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Induction of tissue plasminogen activator (tPA) by pituitary adenylate cyclase-activating polypeptide (PACAP) in Schwann cell-like cultures

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Peripheral nerve regeneration is dependent on the ability of regenerating neurites to migrate through cellular debris and altered extracellular matrix at the injury site, grow along the residual distal nerve sheath conduit, and reinnervate synaptic targets. In cell culture, growth cones of regenerating axons secrete PACAP, a peptide known to induce the expression of the protease tPA[1]. Here we tested the hypothesis that PACAP might also stimulate peripheral glial cells to release tPA to participate in nerve regeneration. More specifically, we addressed whether PACAP promoted the release and expression of tPA in the Schwann cell-like culture RT4-D6P2T, which shares biochemical and physical properties with Schwann cells[2]. We found that PACAP dose- and time-dependently stimulated tPA expression. Maxadilan, a potent PACAP receptor agonist, mimicked the effect of PACAP, whereas VIP, a PACAP-related peptide, produced only a moderate response. PACAP ability to stimulate tPA expression seemed to be dependent on the Akt/CREB signaling cascade, as inhibition using the PI3K/Akt blocker wortmannin or the TrkA/B inhibitor K252a both significantly dampened PACAP-evoked tPA expression. A similar effect was obtained in cells treated with the PACAP/VIP receptor antagonist PACAP6-38. We conclude that PACAP through the Akt/CREB intracellular pathway, acts as a potent inducer of tPA expression and release in Schwann-cell like cultures.

References

[1] Raoult et al. (2011) Pituitary adenylate cyclase-activating polypeptide (PACAP) stimulates the expression and the release of tissue plasminogen activator (tPA) in neuronal cells: involvement of tPA in the neuroprotective effect of PACAP. J Neurochem 119: 920-31.
[2] Castorina et al., (2014) PACAP and VIP increase the expression of myelin-related proteins in rat schwannoma cells: involvement of PAC1/VPAC2 receptor-mediated activation of PI3K/Akt signaling pathways. Exp Cell Res 322: 108-21.

Keywords
Tissue plasminogen activator, PACAP, Schwann cells, nerve injury, serine proteases.