Parathyroid Hormone Related Peptide (PTHrP): A Mini-Review

Abstract

In this mini-review the role of parathyroid hormone-related peptide (PTHrP) in physiology and pathophysiology is discussed. Evolving from an unknown humoral factor in the HHM (Hypercalcemia of malignancy) syndrome its role as a "masterregulator" in the PTH family following identification is reviewed. PTHrP has more paracrine and autocrine functions in virtually all tissues than classical endocrine functions and is essential in embryonic, fetal and post-natal life. The physiological functions are near endless. The development of PTH/PTHrP receptor antagonist and agonists has been difficult and disappointing. Its role as a possible cytokine itself and as a regulatory thermogenesis factor in brown adipose tissue in cancer cachexia is discussed. PTHrP assays must be improved for PTHrP to be a reliable biomarker in oncology and to resolve the function of local proteolytic PTHrP fragments which are largely a mystery until now.

Keywords: Parathyroid hormone-related peptide; PTHrP; Hypercalcemia; HHM; HHM syndrome

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Abbreviations: PTHrP: Parathyroid Hormone-Related Peptide; PHP: Primary Hyperparathyroidism; MS: Mass Spectrometry; HHM: Hypercalcemia of Malignancy

Introduction

In most clinical situations hypercalcemia is caused by primary hyperparathyroidism (PHP) or malignancy [1,2]. Because the excretion of urinary cAMP (cyclic 3',5' adenosine monophosphate) has been proven to be a good measurement of the biological activity of parathyroid hormone (PTH) in PHP some investigators started measuring urinary cAMP excretion in hypercalcemic patients with a malignant tumor in an attempt to differentiate between the hypercalcemia of PHP and of malignancy [3-5]. Soon it appeared that a considerable part of patients with Hypercalcemia of Malignancy (HHM) also showed an increased urinary cAMP excretion. This was found in particular in hypercalcemic patients without bone metastases (6-8). Like in PHP these patients also had a decreased tubular reabsorption of phosphate (TmPO4/GFR). However in contrast to patients with PHP normal or low levels of 1.25 di-(OH)D3 were found and the tubular reabsorption of calcium was not increased [8].

According to Stewart et al the humoral factor that leads to an increased urinary cAMP excretion and Hypercalcemia in patients with a malignancy without skeletal metastases is not identical to PTH and couldn’t be measured with a PTH radioimmunoassay. Nevertheless this humoral factor resembles PTH in decreasing TmPO4/GFR and increasing nephrogenous cAMP excretion. For that reason it was called a “PTH-like factor” resulting in Hypercalcemia in patients with malignancy and it was named the “Humoral Hypercalcemia of Malignancy (HHM) syndrome” [8]. The HHM syndrome occurred in particular in patients with squamous cell solid tumors of the bronchus, head and neck and in the renal adenocarcinoma [8].

Ralston et al. [9] showed there was no association between the number of skeletal metastases and the serum calcium concentration in patients with solid tumors. Based on this study Mundy estimated that the HHM syndrome occurs in 75% of patients with a solid tumor, including breast cancer patients [10]. Hypercalcemia in malignancy is caused in 50% by breast cancer and multiple myeloma. Therefore it was important that the occurrence of the HHM syndrome in breast cancer was demonstrated by Isales et al. [11].

Several investigators studied nephrogenous cAMP excretion in normocalcemic tumor patients and found nephrogenous cAMP excretion increased in 30% of patients, including breast cancer patients [6,12,13]. If this is a harbinger for the development of Hypercalcemia is not known. What is well known that with resection of the tumor all biochemical parameters disappear. It is also known that the renal adenyl cyclase system in these patients shows a diminished stimulation capability [17]. It was in the late 1980's the "PTH-like factor" was identified as the Parathyroid Hormone Related Peptide (PTHrP) [18-20]. In this mini -review the identification, physiological and pathophysiological role and future possible developments of PTHrP will be discussed.

Identification of PTHrP

Human PTHrP proved to be encoded by a single gene on the short arm of chromosome 12 [18-22]. Alternative splicing generates many different mRNA species which encode three separate is forms of 139, 141 or 173 amino acids. From the outset it was evident that the PTHrP and PTH gene were related. The portions of the genes encoding the amino-terminal part are highly homologous such that the peptides share 8 of the first 13 amino acids and a similar secondary structure over the next 21 amino acids. The amino-terminal end of PTH contains 34 amino acids. PTHrP is produced in low concentrations in virtually all
tissues. The physiological role of PTHrP remains incompletely understood. PTHrP has a function in:

1. Transepithelial calcium transport in the kidney and mammary gland.
2. Smooth muscle relaxation in the uterus, bladder, gastrointestinal tract and arterial wall.
3. Cellular differentiation and apoptosis of multiple tissues.
4. PTHrP is an indispensable component of successful pregnancy and fetal development. Embryonic gene deletion is lethal in mammals.

When the receptor was discovered it was evident that this receptor functioned to relay both PTH and PTHrP biological activity [24]. This PTH1 receptor belongs to the G protein-coupled receptor family. Knock out of this PTH/PTHrP receptor (PPR) showed the importance of PTHrP [25,26]. PTHrP is the master regulator and has widespread paracrine actions. The actions of recombinant PTH 1-34, as an anabolic agent in the treatment of osteoporosis mimic PTHrP actions locally in the bone microenvironment [27]. There are three identified circumstances in which PTHrP species are present in the circulation and act in an endocrine manner:

A. The HMM syndrome in which PTHrP is produced by tumors and circulates to the bone to stimulate bone resorption [28,29].
B. Lactation in which PTHrP is made in the breast and reaches the circulation [30].
C. Fetal life, where PTHrP regulates maternal-to-fetal calcium transport [31,32].

Hence the vast majorities of PTHrP actions are paracrine in nature.

Skeletal actions of PTHrP

The generation of mice missing the PTHrP gene, the PTH/PTHrP receptor gene or the PTH gene provided important models for testing the physiological roles of PTHrP [25,33,34]. Mice lacking PTHrP die at birth because all bones resulting from endochondral bone formation develop improperly. As a result the rib cage is small and inappropriately mineralized. Abnormalities in the growth plate result from aberrant control of chondrocyte proliferation and differentiation in the PTHrP (-/-) growth plates and also in the growth plates of the PTH/PTHrP receptor (-/-) mice. These similarities support the idea that PTHrP affects the proliferation and differentiation in the PTHrP (-/-) growth plates in the growth plate result from abberant control of chondrocyte proliferation [35]. The PTHrP (1-84) knock-in mice exhibited also early senescence in multiple tissues. The brain showed decreased neural proliferation and increased apoptosis with abnormal shape. PTHrP is needed in maintaining normal synapsis and plasticity. These effects are partly mediated by the PTH2 receptor [42].

In a second model, knock-in of PTHrP(1-66), which excludes a significant portion of the mid-region, resulted in a an even more severe phenotype with similar skeletal abnormalities as chondrodysplasia but also impaired hemopoiesis and mammary development, deregulated energy metabolism and death by 5 days of age. So many actions of PTHrP are not mediated solely by the amino-terminal fragment [43].

PTHRP in lactation

Not long after its discovery PTHrP mRNA was found in the lactating and PTHrP was measured in high concentrations in milk [44,45]. In mice as soon as the mammary bud begins to form epithelial cells produce PTHrP which interacts with the PTH1 receptor expressed on surrounding mesenchymal cells. This interaction is necessary for proper differentiation of the dense mammary mesenchym. PTHrP or PTH1 R knock-out mice lack mammary glands. The formation of the human breast in human...
fetus is similar to that in mice and PTHrP is indispensable for that as well [46]. During puberty PTHrP seems to regulate the growth of the mammary ducts in response to estrogen [47,48]. PTHrP is also made by breast epithelial cells during lactation and large quantities are secreted in milk [49,50]. Milk production requires a great deal of calcium, an important source of which is the maternal skeleton. During lactation elevated levels of PTHrP correlate with bone loss in human and circulating levels of PTHrP correlate directly with rates of bone resorption and inversely with bone mass in mice [51,52]. The lactating breast also expresses the CaR which signals to suppress PTHrP secretion in response to calcium delivery to the breast [52]. These interactions define a classical negative feedback loop whereby mammary cells secrete PTHrP to mobilize calcium from the bone. Calcium in turn feeds back to inhibit further PTHrP secretion from the breast. Therefore during lactation the breast and bone engage in a conversation which leads to the mobilization of skeletal calcium to ensure a steady supply of calcium for milk production. Interestingly fish PTHrP shows a similar function to mobilize calcium stored in scales to be used for egg production [53].

**PTHrP and the placenta**

During pregnancy calcium must be actively transported across the placenta from mother to fetus. The calcium concentration in the fetus is higher than in the mother so that calcium must be transported against a gradient [54]. In PTHrP(-/-) mice this gradient is lost and PTHrP deficient fetuses are hypocalcemic. This suggests that fetal PTHrP is important in placental calcium transport from the mother [32]. Placental production of PTHrP has been shown to be regulated by the CaR [55,56]. Experiments in sheep and mice showed that the midregion PTHrP is responsible for placental calcium transport and not the amino-terminal portion [32,57]. PTHrP levels in umbilical cord blood are approximately 10 fold higher than PTH levels. Placental calcium transfer requires PTHrP and possibly PTH but not calcitriol or calcitonin. It is in the neonatal period that intestinal calcium absorption and thereby skeletal development and mineralization become dependent upon vitamin D3 and calcitriol [58]. A few cases of overproduction of PTHrP in the placenta resulting in hypercalcemia have been described [59,60].

**PTHrP in smooth muscle and the cardiovascular system**

PTHrP expression is present in many different smooth muscle cell beds [22]. Stretching of the muscular cell or structure increases the expression of PTHrP. PTHrP works as a relaxant then in turn on the structure that has been stretched in an autocrine or paracrine way [22,61,64]. For organs like the bladder, stomach or uterus this may be an important feedback loop allowing gradual filling. In the vascular wall PTHrP is expressed by vasoconstrictive agents, stretch it and acts as a vasodilator to resistance vessels. In this way PTHrP may act as a local modulator of blood flow [65]. PTHrP expression is also stimulated by pathologic stimuli including atherosclerosis, restenosis after balloon angioplasty and hypertension [66]. In addition to its relaxant effect PTHrP inhibits vascular smooth muscle cell proliferation through its interaction with the PTH1R and stimulation of the cAMP-protein kinase a pathway resulting in cell cycle blockade in the G1 phase. These effects are mediated by the amino-terminal fragments of PTHrP. PTHrP may also have proliferative effects on vascular smooth muscle cells by translocating in the nucleus leading to inhibition of vascular proliferation. These effects are mediated by the mid-region fragments of PTHrP [67,68]. Endogenous PTHrP is mitogenic in the renovascular smooth muscle cell while exogenous added PTHrP was anti-mitogenic in the SHR (Spontaneously Hypertensive Rat) model of genetic hypertension. These results suggest that a single molecule may have opposite effects under physiological and pathological conditions [69]. PTHrP has been found in cardiomyocytes and co-localizes with atrial natriuretic peptide in granules within the atrial cells in the rat heart [70]. In PTH1R deficient mice widespread cardiomyocyte death occurred in midgestation. This was not seen in PTHrP(-/-) mice. PTHrP has both positive inotropic and chronotropic effects and may affect coronary blood flow [71,72].

**PTHrP and the pancreas**

PTHrP is expressed in all four different types of neuroendocrine cells in the pancreas. In beta-cells it is stored within secreting granules and co-released with insulin [73]. Pancreatic islet cells express the PTH1 receptor. Overexpression of PTHrP in beta cells leads to an increased beta cell mass, hyperinsulinemia and hypoglycemia due to increased beta cell proliferation, increased insulin production and inhibition of beta cell apoptosis [74,75]. PTHrP(-/-) mice have no defects in islet cell development. Because of the death of these mice at birth the role of PTHrP in the physiology of islets is not known. Neuroendocrine tumors secreting PTHrP resulting in hypercalcemia has been described [76,78].

**PTHrP and the central and peripheral nervous system**

PTHrP and the PTH1 receptor are both widely expressed within the brain including the cortex, the cerebellum, the hippocampus, hypothalamus and pituitary [79,80]. PTHrP secretion by neurons is regulated by calcium influx through L-type channel activity on depolarization. In turn PTHrP can dampen L-type channel activity to protect neurons from damage to prolonged or repeated depolarization so called “excitotoxicity” creating an autocrine or paracrine short feedback loop [81]. PTHrP is also present in glia and astrocytes. High PTHrP levels in glial tumors correlate with a poor prognosis [82-85]. PTHrP expression increases in sites of ischemic brain injury where it may play a protective role by enhancing blood flow [83]. PTHrP inhibits the proliferation of damaged and dedifferentiated Schwann cells in peripheral nerves in this way contributing to nerve regeneration [86]. The brain contains also PTH2 receptors. These receptor scan bind PTH and the tuberoinfundibular peptide (TIP39) but do not bind PTHrP. The TIP39-PTH2R neuromodulatory system is predominantly involved in auditory processing and in neuroendocrine modulation. TIP39 influences somatostatin and CRH (Corticotrophin Releasing Hormone) neurons. PTHrP has no role in this system [87].

**Teeth and PTHrP**

Developing teeth are surrounded by bone and must erupt through the roof of the dental crypt to emerge into the oral cavity. This requires spatial coordination of bone cell activity. Osteoclasts

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must resorb the bone overlying the crown of the tooth to allow it to emerge and osteoblasts must form bone at the base of the tooth to propel it upward out of the crypt. PTHrP is produced by stellate reticulum cells and it signals to dental follicle cells to promote the formation of osteoclasts above the crypt. In the absence of PTHrP these osteoclasts do not appear; eruption fails to occur and the teeth become impacted [88,90].

**PTHrP in the HHM syndrome**

After the identification of PTHrP an assay had to be developed. PTHrP is cleaved into N-terminal [1-86] and C-terminal [109-141] peptides. Various attempts have been made to develop assays that target the N-terminal or C-terminal peptide. The original sandwich radioimmunoassay was using two different antibodies targeting different PTHrP peptides showed to be specific for PTHrP but has now been discontinued (Nichols Lab). Quest offers currently a C-terminal PTHrP assay. This assay is however impacted by declining renal function producing higher values and more false positive results. N-termin al fragments are less influenced by renal function, producing less false positive results. For this reason detection of the N-terminal is a more useful indicator of HHM. Mayo Medical Laboratories developed a sandwich assay capturing the mid-region and the N-terminal fragment of PTHrP. Beckman offers a similar assay that captures the PTHrP 1-86 sequence. Others developed liquid chromatography mass spectrometry (MS) assays for the midportion region of PTHrP but it had very poor correlation with the immunoassay. Competetive immunoassays have lower specificity, precision and analytical sensitivity compared to sandwich or MS assays. So when PTHrP should be a reliable biomarker there is still some work to do. At this time nephrogenous cAMP excretion remains the golden standard as a reliable biomarker there is still some work to do. At this time nephrogenous cAMP excretion remains the golden standard as a bio-assay until the PTHrP or other protein assays are able to achieve maximal clinical sensitivity and specificity [91].

**PTHrP/PTH1R antagonists and agonists**

The development of PTHrP or PTHrP/PTH1R antagonists and agonists has been difficult and disappointing. Binding modes used by agonists and antagonists of the PTH1 receptor utilizes a two-site binding site mechanism that involves the putatively helical N-and C-terminals of the ligand. The N-terminal domain of the receptor provides the major binding energy while the juxtamembrane region of the receptor induces activation of the receptor. N-terminally truncated antagonists as PTHrP(5-36) bind mainly to the N-domain with some overlap to the J-domain. These N-terminal antagonists are not effective inhibitors of the two-site agonists such as PTH(1-34). Recently however highly potent and longacting PTH1R monoclonal antibodies were developed for the treatment of elevated levels of PTH as in primary hyperparathyroisism (PHP) or PTHrP as in the HHM syndrome. PTH1R antagonism to both PTH and PTHrP was determined by cAMP accumulation in osteosarcoma cell lines of both human and rat origin. This antibody showed roughly equivalent inhibition of cAMP in human and murine cell Lines. The antibody inhibited both PTH and PTHrP induced osteoclast differentiation by tenfold. The expression of RANKL was also inhibited. The monoclonal antibody reduced serum calcium levels in a dose dependent manner when infused [92-94]. These studies were scheduled in the poster sessions of the Endocrine Society and the American Society of Cancer Research and not in the oral.

Presentations implying clinical application of this monoclonal antibody will take some time.

As depicted above the physiologically functions of PTHrP are enormous and widespread. Systemic application of an anti-PTH/PTHrP receptor antibody could have also widespread adverse effects for that reason. Topical administration of such an antagonist would be less risky: PTH and PTHrP influence hair follicles through paracrine and intracranial routes. The PTH/PTHrP receptor plays an important role in the hair follicle cycle and may induce premature catagen-telogen transition [95]. Transgenic mice with an overexpression or blockade (PTH/PTHrP receptor knock-out mice) of PTHrP activity revealed lessened or increased hairgrowth respectively. Antagonists of the PTH/PTHrP receptor have been shown to stimulate proliferation of hair follicle cells and hair growth [96]. A hair stimulating effect of such an antagonist has been observed in hairless mice and mice treated with cyclofosfamide [96-98]. So these topical PTH/PTH1R antagonists might be useful in chemotherapy induced alopecia [98]. Sporadic cases of PTH-related hair symptoms were reported in familial syndromes of hyper/hypoparathyroisism [99,100]. PTHrP antagonists have been studied also in enchondroma’s, patients with Olliers syndrome, chondrodystrophia’s and chondrosarcoma’s. Research with structurally modified PTH1R ligands has revealed deeper insights in the function of the receptor but didn’t result in clinical applications yet [102].

The role of PTHrP in the “cytokine excess” has been investigated too. As PTH and PTHrP bind to the PTH1R and stimulate osteoblasts via A-kinase IL-6(interleukine-6) and TNF alpa (tumor necrosis factor alpha) production is also stimulated by this pathway. Marked elevated levels of IL-6 and TNF alpha are present in PHP and in the HHM syndrome. These increases in cytokines normalize after parathyroideectomy [103]. Levels of circulating cytokines as IL-6, IL-8 and TNF-alpha are also increased in cancer patients with high PTHrP levels [104]. PTHrP has been found to be a key factor not only in HHM but also in local osteolytic Hypercalcemia in myeloma patients and osteolytic bone metastases [105,106]. If PTHrP is a cytokine itself or only stimulates the production of the interleukins and TNF alpha is not known. How they interplay is also not completely understood.

For PTHrP as well as the cytokines the RANKL-RANK pathway represents a final common pathway to osteoclastogenesis and stimulation of bone resorption [107]. Bone remodelling is a continuous process achieved by osteoblasts and osteoclasts. The balance of this process is maintained by a trimolecular control factor complex composed of osteoprotegerin (OPG), RANKL (osteoprotegerin ligand) and RANK (receptor activator of nuclear kappa beta, NFkB ligand). Osteocytes regulate the recruitment of osteoclasts to sites of bone resorption by inducing the expression of RANKL by osteoblastic cells. This system is part of the TNF family and can be unregulated by PTHrP; TNF alpha or macrophage colony stimulating factor (M-CSF) [108,109].

Denosumab is a fully human Ig-G2 monoclonal neutralizing antibody to RANKL. It differs from bisphosphonates that inhibit bone resorption by inducing apoptosis in mature osteoclasts. Denosumab inhibits not only bone resorption by mature osteoclasts but also osteoclast formation from hematopoetic precursors [110-112]. Denosumab was effective in controlling serum calcium levels in patients with HHM and was approved by
the FDA for the treatment of skeletal metastases in malignancy, HHM and postmenopausal osteoporosis based on the trials delivered [113,114].

**PTHrP in cancer cachexia**

In 2014 the Spiegelman group suggested that PTHrP is a mediator of adipose tissue browning and tumor-induced cachexia [115]. PTHrP drives the expression of thermogenesis in adipose tissue. Neutralizing of PTHrP in tumor-bearing mice blocked adipose tissue browning and the loss of muscle mass and strength. Cachexia is a wasting syndrome that accompanies many chronic diseases. The PTH/PTHrP receptor was shown also mediating the cachexia of chronic kidney failure. PTHrP proved to be involved in stimulating atherogenic gene program in 5/6 nephrectomized mice that suffered from cachexia. Fat-specific knock-out of PTHrP blocked adipose tissue browning and wasting. Loss of PTH1R in fat tissue preserved muscle mass and improved muscle strength. So PTHrP and PTH mediate wasting through a common mechanism involving a crosstalk between wasting of fat tissue and skeletal muscle [116]. Patients with upper gastrointestinal and pancreatic cancers are the likeliest to develop cachexia which affects about 80% of terminal cancer patients [118]. Blocking the “excess cytokines” syndrome could not reverse cachexia in terminal cancer patients as did the use of anabolic steroids neither [119]. Blocking the PTH/PTHrP receptor in cancer cachexia will not be the ultimate answer because of the widespread systemic adverse effects to be expected as discussed before.

**Conclusion**

Evolving from an unknown humoral factor in the “hypercalcemia of malignancy” (HHM) syndrome in the late 1970’s and 1980’s to the identification of this factor as “parathyroid hormone related peptide” (PTHrP) in 1987 has been a major step in the research of the function of members of the PTH-family in physiology and pathophysiology. Soon it appeared that most functions of PTHrP are paracrine or autocrine. Only its role in the HHM syndrome, lactation and in placental maternal-fetal calcium transport is classical endocrine in nature. PTHrP regulates endochondrial bone formation in fetal life and bone remodeling, formation and resorption in post-natal life. During lactation PTHrP provides a steady supply of calcium from the maternal skeleton to assure calcium-rich milk production. PTHrP is essential in pregnancy for regulating fetal-maternal calcium transport. Without PTHrP there is no fetal life. In the cardiovascular system PTHrP works as a vascular relaxant by its effect on the smooth muscles in the vessel wall and has it a chronotropic and inotropic effect on the heart. In the pancreas PTHrP is involved in beta cell proliferation, insulin production and inhibition of beta cell apoptosis. In the central nervous system PTHrP has a role in protecting neurons from damage of “excitotoxicity” due to repeated or prolonged depolarization. Without PTHrP teeth will not erupt and become impacted in early life. PTHrP has also a function in the growth of the hair follicle. Antagonists of the PTH/PTHrP receptor stimulate the proliferation of hair follicle cells and may be used in the future for chemotherapy-induced alopecia. PTHrP plays a role in the “cytokines excess” syndrome in cancer patients and may be a cytokine in itself. By bringing a thermogenesis gene program to expression in brown adipose tissue PTHrP plays a role in cancer cachexia too. Blocking excess cytokines does not relieve cancer cachexia and blocking the PTH/PTHrP receptor wills not either because of the expected widespread adverse effects. When PTHrP should be a reliable tumor marker in oncology problems with the specificity, sensitivity and analytical precision of the PTHrP assays must be resolved in the near future. This is rather urgent as the function of PTHrP fragments formed by local proteolysis stays otherwise largely unknown.

**Conflict of Interest**

None.

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