ENDOCRINOLOGY SEMINARS

An Update on the Discovery, Pathophysiological Actions, Clinical Manifestations and Possible Physiology of Parathyroid Related Peptide

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ABSTRACT. PTHrP has had an unidentified role in medicine since 1930, when Albright described a patient with renal cortical cell carcinoma with hypercalcemia. Since then hypercalcemia has been recognized as the most common paraneoplastic syndrome. At that time the concept of "ectopic PTH syndrome" was introduced, and remained in literature until the true etiology was finally described. In the early 1970's Roof and Benson presented evidence that PTH in humoral hypercalcemia differed from "authentic" PTH. This marked the starting point for researchers to try identifying the molecule that mimicked PTH action and structure. This molecule, named parathyroid-related peptide, has been associated to hypercalcemia seen with solid tumors, such as squamous cell carcinoma of the lung and renal cortical cell carcinoma. PTHrP has been demonstrated to have similar actions to PTH but to differ in decreasing osteoblastic activity while increasing osteoclastic activity. The more fascinating finding was the presence of the PTHrP genes throughout the body, mostly the lactating breast as well as the heart, lungs and skin among others. Despite its identification, finding its physiological roles on normal tissue still remains to be clarified.

Since the late sixties, humoral hypercalcemia had been theorized to be caused by a factor mimicking the effects of parathyroid hormone. The discovery of this factor, parathyroid related protein, marked the birth of a family of hormones with physiological importance not established yet. A literature review on this subject depicts fragments of a complicated puzzle. However, little has been put together to help clarify the physiologic role(s) of this novel hormone. In this article, we attempt to assemble pieces of the puzzle, in order to learn more about Parathyroid-Related Peptide(s).

PTHrP: The discovery

Humoral hypercalcemia has been long recognized as the most common paraneoplastic syndrome. In 1930, Fuller Albrigth described a patient with renal cortical carcinoma and a single bony metastasis, with biochemical features similar to those of primary hyperparathyroidism. Hypercalcemia in this patient was corrected by X-ray therapy to the metastasis after removal of the primary tumor. At that time Albright suggested that hypercalcemia might be due the ectopic production of parathyroid hormone (PTH) by the tumor. This introduced the concept of the "ectopic PTH syndrome", which became established in the literature and remained as such until very recently.

In 1966 Berson and Yalow, using a radioimmunoassay (RIA) developed by them, found significantly elevated PTH levels in an unselected group of patients with bronchogenic carcinoma (1). Subsequently there were several reports of measurements of PTH by RIA in plasma or extracts of cancers from patients with this syndrome. In none of these instances, however, was the circulating level of PTH as high as in patients with primary hyperparathyroidism (PHPTH) at comparable degrees of hypercalcemia. The general view into the 1970's was that the syndrome of hypercalcemia in cancer without significant bony metastases was really due to ectopic production of PTH. However as the PTH RIA's specificity began to improve during the 1970's, Roof and Benson presented evidence that circulating PTH in humoral

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hypercalcemia of malignancy (HHM) differed from authentic (1-84)PTH(2, 3). In 1973 Powell found that PTH could not be detected either in plasma nor in tumor extracts in patients with HHM despite the use of a wide range of PTH antisera directed against several different parts of the molecule (4). Atkins in 1977 showed that tumor cells could produce bone resorbing activity in vitro by a factor other than PTH.

In the early 1980's three groups working at separate laboratories demonstrated that in addition to hypercalcemia, hypophosphatemia and hyperphosphaturia, HHM displayed additional features that were similar to PHPTH(5-7). One such similarity included increased nephrogenous cAMP excretion. However, important differences between HHM and PHPTH were observed, normal or low levels of circulating immunoreactive PTH concentrations, reduced circulating 1,25 dihydroxy-vitamin D ($1,25(OH)_2D_3$) concentrations and a relatively high fractional Ca^{++} excretion. In 1982 Stewart reported that quantitative bone histomorphometric studies on patients with HHM disclosed an increased bone osteoclastic activity and decreased osteoblastic activity in contrast to the coupled activity seen in patients with PHPTH (8). All this was strong evidence that HHM neoplasms produced a substance chemically distinct from PTH, but which acted on PTH target cells through or in close association with the PTH receptor-adenylyl cyclase complex.

In 1987 groups in New Haven, San Francisco and Melbourne succeded in purifying the tumor-derived adenylyl cyclase stimulating factor from human HHM-associated tumors. The N-terminal aminoacid sequences of the peptides identified by each group were identical when compared to the other two peptides. Sequences of these peptides confirmed that the HHM factor was indeed "PTH-like" in some ways yet "PTH-non-like" in others. The partial N-terminal homology to the N-terminal region of PTH has earned this family the name of "PTH-related protein (PTHrP)" or "PTH-like protein (PTHLP)", names still in use.

Specificity of 1-84 PTH by IRMA

Promptly after RIA techniques were initiated in 1959-60, their inventors, Solomon Berson and Rosalyn Yalow, described the heterogeneity of PTH in sera of various origins. It became established that C-terminal PTH was rather inactive and had a longer half-life than the N-terminus, particularly in patients with impaired renal function.

Subsequent efforts were directed at developing RIA's that would discriminate in favor of the active PTH form. This lead to mid-region and N-terminal PTH radioimmunoassays. However, these did not completely separate primary hyperparathyroidism from its most important mimic: hypercalcemia of malignancy.

Nichols Institute finally came forth with an immunoradiometric assay (IRMA) in what came to be known as the Allegro "sandwich" technique. It employed two labeled antibodies that would select the intact 1-84 PTH (Fig. 1). This became the standard way to distinguish between PTH and the much sought-after but still unidentified, PTHrP.

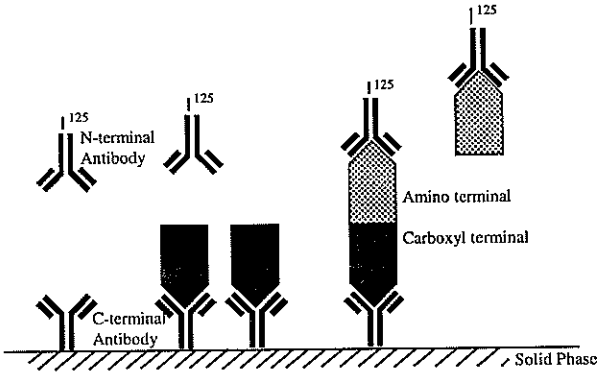

Figure 1. Principle of the two-site immunoradiometric assay. The antigen reacts with a C-terminal antbody immobilized on a solid phase (capture antibody). Subsequently, an antibody labeled with ^{125}I and directed against the NH_2-terminal region of the peptide (signal antibody) is added and produces a "sandwich" complex. Both capture and signal antibodies are added in excess to ensure complete extraction of the antigen. Note that only circulating peptides reacting with both NH_2- and COOH-terminal antibodies can be measurd. Excess labeled antibody, which is free or complexed to the NH_2-terminal fragments of the peptide, is removed during the washing procedure. In contrast to traditional RIAs, there is a direct linear relationship between the amount of antigen and the radioactive signal. Note that the capture and signal antibodies could be either COOH or NH_2 terminal.

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PTHrP structure, PTH and PTHrP receptor genes

PTHrP was shown to have partial homology between its own N-terminus and PTH's first amino acids at the same terminus, where 8 out of 13 aminoacids were identical and another three (1,8 and 10) represented conservative substitutions (Fig. 2). Also, both peptides were separated from their own "propeptides" by a common Lys-Arg arrangement in the -2,-1 positions.

The human PTHrP gene is a single-copy gene which resides in the short arm of chromosome 12. Given the "geographical" similarity to the PTH gene (located in the same position on chromosome 11) and the homology of the two genes encoding the first 13 amino acid sequence, it is believed that the two genes arose from a common ancestral gene through an ancient duplication event. In contrast to the PTH gene, which has a relatively simple structure, the PTHrP gene is a very complex transcriptional

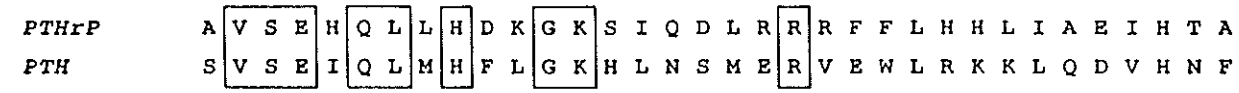

Figure 2. Amino acid sequences of PTH-(1-34) and PTHrP-(1-34).

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unit. The PTHrP gene contains at least 6 exons which give rise to three mature mRNA transcripts encoding three mature PTHrP species 139, 141, and 173 amino acids in length. All of these mature PTHrP species have identical sequences from position 1 to position 139 and an identical 36 amino acids long "prepro" sequence.

Rabbani in 1988 showed that removal of the first two aminoacids dramatically reduced the ability of PTHrP to stimulate adenylyl cyclase, indicating that PTH-like bioactivity requires the presence of an intact N terminus as expressed on the three peptides (9). Other studies have demonstrated that amino acids 14-34, despite having no homology with their counterparts in the PTH molecule, play an important role in the binding to the PTH receptor. Apparently, these amino acids mold in PTHrP a tertiary structure which is similar to that of PTH and thus, is able to interact with the PTH receptor. In adition, amino acids 35-111 are believed to have a yet unknown critical role, as this peptide region shows extraordinary high conservation among species. This 35-111 region shows even more strict conservation than other important peptides such as insulin and growth hormone. On the contrary amino acids 112-139 display little species homology.

In 1994 through cell mapping panels, Gelbert, showed that the human PTH receptor gene is located on chromosome[3](10). It has been demonstrated tha both PTH and PTHrP molecules interact with the same affinity with this receptor, both stimulating multiple intracellular signals including cAMP,inositol phosphates and protein kinase A and C. The PTH receptor, as suggested by endoglycosidase digestion, is believed to be a glycoprotein whose hydrophobicity plot suggests the presence of seven membrane-spanning domains along with extracellular amino-terminal and intracellular carboxy-terminal tails.

Striking homology of the PTH receptor with the calcitonin (30%) and secretin (40%) receptors would suggest a new subfamily of seven transmembrane peptide hormone receptors. In comparison to the calcitonin receptor, seven of the eight functionally important extracellular cysteine residues are conserved, suggesting that they are critical for proper binding to the ligand.

Tissue surveys have shown that kidney and bone express PTH receptor at the highest levels, but, interestingly many other tissues have been demostrated to express tanscripts at lower levels, including: adrenal gland, bladder, breast, heart, liver, lung, skeletal muscle, ovary, placenta, skin and stomach. This "universal" location makes one believe there are effects mediated by this receptor other than just bone turnover. These effects may be "exaggerated" in neoplastic syndromes. PTHrP receptor(s) gene expression has been demonstrated in many adult and embryo tissues (Tables 1 and 2)

Table 1. PTHrP gene expression in adult mammalian tissues

Adrenal cortex
Adrenal medulla
Amnion
Bone
Brain
Endothelium
Epidermis and other epithelia
Heart
Kidney
Lung
Mammary gland
Ovary
Pancreatic islets
Parathyroid
Pituitary
Placenta
Prostate
Skeletal muscle
Small intestine
Smooth muscle
Vascular
Uterine
Bladder
Gastric
Spleen
Stomach mucosa
Testis
Thyroid
Thymus
Urothelium
Uterus (endometrium)

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PTHrP as a cause of humoral hypercalcemia of malignancy

It is clear that patients with HHM resemble PHPTH in their main biochemical features. Exceptions to this similarity are a higher serum concentration of HCO_3^- and a low serum concentration of 1,25 $(OH)_2D$.

Table 2. PTHrP gene expression during embryogenesis

Chicken	Human and rat
Day 3-10 embryo	Nervous system
Body and head	Brain
Allantois	Spinal cord
Yolk sac	Dorsal root ganglion
Chorioallantoic membrane	Developing eye
Day 15 embryo	Epithelia
Brain	Epidermis and hair follicles
Gizzard	Pharynx and larynx
Intestine	Bronchial epithelium
Liver	Stomach and intestine
Lung	Pancreatic acini
Skeletal muscle	Liver
Chorioallantoic membrane	Salivary ducts
and yolk sac	Endocrine glands
	Parathyroid
	Thyroid
	Adrenal
	Gonad
	Muscle
	Cardiac muscle
	Striated muscle
	Smooth muscle
	Urogenital tract (human)
	8-10 weeks: glomeruli, mesonephros, and metanephros
	20 weeks and beyond: proximal tubule, distal tubule, collecting duct, urothelium
	Bone and teeth
	Dental lamina
	Immature chondrocytes
	Mature chondrocytes
	Osteoblast-like cells

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The term HHM was introduced to describe patients with certain cancers in whom blood Ca^{++} is increased in the absence of bony metastases. The most common of these are squamous cell CA of the lung and renal cortical cell carcinoma. Squamous cell carcinoma of the skin, primary carcinoma of the liver, pancreatic carcinoma, bladder and prostatic carcinoma as well as melanoma may all be associated with humoral hypercalcemia. There is little doubt that PTHrP is the major, if not the sole, mediator of hypercalcemia in HHM.

In some cases it is possible that other bone resorbing factors contribute to the development of increased serum Ca^{++}. A number of tumor-derived factors have been identified that are potent resorbers of bone: interleukin-I (IL-1), alpha and beta tumor necrosis factor (TNF) and tumor growth factor (TGF) alpha.

In patients with increased serum Ca^{++} and solid tumors without bony metastases PTHrP has been frequently detected in plasma. Also 75% of patients with metastases to bone, from sources other than breast have PTHrP levels well above normal subjects. Therefore, patients with metastases to bone may suffer both from humoral and osteolytic mechanisms for their hypercalcemia.

The factors regulating the expression of PTHrP are currently the subject of much interest. Agents that increase cAMP, such as calcitonin, TGF alpha and estrogen; have been shown to increase PTHrP gene expression. The effect of lowering ionized calcium on circulating PTH and PTHrP was assesed in hypercalcemia of malignancy following treatment with pamidronate: a rapid rise in PTH was seen but neither PTHrP levels nor urinary cAMP changed significantly. The logical conclusion: plasma Ca^{++} does not influence tumor production of PTHrP.

PTHrP has also been proposed and, sometimes, shown to be a cause of hypercalcemia in such non-malignant conditions as: pheochromocytoma, pancreatic somatostatinoma, benign breast hyperthrophy and, William's Syndrome (supravalvular aortic stenosis, elfin-like facies and hypercalcemia in the first year of life).

PTHrP Pharmacokinetics

Fraher in 1995 investigated whether difference in potency observed with the infusion of PTH and PTHrP (the former, previously found to be 3-10 times more potent) could be associated to differences in either metabolic clearance of the 2 peptides or the target tissue responsiveness to them (11). They found PTH to be 9 times more potent than PTHrP when assesed by plasma cAMP and, 5 times more potent when assesed by urinary output of cAMP. PTHrP has a metabolic clearance rate twice as high as PTH. However, other mechanisms must exist to explain the two hormones differing potencies on adenylylcyclase and yet similar renal handling of Ca^{++} and Na^{+}.

Skeletal and Renal actions of PTHrP

Bone resorption. Although there have been several lines of evidence that GH receptors are present in osteoblasts but not in osteoclasts, it has been reported that PTHrP stimulates bone resorption through the release of a 9Kd bone resorbing protein from osteoblasts; until 1993 it was not known whether PTHrP could stimulate osteoclast formation through soluble factors released from osteoblasts.

Hiroshi Kaji in 1993 demonstrated that PTH and PTHrP can cause osteoblast-mediated stimulation of osteoclast cell formation and that PTH/PTHrP responsive dual signal transductor system (cAMP dependent PKA and PKC) is involved in the release of soluble factors stimulating the

osteoclast formation (12). Sugimoto investigated this second messenger signaling of PTH and PTHrP stimulating osteoclast formation in mouse hematopoietic blast cells possesing PTH binding site, using these cAMP analogue and 2 types of PKC inhibitors (13). It was found that PTH(1-34) and PTHrP(1-34) caused a dose-dependent stimulation of multinucleated cell formation and that pretreatment with PTH(3-34), a PTH receptor antagonist, significantly blocked this response. In their study, all known activators of PKA increased the multinuclear cells activity while the antagonists blocked this action, suggesting the involvement of PKA in the stimulation of osteoclast-like cell formation. Also agents that increased Ca^{++} and activated PKC increased multinuclear cells activity, but to a lesser extent than PKA.

Effect on coupling of bone formation and bone resorption. It has been observed that patients with malignancies complicated by humoral hypercalcemia display markedly reduced bone formation in the presence of accelerated bone resorption. This is in contrast to most other states of high bone resorption, including PHPTH, where coupling between bone formation and resorption is observed. This finding raises the question of whether PTHrP might have a distinctive effect on bone remodeling, leading to uncoupling of bone formation and bone resorption.

In studies with parathyroidectomized rats, infusion of PTHrP(1-34) leads to increased bone formation, but did not uncouple bone formation and bone resorption in these rodents. Given continuously PTH(1-34) and PTHrP(1-34) both inhibit collagen synthesis but when infused intermittenly, stimulate its synthesis. This anabolic effect may involve IGF-1 as a mediator, since these effects are blocked by antibodies against IGF-1. Neither the effects of infusing PTHrP nor its cellular effects give a satisfactory explanation for the low bone formation rates observed in patients with HHM, other than the marked rate of bone resorption per se, not allowing for adequate accretion.

Indeed, it is notable that depressed bone formation rates occur in hypercalcemic patients with multiple myeloma, in which PTHrP levels are rarely increased. The uncoupling phenomenon could be a non-specific effect of innanition, could be related to suppressed $1,25(OH)_2D_3$ or could result from the secretion of another cytokine, as for example Interleukin I, sometimes cosecreted with PTHrP- inhibiting-osteoblast-function.

Renal actions of PTHrP

UcAMP excretion. In normal individuals nephrogenous cAMP production is largely attributed to PTH receptor mediated stimulation of renal tubular adenylyl cyclase. In a large proportion of patients with HHM, UcAMP is increased despite normal or supressed levels of PTH, thus suggesting the presence of a PTH-like factor capable of increasing renal tubule cAMP levels. In most studies PTHrP(1-34) displayed a potency similar to that of PTH(1-34).

Studies by Beech demonstrated that in HHM renal calcium reabsorption was increased 50% and phosphorus reabsorption was decreased by 77% in association to *decreased* cAMP, thus suggesting a humoral factor other than PTHrP which may contribute to the decrease in serum phosphate in HHM. Law evaluated the potential interaction between TGF alpha and PTHrP effects in renal epithelial cells (14). They examined the influence of TGF alpha on PTHrP induced P_i transport inhibition and cAMP stimulation, and suggested TGF alpha could modulate the action of PTH/PTHrP in renal P_i handling under physiological and pathological conditions.

Renal calcium handling. Stewart and his group found that patients with HHM exhibited increased calcium excretion when compared to patients with PHPTH with equivalent levels of serum calcium, suggesting that the PTH-like factor might lack the anticalciuric action of PTH. However subsequent studies have evidenced increased renal calcium reabsorption although less than that seen with PTH.

Regulation of 25(OH)D 1-alpha hydroxylase. An interesting aspect of mineral homeostasis in patients with HHM is the tendency to demonstrate low normal to low levels of $1,25(OH)_2D_3$. It has been demonstrated that PTH and PTHrP amino terminals increased the levels of $1,25(OH)_2D_3$ in rodents and humans. However, chronic infusion of PTH into dogs and humans is associated with increased CA^{++}, decreased PO_4^{-3}, but decreased levels of $1,25(OH)_2D_3$. This suggests that similarly, constant PTHrP stimulation, as present in HHM, could produce a desensitization (down regulation) to its stimulus on $1,25(OH)_2D_3$ synthesis.

Physiological functions of PTHrP

PTHrP in skin. PTHrP has been demonstrated in keratinocytes from human skin biopsies (both adult and fetal) and, in the fetal amniotic membranes which trough the umbilical cord are continuous with the fetal epidermal keratinocyte layer. Molecular evidence is beginning to emerge which may indicate the presence of unique PTHrP receptors in keratinocytes.

The most pressing question concerning keratinocyte-PTHrP interaction involve the normal physiological role in the keratinocyte as well as how PTHrP gene expression relates to the malignant transformation into squamous cell carcinoma. Two tentative models of PTHrP actions in skin have been proposed.

In the first, PTHrP made by differentiated cells in the outer layers of the epidermis is seen as acting to inhibit proliferation and stimulate differentiation of basal inner layer keratinocytes. When the outer layer is damaged or removed the basal layers are free to proliferate, which ends as soon as a new outer layer has emerged and can once again secrete PTHrP. In this model, PTHrP overproduction in squamous cell carcinoma is seen as a result of dysregulated expression of the PTHrP gene.

In the second model PTHrP is seen as a factor that coordinates the normal interaction of epidermal keratinocytes and dermal fibroblasts. Complete understanding of the role of PTHrP in keratinocytes and dermal fibroblast biology will have to take into account the complex regulation of PTHrP production by keratinocytes, the complexities of PTHrP post translational processing and the possible opposing effects of different PTHrP secretory species on keratinocyte and dermal fibroblast functions.

PTHrP and the lactating breast. It is an established fact, that the richest source of PTHrP in a physiologic state is maternal breast milk during lactation. Thus, there are 4 proposals as to what milk PTHrP does in maternal/neonatal physiology:

1. PTHrP presence in developing nests of epithelialcells in rat mammary tissue as early as 14 day of pregnancy has led to the suggestion that the peptide might have some effect in the mammary epithelial growth and development. Fact: There is no evidence for an actual effect of PTHrP on cell proliferation and/or differentiation.
2. PTHrP might regulate the tone of myoepithelial cells during lactation. Blood flow to the breast increases during lactation and PTHrP can induce relaxation of smooth muscle in other tissues. Therefore it has been proposed that PTHrP might regulate vascular tone and blood flow during lactation. Fact: is not known whether PTHrP gene is expressed in smooth muscle of the vessels feeding the breast, although it seems likely.
3. PTHrP might be involved in the active transport of Ca^{++} from blood to milk during lactation. Fact: in longitudinal studies, milk Ca^{++} has been found relatively constant throughout lactation, whereas PTHrP concentration increases.
4. PTHrP derived from maternal breast may enter the systemic maternal circulation and be responsible for Ca^{++} mobilization from skeleton and possibly Ca^{++} conservation by the distal nephron. Fact: There is disagreement on whether circulating plasma levels of PTHrP are increased in lactating women compared to normal subjects or pregnant non-lactating women.

In summary, in spite of the clear evidence of physiological regulation of PTHrP expression in the lactating breast, no clear function has been established in the breast or in the neonate.

PTHrP and the cardiac muscle. PTH and PTHrP have been regarded to have positive inotropic effect on the heart as well as chronotropic and vasodilatory effects. Ogino demonstrated that both hormones are inotropic by virtue of their influence on coronary flow and heart rate but not by any direct effect on contractile elements in the heart (15).

PTHrP in meninges and its receptor in astrocytes: a paracrine meningo-astrocytic loop. Struckhoff and Turzynski concluded, after confirming activation of adenylyl cyclase in astrocytes and the rapid development of cellular processes following incubation with PTHrP, that PTHrP secreted by meninges forms a paracrine meningo-astrocytic loop and may cause astrocytic differenciation. Thus, PTHrP could possibly be involved in the formation of the glial limiting membrane (16).

PTHrP expression in the lung. Hastings, in 1994, showed that freshly isolated type II alveolar epithelial cells contained PTHrP whereas macrophages did not (17). Although the function in the adult lung is unknown, it could involve control of the cell growth and differentiation or control of surfactant lipid secretion.

PTHrP in human seminal plasma. Iwamura demonstrated detectable levels of PTHrP in normal and vasectomized men with negative immunostaining in the seminal vesicles, indicating that PTHrP in semen is predominantly of prostatic origin (18). There were significant correlations between PTHrP and seminal Ca^{++} which may suggest a role for regulation of Ca^{++} secretion in the prostate.

PTHrP and the placenta. There is growing evidence suggesting that PTHrP, principally derived from the fetal parathyroids, is responsible for maintaining the Ca^{++} gradient acting as a fetal hormone in the conventional endocrine sense. To date, this is the only normal PTHrP effect involving actions in distant target tissues.

Postulated actions of PTHrP in the utero-placental unit include: transport of Ca^{++} across the placenta, stretching of membranes, inhibition of uterine contractility, growth and differentiation, and vasoregulation.

Action in bone. The PTH/PTHrP receptor gene is expressed in the zone of mating (pre-hypertrophic) chondrocytes. PTH (presumably PTHrP) is mitogenic to embryonic chick and rabbit chondrocytes (thought to reflect induction of cytokines). PTH/PTHrP inhibits the mineralization of cartilage mediated by hypertrophic

chondrocytes. In essence, such effects are envisioned as leading to linear growth of the zone of proliferating chondrocytes that lies first above the hypertrophic zone and, inhibition of mineralization below this zone; both effects are presumably mediated by paracrine signals downstream of the PTH/PTHrP receptor interactions.

Smooth muscle effects. PTHrP peptides containing amino terminus have been found to relax a number of smooth muscle systems: aortic strips, renal artery segments, gastric strips and acetylcholine stimulated rat uterine horns in vitro.

PTHrP effect on the rat *in vivo* result from a decrease in systemic vascular resistance (SVR) with a redistribution of flow that favor some vascular beds such as coronaries and vessels of the skin. Also PTHrP has been found to have positive chronotropic and inotropic effects in perfussed rat heart.

It seems clear that mechano-transduction (the means by which physical forces are converted into cellular signals) is a major stimulus controlling PTHrP gene expression in smooth muscle. This is an area of considerable recent interest in cardiac muscle and smooth muscle physiology and appears to involve membrane-associated signal transduction pathways such as stretch-activated/inactivated channels and adenylyl cyclase. In the case of the PTHrP gene, stretch induction would result in the local production of a molecule capable of counterbalancing the mechanical force being applied.

The specific PTH/PTHrP receptor targets and the resultant physiological effects may well differ depending on the tissue in question: 1) vasculature, serosal vessels of oviduct and villous vessels where it increases blood flow; 2) bladder and smooth muscle of chicken oviduct, where it produces gradual relaxation to accomodate volume; 3) rat myometrium where it exerts complex control of the force and rhythmicity of myometrial contractility that ultimately leads to parturition.

Resumen

PTHrP ha tenido un rol (no identificado en la medicina moderna) desde que en 1930 Albright describió un paciente con carcinoma de la celula cortical renal e hypercalcemia. Desde entonces la hipercalcemia se reconoce como el síndrome paraneoplastico mas común. En ese momento se introdujo el concepto del "síndrome de PTH ectópico', el cual se mantiene en la literatura hasta que se descubre su etiologia más frecuente. Al principio de los 1970's Roof y Benson presentaron evidencia de que la PTH en la hipercalcemia humoral era diferente a la PTH "auténtica". Esto marcó el comienzo para que varios investigadores trataran de identificar la molécula que no solo se comporta como la PTH, sino también, de una estructura parecida. Esta molécula, llamada peptido relacionado a la PTH (PTHrP), ha sido asociada a la hipercalcemia en tumores sólidos, tales como el carcinoma de la celula escamosa del pulmón y el carcinoma de la celula cortical renal. El PTHrP ha demostrado comportarse como la PTH, pero difiere en que disminuye la actividad de los osteoblastos en relación a la estimulación de los osteoclastos. El hallazgo mas fascinante ha sido el demostrar los genes de PTHrP dispersos por todo el cuerpo, mayormente en el tejido mamario, además del corazón, los pulmones, la piel y otros.

Aunque propiamente identificado, falta aún por descibirse las acciones fisiológicas concretas del PTHrP antes de poder postular una noción fisiológica de esta interesante molécula.

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