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Gene Section

Review

ADCYAP1 (adenylate cyclase activating polypeptide 1 (pituitary))

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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).

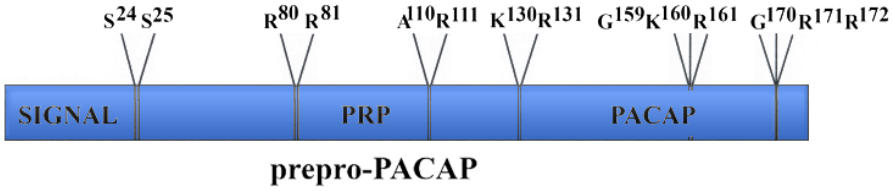
PACAP-27 was isolated from ovine hypothalamus and had the same N-terminal 27 amino acids as does PACAP-38 (Miyata et al., 1990).

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).



Structure of human prepro-PACAP. Human prepro-PACAP (1-176) is metabolized by signal proteases 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 be further 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 adrenals, brain, gastrointestinal (GI) tract, pituitary and testis (Ghatei et al., 1993). Addition of PACAP to adrenal chormaffin 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 prolactnomas (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 (Filipsson 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 DISCI-binding zinc-finger protein with DBZ (Katayama et al., 2009).

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