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Cardiovascular Research 37 (1998) 34–41

Cardiovascular Research

Review

Cardiovascular actions of parathyroid hormone and parathyroid hormone-related peptide

Klaus-Dieter Schlüter *, Hans Michael Piper

Physiologisches Institut, Justus-Liebig-Universität Giessen, Aulweg 129, D-35392 Giesen, Germany

Received 9 April 1997; accepted 28 July 1997

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Abstract

Cardiovascular cells (cardiomyocytes and smooth muscle cells) are target cells for parathyroid hormone (PTH) and the structurally related peptide parathyroid hormone-related peptide (PTH-rP). PTH activates protein kinase C (PKC) of cardiomyocytes via a PKC activating domain previously identified on chondrocytes. Activation of PKC leads to hypertrophic growth and re-expression of fetal type proteins in cardiomyocytes. This hypertrophic effect of PTH might contribute to left ventricular hypertrophy in hemodialysis patients with secondary hyperparathyroidism. PTH-rP is expressed in cardiovascular cells (endothelial cells and smooth muscle cells). It does not mimic the above described actions of PTH but exerts effects of its own on cardiomyocytes. These effects involve activation of protein kinase A, via a N-terminal domain distinct from that identified on PTH, and activation of PKC, via a C-terminally located domain distinct from that found on PTH. On smooth muscle cells PTH and PTH-rP reduce the influence of extracellular calcium, through cAMP-dependent mechanisms. These inhibitory effects on voltage-dependent L-type calcium channels of smooth muscle cells cause vasorelaxation. Present studies concerning cardiovascular actions of either PTH and PTH-rP suggest that increased plasma levels of PTH and PTH-rP influence cardiomyocyte and smooth muscle cell physiology. It can be assumed that PTH-rP acts as a paracrine or autocrine modulator in heart and vessels. © 1998 Elsevier Science B.V.

Keywords: Hormones; Hypertrophy; Myocytes; Smooth muscle; Vasoactive agents

1. Introduction

Parathyroid hormone (PTH) is a peptide hormone that is secreted from the parathyroid gland. It acts on bone and kidney cells and is involved in systemic calcium homeostasis. In the initial description of the isolation of a parathyroid extract in 1925 a hypotensive effect of PTH was reported [1]. This observation indicated that PTH also acts on cardiovascular cells. The exploration of cardiovascular effects of PTH has gained increasing interest in the eighties, after synthetic and defined PTH peptide preparations had become available. Interest to study cardiovascular actions of PTH is also based on clinical data supporting the idea that PTH contributes to the progression of several cardiovascular diseases. For example, hemodialysis patients with increased plasma concentrations of PTH and end-stage renal disease develop left ventricular hypertrophy and approximately 50% of the annual mortality in patients with end-stage renal disease is attributed to cardiovascular events [2]. In order to identify potential target cells of PTH in the cardiovascular system, several investigators studied the effects of PTH on cardiomyocytes, endothelial cells, and smooth muscle cells.

In 1988 it was found that parathyroid hormone-related peptide (PTH-rP), a peptide hormone structurally related to PTH, is expressed in the heart [3]. PTH-rP was initially identified as a secretion product of squamous tumors [4]. It is now known that PTH-rP is constitutively expressed in various tissues including the heart. On various target cells PTH-rP can bind to and stimulate the same receptor as PTH. From these findings it has been argued that PTH-rP acts as a paracrine or endocrine modulator in cardiovascular organs. PTH-rP is supposed to influence the

* Corresponding author. Tel.: (+49-641) 9947243; Fax: (+49-641) 9947239; E-mail: klaus-dieter.schlueter@physiologie.med.uni-giessen.de

Time for primary review 35 days.

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hemodynamic behavior of the heart as well as angiogenesis and arteriosclerosis [5,6].

For an insight in the physiological role of PTH and PTH-rP on cardiovascular cells, it is necessary to study the specific structure–function relationship of the two related peptide hormones and the intracellular signaling cascade in responsive cardiovascular cells. It is generally assumed that peptide hormones like PTH and PTH-rP bear regions that are configured for high affinity to a receptor (binding regions) and regions that interact with the receptor to initiate a cascade of intracellular signals (functional domains). Additional orders of complexity are added by findings that one peptide hormone may interact with more than one class of receptors. Expression of different receptors and involvement of different functional domains of a given peptide hormone may vary among target cells. This review summarizes the present knowledge about the action of PTH and PTH-rP on cardiovascular target cells with a focus on cellular aspects.

2. Contractile effects of PTH on cardiomyocytes

Neonatal cardiomyocytes were identified as potential target cells for PTH early in the history of this field of cardiovascular research. Neonatal cardiomyocytes beat spontaneously and PTH increases their beating frequency by 47%, compared to 61% achieved by addition of the β-adrenoceptor agonist isoprenaline [7]. Surprisingly, the effect of intact full-length PTH, PTH(1–84), was 3.3-fold greater than that of the truncated 1–34 moiety [8]. This was the first evidence that the structure–function relationship of PTH on cardiomyocytes differs from that on classical target cells, like osteoblasts, chondrocytes or kidney cells, because on classical target cells the 1–34 moiety of PTH is a full biological agonist compared with intact PTH. In these cells PTH causes activation of intracellular signaling, leading to either proliferation of the cells or altered ion handling. An increased activity of intact PTH compared to PTH(1–34) was also found on adult cardiomyocytes when PTH dependent Ca^{2+} influx [9] and the induction of cytosolic creatine kinase [10] were investigated. This increased activity of full-length PTH compared to PTH(1–34) could not be explained by an intrinsic activity of C-terminally located peptide sequences like PTH(39–69) or PTH(53–84) [8,11]. The exact molecular mechanism to explain this unexpected behavior has still to be elucidated.

The chronotropic effect of PTH on neonatal cardiomyocytes seems mediated by an activation of adenylate cyclase and, subsequently, cardiac L-type Ca^{2+}-channels. In presence of PTH(1–34), cAMP accumulated in neonatal cardiomyocytes prior to the increase of the beating frequency [8,12]. An increase in L-type Ca^{2+} currents of neonatal cardiomyocytes by PTH(1–34) was also demonstrated [13] and this increase was abolished by Rp-cAMPS, an inhibitory cAMP analogue. Ca^{2+} influx into neonatal cardiomyocytes was also demonstrated in the presence of PTH. This influx was not observed in cells pretreated with cholera toxin and prestimulation of G_s proteins [12]. Thus, PTH seems to activate L-type Ca^{2+} channels via a G_s mediated activation of adenylate cyclase. No effects on T-type Ca^{2+} channels were found [14]. These studies with neonatal cardiomyocytes suggested that PTH acts as a modulator of cardiac L-type Ca^{2+} channels. Cellular changes, related directly or indirectly to PTH and responsible for myocardial dysfunction seen in patients with chronic renal disease, are generated, however, on adult rather than neonatal cardiomyocytes. It was important therefore to compare the actions of PTH on neonatal cardiomyocytes with those evaluated on adult cardiomyocytes.

On adult cardiomyocytes PTH also causes a Ca^{2+} influx [9]. As in neonatal cardiomyocytes, full-length PTH is more potent to increase Ca^{2+} influx than PTH(1–34). In contrast to neonatal cardiomyocytes, however, Ca^{2+} influx in adult cardiomyocytes is pertussis toxin sensitive and not affected by cholera toxin [9]. This indicates that in adult cardiomyocytes either G_i or G_o proteins instead of G_s proteins are involved in the PTH signaling towards Ca^{2+} influx. In contrast to neonatal cardiomyocytes cAMP seems not involved in this effect of PTH, because neither dibutyryl-cAMP, a cell permeable cAMP analogue, nor forskolin, a direct activator of adenylate cyclase, could mimic the PTH effects on Ca^{2+} influx in adult cardiomyocytes [9]. In addition, PTH(1–34) did not cause accumulation of cAMP in adult cardiomyocytes [15] or adult myocardium [16]. Furthermore PTH(1–34) did not cause functional alterations linked to adenylate cyclase activation, such as the contractile behavior of adult cardiomyocytes [15] or of papillary muscle from right rat ventricle [16]. The differences in the pathways leading to an increase in Ca^{2+} influx between neonatal and adult cardiomyocytes are summarized in Fig. 1.

Several studies cited above have documented that PTH increases movement of calcium into cardiomyocytes. Severe calcium overload of the myocardium is associated with a deficiency of high energy phosphate compounds from the tissue [24]. Baczynski et al. [25] injected rats approximately 10 μmol full-length PTH and evaluated whether PTH influences myocardial high energy phosphate contents. They found that myocardial ATP and creatine phosphate contents were significantly reduced in rats treated with PTH compared to untreated control animals. Verapamil, which inhibits Ca^{2+} influx, abolished these effects of PTH. PTH did not cause a significant rise in the blood levels of calcium under these experimental conditions. From these data the authors concluded that PTH may influence myocardial energy metabolism by forced accumulation of Ca^{2+} in cardiomyocytes. The significance of these findings remains unclear.

Although no direct contractile effects of PTH on adult cardiomyocytes have been found, there is evidence that

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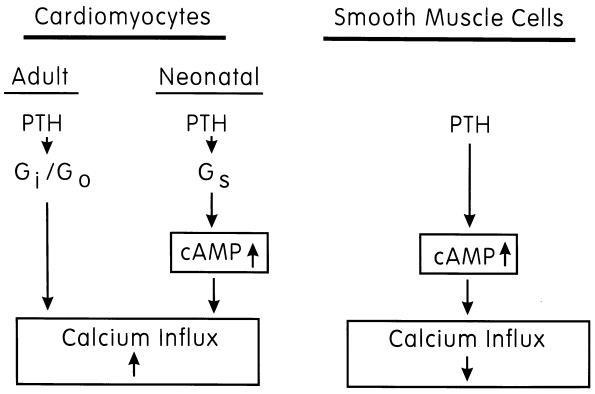

Fig. 1. Intracellular signaling by which PTH influences the increase of intracellular calcium by influx of extracellular calcium into cardiovascular cells. PTH increases calcium influx, in adult cardiomyocytes via pertussis toxin sensitive G-proteins, e.g. G_i or G_o, in neonatal cardiomyocytes via cholera toxin sensitive G-proteins, e.g. G_s, and activation of adenylate cyclase. PTH decreases calcium influx in smooth muscle cells in a cAMP-dependent manner.

PTH can influence the contractile behavior of cardiomyocytes in an indirect way. It was demonstrated first on neonatal cardiomyocytes, that PTH interferes with β-adrenoceptor mediated contractile effects. When beating of neonatal cardiomyocytes was stimulated by addition of isoprenaline, a β-adrenoceptor agonist, PTH(1–34) attenuated significantly the β-adrenoceptor mediated effect by 54% [7]. Similar results were also found on adult cardiomyocytes and in these studies the mechanism by which PTH(1–34) interferes with β-adrenoceptor stimulation was analyzed in more detail. The inhibition by PTH of the contractile effect of β-adrenoceptor stimulation on adult cardiomyocytes was abolished in presence of calphostine, a protein kinase C inhibitor, and in presence of a phosphodiesterase inhibitor [15]. From these studies it is concluded that PTH attenuates the contractile effect of β-adrenoceptor stimulation by a protein kinase C-dependent activation of a phosphodiesterase, which lowers the cellular accumulation of cAMP.

The functional domain involved in this indirect contractile inhibitory effect on adult cardiomyocytes covers the amino acids 28–34. This part of PTH was identified as a functional domain first on chondrocytes [17]. It activates protein kinase C in classical target cells like osteoblasts [18] and non-classical target cells like adult cardiomyocytes [15].

In summary, PTH activates adenylate cyclase in neonatal cardiomyocytes but not in adult cardiomyocytes. The mechanisms underlying these differences have yet to be elucidated. It is not clear whether neonatal and adult cardiomyocytes behave differently because they express different receptor subtypes or different transduction mechanisms for the receptor signals. PTH attenuates the contractile effect of cardiomyocytes to β-adrenoceptor stimulation indirectly in a protein kinase C-dependent way.

3. PTH and myocardial hypertrophy

As noticed above, PTH activates protein kinase C in adult cardiomyocytes [15]. On isolated adult ventricular cardiomyocytes several humoral factors have been identified that induce signs of myocardial hypertrophy, i.e. increase in protein synthesis, cellular protein mass, and re-expression of fetal type proteins like creatine kinase BB (reviewed in Ref. [19]). Among these, several factors act, like PTH, via an activation of protein kinase C. From this the question arises whether elevated plasma concentrations of PTH contribute to the genesis of myocardial hypertrophy in vivo. Clinical data support this hypothesis: Severe left ventricular hypertrophy was found in 70% of patients with end-stage renal disease, which exhibit elevated plasma PTH levels [20,21]. In two clinical studies patients with extremely high serum PTH levels, caused by secondary hyperparathyroidism, and accelerated left ventricular mass underwent parathyroidectomy. This resulted in a marked reduction of both plasma PTH levels and left ventricular mass [22,23].

Direct evidence for a hypertrophic effect of PTH on cardiomyocytes has been shown by the use of ventricular cardiomyocytes isolated from adult rats. On isolated ventricular cardiomyocytes a hypertrophic response can be characterized by increased protein synthesis, protein mass, and re-expression of fetal type proteins. On these cells the PTH peptides PTH(1–34) and PTH(28–48) stimulated ^{14}C-phenylalanine incorporation, used to determine protein synthesis, whereas PTH(39–69) did not [11]. This was accompanied by an increase in total cellular protein mass. PTH(1–34) and PTH(28–48), but not PTH(39–69), were similarly potent in induction of cytosolic creatine kinase. Induction of cytosolic creatine kinase was mainly due to a re-expression of the fetal type creatine kinase isoform, CK-B [10]. An increase of CK-BB activity by PTH could be mimicked by addition of phorbol myristate acetate, a protein kinase C activator, and attenuated by staurosporine, a protein kinase C inhibitor. It is concluded from these data that PTH exerts a direct hypertrophic effect on cardiomyocytes via activation of protein kinase C and that a functional domain covering the amino acids 28–34 is responsible for this effect.

4. Conclusive remarks about the effects of PTH on cardiomyocytes

PTH exerts distinct effects on neonatal and adult cardiomyocytes (summarized in Table 1). On neonatal cardiomyocytes PTH seems to activate adenylate cyclase and Ca^{2+} influx in a cAMP-dependent way. These effects of PTH are blunted by truncation of the first two amino acids of PTH [12]. This is in accordance with the structure–function relationship (Fig. 2) of PTH on classical target cells [48]. On adult cardiomyocytes there is no evidence that

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Table 1
Effects of PTH on cardiomyocytes

Biological effect	Region	Activity	Target	Literature
Beating activity	1–34	+	neonatal	[8,7]
	1–84	+ +	neonatal	[8]
	53–84	−	neonatal	[8]
Ca^{2+} influx	1–34	+	neonatal	[12]
	3–34	−	neonatal	[12]
	1–34	+	adult	[9]
cAMP accumulation	1–34	+	neonatal	[8,12]
	1–34	−	adult	[15]
L-type Ca^{2+} current	1–34	+	neonatal	[12]
	1–34	+	neonatal	[14]
T-type Ca^{2+} current	1–34	−	neonatal	[14]
Protein synthesis	1–34	+	adult	[11]
	28–48	+	adult	[11]
	39–69	−	adult	[11]
CK activity	1–84	+ +	adult	[10]
	1–34	+	adult	[11]
	28–48	+	adult	[11]
	39–69	−	adult	[11]

Activity: + + = very high; + = high effect; − = no effect.
Calcium influx represents experiments in which the increase in intracellular calcium depends on an increased flux of extracellular calcium into the cell.

PTH activates adenylate cyclase. In some of these studies PTH(1–34) was replaced by N-terminally truncated peptides. These peptides are active, i.e. increase protein synthesis on cardiomyocytes, as long as they cover amino acids 28–34, which has previously been described as a core of a functional domain activating protein kinase C. PTH effects on adult cardiomyocytes seem exclusively due to an activation of protein kinase C. In accordance with this a direct protein kinase C activation of PTH on adult cardiomyocytes has been shown. Interestingly, although PTH increases Ca^{2+} influx in neonatal and adult cardiomyocytes, both cell types differ significantly in the intracellular signaling leading to this response.

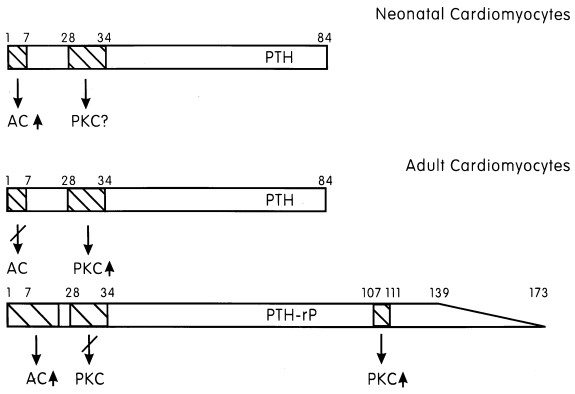

Fig. 2. Structure–function relationship of PTH and PTH-rP determined on neonatal and adult cardiomyocytes. PTH activates adenylate cyclase (AC) of neonatal cardiomyocytes via a domain covering the first N-terminal amino acids. It has to be determined whether PTH activates protein kinase C (PKC) of neonatal cardiomyocytes via a domain covering amino acids 28–34. PTH does not activate adenylate cyclase of adult cardiomyocytes. It activates PKC via its classical PKC activating domain. PTH-rP activates adenylate cyclase in adult cardiomyocytes, but the responsible domain has not yet been identified. PTH-rP also exerts PKC-dependent effects, but via a C-terminally located domain covering amino acids 107–111 and not the classical PKC-activating domain covering amino acids 28–34.

5. Vasodilatory effects of PTH and interaction on smooth muscle cells

Vasodilatory actions of PTH have been described in several species, e.g. in dogs [26], rats [27], chicken [28], frogs [29], and snakes [30]. Pang et al. [28] showed that synthetic PTH(1–34) decreases the mean arterial pressure in anaesthetized rats in a dose-dependent fashion. PTH has also been shown to lower blood pressure in hypertensive rats [31]. The relaxant action of PTH on blood vessels does not require an intact endothelial cell layer [32]. This indicates a direct vasorelaxant mechanism for PTH on vascular smooth muscle cells. Responsiveness in vivo of small arterioles to PTH(1–34) but not PTH(3–34) indicated that N-terminally located amino acids are important for vascular dilatation [33]. These first two amino acids are required for activation of adenylate cyclase on classical target cells of PTH. Indeed, PTH(1–34) was also found to increase cAMP accumulation in primary cultures of smooth muscle cells isolated from rabbit or rat aortas and bovine pulmonary arteries [34].

Vasorelaxation of smooth muscles cells can be caused by an inhibition of L-type calcium channels. Inhibition of L-type calcium channels of smooth muscle cells by PTH(1–34) has been demonstrated directly [13,14,27]. In contrast, N-truncated PTH peptides, e.g. PTH(3–34) and PTH(7–34), could not mimic these effects of PTH(1–34) but they antagonized the effects of PTH(1–34). As mentioned above these N-terminal truncated PTH peptides do not activate adenylate cyclase of classical target cells. In addition, PTH inhibited the vasopressin-induced vascular smooth muscle contraction and this effect of PTH was abolished by antagonists of cAMP-dependent protein kinases [13]. PTH did not influence T-type calcium channels in smooth muscle cells [14]. All together, work with isolated smooth muscle cells suggests that the vasodilatory action of PTH is mediated by a cAMP-dependent inhibition of L-type calcium currents. It has to be emphasized here that PTH increases calcium influx in cardiomyocytes (see above) but decreases calcium influx in smooth muscle cells (see Fig. 1).

In sharp contrast to this vasodilatory action of PTH is that PTH raised intracellular Ca^{2+} in a cell line of smooth muscle cells [35]. This effect of PTH was strictly limited to PTH(1–34), could not be mimicked by PTH(3–34) and

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seemed to be cAMP-dependent, too. At present the discrepancy between this cell line and the physiological behavior described above cannot be easily explained. An assumption may be that the cell line does not reflect the physiological situation found in vivo.

6. Conclusive remarks about the vasorelaxant effects of PTH

PTH is a vasorelaxant agent that acts directly on vascular smooth muscle cells. As known so far, this action of PTH represents the classical way of PTH signaling, involving the functional domain covered by the very first N-terminal amino acids and activation of adenylate cyclase. Experimental data suggest that PTH exerts its vasorelaxant action via cAMP-dependent inhibition of L-type Ca^{2+} channel currents.

7. Expression of PTH-rP in cardiovascular cells

Cardiovascular effects of PTH have been described for many years and indicated that cardiovascular cells express PTH-receptors. It is evident that excess serum PTH causes cardiovascular dysfunction. The physiological role of PTH in the regulation of the cardiovascular system remained an open question. Cloning and sequencing of a peptide hormone initially named hypercalcemic factor of malignancy and now named parathyroid hormone-related peptide (PTH-rP) have enabled studies on the expression of this structurally to PTH related peptide hormone in various tissues. In contrast to PTH, PTH-rP is expressed in several tissues, including the heart [3]. Within the heart PTH-rP is expressed predominantly in the atria and to a smaller extent in ventricles [39,42]. PTH and PTH-rP are highly homologous. Among the first 6 amino acids at the N-terminal part 5 amino acids are identical. Due to this strong homology PTH-rP can bind to the same receptor as PTH and mimic the cell physiological effects of PTH in classical target cells, e.g. osteoblasts, chondrocytes, and kidney cells.

Within the vascular system expression and release of PTH-rP was detected in smooth muscle cells [36]. Vasoactive peptides, like endothelin, norepinephrine, thrombin, and angiotensin II or mechanical stimuli increased the expression of PTH-rP in smooth muscle cells [36–38]. The concentrations of the PTH-rP peptide in smooth muscle cells surrounding the aorta and vena cava were comparable to those concentrations found in the atria but the RNA concentrations of PTH-rP were 3-fold lower [39]. This difference in the ratio of peptide versus RNA contents in vessels and atria suggests differences in the regulation of expression. In the atria, PTH-rP expression seems regulated predominantly on the transcriptional level. In aorta and vena cava it seems regulated predominantly on the posttranslational level.

Within the vessel wall, expression of PTH-rP is not limited to smooth muscle cells. It also occurs in endothelial cells, as shown with endothelial cells from human umbilical vein [5] and bovine carotid artery [40]. In contrast to smooth muscle cells, which express PTH-rP and possess PTH/PTH-rP receptors [41], endothelial cells express PTH-rP but not the corresponding receptor [5].

PTH-rP is a peptide hormone that is expressed in three different mRNA forms, namely mRNA encoding for PTH-rP(1–139), PTH(1–141), and PTH-rP(1–173). These three different mRNA forms are generated by the selective use of specific promoter regions of the PTH-rP gene and specific RNA splicing. Posttranslational modifications of these three different PTH-rP peptides lead to the production and release of either N-terminal PTH-rP peptides or C-terminal PTH-rP peptides. Positive immunostaining was detected in hearts with PTH-rP(1–34) antibodies [5], but immunoreactivity determined by PTH-rP(109–141) antisera revealed a 3- to 5-fold higher amount of PTH-rP peptides covering the C-terminal part than those covering the N-terminal part [39]. This indicates that cardiovascular cells preferentially release PTH-rP peptides representing C-terminal parts of the molecule. This part has no homology to PTH and therefore this pattern of PTH-rP release suggested separate roles for PTH-rP and PTH in cardiovascular physiology.

8. Cardiovascular effects of PTH-rP

The characterization of cardiovascular effects of PTH-rP has focused on its hypotensive effect. It was investigated whether PTH-rP(1–34), the N-terminal part of the molecule with a high homology to PTH, can mimic the effects of PTH(1–34) on vasodilatation. As mentioned above PTH(1–34) exerts its vasodilatory effects via activation of adenylate cyclase mediated by the first two amino acids, which are identical in PTH and PTH-rP. Thus, one might expect that PTH-rP(1–34) mimics the effects of PTH on smooth muscle cells. The experiments show, however, that PTH-rP(1–34) is more potent than PTH(1–34) in lowering blood pressure. This result was found independently of the experimental system used, i.e. vasodilatation in rats [43,44], increase in blood flow [44], preglomerular vasodilatation [45], or relaxation of aortic rings precontracted with norepinephrine [37]. These findings cannot be explained by a similar structure–cardiovascular function relationship of the N-terminal region of PTH and PTH-rP. They rather suggest that parts of PTH-rP(1–34) other than the first two amino acids contribute to its cardiovascular effects. To date, effects of PTH-rP on smooth muscle cells cannot finally be judged because experimental data on peptides covering C-terminal parts of PTH-rP are not available. This is an important field for future research because cardiovascular cells seem to release preferentially PTH-rP peptides covering the C-terminal part of the whole molecule.

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On cardiomyocytes it was also investigated whether PTH-rP can mimic effects of PTH. PTH-rP(1–34) did not promote Ca^{2+} influx in neonatal cardiomyocytes [46], in contrast to PTH(1–34). On adult cardiomyocytes PTH, but not PTH-rP, induced cytosolic creatine kinase. PTH-rP could attenuate this hypertrophic effect of PTH, indicating that cardiomyocytes are target cells for PTH-rP [10]. The structure–function relationship was studied in more detail on adult cardiomyocytes. As mentioned above, induction of creatine kinase by PTH is mediated by a functional domain covering amino acids 28–34. In this part of PTH and PTH-rP molecules only one amino acid is identical (histidine at position 32). The secondary structure between both peptides is, nevertheless similar, except for position 29, where the hydrophilic glutamine of PTH corresponds to the hydrophobic alanine of PTH-rP. The similar secondary structure seems to explain why PTH-rP activates protein kinase C on osteoblasts with the same functional domain as PTH [18]. On adult cardiomyocytes, however, PTH-rP cannot replace PTH for its physiological effects. To clarify the structural basis for this discrepancy a synthetic hybrid peptide was synthesized, [Ala^{29}]PTH(28–48), in which alanine replaced glutamine at position 29, as in PTH-rP. In contrast to PTH(28–48) this mutated peptide had no intrinsic activity but antagonized the effect of full-length PTH on cardiomyocytes. The hydrophobic replacement at position 29 thus causes functional antagonism of PTH-rP and PTH on adult cardiomyocytes.

It was further investigated whether PTH-rP can influence mechanical performance of cardiomyocytes in different ways from PTH. On isolated and perfused rat hearts, PTH-rP(1–34) produced positive chronotropic and inotropic effects [43] not found for PTH. On the cellular basis PTH-rP(1–34), in contrast to PTH(1–34), activated adenylate cyclase in adult ventricular cardiomyocytes and stimulated their contractile response [15,47].

Recently it was investigated whether other parts of PTH-rP, e.g. PTH-rP(107–111), mediate protein kinase C dependent effects on adult cardiomyocytes. This C-terminal pentapeptide represents a protein kinase C activating domain of PTH-rP completely distinct from those identified on PTH. PTH-rP(107–111) was found to activate mitogen activated protein kinase (MAPK) in adult cardiomyocytes, increase protein synthesis, and the specific activity of creatine kinase BB [47]. These data indicate that PTH-rP can exert effects of its own on cardiomyocytes which are completely distinct from those previously reported for PTH.

9. Conclusive remarks about the expression and function of PTH-rP in the cardiovascular system

PTH-rP is secreted in various parts of the cardiovascular system, i.e. smooth muscle cells, endothelial cells, and atrial cardiomyocytes. Smooth muscle cells, atrial and ventricular cardiomyocytes, but not endothelial cells, are target cells for PTH-rP. PTH-rP exerts direct effects on these target cells, which are summarized in Table 2. These actions seem to be independent from those exerted by PTH, the structurally related hormone. In conclusion, PTH and PTH-rP influence cardiovascular cell physiology in a way different from their influence on classical target cells, i.e. osteoblasts, chondrocytes, or kidney cells.

Table 2
Effects of PTH-rP on cardiovascular cells

Biological effect	Region	Activity	Target	Literature
Beating activity	1–34	+	isolated heart	[43]
	1–34	(+)	adult CM	[47]
	7–34	(+)	adult CM	[47]
cAMP accumulation	1–34	(+)	adult CM	[47]
L-type Ca^{2+} current	1–34	–	neonatal CM	[46]
Protein synthesis	107–111	+	adult CM	[47]
CK activity	1–34	–	adult CM	[10]
	7–34	–	adult CM	[10]
	107–111	+	adult CM	[47]
Vasodilatation	1–34	++	aortic rings	[37]

Activity: ++ = very high; + = high effect; (+) = moderate effect; – = no effect.
CM = cardiomyocytes.

Acknowledgements

This study was supported by the Deutsche Forschungsgemeinschaft, Sonderforschungsbereich 547, project A1.

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