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Vasoactive Intestinal Polypeptide or VIP

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Gene Name: VIP

1. General Information

Vasoactive intestinal polypeptide (VIP) was isolated by Said and Mutt in 1970 from pig small intestine based on its vasodilating activity (64). In their initial studies using dogs, the peptide was shown to cause hypotension, increased cardiac output, stimulation of respiration and hyperglycemia. The purified substance was determined to be a highly basic, single chain polypeptide of 28 amino acids with sequence similarity to secretin (27 aa) and glucagon (29 aa) (53). Said and Mutt named the peptide vasoactive intestinal polypeptide and also showed that it stimulated pancreatic bicarbonate secretion in the cat although was only 5-10% as potent as secretin (63). These early studies also showed that injected VIP was inactivated in the liver. VIP is well conserved evolutionarily from fish to mammals except for the guinea pig and chicken. The sequence of cow, pig, human, goat, dog, rabbit, and rat are identical; guinea pig and chicken VIP differs in 4 amino acids (16, 17). VIP was cloned from human neuroblastoma cells and from a human tumor of VIP producing cells (37, 67). The mRNA sequence predicts a 170 amino acid precursor with a N-terminal signal peptide. VIP and another potential physiologically active peptide termed PHM for its amino terminal histidine and carboxy terminal methionine. PHM is somewhat similar in structure and actions to VIP and PHI (Peptide with amino terminal histidine and carboxy terminal isoleucine), another peptide isolated from the intestine. VIP is released from pro-VIP by prohormone convertase yielding VIP with the carboxyl amino acid extension GKR which is further processed by a carboxypeptidase like enzyme to cleave the terminal dipeptide and then the glycine is converted to an amidated C-terminal (38). The human gene was found to contain 7 exons spanning about 9 kB of DNA with VIP and PHM/PHI present in adjoining exons (10, 48, 67, 70). The human VIP gene is located on chromosome 6 while rat and mouse VIP genes are on chromosome 1.

Antisera to VIP showed that it is a neuropeptide present in nerve endings and cell bodies throughout the body including the enteric nervous system, brain and pancreas (14, 20, 46). It is abundant in gut neurons but there is no evidence for a GI endocrine cell localization. In neurons it is synthesized by ribosomes in the cell body, undergoes axonal transport and is stored as dense core vesicles about 100 nm in diameter (57). It can be released from nerve terminals following electrical stimulation or physiological neuronal firing and its action is terminated by enzymatic degradation. In the peripheral nervous system, VIPergic neurons regulate blood vessels, the digestive system including smooth muscle, endocrine function, the urogenital system, the

respiratory system and the immune system (20, 38). One important action in the digestive tract is its role along with nitric oxide to relax smooth muscle in the stomach and intestine particularly at sphincters (47). Gene deletion of VIP induces a relatively mild phenotype with alterations in circadian rhythms, reproductive function, behavior, metabolism and bladder function (14).

In the CNS, VIP neurons are present in the cerebral cortex, innervate cerebral vasculature and are believed to couple neuronal activity to blood flow (30). VIP receptors (VPAC1) are present on circular smooth muscle cells of cerebral arterioles (21). Moreover, VIP antibodies block the increase in blood flow. Increasing evidence suggests that VIP and VPAC receptors in the suprachiasmatic nucleus (SCN) play a role in generation of circadian rhythms (28, 29). VIP applied to brain slices increases the firing of SCN neurons (59) and increases the expression of Per genes (54).

In the immune system, VIP neurons innervate lymphatic tissue and VIP is produced by many immune cells (1). Immune cells also bear VPAC receptors especially VPAC1 (see below). VIP can act as an immunomodulatory (15) and blocks inflammation, modify the Th response favoring Th2 and induce regulatory T cells (1).

The two receptors recognizing VIP with high affinity are termed VPAC1 and VPAC2 because they recognize both VIP and PACAP (Pituitary adenylyl cyclase activating peptide) (16, 28). They and PAC1, which specifically binds PACAP and not VIP are a subfamily of Class B, G-protein coupled receptors which also includes secretin receptors. Class B receptors have a long extracellular N-terminal which is involved in binding ligand. The three receptors were originally identified by radioligand binding, development of specific agonists and antagonists and then by molecular cloning (16, 29, 45). Both VPAC receptors couple through the heterotrimeric G protein Gs to adenylyl cyclase and are broadly distributed throughout the body. Functions of the receptors have been shown using mouse genetic models where knockout of VPAC1 and VPAC2 effect different physiological actions of VIP. VPAC1 KO mice show impaired growth with intestinal obstruction and smaller pancreatic islets (19). VPAC2 KO mice show growth impairment, decreased fat mass, reduced metabolic rate and impaired circadian rhythm (5).

Endocrine tumors with islet characteristics that are most commonly located in the pancreas are associated with a syndrome of watery diarrhea and hypokalemia described initially by Werner and Morrison in 1958 (69). The syndrome is also known as pancreatic cholera and is due to intestinal secretion that is similar to that induced by cholera toxin. Bloom et al recognized that the patients had elevated VIP levels in plasma and in the tumors (9). The syndrome is due to VIP binding to receptors on enterocytes, activating adenylyl cyclase and stimulating chloride rich fluid secretion (44). The symptoms subside after removal of the tumor or can be blocked by administration of long acting somatostatin.

2. VIP and the Pancreas

Purified or synthetic VIP injected as a bolus or by infusion stimulates pancreatic bicarbonate rich fluid secretion in all mammalian species tested but has only 15-20% of the maximal effect of secretin in most species. It is a partial or lower potency agonist compared to secretin in rats (17), dogs (35, 42, 51, 63) or humans (18, 22). In cats, VIP induced a similar maximal flow to secretin but required much higher concentrations (41, 60). In these in vivo studies there was no increase in digestive enzyme secretion in response to VIP. The effects on fluid and bicarbonate secretion are presumably mediated by the pancreatic ducts. At high concentrations VIP also stimulated insulin secretion and VPAC receptors are known to be present in islet beta cells (6). VIP stimulates insulin secretion in a glucose dependent manner and also stimulates glucagon secretion (72).

This lack of an effect or low potency of VIP administered in vivo is probably due to the fact that

VIP is now known to be a neuropeptide and not a GI hormone (20, 38). VIP is present in a variety of pre- and post- ganglionic autonomic neurons and in the pancreas is localized in neurons innervating both exocrine and endocrine cell in a variety of vertebrate species (3, 7, 32, 34, 46, 49, 66). VIP is also found in nerve fibers which innervate blood vessels as well as secretory cells (2). There is longstanding evidence for a non-cholinergic, non-adrenergic innervation of the exocrine pancreas which is very strong in the pig (31). Both in vivo and in a perfused pancreas preparation, vagal electrical stimulation enhances pancreatic fluid and bicarbonate secretion, releases VIP and insulin into the blood and reduces vascular resistance (23, 34, 39, 71). Most of the secretory effects are blocked by VIP antisera (34). PHI (peptide histidine isoleucine) an intestinal GI hormone which is analogous to PHM in the human VIP precursor also stimulate pancreatic fluid and bicarbonate secretion although less potent than VIP (33). Neural VIP is probably not as important for fluid secretion in other species (71) but contributes to the increase in pancreatic blood flow in dogs (8, 35, 43) and rats (6). VIP is often present in postganglionic parasympathetic neurons along with acetylcholine. While this two transmitter paradigm is best studied in salivary gland innervation. it probably also occurs in the pancreas.

VIP action has been extensively studied on isolated pancreatic acini where its main observable action is to stimulate secretion of amylase and other stored digestive enzymes. These studies use acinar cells as a model cell for studying VIP action. Early studies showed that VIP was a full agonist on amylase secretion from guinea pig isolated cells and acini (25, 27, 56, 65) and induced a partial response from rat and mouse acini (11, 13, 65). VIP was found to increase cyclic AMP in acini and to synergize with stimuli that acted through an increase in intracellular Ca^{2+} such as CCK or cholinergic agonists. These effects are similar to studies using secretin, cholera toxin and dibutyryl cAMP. Thus the species dependence reflects the ability of cyclic AMP to act in a particular species (26). The action of VIP is now known to be mediated by binding to VPAC receptors and both VPAC1 and VPAC2 have been identified in rodent acini at the RNA level by Northern blotting and by Southern blotting after RT-PCR. Most (85-90%) of the physiological effects on cAMP formation and amylase secretion are believed to be mediated by VPAC1 (36) as shown using subtype specific ligands and substantiated by means of specific receptor KO mice.

In addition to amylase release, isolated acini have been used to show other actions of VIP mostly related to signaling initiated by cAMP. VIP increased adenylyl cyclase activity in guinea pig and rat isolated acini and calf pancreas membrane fractions (52), increased cAMP levels (25, 68) and the activity of PKA (39, 62). In mouse acini and ducts, the effect of VIP was mediated by the AC6 isoform of adenylyl cyclase. The cAMP produced activates PKA and leads to the phosphorylation of specific proteins on serine and threonine residues (12, 68). Of these proteins two have been identified as ribosomal protein S6 and CREB. In addition to PKA, cyclic AMP activates EPAC (exchange protein directly activated by cAMP) which is involved in the activation of the small G protein Rap1 (61) and of another protein kinase, PAK4 (58). An additional effect of VIP was to increase the tyrosine phosphorylation of proteins of 115 and 130 kDa similar to the effects of forskolin and dibutyryl cAMP (50).

Isolated pancreatic duct fragments have also been used to show actions of VIP and secretin on pancreatic duct cells. VIP increased cAMP levels in rat and mouse duct fragments (24, 62). However, in another study VIP had no effect on fluid secretion by isolated rat duct fragments (4). VIP was, however, shown to depolarize the basolateral membrane of dissected rat ducts (55). VIP is also known to reduce the severity of experimental pancreatitis in mice (40). VPAC1 agonists also reduced the increase in cytokines including IL-6 and TNF-α.

3. Tools for the Study of VIP

a. Peptides

VIP peptides are sold by Phoenix Pharmaceutical, Peptides International, and Antibodies online.

b. Antibodies

Mouse and rabbit antibodies to VIP are available from Abcam that are primarily designed and validated for immunofluorescence and immunohistochemistry. Antibodies are also available from Santa Cruz, Sigma and Thermo Fisher.

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