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VIP Receptors

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Gene Names: **VIPR1**, **VIPR2**

1. General Information

VIP (vasoactive intestinal polypeptide) and PACAP (pituitary adenylate cyclase-activating peptide) belong to a family of structurally related peptides, the secretin/VIP family which includes VIP, secretin, glucagon, PACAP, GRF (growth hormone-releasing factor), GLP-1 (glucagon like peptide-1), GIP (gastric inhibitory peptide) and PHI (peptide histidine isoleucine, a biologically active peptide contained in the VIP precursor). The structure, function and role in the pancreas for VIP and PACAP are reviewed elsewhere in the Pancreapedia (19, 48). VIP and PACAP bind to three VPAC receptors: VPAC1 (originally VIP1), VPAC2 (originally VIP2), and PAC1 (PACAP preferring) which are distinct from receptors for the other members of the family (12). While these receptors were initially defined by ligand binding and second messenger activation, molecular cloning studies in the 1990s showed that their receptors were members of a distinct group of 7-transmembrane, G-protein coupled receptors characterized by a long external amino terminal (N-ted) of around 140 amino acids and termed Class B or Class II GPCRs (9, 21). Overall, the VPAC receptors contain around 540 amino acids. Photoaffinity cross-linking and NMR studies have shown that the alpha helical portion of VIP interacts with the N-ted region of the receptor (7, 28). The remainder of the receptor structure is similar to other GPCR with three intracellular loops and a C terminal intracellular tail.

The two receptors recognizing VIP with high affinity are termed VPAC1 and VPAC2 because they recognize both VIP and PACAP with similar affinity (2, 25, 30, 40, 47). They have 50% homology to each other and 30 to 50% homology to other Class B GPCRs. The PACAP receptor, termed PAC1 specifically binds PACAP and not VIP with high affinity (35). Since VIP is primarily a neuropeptide and is released locally near VPAC receptors, VIP and PACAP can function differently even though their receptors are homologous. VPAC receptors signal primarily through cyclic AMP while PAC1 signals through an increase in intracellular Ca^{2+}. VPAC1 has three glycosylation sites in the N terminal and at least one needs to be glycosylated for the receptor to reach the plasma membrane (8). Some GPCR can interact with additional intracellular proteins such as RAMPS (receptor activity modifying proteins) which VPAC1 but not VPAC2 can interact with through a PDZ domain in the carboxyl terminal of the receptor (6). This does not affect the ligand binding specificity but may mediate the ability of VIP to act through Ca^{2+} in some circumstances. VPAC1 receptors can homodimerize and heterodimerize with VPAC2 or secretin receptors although the significance of this is not clear (20).

Selective agonists and antagonists, largely mutated peptides, have been developed (28). Ala^{11,22,28}VIP is a selective VPAC1 agonist (33) and PG 97-269 is a VPAC1 antagonist (17). For VPAC2, a cyclic VIP peptide analog termed Ro 25-1392 is a potent and selective agonist (18) but there are not yet well defined antagonists.

VPAC1 receptors are widely distributed in the brain and are located on both neurons and blood vessels particularly in the cerebral cortex and hippocampus (21, 25, 45). In peripheral tissues it is present most abundantly in the liver, lung and intestine. VPAC2 receptors in the brain are most abundant in the thalamus and suprachiasmatic nucleus with lesser amounts in the hippocampus, brainstem and spinal cord (44). VPAC2 is present in peripheral tissues especially smooth muscle in the cardiovascular, gastrointestinal and reproductive system. VIP and its receptors also play a role in the immune response and inflammatory disease (11).

The role of VIP and its receptors has also been augmented by studies of genetically modified mice in which specific receptors have been deleted which affects different physiological actions of VIP. VPAC1 KO mice show growth impairment with small islets and intestinal obstruction (13). These mice also show an abnormal immune response (1). VPAC2 KO mice show growth impairment, decreased fat mass, and increased metabolic rate (3). In a different study the VPAC2 receptor was shown to be essential for circadian function in the suprachiasmatic nucleus (22).

2. VIP Receptors in Pancreas

The initial studies characterizing VIP receptors on pancreatic acini were carried out using radioiodinated VIP (^{125}I-VIP) and isolated guinea pig acinar cells prepared using collagenase digestion (5). Binding was reversible, saturable and could be displaced with unlabeled VIP or secretin but not CCK or glucagon. Displacement curves suggested two separate classes of binding sites one with high affinity for VIP and low affinity for secretin and the other with a high affinity for secretin and low affinity for VIP. Subsequent studies on rat acini also revealed a high affinity VIP receptor whose occupancy correlated with an increase in cyclic AMP and amylase secretion induced by VIP (4, 39). Studies with a variety of VIP and secretin analogues as well as using ^{125}I-secretin as ligand confirmed the presence of distinct VIP and secretin receptors (14, 15, 43, 50, 51). VIP receptors on acini also bind helodermin, a peptide from Gila monster venom (10, 37), PHI (50), and GRF (50) with high affinity and stimulate adenylyl cyclase in the plasma membrane (15, 29). Using ligand binding assays, [4Cl-D-Phe^{6}, Leu^{17}] VIP and [N-Ac-Tyr^{1}, D-Phe^{2}] GRF-1-29 NH2 were developed as antagonists for VIP binding to acini (34, 46). Covalent cross-linking studies suggested that the VIP receptor on guinea pig acini was a single protein with an apparent molecular mass of 45,000 (31). However, Svoboda et al concluded that the receptor was a 77,000 molecular mass protein which is similar to other tissues (41). Le Meuth et al labelled a glycoprotein of 55 kDa in calf pancreas membranes (29). These numbers are less important after molecular cloning but also reflect additional glycosylation that may differ between cell types and species. These binding studies have been summarized by Gardner and Jensen (15, 16).

Following the cloning and description of VPAC1 and VPAC2 receptors, Northern blotting has been used to show the presence of mRNA for both receptors in pancreas and isolated acini of guinea pig, mouse, and rat (23, 26). Earlier studies had also shown both receptor mRNAs in the human pancreas but primarily localized to blood vessels and islets (47). Ito et al then used [Lys^{15}, Arg^{16}, Leu^{27}] VIP(1-7)-GRF(8-27), a VPAC1 selective agonist (17) and Ro-25-1553 a VPAC2 selective agonist (45) to show that both receptors on acini would bind VIP resulting in stimulation of amylase release and that 85-90% of the effects of VIP on rat and guinea pig acini were mediated by the VPAC1 receptor. However, based on adenylyl cyclase activation, VPAC2 was the predominate VIP receptor in calf pancreas (32). On rat acini, 125I-VIP also bound to VIP and PACAP receptors (39).

At another level, both VPAC1 and VPAC2 receptor activation increased pancreatic blood flow (24).

VPAC2 has been shown to play a role in the embryonic development of the pancreas. The presence of VPAC2 was shown by Northern blot in rat pancreas between E12 and E16. In vitro, VIP and Ro25-1553 increased cyclic AMP, cellular proliferation and survival in pancreatic organ culture (36). VIP receptors are present in most pancreatic ductal adenocarcinoma tissue and in tumor derived cell lines where VIP stimulates cyclic AMP formation (27). In addition, VPAC2 receptors are present in islets (44) and on normal beta cells (49) and a VPAC2 specific peptide (BAY 55-9837) stimulates insulin secretion (42),

Considering the importance of VIP to stimulate ductal fluid secretion, there is unfortunately less information on the type of VIP receptors on normal pancreatic ductal cells. In a autoradiographic study of human pancreatic tumors and surrounding normal tissue VIP binding to a normal duct was displaced by a VPAC1 specific ligand (38).

3. Tools for the Study of VIP Receptors

a. Peptides – Synthetic agonist and antagonist peptides against the two VPAC receptors are available from Sigma, Calbiochem, and Tocris

b. Antibodies – Antibodies to VPAC1 (ab138260) and VPAC2 (ab 194383) are available from Abcam but have not been tested by us. Other polyclonal rabbit antibodies from MyBioSource.

c. Knockout mice – Whole body genetic deletions of VPAC1 and VPAC2 have been reported (13, 22).

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