Thromboxane in ocular pathophysiology

Thought provoking communications are the lifeblood of the British Journal of Ophthalmology. Chen et al, in this issue, provide us with such a report, describing the localisation, at the cellular level, of thromboxane A$_2$ receptors and their corresponding mRNA levels in whole human eyes. The significance of their findings appears to be broad based, touching upon several well known but poorly understood phenomena.

Thromboxane A$_2$ (TxA$_2$) is a cell membrane derived lipid, a metabolite of arachidonic acid that exerts four major biological activities: vasoconstriction, platelet aggregation, bronchoconstriction, and membrane destabilisation. It is widely recognised as an important agent in cardiovascular diseases. However, recent evidence suggests a role in the modulation of immunological and inflammatory reactions. Platelets, by far, have the highest synthetic capacity although TxA$_2$ has been identified as a metabolite of other tissues including ocular tissues where its function was postulated primarily in a proinflammatory role. Chen et al have taken these findings to the next level by identifying the TxA$_2$ effector cells, those that express the TxA$_2$ receptor using contemporary autoradiographic binding assays and in situ hybridisation techniques. Their findings indicate that TxA$_2$ receptors are specifically concentrated in the corneal epithelium, the ciliary processes, retina, and the posterior ciliary arteries. From this it seems clear that TxA$_2$ is more than just a vasoactive lipid.

The significance of TxA$_2$ receptors on the corneal epithelium is a matter of speculation but the abundant presence of mast cells in the adjacent conjunctiva, cells known to be laden with TxA$_2$, synthesize and to participate in the early phase of inflammation, especially of an allergic nature, indicates a role in the effector limb of the response to corneal surface injury.

The presence of TxA$_2$ receptors in the non-pigmented epithelium in the ciliary body and retina might explain some of the pathophysiological changes seen in experimental autoimmune uveoretinitis (EAU), a well established model for human autoimmune conditions. In EAU, a massive inflammation occurs in rats with widespread destruction of retinal photoreceptor cells 2 weeks after immunisation with bovine S-antigen, a protein derived from photoreceptor cells. Chen et al recently reported that oral feeding of a TxA$_2$ synthase inhibitor, CGS-13080, postponed the onset of overt EAU, decreased both the incidence and severity of the condition, and inhibited the lymphocytic proliferation response in a dose dependent fashion. This report makes clear the importance of TxA$_2$ in EAU. Li et al, in an earlier report, studied the role of mast cells, presumably, as a source of TxA$_2$, in the immunogenesis of EAU. The breakdown in the blood-aqueous barrier and the massive destruction of photoreceptor cells may be a consequence of the concentrations of TxA$_2$ receptors in the retina and the non-pigmented epithelium of the ciliary body. These speculations should be followed by additional experimental evidence that these receptors function in the binding of TxA$_2$, resulting in cell destruction.

Autoregulation of blood flow, defined as the intrinsic ability of an organ to maintain its blood flow relatively constant despite changes in perfusion pressure, has been described in the choroidal circulation of rabbits and piglets. Thus, the observation that TxA$_2$ receptors are concentrated...
in the posterior ciliary in the human eye is highly significant since these vessels are thought to supply the anterior surface of the optic nerve as well as the choroid. TxA₂ must be considered to be an important mediator in maintaining the fine balance between vasodilatation and vasoconstriction in the maintenance of autoregulation of choroidal blood flow; Chen et al speculate as to the importance of their findings in the pathogenesis of glaucomatous and ischaemic optic atrophy.

One has to keep in mind that the so-called TxA₂ receptor has another equally potent endogenous agonist, the prosta
glandin endoperoxide (PGH₂) which is the final unstable metabolite of the cyclo-oxygenase activity on arachidonic acid and the substrate for the TxA₂ synthase. PGH₂ is also a potent vasoconstrictr and a platelet aggregator. The emerging information regarding different cyclo-oxygenase (COX) genes, in particular the existence of the inducible form, opens a new front in the role of prostanooids in inflammatory and immune related disorders. To date no information is available regarding COX-2 inducibility in ocular inflammation. However, since COX-2 has been shown to be induced in response to inflammatory and immune cytokines in many tissues, it is possible that such activity could exist in inflamed ocular tissues and therefore could increase the amount of TxA₂, receptor agonists, PGH₂ and TxA₁, to significant levels.

Localisation of receptors is a very important step in understanding the pathophysiological impact of any modulator, either endogenously formed or exogenously added as a foreign compound. Localisation should be followed by identification of those receptors as functional receptors – that is, the receptors bind their ligand and this binding provokes a receptor mediated signal transduction ending with the final effect. Chen et al provide us with evidence of functional receptors by presenting a correlation between receptor mRNA and ligand binding. This should follow with functional studies which in all together will bring a promise of new therapeutic opportunities.

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