Pituitary Adenylate Cyclase Activating Polypeptide (PACAP): A Novel Brain-Gut Peptide

PACAP: YENİ BİR BEYİN-BARSAK PEPTİDİ

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SUMMARY

PACAP is a novel neuropeptide and it has been accepted as a new member of glucagon/VIP/secretin peptides family. It shows general characteristics of this family. Although Its physiological roles are not known its biological activities are in a wide spectrum. It is considered to be à new brain-gut peptide. It stimulates exocrine pancreas secretion, inhlbitis gastric acid secretion, stimulates colonic secretion and relaxes smooth muscle contractions and it is also possible to have regulatory role on sphincter functions and blood flow in gastrointestinal system.

Key Words: **PACAP, VIP, Peptide gastrointestinal system**

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ÖZET

"Pituitary Adenylate Cyclase Activating Polypeptide (PACAP)" 1989 yılında tanımlanmış bir nöropeptittir. Glucagon/VIP/secretin peptidler ailesinin genel özelliklerini gösterdiğinden bu peptid ailesinin yeni bir üyesi olarak kabul edilmektedir. Fizyolojik rolleri henüz tam olarak gösterilmemiş olmasına rağmen çeşitli biyolojik aktiviteleri gösterilmiştir. Yeni bir beyin-barsak peptidi olduğu düşünülmektedir. Bugüne kadar yapılan çalışmalarda PACAP'ın ekzokrin pankreas salgısını arttırdığı, mide asit salınımını azalttığı, kolonik sekresyonu arttırdığı ve gastrointestinal traktüste düz kasları gevşettiği gösterilmiştir. Ayrıca PACAP'ın gastrointestinal sistemde sfinkter fonksiyonlarını ve kan akımını düzenlemesi mümkündür.

Anahtar Kelimeler: **PACAP, VIP, Peptid gastrointestinal system**

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A novel bioactive neuropeptide with adenylate cyclase stimulating activity in the rat pituitary cell culture was isolated from sheep hypothalamus in 1989 (1) and named pituitary adenylate cyclase activating polypeptide (PACAP). The structure of PACAP appears to be well preserved in various species. The structures of rat, human and sheep PACAP were identical (2,3). This novel neuropeptide has two bioactive forms, PACAP-38 and PACAP-27 with 38 and 27 amino acid residues, respectively (1,4). It is a new member of the glucagon/vasoactive intestinal peptide (VIP)/secretin peptides family with 70% sequence homology with VIP (Figure 1). Even though PACAP shows important amino acid sequence homology with VIP in the N-terminal 28 residues, it is 1000 times more potent than VIP in stimulating adenylate cyclase in pituitary cell cultures (1).

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DISTRIBUTION OF PACAP

PACAP was originally isolated from sheep hypothalamus, but its presence has been shown in different peripheral tissues by immunohistochemical (5-7), radioimmunoassay (RIA) (8) and binding studies (9). The highest tissue concentration of immunoreactive PACAP was found in hypothalamus, testis, posterior pituitary, hippocampus, cortex, adrenal gland, respectively. The highest concentration in gastrointestinal system was found in duodenum and stomach (8). Using immunohistochemical method PACAP-lmmunoreactivity has been shown in different layer of gastrointestinal tract in different species (5-7). The small arteries and arterioles were also Innervated by PACAP (7). In one

PACAP-38 His-Ser-Asp-Qly-Ite-Phe-Thr-Asp-Ser-Tyr-Ser-Arg-Tyr-Arg-Lys-Gln-Met-Ata-Val-Lys-
VIP fcSter-A^Ala-Val-I^-TM-^A^^
Secretin ^-Ser-A^G^-Thr-Phj-TjW'Se^
Glucagon Hio-Sw^In-^-Thr-Plw^
Lys-Tyr-L8u-Ala-Ala-Val-LeuieiyLyS-Arg-Tyr-Lys-Gln-Arg-Va:-Lyr,.Asn-l.ys-MH,
Lys-TyN-eu-Asn-SeHle-Leu-Asn-NHg (70%)
Arg-Lea-L£j-Gln-Gly-Leu-Val'NH,i3?%)
Asp-Phe-VaM3In-Trp-Leu-Mst-Asn-THr-NH2(a9%)

Figure 1. Amino acid sequence of PACAP-38 as compared to those of ViP, secretin and glucagon [Amino acid residues identical with those in PACAP-38 are underlined. Percentage homology with PACAP-27 (ending at vertical line) in parenthesis],

study it was shown that Brunner's glands in the submucosal layer of duodenum were surrounded by PACAP-immunoreactive fibers (7). PACAP immunoreactivity was also observed in both exocrine and endocrine parts of pancreas (10), PACAP-immunopositive fibers innervated the exocrine acini, islets of Langerhans and the small arteries in the connective tissue. These data suggested that PACAP regulates the activity on the digestive system such as motility of the intestine, blood supply, secretory activity of Brunner's glands, and both exocrine and endocrine functions of the pancreas (10).

RECEPTORS OF PACAP

At least two type PACAP receptors has been described as type I receptors, which are spesific for PACAP, and type II (PACAP/VIP) receptors, which are shared with VIP (9,11), The presence of spesific PACAP receptors (type i) have been reported in hypothalamus, anterior pituitary, cultured astrocytes, epididymis, testis, adrenal glands and intestinal muscle (9,11,12), Type II receptors were found in lung, liver, prostate gland, seminal vesicle and cultured splenocytes (9,11).

EFFECTS OF PACAP ON GASTROINTESTINAL SYSTEM

Because of the similarity between the effect of PACAP and VIP in several biological systems, as well as their similarity In amino acid sequence, and presence of PACAP-immunoreactivity in all gastrointestinal system (5-7), the effects of PACAP on different gastrointestinal functions have been investigated.

Effect of PACAP on exocrine pancreas secretion

PACAP has been shown stimulatory effect on exocrine secretion of rat panceras in vivo and in vitro studies (13,14). cAMP stimulation in dispersed acini from rat pancreas was similar to the stimulation of amylase secretion. Inhibition of PACAP-induced cAMP production and amylase release by VIP receptor antagonist indicated that the secretory effect of PACAP was mediater by interaction with VIP receptors (14).

*Effect of **PACAP** on gastric secretion*

We investigated the effect of PACAP on gastric acid secretion in rats (15,16). PACAP showed significant inhibitory effect on pentagastrin- and hlstamlne-stimulated gastric acid secretion, but no effect on basal or carbachol-stimulated secretions. PACAP did not alter serum gastrin levels. Inhibition of prostaglandin synthesis with indomethacln and immunoneutralizatlon of somatostatin with anti-somatostatin serum did not prevent the inhibitory effect of PACAP on gastric acid secretion (Unpublished data). We conclude that PACAP most likely has a direct effect on parietal cells and that this effect may be mediated, at least partially, by inhibition of the action of histamine on parietal cells. In another study it was shown that PACAP stimulated pepsinogen release from isolated chief cells from guinea pig stomach and this effect was equal to the effect of VIP (17).

Studies have indicated that the Injection of a number of peptides into the cerebroventricular fluid alter gastric acid secretion and It has been concluded that some peptides has a physiologic role In the central regulation of gastric acid secretion (18). Since PACAP is densely found In the hypothalamus (8) and because it has varied actions on gastrointestinal functions, we also Investigated the effect of PACAP on gastric acid secretion after Intracerebroventrlcular (ICV) administration. Our results showed that: (1) ICV injection of PACAP had a dose-dependent Inhibitory effect on basal acid secretion at the dose range of 0.01-0.3 nmol/rat. PACAP also inhibited pentagastrin-stlmulated gastric acid secretion. (2) PACAP did not alter serum gastrin level. (3) VIP at 0.1 nmol/rat (the submaximal effective dose of PACAP) had no effect on gastric acid secretion and serum gastrin level. (4) Pretreatment with antl-somatostatin serum did not prevent the inhibitory effect of PACAP. (5) The inhibitory effect of PACAP was not vagal-dependent. We suggest that PACAP is new candidate peptide for the central regulation of gastric acid secretion (16, unpublished data of author).

Effecf *of **PACAP** on colonic secretion*

PACAP potently stimulated colonocyte ion transport via mechanism mediated by the VIP receptors and cAMP-dependent signaling (19). The presence of PACAP in some gastrointestinal endocrine tumors was also reported (by Dr.Bloom SR in the Second Annual PACAP Symposium, New Orleans, 1991). Therefore It seems reasonable to speculate that PACAP may contribute to the pathogenesis of some unexplained diarrhea syndromes.

*Effect of **PACAP** on gastrointestinal smooth muscle contractions*

Immunohistochemical studies showed PACAP-immunoreactivity In muscle layers In all parts of gastrointestinal tract in different species including human (5-7). Therefore, we investigated effect of PACAP in rat gastrointestinal tract by using muscle strips in organ bath system. PACAP showed dose-dependent (10^{-9}-10^{-7} M) inhibitory effect on basal smooth muscle contractions in all tested parts (fundus, antrum, pylo-

rus, duodenum, jejunum, ileum, cecum, mid- and descending colon). The inhibitory effect of PACAP was approximately 100 contractions which induced by acetylcholine, carbachol, substance P, CCK-8, galanin and VIP on longitudinal smooth muscle contractions of jejunum and/or duodenum. This inhibitory effect was not prevented by pretreatment with hexamethonium, atropine and tetrodotoxin (20,21). Similar type results were also obtained by using human colonic tissues (22). This study showed that PACAP and VIP receptors. The PACAP receptors (type I) seems to be coupled to an apamin-sensitivite calcium-activated potassium channel, while the VIP receptors (type II PACAP/VIP receptor) probably mediates the VIP effect through a tetraethylammonium-sensitive potassium channel. Formation of endogenous nitric oxide and/or cAMP was not involved in the relaxant activity of both peptides. In another study, PACAP stimulated gallbladder contraction dose-dependently through the preganglionic cholinergic pathway in conscious dogs (23). In guinea pig ileum PACAP stimulated smooth muscle contractions (24). In the lower esophagus of cat, sheep and man presence of PACAP-containing nerve cell bodies was shown by using immunohistochemical and radioimmunoassay technic (6). Although it can be some species differences, it is possible conclude that PACAP may play a regulatory role in the gastrointestinal smooth muscle contractions and sphincter functions.

OTHER BIOLOGICAL ACTIONS OF PACAP

PACAP decreased blood pressure in rat (1) and has been found potent, long -lasting endothelium- independent vasodilators (25). In the trachea a moderate supply of PACAP-immunoreactive nerve fibers found around smooth muscle bundles, glands and small vessels. In the lung, PACAP-immunoreactivite nerve fibers were distributed around small glands and bronchi. A rich supply of PACAP immunoreactive nerve fibers was found around blood vessels in the lung (26). PACAP increased release of GH, prolactin, ACTH and LH but not TSH or FSH from superffused rat pituitary (1). PACAP prevented GP-120 induced neuronal cell death. The preventive effect of PACAP from this toxic envelope protein of HIV was found 100 times more potent than VIP (10,27). PACAP also showed stimulatory effect on endocrine function of pancreas. It stimulated Insulin release in a glucose dependent manner from the isolated perfused rat pancreas (28).

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