

Vasoactive Intestinal Peptide (and Related Peptides) Receptors

Key References

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Overview

Vasoactive intestinal peptide (VIP) is an amidated 28 amino acid peptide first isolated from porcine duodenum. It functions as a neurotransmitter and neuroendocrine hormone, activating adenylyl cyclase through G protein-coupled receptors. VIP has a number of actions in the periphery, including vascular and non-vascular smooth muscle relaxation, vasodilatation and electrolyte secretion. The presence of VIP and VIP receptors in defined pathways in brain indicates that it may play important roles in CNS function, including regulation of cerebral energy metabolism, cerebral blood flow and neuronal survival. Exogenous VIP stimulates prolactin secretion from the pituitary and catecholamine release from the adrenal medulla. In the immune system, it inhibits mitogen-activated proliferation of T cells by inhibiting interleukin-2 production. Its anti-inflammatory and anti-injury effects have been demonstrated at several sites and include inhibition of TNF- α and other pro-inflammatory cytokines, and suppression of nuclear transcription factor NF κ B activation. Lastly, VIP is present in the ovary and can stimulate oocyte maturation and induce steroidogenesis.

Pituitary adenylyl cyclase activating polypeptide (PACAP) was identified and purified on the basis of its ability to stimulate the accumulation of cAMP in rat pituitary cells in culture. Two forms of PACAP have been isolated from the hypothalamus, one of 38 amino acids (PACAP-38) and a C-terminally truncated form of 27 amino acids (PACAP-27). PACAP is closely related to VIP (68% sequence homology within the N-terminal 28 residues) and more distantly related to glucagon, glucagon-like peptide I (GLP), peptide histidine isoleucine amide (PHI),

secretin and growth hormone releasing factor (GRF). PACAP has a distinct distribution in the central and peripheral nervous systems, where it is thought to function as a neurotransmitter. In addition, PACAP has been proposed to control the synthesis and secretion of catecholamines from the adrenal medulla and to regulate pancreatic exocrine activity. The presence of PACAP receptors in the reproductive tract has led to the suggestion that PACAP may have a role in the control of spermatogenesis.

Receptors for VIP and PACAP are members of a distinct family of seven transmembrane receptors coupled to G proteins. Other members of this family include receptors for secretin, GRF, glucagon, glucagon-like peptide, calcitonin, calcitonin gene-related peptide, parathyroid hormone and corticotrophin releasing factor. PACAP exhibits a high affinity for three distinct receptors (PAC₁, VPAC₁ and VPAC₂ receptors). Two of these, VPAC₁ and VPAC₂, are also high affinity receptors for VIP. The three receptors are preferentially coupled to G_s (adenylyl cyclase activation); the PAC₁ and VPAC₁ are also coupled to G_q and G_o respectively (calcium mobilization). In human, the chromosomal location is 7p15-p14, 3p22 and 7q36.3 for PAC₁, VPAC₁ and VPAC₂ receptors, respectively. Splice variants are described for the PAC₁ receptor although their physiological significance is not yet fully established.

Vasoactive Intestinal Peptide (and Related Peptides) Receptors

CURRENTLY ACCEPTED NAME	VPAC ₁	VPAC ₂	PAC ₁
PREVIOUS NAMES	PVR2 VIP ₁ PACAP type II VIP	PVR3 VIP ₂ PACAP-3 Helodermin-preferring	PVR1 PACAP PACAP type I
STRUCTURAL INFORMATION	457 aa (human)	438 aa (human)	525 aa (human)
NATURAL LIGANDS	VIP (V 3628 , V 6130) PACAP(1-27) (A 9808) PACAP(1-38) (A 1439) ^a	VIP (V 3628 , V 6130) PACAP(1-27) (A 9808) PACAP(1-38) (A 1439) PHI	PACAP(1-27) (A 9808) PACAP(1-38) (A 1439)
RECEPTOR SELECTIVE AGONISTS	[Lys ¹⁵ ,Arg ¹⁶ ,Leu ²⁷]-VIP(1-7) GRF(8-27)-NH ₂ [Ala ^{11,22,28}]VIP	Ro 25-1553 Ro 25-1392 [Hexanoyl-His ¹]VIP	Maxadilan
RECEPTOR SELECTIVE ANTAGONISTS	[Acetyl-His ¹ , D-Phe ² , Lys ¹⁵ , Arg ¹⁶] VIP(3-7)GRF(8-27)-NH ₂	PG 99-465	D(24-42)Maxadilan PACAP(6-38) ^b
SIGNAL TRANSDUCTION MECHANISMS	G _s (increase cAMP)	G _s (increase cAMP) G _{q/11} (increase IP ₃ /DAG)	G _{q/11} (increase IP ₃ /DAG)
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-VIP [¹²⁵ I]-PACAP	[¹²⁵ I]-VIP [¹²⁵ I]-PACAP [¹²⁵ I]-Ro 25-1553	[¹²⁵ I]-PACAP

ABBREVIATIONS

GRF: Growth hormone releasing factor

PACAP: Pituitary adenyl cyclase activating peptide

PHI: Peptide Histidine Isoleucine-amide

Ro 25-1553: Ac-His¹[Glu⁸,Lys¹²,Nle¹⁷,Ala¹⁹,Asp²⁵,Leu²⁶,Lys^{27,28},Gly^{29,30},Thr³¹]-NH₂ VIP (cyclo-21-25)

Ro 25-1392: Ac-His¹[Glu⁸,OCH₃-Tyr¹⁰,Lys¹²,Nle¹⁷,Ala¹⁹,Asp²⁵,Leu²⁶,Lys^{27,28}] VIP (cyclo-21-25)

PG 99-465: Myr-His¹[Lys¹²,Lys^{27,28},Gly^{29,30},Thr³¹]-NH₂ VIP

VIP: Vasoactive intestinal peptide

FOOTNOTES

a Secretin, GRF and PHI interact with VPAC₁ receptor, probably at supraphysiological concentrations.

b Displays significant affinity for VPAC₂ receptors.