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Effects of PACAP and VIP on hyperglycemia-induced cell proliferation in murine microvascular endothelial cells

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Hyperglycemia is implicated both in micro- and macrovascular complications in diabetes mellitus. Pituitary adenylate cyclase-activating polypeptide (PACAP) and vasoactive intestinal polypeptide (VIP) are two known nonclassic regulators of angiogenesis, although their biological role on endothelial cell proliferation remains poorly defined. In the present study we investigated both peptides effect on cell proliferation of murine microvascular endothelial cells (H5V) cultured both under normoglycemic and hyperglycemic (25mM glucose) conditions for 24h, 48h, 7 and 15 days.

Results demonstrated that high glucose treatment induced a time-dependent increase in cell viability within 48h ($p<0.05$), which was much more evident after 7 and 15 days ($p<0.001$). Similar effects were observed in cell proliferation, although significant changes were obtained after prolonged exposures to high glucose (7 and 15 days; $p<0.001$). The proliferative response to the glucose-enriched environment was correlated to changes in the expression of PAC1, but not VPAC1 and VPAC2 receptors, as measured by quantitative real time PCR. These results were further confirmed by Western blot and immunofluorescence analyses. Interestingly, 100nM PACAP or VIP treatment significantly attenuated hyperglycemia-induced cell viability and proliferation after 7 and 15 days. Taken together, our findings demonstrated that both PACAP and VIP peptides exert an inhibitory activity on hyperglycemia-induced endothelial cell proliferation, and further suggest that the effect might be mediated by PAC1 receptors.

Key words
PACAP, VIP, endothelial cells, proliferation