Pituitary Adenylate Cyclase Activating Polypeptide (PACAP) An Antimitogenic Signal for Neuronal Precursor Cells

Background

The developing forebrain contains precursor neuronal cells that give rise to the various types of neuronal cells of the hippocampus, cortex and subventricular zone. In a developing brain, a tight control over the proliferation of neuronal precursors is required for regulating the final size of the cortex. Pituitary Adenylate Cyclase Activating Polypeptide (PACAP) has been implicated in neurogenesis although its precise role *in vivo* has not been determined.

Pituitary Adenylate Cyclase Activating Polypeptide (PACAP) is a 38 amino acid hypothalamic neuropeptide with adenylate cyclase stimulating activity. PACAP has significant homology to Vasoactive Intestinal Polypeptide (VIP) and interacts with three well-characterized G-protein coupled receptors termed VPAC 1, VPAC2, and PAC_1. The VPAC 1 and VPAC2 receptors bind to both PACAP and VIP, while PAC_1 is highly specific to PACAP. PAC_1 is expressed in both neuronal and non-neuronal tissues such as pancreas, ovaries and adrenal glands. Previous studies with PACAP have revealed this neuropeptide to be expressed during neurogenesis in both central and peripheral nervous systems. Also, PACAP and its receptors are expressed in the neurons of developing embryos, in neonatal brain, and the mature forebrain, suggesting roles in neural development and adult neurogenesis. **Determination of the factors that influence neuron regeneration would be medically beneficial to the modulation and management of diseases affecting the forebrain such as epilepsy, dementia, prion disorders, brain injury and stroke.**

Description of the Technology

Using immunohistochemical analysis both PACAP and PAC_1 receptor were detected in the embryonic cortical precursor cells but not in the corresponding skull or skin regions. Administration of PACAP inhibited mitosis and neurogenesis in the lateral ventricles of the embryonic brains. Further, to define the role of PACAP signaling, P-CREB signal was assessed and found to be enhanced in cortical precursors with a subsequent reduction in DNA synthesis. This inhibition of DNA synthesis was determined to be due to a decrease in the number of precursor cells entering the S-phase of mitosis suggesting a definitive role for PACAP in the control of proliferation of precursor cells of the embryonic forebrain. Next, a sand fly peptide antagonist termed M65 was used to assess if PACAP interferes with ongoing mitosis. The antimitogenic effects of endogenous PACAP were reversed significantly thereby indicating that PACAP is anti-mitogenic *in vivo*. These studies open the possibility of exploiting PACAP and its receptors in the regulation of cellular proliferation in diseases affecting the forebrain in both developing and adult brain.

Applications

. • For the treatment of neurodegenerative diseases of the forebrain such as stroke, dementia, prion disorders, and brain injury.
. • For the treatment of developmental diseases such as epilepsy, cerebral palsy and brain injury.
. • For the inhibition of brain neoplasms including medulloblastoma, primitive neuroectodermal tumors, gliomas and glioblastomas.
. • For the development of agonists of PACAP receptor or antagonists of PACAP
. • For the manipulation of proliferation of neuronal cells (either regeneration or

suppression of the proliferation of neuronal cells).

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Patent Status

. •United States application filed.
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Licensing Opportunity

This technology is available for exclusive license.

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