

# Vasoactive Intestinal Peptide Receptors

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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 adenyl 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. In addition, it has also been shown to possess both anti-inflammatory and anti-apoptotic properties. 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, neuronal survival and control of circadian rhythms. Exogenous VIP stimulates prolactin secretion from the pituitary, catecholamine release from the adrenal medulla and insulin secretion from pancreatic islets. 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- $\alpha$  and other pro-inflammatory cytokines, and suppression of nuclear transcription factor NF $\kappa$ B activation. VIP is present in the ovary where it has been shown to stimulate oocyte maturation. Finally, it has also been shown to induce steroidogenesis in the adrenal medulla.

Pituitary adenyl 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 domain receptors coupled to G proteins. Other members of this family include receptors for secretin, growth hormone releasing factor, glucagon, glucagon-like peptide, calcitonin, calcitonin gene-related peptide, parathyroid hormone and corticotrophin releasing factor. PACAP exhibits a high affinity for three distinct receptors (PAC<sub>1</sub>, VPAC<sub>1</sub> and VPAC<sub>2</sub> receptors). Two of these, VPAC<sub>1</sub> and VPAC<sub>2</sub>, are also high affinity receptors for VIP. The three receptors are preferentially coupled to G<sub>s</sub> (adenyl cyclase activation); the PAC<sub>1</sub>, VPAC<sub>1</sub> and VPAC<sub>2</sub> (with lower efficiency) are also coupled to G<sub>q</sub>, G<sub>i</sub>/G<sub>o</sub> and G<sub>o</sub>, respectively (calcium mobilization). In man, the chromosomal location is 7p15-p14, 3p22 and 7q36.3 for PAC<sub>1</sub>, VPAC<sub>1</sub> and VPAC<sub>2</sub> receptors, respectively. mRNA encoding the PAC<sub>1</sub> receptor is found predominantly in CNS and adrenal medulla. mRNA encoding VPAC<sub>1</sub> and VPAC<sub>2</sub> receptors is widely distributed in the CNS and in peripheral tissues. In immune cells, the VPAC<sub>1</sub> receptor is constitutively expressed, whereas the

VPAC<sub>2</sub> receptor expression is induced by immunological stimuli such as lipopolysaccharide. As tissue expression is in part overlapping, only some studies allow attributing to a receptor subtype precise physiological effects. Splice variants are described for the PAC<sub>1</sub> receptor although their physiological significance is not yet fully established. A deletion mutant of mouse VPAC<sub>2</sub> receptor, lacking 13 amino acids in the seventh transmembrane domain, has also been identified in immune cells. This mutant is expressed at the cell surface, binds VIP with high affinity but fails to transduce VIP induced signaling in immune cells. PAC<sub>1</sub>, VPAC<sub>1</sub> and VPAC<sub>2</sub> receptors have been proposed as potential targets for treatment of inflammation, autoimmunity, organ failure, neurodegeneration and pulmonary hypertension.

# Vasoactive Intestinal Peptide Receptors

<b>CURRENTLY ACCEPTED NAME</b>	VPAC <sub>1</sub>	VPAC <sub>2</sub>	PAC <sub>1</sub>
<b>PREVIOUS NAMES</b>	PVR2, VIP <sub>1</sub> , PACAP type II, VIP	PVR3, VIP <sub>2</sub> , PACAP-3, Helodermin-preferring	PVR1, PACAP PACAP type I
<b>STRUCTURAL INFORMATION</b>	457 aa (human)	438 aa (human)	525 aa (human)
<b>NATURAL LIGANDS</b>	VIP ( <b>V3628</b> , <b>V6130</b> ), PACAP(1-27) ( <b>A9808</b> ), PACAP(1-38) ( <b>A1439</b> ) <sup>a</sup>	VIP ( <b>V3628</b> , <b>V6130</b> ), PACAP(1-27) ( <b>A9808</b> ), PACAP(1-38) ( <b>A1439</b> ), PHI	PACAP(1-27) ( <b>A9808</b> ), PACAP(1-38) ( <b>A1439</b> )
<b>RECEPTOR SELECTIVE AGONISTS</b>	[Lys <sup>15</sup> ,Arg <sup>16</sup> ,Leu <sup>27</sup> ]-VIP(1-7), GRF(8-27)-NH <sub>2</sub> , [Ala <sup>11,22,28</sup> ]VIP	Ro 25-1553, Ro 25-1392, [Hexanoyl-His <sup>1</sup> ]VIP	Maxadilan
<b>RECEPTOR SELECTIVE ANTAGONISTS</b>	[Acetyl-His <sup>1</sup> , D-Phe <sup>2</sup> , Lys <sup>15</sup> , Arg <sup>16</sup> ] VIP(3-7)GRF(8-27)-NH <sub>2</sub>	PG 99-465	D(24-42)Maxadilan, PACAP(6-38) <sup>b</sup>
<b>SIGNAL TRANSDUCTION MECHANISMS</b>	G <sub>s</sub> (increase cAMP), G <sub>q/11</sub> G <sub>i</sub> (increase IP <sub>3</sub> /DAG)	G <sub>s</sub> (increase cAMP), G <sub>q/11</sub> (increase IP <sub>3</sub> /DAG)	G <sub>s</sub> (increase cAMP), G <sub>q/11</sub> (increase IP <sub>3</sub> /DAG)
<b>RADIOLIGANDS OF CHOICE</b>	[ <sup>125</sup> I]-VIP, [ <sup>125</sup> I]-PACAP	[ <sup>125</sup> I]-VIP, [ <sup>125</sup> I]-PACAP, [ <sup>125</sup> I]-Ro 25-1553	[ <sup>125</sup> I]-PACAP
<b>TISSUE EXPRESSION</b>	Liver, breast, kidney, prostate, ureter, bladder, pancreatic ducts, lung, thyroid, lymphoid tissues, gastrointestinal mucosa	Smooth muscle (blood vessels, GI tract, reproductive system) pancreatic endocrine cells	Anterior pituitary, adrenal medulla, pancreatic endocrine cells, all brain areas
<b>PHYSIOLOGICAL FUNCTION</b>	Reproduction, development, growth, cardiovascular, respiratory, digestive function, immune response, circadian rhythms		
<b>DISEASE RELEVANCE</b>	Septic shock, rheumatoid arthritis, Crohn's disease, Parkinson's disease, brain trauma, pulmonary hypertension		

## Abbreviations

**GRF:** Growth hormone releasing factor

**PACAP:** Pituitary adenyl cyclase activating peptide

**PHI:** Peptide Histidine Isoleucine-amide

**Ro 25-1553:** Ac-His<sup>1</sup>[Glu<sup>8</sup>,Lys<sup>12</sup>,Nle<sup>17</sup>,Ala<sup>19</sup>,Asp<sup>25</sup>,Leu<sup>26</sup>,Lys<sup>27,28</sup>,Gly<sup>29,30</sup>,Thr<sup>31</sup>]-NH<sub>2</sub> VIP (cyclo-21-25)

**Ro 25-1392:** Ac-His<sup>1</sup>[Glu<sup>8</sup>,OCH<sub>3</sub>-Tyr<sup>10</sup>,Lys<sup>12</sup>,Nle<sup>17</sup>,Ala<sup>19</sup>,Asp<sup>25</sup>,Leu<sup>26</sup>,Lys<sup>27,28</sup>] VIP (cyclo-21-25)

**PG 99-465:** Myr-His<sup>1</sup>[Lys<sup>12</sup>,Lys<sup>27,28</sup>,Gly<sup>29,30</sup>,Thr<sup>31</sup>]-NH<sub>2</sub> VIP

**VIP:** Vasoactive intestinal peptide

## FOOTNOTES

<sup>a</sup> Secretin, GRF and PHI interact with VPAC<sub>1</sub> receptors, probably at supraphysiological concentrations.

<sup>b</sup> Displays significant affinity for VPAC<sub>2</sub> receptors.