ADCYAP1 (adenylate cyclase activating polypeptide 1 (pituitary))

Terry Moody
National Cancer Institute, Center for Cancer Research, Office of the Director, 9609 Medical Center Drive, Rm 2W130, Bethesda, Maryland 20892, USA (TM)

Published in Atlas Database: September 2014
Online updated version: http://AtlasGeneticsOncology.org/Genes/ADCYAP1ID43656ch18p11.html
DOI: 10.4267/2042/62257
This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2015 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Abstract
Review on ADCYAP1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity
Other names: PACAP
HGNC (Hugo): ADCYAP1
Location: 18p11.32
Local order:
The PACAP gene has 5 exons.
Note: PACAP-27 or PACAP-38 are secreted proteins which binds to membrane G-protein coupled receptors (GPCR) increasing intracellular cAMP signaling.

DNA/RNA
Note
The ADCYAP1 gene encodes 5 exons and is localized to chromosome 18p11 (Kimura et al., 1990). Exons 1 and 2 encode for the 5'UTR and the signal peptide. Exon 3 encodes for the N-terminal of pro-PACAP upstream from PRP. PRP is encoded by Exon 4. Exon 5 encodes for the C-terminal of pro-PACAP including PACAP-27, PACAP-38 and the 3'UTR (Vaudry et al., 2009).

Description
The PACAP gene which contains 7230 bases is highly conserved in nature (Sherwood et al., 2000).

Transcription
The gene transcript is 2.7 kb (Ghatei et al., 1993).

Protein
Note
Pituitary adenylate cyclase-activating polypeptide (PACAP) was isolated from ovine hypothalamus and contains 38 amino acids.
PACAP-38 elevates cAMP in rat pituitary cells in culture (Miyata et al., 1989).
PACAP-27 was isolated from ovine hypothalamus and had the same N-terminal 27 amino acids as does PACAP-38 (Miyata et al., 1990).
PACAP-27 has high homology with vasoactive intestinal peptide (VIP) and moderate homology with PRP.
The PACAP-38 amino acid sequence is identical in mammals.
PACAP has a β-turn at residues 9-12, followed by an α-helix at residues 12-14, 15-20 and 22-24 (Inooka et al., 1992). PACAP binds with high affinity to 3 GPCR (VPAC1, VPAC2 and PAC1) which are members of the class II or class B secretin-like receptors (Harmar et al., 2012).
The activated VPAC1, VPAC2 or PAC1 interacts with a stimulatory guanine nucleotide binding protein (Gs) increasing adenylylcyclase activity resulting in elevated cAMP (Arimura et al., 1992).
The increased cAMP activates protein kinase (PK) A causing phosphorylation of various proteins such as CREB leading to altered gene expression (Moody et al., 2003).
ADCYAP1 (adenylate cyclase activating polypeptide 1 (pituitary))

Moody T

Atlas Genet Cytogenet Oncol Haematol. 2015; 19(8) 496

Structure of human prepro-PACAP. Human prepro-PACAP (1-176) is metabolized by signal peptidases to generate pro-PACAP (26-176). Pro-PACAP is metabolized by pro-hormone convertases to (26-79), big PACAP-related peptide (82-129; PRP) and PACAP-38. Pro-PACAP (26-176) can further be metabolized to PRP (82-109) and PACAP-27 by other enzymes. PACAP is derived from the 176 amino acid precursor protein prepro-PACAP. Initially the signal peptide (1-25) is cleaved by signal proteases to generate pro-PACAP (26-176). Pro-PACAP is metabolized by pro-hormone convertases and carboxypeptidases to (26-79), (82-129) and (132-170). The C-terminal peptides (132-170) and (132-159) are metabolized to by peptidylglycine alpha-amidating monooxygenase enzymes to PACAP-38 and PACAP-27, respectively, which have amidated C-terminals.

In addition, PAC1 interacts with Gq causing phosphatidylinositol (PI) turnover (Pisegna and Wank, 1996). The resulting metabolites inositol-1,4,5-trisphosphate and diacylglycerol increases cytosolic calcium and activates protein kinase C, respectively.

Expression
PACAP is produced in neurons within the adenals, brain, gastrointestinal (GI) tract, pituitary and testis (Ghatei et al., 1993). Addition of PACAP to adrenal chromaffin cells causes catecholamine release (Watanabe et al., 1990). High densities of PACAP are present in the hypothalamus and PACAP as well as glutamate shift the circadian rhythm in the suprachiasmatic nucleus (Vaudry et al., 2009). In the gastrointestinal tract PACAP stimulates the secretion of saliva, gastric acid, bicarbonate and peptides leading to myorelaxation (Moody et al., 2011). In PACAP knockout mice or mice treated with PACAP (6-38) there is reduced insulin secretion after glucose challenge (Shintani et al., 2003). In pituitary cells, PACAP elevates cAMP increasing the secretion of LH, GH, PRL, ACTH and TSH (Vaudry et al., 2009). The results indicate that PACAP is present in the normal CNS and periphery.

Localisation
Prepro-PACAP is stored in dense core neurosecretory granules in cells. In cellular extracts approximately an order of magnitude more PACAP-38 is detected than PRP or PACAP-27. PACAP-38 and PACAP-27 have approximately an order of magnitude more biological activity than does PRP (Fahrenkrug, 2010). PACAP is metabolized by neutral endopeptidase and has a half life of 5 min.

Function
PACAP alters neurotransmitter release in the CNS, causes increased insulin and histamine secretion in the periphery, controls vasodilation, bronchodilation alters intestinal motility and stimulates cellular proliferation as well as differentiation (Vaudry et al., 2009).

Homology
VIP has 67% sequence homology with PACAP-27. The sequence for PACAP-38 is identical in mammals (Fahrenkrug, 2010).

Mutations
Note
Sequence mutations of PACAP-38 are rare. Numerous mutations of PAC1 have been reported including deletions, which affect PACAP binding (PAC1 short; PAC1 very short) and splice variants, which affect signal transduction (hip, hop1, hop2; Blechman and Levkowitz, 2013). SNP rs2267735 of PAC1 is associated with post-traumatic stress disorder (PTSD) in females (Ressler et al., 2011).

Implicated in
Lung cancer
PACAP-38 immunoreactivity is higher in the human lung cancer than normal lung biopsy specimens (Szanto et al., 2012). PAC1 is present in lung cancer cells and PACAP (6-38) inhibits their proliferation (Zia et al., 1995). PACAP-27 may stimulate lung cancer proliferation as a result of EGFR transactivation (Moody et al., 2012).

Breast cancer
A 19.9 kDa prepro-PACAP was detected in human breast cancer biopsy specimens (Garcia Fernandez et al., 2004). PACAP-27 stimulated and PACAP (6-38) inhibited the growth of breast cancer cells (Leyton et al., 1999).

Colon cancer
PACAP knockout mice but not wild type mice develop colitis and colorectal tumors after treatment with dextran sulfate sodium (Nemetz et al., 2008). PACAP-38 stimulates the growth of colon cancer cells (Le et al., 2002).
**Pheochromocytoma**

PACAP increases the cAMP after addition to PC12 adrenal pheochromocytoma cells (Watanabe et al., 1990) and causes catecholamine secretion (Taupenot et al., 1999). PACAP addition to PC12 cells increases their survival as a result of Trk receptor tyrosine kinase phosphorylation and activation of Akt (Rajagopal et al., 2004).

**Pituitary adenoma**

PACAP inhibits apoptosis caused by TGFβ addition to human pituitary adenoma cells (Oka et al., 1999). PAC1 receptor mRNA was present in all pituitary adenoma cells except prolactinomas (Oka et al., 1998).

**Medulloblastoma**

Disruption of a single copy of the PACAP gene increased medulloblastoma incidence in ptc1 mutant mice 2.5-fold (Lelievre et al., 2008).

**Diabetes**

ADCYAP1 stimulates insulin secretion in a glucose-dependent manner (Filippson et al., 2001). Two SNPs g.9863G>A, G54D in exon 3, and g.12712C>G in exon 5 were found in European type 2 diabetic patients (Gu et al., 2002).

**Neuronal survival**

PACAP stimulates neurite outgrowth and enhances neuronal cell survival (Canonico et al., 1996). PACAP addition to rat cerebellar neurites increases cAMP and inhibits caspase-3 activity (Vaudry et al., 2009).

**Schizophrenia**

In PACAP knockout mice and schizophrenic patients, brain strathmin I is up-regulated (Hashimoto et al., 2007). PACAP reduces Strathmin I in animal models of schizophrenia by inhibiting the association of the DISC1-binding zinc-finger protein with DBZ (Katayama et al., 2009).

**References**


Gu HF. Genetic variation screening and association studies of the adenylate cyclase activating polypeptide 1 (ADCYAP1) gene in patients with type 2 diabetes. Hum Mutat. 2002 May;19(5):572-3

Le SV, Yamaguchi DJ, McArdle CA, Tachiki K, Pisegna JR, Germaino P. PAC1 and PACAP expression, signaling, and
Fahrenkrug J. VIP and PACAP. Results Probl Cell Differ. 2010;50:221-34
Moody TW, Ito T, Osefo N, Jensen RT. VIP and PACAP: recent insights into their functions/roles in physiology and disease from molecular and genetic studies. Curr Opin Endocrinol Diabetes Obes. 2011 Feb;18(1):61-7