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PACAP and VIP increase the expression of myelin-markers in rat schwannoma cells

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Defining the mechanisms regulating peripheral myelinogenesis in vitro remains a daunting task. One of the major complications is related to the inability of Schwann cells to produce myelin in vitro. However, a limited number of schwannoma cell lines are now being accepted as adequate model systems to study myelin expression since they present most of the features that characterize normal myelinating Schwann cells. PACAP and VIP peptides have been shown to play part in myelin maturation and synthesis in the central nervous system, but no data regarding their potential actions have been reported in the peripheral nervous system, particularly in vitro. In this study, we investigated the effects of both peptides on the expression of myelin-specific markers using the well-established rat RT4 schwannoma cell line. In addition, we endeavored to partly unravel the underlying molecular mechanisms involved. Expression of myelin-specific markers (MAG, MBP and MPZ, respectively) was assessed in cells grown either in the presence of normal serum (10% FBS) or serum starved and treated with or without 100nM PACAP or VIP. Effects of pharmacological blockade of PACAP and VIP receptors as well as of the main signaling pathways on the expression of myelin-markers were also determined. Our data shows that serum starvation (24h) was sufficient to induce a significant increase in the expression of myelin markers. This result was paralleled by a concurrent increase in the endogenous expression of both peptides, as well as of the non-specific PACAP/VIP receptor 2 (VPAC2), but not of VPAC1 or PAC1. Exogenous PACAP or VIP treatment further exacerbated starvation-driven expression of myelin markers, suggesting an active role of these peptides in myelin generation. Interestingly, stimulation with either peptides increased phosphorylation levels of Akt at Ser473 residue whereas they did not affect Erk1/2 activation. Treatment with the PAC1 receptor antagonist (PACAP6-38) had no effects on myelin markers expression while a non-specific VPAC receptor antagonist completely abrogated both starvation and/or starvation + peptide-induced expression of myelin markers. Similar effects were obtained in cell pretreated with the PKA inhibitor (H-89, 10μM), suggesting that peptide-driven induction of myelin markers occurs preferentially via the canonical PKA/Akt signaling pathway. In conclusion, the results here presented provide the basis for future studies on the role of these peptides in physiological myelination and in demyelinating pathologies such as Charcot-Mary-Tooth disease.

Key words

Myelin, PACAP, VIP, peripheral nerve sheath tumor, myelin-associated glycoprotein, myelin basic protein, protein zero.

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