Phospholipase A2, the neurotrophin pigment epithelial derived factor and lipid mediators regulate corneal nerve regeneration

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The cornea is densely innervated and corneal nerves play a pivotal role in maintaining a healthy ocular surface. Many diseases as well as surgical procedures that affect the cornea can compromise corneal innervation and produce a decrease in tear secretion and epithelial wound healing.

Our previous studies had shown that treatment of rabbit corneas with pigment epithelium-derived factor (PEDF) + docosahexaenoic acid (DHA) increase neuroprotectin D1 (NPD1) synthesis and promote nerve regeneration after experimental surgery. Synthesis of NPD1 occurs after stimulation of phospholipase A2 (PLA2)-15-lipoxygenease-1 (15-LOX-1).

We now show that a PEDF-receptor (PEDF-R) that shares strong homology with members of the Ca-independent PLA2 (iPLA2) is expressed in the plasma membrane of corneal epithelial cells. To investigate the action of PEDF on the release of DHA, rabbit corneas were incubated with 40ng/ml of PEDF for different times, and lipids from epithelia and media were extracted and analyzed by liquid chromatography-mass spectrometry (LC-MS/MS). After 5 minutes of incubation, there was an increase in the release of DHA and in the synthesis of 15-hydroxyeicosatetraenoic acid (15-HETE), a product of the 15-LOX. In the presence of the iPLA2 inhibitor bromoenol lactone (BEL, 50μM), there was inhibition of DHA release and 15-HETE synthesis. Our results show that the mechanism of corneal nerve regeneration induced by PEDF requires the activation of a PEDF-R with activity of iPLA2 and the release of DHA to synthetize NPD1.

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