PERSPECTIVE

Macular oedema: the role of soluble mediators

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Extracellular accumulation of fluid resulting in oedema is well tolerated in most tissues of the body, but in the retina, it results in dysfunction of retinal neurons. Collection of fluid in the macula is called macular oedema and when the fovea is involved, it results in decreased visual acuity. Macular oedema occurs in a wide variety of ocular diseases and is one of the most prevalent causes of vision loss in developed countries. It is the most common cause of vision loss in patients with diabetic retinopathy¹ and in other ischaemic retinopathies such as branch and central retinal vein occlusion.²⁻³ Macular oedema is also a major cause of decreased vision following intraocular surgery. In the literature, the term cystoid macular oedema (CMO) is often used to describe oedema occurring after surgery,⁴ because collection of fluid in the macula often results in cystic changes that are visible by ophthalmoscopy. However, cystic changes can occur with any type of macular oedema, and therefore the term post-surgical macular oedema is preferred when referring to oedema occurring after any type of intraocular procedure. Macular oedema is also a frequent complication of uveitis regardless of aetiology⁵ and is commonly seen in patients with retinitis pigmentosa.⁶ Thus, macular oedema is a component of many different types of pathological conditions and is an enormous clinical problem.

Macular oedema results from breakdown of the blood-retinal barrier

Extravascular accumulation of fluid in the retina is normally prevented by the blood-retinal barrier (BRB). The BRB consists of adaptations of retinal blood vessels (inner BRB) and the retinal pigmented epithelium (RPE; outer BRB) that control access of fluid and solutes to the retina. One adaptation is the presence of tight junctions between adjacent retinal vascular endothelial (RVE) cells and between adjacent RPE cells. Other adaptations include an abatement in vesicular transport in RVE cells compared with vascular endothelial cells in skin⁷⁻⁸ and asymmetrical distribution of proteins that regulate vectorial transport across RPE cells.⁹

Breakdown of the BRB can occur in a variety of ways. Any insult involving RVE or RPE cells results in BRB breakdown that is usually repaired rapidly unless the source of damage is persistent. For example, laser photocoagulation results in death of RPE cells with accompanying BRB breakdown, but the barrier is rapidly re-established by repopulation of the involved area with RPE cells that form tight junctions.¹⁰ In patients with diabetic retinopathy, death of pericytes results in microaneurysm formation and focal vascular leakage.¹¹⁻¹² Focal leakage may be due to loss of pericyte and/or glial derived signals or structural changes in endothelial cells caused by microaneurysm formation.¹³ In addition, there is often diffuse breakdown of the BRB in these patients and in patients with other ischaemic retinopathies, which is not associated with identifiable structural changes.¹⁴ Fluores-

cein angiography demonstrates staining of vessel walls and leakage from retinal vessels adjacent to areas of ischaemic retina,¹⁵ suggesting that a diffusible agent released by ischaemic retina may be involved. In patients with macular oedema occurring after cataract surgery, the surgical wound is remote from RVE and RPE cells, while in patients with macular oedema due to uveitis, inflammatory cells are often limited to the anterior chamber and/or anterior vitreous, again suggesting that diffusible factors are involved.

Current treatments for macular oedema are empirical and often ineffective

Since the molecular mechanisms of various types of macular oedema are unknown there are no specific treatments. Instead, non-specific anti-inflammatory treatment is used for all types of macular oedema except that associated with ischaemic retinopathies for which laser treatment is used. After cataract surgery, topical non-steroidal anti-inflammatory drugs (NSAIDs) help to prevent angiographic macular oedema and result in some improvement in vision in some patients who have had macular oedema for more than 6 months.¹⁶⁻¹⁷ However, some NSAIDs have been implicated in corneal melts occurring after cataract or refractive surgery. Corticosteroids have not been proved to be effective in a randomised, placebo controlled study, but are frequently used for the treatment of macular oedema. Acetazolamide provides some small benefit for certain types of macular oedema.¹⁸ Many patients with macular oedema do not benefit from current treatments, and therefore new, specific treatments are needed.

Soluble factors implicated in BRB breakdown

In ischaemic retinopathies, vascular endothelial growth factor (VEGF) and adenosine, released from the ischaemic tissue, are capable of causing BRB breakdown and contributing to macular oedema.¹⁹⁻²¹ Histamine has also been implicated as a possible mediator of BRB dysfunction in patients with diabetes.²²⁻²³ Systemic administration²⁴ or sustained intravitreal release²⁵ of insulin-like growth factor 1 (IGF-1) causes breakdown of the BRB. Recently a somatostatin analogue that antagonises IGF-1 has been demonstrated to decrease idiopathic macular oedema²⁶ and macular oedema associated with ocular inflammatory disease (PM van Hagen, personal communication, March 1999), suggesting that IGF-1 may play a part in several types of macular oedema.

Ocular tissues respond to injury, including surgical trauma, by the activation of phospholipases which in turn cause release of membrane phospholipids. Activation of phospholipase A2 is the first step in the synthesis of lipid second messengers, including prostaglandins (PGs), leukotrienes, and platelet activating factor (PAF). PAF, the most active inflammatory mediator known,²⁷ has been shown to promote vascular permeability in a number of different vascular beds²⁷⁻³⁰ including the retinal

vasculature.³¹ PGs are thought to contribute to the pathogenesis of post-surgical and inflammatory macular oedema for several reasons. Firstly, PGE1, PGE2, and PGF2 α are produced in the iris as a result of surgical trauma and increased levels may persist for weeks after surgery.^{4 32 33} Secondly, PGs can cause disruption of the blood-retinal and the blood-aqueous barriers.^{19 34 35} Finally, indomethacin, an inhibitor of PG synthesis, reduces both the incidence and severity of macular oedema after lens extraction^{4 36} and the PGE activity in the aqueous humour of postoperative eyes.^{4 33}

Tumour necrosis factor α (TNF α) and interleukin 1 (IL-1) α and β are proinflammatory cytokines that have been implicated in ocular inflammatory diseases.³⁷ Intravitreal injection of TNF α or IL-1 β causes BRB breakdown and infiltration with inflammatory cells similar to that seen in experimental autoimmune uveoretinitis (EAU) and other models of inflammatory eye diseases.³⁸⁻⁴² In addition, rats with EAU show dramatic upregulation of VEGF that is temporally and spatially correlated with BRB breakdown.^{43 44} Therefore, VEGF, which is known to be associated with macular oedema in ischaemic retinopathies, may also contribute to macular oedema in ocular inflammatory disorders. The finding that octreotide, a somatostatin analogue, shows some benefit for macular oedema in ocular inflammatory diseases would also tend to support a role for IGF-1.

Animal models for macular oedema

It is difficult to model macular oedema, because only higher animals have a macula and because it is a chronic disease process. In addition, the pathophysiology may be very different in different disease settings and our understanding of its pathophysiology in any setting is incomplete. For these reasons, much of our efforts have focused on pathological specimens from patients with macular oedema.^{13 45-49} These studies have provided important insights. For instance, the correlation of VEGF expression with sites of BRB breakdown in eyes of patients with choroidal melanomas⁴⁹ was the first suggestion that VEGF may contribute to BRB breakdown, both in ischaemic retinopathies and other disease processes. However, testing mechanistic hypotheses requires animal models.

Models of post-surgical macular oedema in monkeys mimic important features of the disease in humans,^{50 51} but are extremely expensive and are not feasible for biochemical or molecular investigations. Diabetic animals, including humans, develop mild breakdown of the BRB soon after the onset of hyperglycaemia,⁵² but it is not clear if this has any relevance to macular oedema, which does not develop until years later.

There are models of ocular inflammatory disease, the best characterised of which is EAU which has been established in both rats^{53 54} and mice.^{55 56} EAU is a very severe form of uveitis, which provides a brief period in its early stages when it can be used to study the effects of ocular inflammation on the BRB, after which there is destruction of the retina. IL-1 β and TNF α ⁵⁷ have been implicated as mediators of inflammatory cell recruitment and, although it has not been directly demonstrated, it is thought that these mediators may also contribute to BRB breakdown.

An alternative approach to the modelling of disease processes associated with macular oedema is to perform intravitreal injections of mediators suspected to play a part in these disorders to study their effects on the BRB. Studies of this type in rabbits have provided insights regarding potential mediators and the mechanisms by which they compromise the BRB,^{19 31 37 58-60} but although rabbit retinal vessels have tight junctions and form a BRB, their limited distribution to the central retina and the rela-

tive lability of the BRB in rabbits, raise questions regarding the relevance of findings in rabbits to human disease processes. Rats and mice have holangiotic retinas that are similar to humans in most respects, except for the absence of a macula. This is probably not of major consequence because while macular oedema derives its name from the part of the retina where oedema has visual significance, leakage and oedema are not limited to the macula; there is diffuse leakage from retinal vessels, and to a lesser extent through the RPE.^{13 48}

Investigations aimed at understanding the causes of BRB breakdown and how it can be treated or prevented can therefore be done in rodents. Intravitreal injection of TNF α , IL-1 β , or IL-8, but not IL-6, causes BRB breakdown in Lewis rats.³⁸⁻⁴¹ Comparison of the effects on the BRB of injection of TNF α , IL-1 β , or VEGF to ultrastructural changes seen in the BRB in rats with EAU showed many similarities supporting the validity of this approach and suggesting that these particular mediators may be involved.⁴² A histamine H₂ receptor antagonist significantly inhibited the IL-1 β induced breakdown of the BRB in rats, suggesting that the IL-1 β effect on the BRB is mediated, at least in part, through histamine.⁴⁰ Additional studies such as these are needed to compare and contrast the acute effects on the BRB of potential mediators of macular oedema, but it is also important to investigate long term effects.

One way to investigate long term effects is to utilise sustained release of agents from implants in the vitreous cavity. To investigate this issue, we incorporated VEGF into sustained release polymers and implanted them into the vitreous cavity of rabbits or primates.²⁰ There were some differences in the effect of VEGF on the retinal vasculature between primates and rabbits, adding to our reservations regarding the use of rabbits for these types of studies, but in both rabbits and primates, there was severe BRB breakdown. In primates, there was retinal oedema, including macular oedema, confirming that sustained exposure of VEGF to the retina results in macular oedema.

A more practical approach to investigate the long term effects of VEGF on the retina is to generate transgenic mice with sustained increased expression of potential mediators in the eye. We are currently utilising *Rhodopsin promoter/VEGF* transgenic mice with photoreceptor specific expression of VEGF⁶¹ to determine the effect of sustained increased expression of VEGF on the BRB.

Direct and indirect actions of potential mediators of macular oedema

Based upon vascular leakage studies in rabbit skin, VEGF, histamine, and bradykinin have been classified as direct action mediators because the onset of leakage is rapid and peaks within 30 minutes, no neutrophils are required, and antagonists to PAF have no effect.⁶² The same conclusion regarding VEGF being a direct acting agent was reached based upon studies in rat brain,⁶³ but a study using the Miles assay in guinea pigs⁶⁴ has suggested that VEGF increases permeability indirectly through nitric oxide and PGs. Measuring vascular permeability in several tissues after intradermal injections of VEGF in rats, Sirois and Edelman⁶⁵ found that in some tissues, but not others, VEGF appears to act through PAF. Conversely, in other studies, PAF has been suggested to increase permeability through VEGF,⁶⁶ nitric oxide,^{66 67} or PGs.^{28 30} Therefore, the situation is complex and it is difficult to predict what interactions exist in the retina based upon studies in other vascular beds.

With regard to the retinal vasculature, there is a paucity of information, mostly derived from studies in rabbit eyes. It has been suggested that TNF α and IL-1 β act synergisti-

cally in rabbit eyes to increase permeability of retinal vessels, partially mediated through PGs, but independent of PAF,^{59,60} while, in another study, IL-1 α was found to act indirectly through both PGs and PAF.⁵⁸ In Lewis rats, IL-1 β appears to act indirectly through histamine.⁴¹ Additional studies are needed to clarify the interactions, because there are important therapeutic implications.

In summary, macular oedema is a major cause of visual loss in a large number of ocular conditions. Treatments are empirical and often ineffective. There is evidence suggesting that soluble mediators play a part, but the specific agents involved in each disease process and the manner in which they interact is unknown. Defining the details of the molecular mechanisms in various disease processes is critical for the development of specific therapies.

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