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Ameliorative effect of PACAP and VIP against increased permeability in a model of outer blood retinal barrier

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Diabetic retinopathy (DR) is one of the leading causes of blindness and vision loss in adults. A recent study has demonstrated that compromised tight junctions, basement membrane thickening and increased vascular permeability contribute to the disruption of the outer blood-retinal barrier (BRB) in DR. The outer BRB is formed by retinal pigmented epithelial cells and controls the flow of solutes and fluid from the choroidal vasculature to the outer retina. Previous studies have shown that pituitary adenylate cyclase activating polypeptide (PACAP) and the related peptide vasoactive intestinal polypeptide (VIP) are protective against several types of retinal injuries, including DR. However, whether these peptides are involved in maintenance of outer BRB function during DR remains to be elucidated. Here, using an *in vitro* model of dysfunctional outer BRB, we explored the effects of both PACAP and VIP. Retinal pigment epithelial cells (ARPE19) were cultured for 18 days either in normal glucose (NG, 5.5 mM) or in high glucose (HG, 25mM). In addition, to mimic the inflammatory aspect of the diabetic milieu, HG cells were also treated with IL-1β (HG + IL-1β). Effects of PACAP or VIP on cells permeability were evaluated by measuring both transepithelial electrical resistance (TEER) and apical-to-basolateral movements of fluorescein isothyocyanate (FITC) dextran. mRNA and protein expression of tight junction-related proteins (ZO-1, occludin and claudin, respectively) were evaluated by real-time PCR (RT-PCR) and Western blot analyses. Our results show that cells grown in HG or in HG + IL-1β show significantly increased FITC-dextran diffusion, which is paralleled by a decrease in TEER as compared to NG cultures. Treatment with either PACAP or VIP were able to reverse both of these effects. Induction of claudin expression was observed both in cell cultures grown in HG alone or cotreated with IL-1β, which was totally abrogated by PACAP and, to a minor extent, by VIP. Neither ZO-1 nor occludin seemed to be affected in our experimental model. In conclusion, the present finding show that PACAP and VIP are able to counteract HG- or HG + IL-1β-induced damage in ARPE19 cells, suggesting that both peptides might be relevant to the maintenance of outer BRB function during DR, possibly through the modulation of claudin.

Keywords: PACAP, VIP, outer blood retinal barrier, diabetic retinopathy.