

## Ameliorative effect of VIP family members on blood retinal barrier breakdown in diabetic macular edema

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Diabetic macular edema (DME) is one of the main complications of diabetic retinopathy [1]. This pathology is owed to impairment of the blood-retinal barrier (BRB) [2]. Many factors, such as hypoxia, contribute to barrier dysfunction and progression of the disease. Low oxygen tension is one of the main events involved in the formation of new blood vessels that characterize the typical uncontrolled angiogenesis in proliferative stage of diabetic retinopathy. In the last decades, various studies have focused their attention on the role of pituitary adenylate cyclase-activating polypeptide (PACAP) and vasoactive intestinal peptide (VIP) in the pathophysiology of DME. However, the effects of these peptides in maintaining the integrity of the BRB exposed to hypoxia remains to be elucidated. In the present work we have studied, for the first time, the effect of these peptides on outer BRB integrity following hypoxic insult in an experimental model of DME. To this end, we have used the human retinal pigment epithelial cells (ARPE-19) to test the effect of both peptides on cellular permeability, transepithelial electrical resistance, tight junctions expression and hypoxia-induced apoptosis. Results have demonstrated that both PACAP and VIP are able to rescue the integrity of cell monolayer during the hypoxic event, minimizing apoptotic damages induced by low tissue oxygen tension through the activation of phosphoinositide 3 kinase /Akt and mammalian mitogen activated protein kinase/Erk kinase signaling pathways. Furthermore, these peptides modulate the expression of vascular endothelial growth factor which is one of the downstream transcription factor activated during the hypoxic process. In conclusion, we have demonstrated that PACAP and VIP are able to counteract the damage induced by hypoxia on BRB through the modulation of hypoxia inducible factors expression.

### References

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### Keywords

PACAP; VIP; diabetic macular edema; blood-retinal barrier.