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Localization and function of VIP and PACAP in the heart

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ABSTRACT

Vasoactive intestinal polypeptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP) are structurally closely related neuropeptides, which exert prominent pharmacological effects on heart function through three types of receptors: VPAC1, VPAC2, and PAC1. All of them are present in the heart. Localization and function of these endogenous peptide molecules and their receptors in the heart will be presented

Keywords: Heart, Peptide molecules, Pituitary adenylate cyclase-activating peptide (PACAP), Vasoactive intestinal polypeptide (VIP)

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INTRODUCTION

Vasoactive intestinal peptide (VIP) is a linear 28-amino-acid peptide with molecular weight of 3,326 Da that is generated by enzymatic cleavage from its precursor molecule, preproVIP. The 170 amino-acid precursor is metabolized by a signal peptidase in the endoplasmic reticulum to yield the 148-amino-acid proVIP. ProVIP is cleaved by prohormone convertases to prepro VIP125–155 and prepro VIP81–110 (precursor of peptide histidine methionine, PHM). Both of them are then cleaved by carboxypeptidase-B like enzymes to VIP-G and PHM-G. The VIP-G and PHM-G can then be metabolized by PAM enzymes to VIP and PHM [1]. VIP was first isolated as a vasorelaxant from porcine gut by Said and Mutt [2]. The amino acid sequence of VIP in human, cow, sheep, goat, dog, rabbit and rat is identical to that of the porcine peptide [1]. VIP is structurally related to another neuropeptide pituitary adenylate cyclase-activating peptide (PACAP). They belong to the secretin peptide family including also secretin, peptide histidine isoleucin, peptide histidine methionine (human counterpart to peptide histidine isoleucin), glucagon, glucagon-like peptide, glucose-dependent insulinotropic polypeptide and growth hormone-releasing factor [3]. VIP and PACAP are best discussed together because they share receptors as well as functions (Table 1).

PACAP was first isolated from the ovine hypothalamic extracts and described as a factor potently stimulating adenylyl cyclase activity in the rat pituitary cell culture [4]. PACAP exists in two amidated forms in mammals: The full peptide contains 38 amino acids (PACAP38) while PACAP27 is C-terminally truncated. Both forms are derived from a 175-amino-acid precursor, preproPACAP, and have similar biological actions and potencies [5].

The human VIP peptide is 70% identical to N-terminus of both PACAP variants (Table 2). VIP sequence has been very well conserved during the evolution from protochordates to mammals, suggesting an important biological function [6]. Both peptides have a broad spectrum of biological functions including neurotransmitter, secretagogue, neuroprotective, neurotrophic and differentiation roles as well as effect on growth and survival of cells in the developing nervous system [7].

Table 1: Size, specific receptors, localization and function of VIP and PACAP in the heart

	VIP	PACAP
Size	28 AA	27 AA or 38 AA
Specific receptors	VPAC1, VPAC2	VPAC1, VPAC2, PAC1
Localization in the heart	Neuronal somas and fibers	Neuronal somas and fibers
Functions in the heart	Direct positive inotropic and chronotropic effect Indirect positive chronotropic effect Smooth muscle relaxation	Direct positive inotropic and chronotropic effect Indirect positive chronotropic effect in the first phase and negative chronotropic and inotropic effects in the second phase Smooth muscle relaxation Stimulation of atrial natriuretic peptide secretion Inhibition of cardiac fibrosis Cardioprotection

Table 2: Chromosomal location of VIP and PACAP gene and their amino acid sequence. Bold letters in the amino acid sequences represent differences between VIP and PACAP-27

	VIP	PACAP 27
	Chromosomal location	
Human	6q25	18p11
Rat	1p11	9q37
	Amino acid sequence	
Human, Rat	HSD**AV**FTD**NY**T**RL**R KQMAVKKYL**NSI**L**N**	HSD**GI**FTD**SYSRY**R KQMAVKKYL**AA**V**L**

Localization

Vasoactive intestinal polypeptide (VIP) is produced (1) by neurons in different areas of the central and peripheral nervous system, (2) by endocrine cells such as cells of the endocrine pancreas and pituitary lactotrophes, and (3) by inflammatory and immune cells. In the nervous systems, it acts as a multifunctional neurotransmitter and neuromodulator. In the peripheral nervous system, VIP-containing neurons are either intrinsic neurons involved in local reflexes, or postganglionic neurons under preganglionic cholinergic control. VIP is synthesized in neuronal cell bodies and is then transported along axons or dendrites to dense core vesicles located in presynaptic nerve terminals [1].

PACAP is produced by neurons of central and peripheral nervous system and several nonneural tissues such as the adrenal gland, gonads, immune cells, and pancreas [6].

In the heart, VIP is of extrinsic (from vagal or sympathetic efferents) or intrinsic origin, however, the predominant part of cardiac VIP-immunoreactive (IR) innervation is intrinsic, which consists of postganglionic parasympathetic nerve cell bodies localized within various atrial subepicardial regions and their fibers innervating the heart. In the heart atria, VIP-IR fibers are observed in the area of sinoatrial (SA) node where a dense network of VIP-IR fibers is seen closely apposed to the nodal cells. Other parts of the conductive system (atrioventricular node and Purkinje fibers) are also innervated by VIP-IR nerve fibers, however, the innervation is much less pronounced. Additionally, VIP-IR fibers have been detected along the terminal arterioles in the vicinity of atrial cardiomyocytes with endocrine activity. In the ventricles, VIP-IR fibers are present very rarely, more in the right than in the left ventricle, mainly surrounding coronary vasculature. In the atrial part of coronary circulation, VIP-IR fibers occur within adjacent small atrial arteries and arterioles in a density exceeding that of VIP-IR nerves in the remaining segments of the coronary vasculature [8]. In the nerve fibers from postganglionic parasympathetic neurons, VIP is co-localized with the “classical” neurotransmitter acetylcholine (ACh). VIP is stored in large dense core vesicles, and its release is enhanced by high frequency vagal stimulation in contrast to the release of ACh from small vesicles, which is favored by low frequency stimulation [7].

PACAP is much more widely distributed than VIP in the central nervous system, while they often appear to be co-localized in the same nerve cell bodies, and nerve fibers in peripheral organs. In tissues, PACAP38 is the predominant form, and PACAP27 makes up less than 10% of the total PACAP content. In the heart, PACAP27 and PACAP38 immunoreactive nerve cell bodies and nerve fibers were identified within cardiac ganglia and interganglionic fibre tracts. Additionally, PACAP38 has been detected in the coronary arteries. Additionally,

immunohistochemical observations suggest that PACAP is localized mainly in the nerve fibres within the intracardiac ganglia, which are predominantly of extrinsic origin [9].

Thus, it is likely that endogenous PACAP and VIP might affect the firing of intracardiac cholinergic neurons in a species-dependent fashion but only VIP would directly influence the sinus node and most other regions of the heart under normal circumstances [10]. Additionally, VIP and PACAP derived from an extrinsic source and coming to heart with blood could play important role in regulation of cardiac functions [11].

Receptors

VIP and PACAP exert their effects through three different specific receptors, which belong to the family of guanine nucleotide binding protein (G protein)-coupled receptors with seven conserved transmembrane domains and a molecular weight of 43-80 kDa. They trigger mainly adenylyl cyclase activation through Gs protein, but also can activate phospholipase C. The balance between couplings to adenylyl cyclase versus phospholipase C may be related to the presence of accessory proteins such as the receptor activity modifying proteins RAMPs [12]. Two subtypes of these receptors possess comparable affinity for VIP and PACAP, and, therefore, have been named VPAC1 and VPAC2. The VPAC1 receptor (but not VPAC2 or PAC1) has been shown to be able to interact with RAMPs; in this case ligand specificity is not altered but the VPAC1 receptor-RAMP2 heteromer displays altered signal transduction specificity, with significant enhancement of agonist-mediated phosphoinositide hydrolysis with no change in cyclic AMP stimulation [13]. The third receptor binds VIP with 1,000-fold lower affinity than PACAP, and has been designated PAC1 [9]. Numerous isoforms of the PAC1 receptor, corresponding to 17 known splice variants of the same gene, were identified. The human PAC1 gene is composed of 18 exons, ten being constitutively expressed (exons 2, 3, 7-13 and 18) while seven (exon 4-6 and 14-17) are regulated. A complex process of differential splicing generates the numerous receptor isoforms that display distinct pharmacological profiles. Recent reports suggest that at least one of these isoforms also acts as a high affinity receptor for both VIP and PACAP [14]. All these receptors (VPAC1, VPAC2 and PAC1) belong to the class II family of G protein-coupled receptors. Northern blot analysis confirms presence of all three types of VIP/PACAP receptors in the heart [5]. Immunohistochemistry showed that in the rat heart, VPAC1 receptor is present in macrophages, while VPAC2 receptor was detected on the smooth muscle cells of coronary arteries. Additionally, small amount of cardiomyocytes express VPAC2 immunoreactivity [15]. PAC1 have been detected in cardiomyocytes and intracardiac neurons [9, 16]. According to our knowledge, expression of the specific PAC1 receptor variants has not been studied in the heart yet.

Actions In The Heart

Cardiac ganglia

Intracardiac ganglia play a major role in neuronal control of the heart and are believed to be capable of independently monitoring and influencing cardiac function. They receive not only cholinergic preganglionic inputs, but also peptidergic afferents and sympathetic postganglionic signals. VIP and PACAP are co-localized with acetylcholine in preganglionic parasympathetic fibers, which densely innervate majority of intracardiac ganglionic cells, additionally, both of this neuropeptide are expressed by cholinergic cardiac neurons. On the surface of these neurons are localized several types of specific receptors for VIP and VPAC meaning, that cell membrane of one neuron may contain VPAC1 and/or VPAC2 and /or some isoform of PAC1 receptor [16]. Simultaneous activation of VPAC2 and PAC1 receptors by PACAP elicits a synergistic enhancement of neuronal excitability and produces changes in the active membrane properties that are not seen with stimulation of either receptor alone. This process is dependent on VPAC2 receptor-induced Ca^{2+} release from caffeine- and ryanodine-sensitive intracellular stores. VIP, by acting exclusively on VPAC receptors, evokes a depolarization of lesser magnitude than PACAP and fails to increase action potential firing [17]. These would offer an explanation for distinct effects of VIP and PACAP on the heart. Whereas both VIP and PACAP have positive chronotropic effect and cause smooth muscle relaxation, PACAP, but not VIP, evokes pronounced negative chronotropic and inotropic effects that are mediated by activation of intrinsic cardiac neurons [9].

Cardiomyocytes

VIP and PACAP exert direct effects on cardiomyocytes. Positive inotropic effects of VIP have been demonstrated on myocardial tissue from different parts of the heart of different species. This seems to be mediated, at least in part, through the activation of VIP receptors on cardiomyocytes [18, 19]. All three receptor isoforms have been detected in cardiomyocytes, although PAC1 seems to be dominant and VPAC1 uncommon or absent [15, 18, 20, 21]. It is possible that not all myocytes contain all receptor isoforms. In the cardiomyocytes, both VIP and PACAP induce cAMP synthesis, but PACAP with higher potency. This stimulating effect of VIP and PACAP is, most likely, mediated by distinct receptors. Increased cAMP can increase protein kinase A activity, which enhances calcium channel phosphorylation, the L-type calcium current, and the release of calcium from the sarcoplasmic reticulum. As a consequence, the intracellular calcium concentration increases, enhancing

cardiac myocytes tension development and the rate and extent of contraction. VIP has a more potent positive inotropic effect on the right atrial than left ventricular muscle in human, which would play an important role in maintaining cardiac output under critical conditions, where atrial contraction is fundamental [9, 22]. However, the inotropic response to VIP may diminish with increasing VIP dose and/or with time, which is probably due to VIP receptor desensitization in the myocardium [1]. PACAP exerts actions on cardiomyocytes very similar to VIP in the first phase, but in the second phase it causes a decrease of heart rate and contractile force by interaction with cardiac parasympathetic nerves via the PAC1 receptor [6]. Different cardiac responses to VIP and PACAP in the atria and ventricles might be due to differences in the expression and density of specific receptors.

Additionally, PACAP stimulates secretion of atrial natriuretic peptide through the PAC1 receptor, which indicates that PACAP could play the role of a neurohumoral factor to inhibit the remodeling at cardiac hypertrophy [21].

Cardiac nonmyocytes

VPAC2 receptor mRNAs have been detected also in cardiac fibroblasts. PACAP inhibits DNA and collagen syntheses in cultured nonmyocytes, which is mediated through a cAMP-dependent process. PACAP is able to inhibit cardiac fibrosis through VPAC2 receptor [21]. Additionally, PACAP immunoreactivity has been detected in macrophages infiltrating heart [23], which could play a role in cardioprotective effect of PACAP demonstrated by several studies [21, 24–26].

Conductive tissue

In the SA node myocytes, VIP augments hyperpolarization-activated pacemaker I_f current, which is directly activated by cytoplasmic cAMP, to more positive voltages without altering its maximal conductance and thereby accelerates the rate of diastolic depolarization followed by an increase of heart rate. Interestingly, the action of VIP is exactly opposite to that of ACh, a principal parasympathetic neurotransmitter co-released with VIP, which produces a negative shift in the activation curve of I_f without changes in maximal conductance, and a decrease in heart rate. Since VIP release occurs predominantly during strong vagal stimulation, the physiological role of this neuropeptide may be one of negative feedback, to counter prolonged inhibition of I_f and activation of the muscarinic potassium conductance under conditions of sustained vagal action and elevated ACh concentration in the SA node, which may lead to arrest of spontaneous activity [27]. Altogether, the co-release of VIP and ACh in the SA and atrioventricular nodes may prevent potentially dangerous neurally mediated bradyarrhythmias. PACAP can directly increases sinus rate due to activation of PAC1 receptor and/or produces negative chronotropic effect by activating intracardiac parasympathetic nerves in the atrium.

Coronary circulation

The presence of VIP and PACAP nerve fibers and their receptors in the coronary circulation strongly suggests that both peptides are important in the regulation of coronary blood flow. They are able to produce a vasodilatation but while PACAP displays identical vascular responses in all vessel segments, the vasodilatory effect of VIP differs from one vascular bed to another. The regional differences in vascular responses to the two peptides may be explained (1) by the involvement of a new unknown receptor, or (2) by the interaction of various substances produced and present in the tissue, or (3) by the presence of vessel-specific different populations of the receptor subtypes [28]. In the heart, the vasodilatory effects of VIP on arteries are much greater than on veins because of the greater VIP receptor density in arterial vessels [29]. The potency of VIP depends on the existing level of coronary vessel tone, which may differ from species to species [30]. Moreover, the vasodilatory effect of the peptides is not limited to the coronary arteries. VIP as well as PACAP produces significant arterial dilatation in other body organs such as brain, endocrine glands, and the respiratory system [28, 31, 32]. The requirement of intact endothelium for the vasodilator effects of VIP depends upon the vascular site studied. VIP induced relaxation of rat aortic aorta and the human uterine artery is largely dependent upon the presence of an intact endothelium [33, 34] but the vasodilator effect of VIP at most other sites is endothelium-independent [35-38].

CONCLUSION

The presence of vasoactive intestinal polypeptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP) peptides in the heart and results of several functional studies suggest that these peptides plays an important role in the regulation of heart functions including e.g. frequency of beating, contractile ability of myocardium or regulation of coronary blood flow.

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Magdalena Chottova Dvorakova – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the

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Jana Slavikova – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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