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Relative Contribution of Different Upper Glycolytic Components in the Maintenance of the Retinal Vascular Endothelial Cell Barrier

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**Relative Contribution of Different Upper Glycolytic Components in the Maintenance of the Retinal Vascular Endothelial Cell Barrier**

**Introduction:** Damage to the retinal vascular endothelium is implicated in the progression of retinal degenerative diseases, including diabetic retinopathy (DR) and diabetic macular edema (DME). The retinal endothelial cells constitute the inner blood-retinal barrier (iBRB), and disruption of this barrier allows for the dysregulation of fluid and solute passage into the retina. Moreover, under normal physiological conditions, glycolytic metabolism is critical to the functioning of endothelial cells and maintenance of the iBRB. Conversely, in hyperglycemic environments, unregulated glycolytic metabolism leads to a buildup of glycolytic intermediates, which is thought to contribute to disruption of the iBRB and is associated with retinal cell damage and neovascularization. However, the metabolic mechanisms underlying these processes remain unclear. In this study, we looked to further characterize the roles of upper glycolytic enzymes, those involved in the ATP consumption phase of glycolysis, in the maintenance of the iBRB.

**Methods:** Electric cell-substrate impedance sensing (ECIS) technology was used to assess in real-time the role of different glycolytic enzymes in maintaining the barrier functionality of human retinal endothelial cells (HREC). Furthermore, the endothelial cellular viability was assessed through lactate dehydrogenase cytotoxicity assay following 24h, 48h, and 72h time intervals.

**Results:** Inhibition with heptelidic acid (glyceraldehyde-3-phosphate dehydrogenase (GA3PDH) inhibitor) significantly reduced the resistance (R) and thus the integrity of the HREC barrier at concentrations of 1.0 μM and 10 μM. PFK158 (phosphofructokinase-1 (PFK1) inhibitor) also significantly reduced R, but only at a concentration of 10 μM. Similarly, administration of PFK158 reduced HREC viability throughout all three time intervals (24h, 48h, and 72h) at a concentration of 10 μM. However, administration of heptelidic acid showed reduced HREC viability only at the 72h time interval, but also at a concentration of 10 μM. The other inhibitors tested did not demonstrate significant reduction in resistance of the HREC barrier or in cellular viability.

**Conclusion:** Our study demonstrates the differential roles of glycolytic enzymes in maintaining the barrier functionality of HRECs. We specifically showed that the functions of GA3PDH and PFK-1 are the most important components in regulating HREC barrier integrity. These observed differences are significant since they could serve as the basis for future pharmacological and gene expression studies aiming to improve the activity of GA3PDH and PFK1 and thereby provide avenues for therapeutic modalities in endothelial-associated retinal diseases.

**Keywords:** ECIS, HREC, diabetic retinopathy (DR), diabetic macular edema (DME), retinal vascular endothelium, iBRB, glycolysis, resistance, barrier integrity