Skeletal

Parathyroid hormone-related protein

Analyte Information

Parathyroid hormone related protein (PTHrP)

Introduction

Parathyroid hormone-related protein (PTHrP) is actually a family of protein hormones produced by most if not all tissues in the body. A segment of PTHrP is closely related to parathyroid hormone (PTH), and hence its name, but PTHrP peptides have a much broader spectrum of effects. PTH and some of the PTHrP peptides bind to the same receptor, but PTHrP peptides also bind to several other receptors.

PTHrP was discovered and isolated in 1987 as a protein secreted by certain tumors that caused hypercalcemia (elevated blood calcium levels) in affected patients. Uncontrolled secretion of PTHrP by many tumor cells induces hypercalcemia by stimulation of calcium resorption from bone and suppression calcium loss in urine, similar to what is seen with hyperparathyroidism.

However, PTHrP has many activities not seen with PTH.

Biosynthesis, metabolism

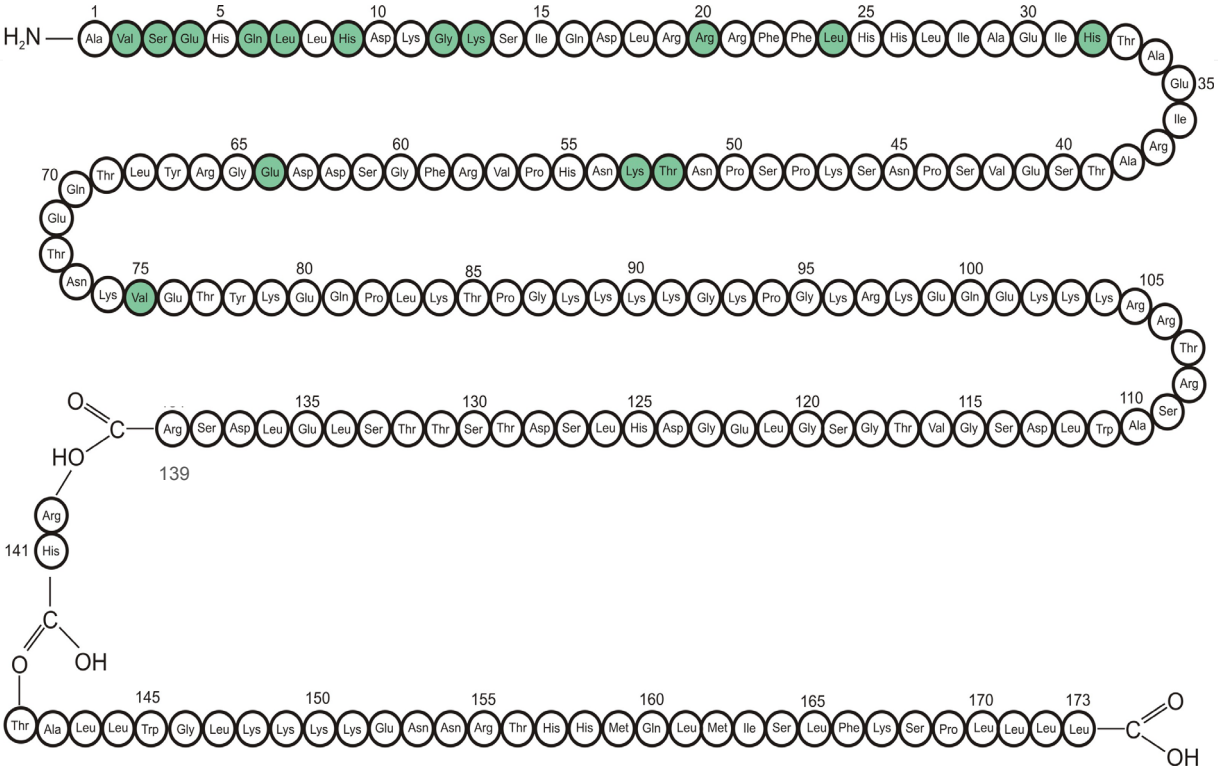
PTHrP is produced in low concentrations de facto in all tissues, including keratinocytes, lactating mammary tissue, the placenta, fetal parathyroid glands and myocardium.

PTHrP is derived from gene on chromosome 12 that is distinct from the PTH gene on chromosome 11.

PTHrP is a single monomeric peptide that exists in several isoforms. Alternate splicing of the primary transcript is a cause why several isoforms with different length are found.

Three main isoforms of 139, 141 and 173 amino acids were recognized (Fig.1).

Fig.1: Amino acid sequence of PTHrP[1]



Although the exact length of circulating PTHrP is unknown, proteins of 139, 141, and 173 amino acids have been predicted from alternative splicing events. The green circles show amino acids that are identical in PTH and PTHrP.

The N-terminal fragments of the molecule shows close homology to PTH (8 of the first 13 amino acids being identical). The common N-terminal explains the ability of PTHrP to interact with the PTH/PTHrP receptors, mimicking the biological action of PTH in classic target tissues, including bone and kidney.

The reminder of the PTHrP molecule shows little homology with PTH. Midregion and carboxyl forms may exert biological actions distinct from the PTH.

The multitude of basic residues in PTHrP suggests that PTHrP undergo extensive posttranslational processing.

Several forms of PTHrP containing the following amino acids have been detected in blood[1]:

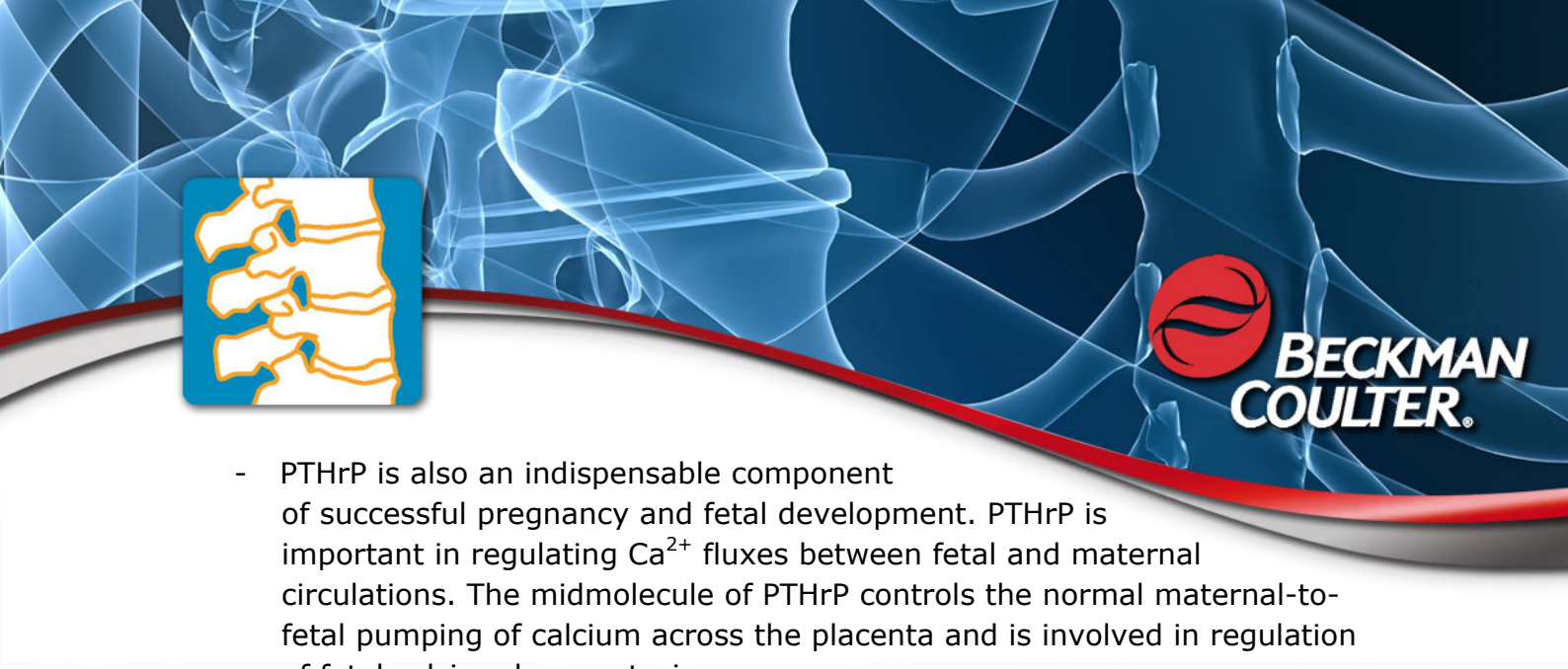
- PTHrP (1-36) – N terminal fragment
- PTHrP (1-74 or 1-86) containing N-terminal and midregion amino acides
- PTHrP (38-70 or 38-80) midregion fragments, beginning at position 38 and extending 70 to 80 amino acids
- Carboxyl fragments beginning at position 107

Physiological Function

The physiological role of PTHrP in not completely understood and its name not adequately describes its activities.

Low circulating concentration of PTHrP does not have a significant effect on calcium homeostasis in normal adult. Nevertheless, there is evidence for its importance in several processes described below. Its functions can be broadly divided into several categories. Not all of them are present in all PTHrP isoforms or in all tissues[2]:

- Like PTH, PTHrP effects transepithelial fluxes of calcium, particularly in the mammary gland. Mammary epithelial cells secrete large amounts of PTHrP, which regulates Ca^{2+} concentrations in breast milk and plays a role in adapting maternal metabolism to the calcium demands during lactation.



- PTHrP is also an indispensable component of successful pregnancy and fetal development. PTHrP is important in regulating Ca^{2+} fluxes between fetal and maternal circulations. The midmolecule of PTHrP controls the normal maternal-to-fetal pumping of calcium across the placenta and is involved in regulation of fetal calcium homeostasis.

But many of PTHrP actions have nothing to do with calcium homeostasis.

- Most prominently, PTHrP peptides exert significant control over the proliferation, differentiation and death of many cell types. They also play a major role in development of several tissues and organs.
- Smooth muscle relaxation in the uterus, bladder, gastrointestinal tract, and arterial wall. PTHrP is secreted from smooth muscle in many organs, usually in response to stretching. It acts to relax smooth muscle, thereby serving as a vasodilating hormone.

PTHrP's diverse functions are mediated through a range of different receptors, which are activated by various portions of PTHrP. Because of similar structure with PTH one of them is PTH receptor. Since most of PTHrP's actions in normal physiology are autocrine or paracrine, with circulating levels being very low, this receptor cross-talk becomes relevant only when there is extreme and sustained over-production of PTHrP.

Levels

Under normal physiological conditions, local production of PTHrP is reflected in circulation only in low concentrations.

Under pathological conditions, PTHrP is produced in excess by malignant or benign processes and the high circulating concentration can be found. Increased PTHrP levels then may cause hypercalcemia.

Production of PTHrP by the fetoplacental unit can cause transient increase during pregnancy, especially in the third trimester. Increased levels can be seen occasionally also in lactation and, rarely, in a variety of non-malignant diseases.

Typical PTHrP levels in serum are given in Table 1.

For each assay, the relevant values are shown in the appropriate Instruction for Use (IFU).

Table 1: Typical PTHrP levels in plasma[3]

Specimen (plasma)	**Reference interval (pmol/L)**
Adults:	<1.5 pmol/L

Equation for the conversion of the units: 1 pmol/L = 10 pg/mL

Diagnostic utility — prospects and possibilities

PTHrP was first identified as a tumor derived product responsible for malignancy associated hypercalcemia and was characterized because of its ability to mimic PTH in kidney and bone.

Elevated PTHrP levels are associated with the following conditions[1]:

- humoral hypercalcemia of malignancy
  - squamous carcinomas (lung, head, neck, esophagus, cervix, vulva, skin)
  - renal cancer
  - bladder cancer
  - ovarian cancer
  - breast cancer
  - lymphomas (human T-cell leukemia virus-1)

Diagnostic utility – Practical applications[4]

Differential diagnosis of hypercalcemia; manage patients with solid tumors and hypercalcemia

Hypercalcemia is most frequently associated with primary hyperparathyroidism with PTH levels elevation, but PTHrP levels stay normal.

The second most common cause of hypercalcemia is hypercalcemia associated with malignancy. This frequent paraneoplastic syndrome is believed to occur primarily through two mechanisms: humoral hypercalcemia of malignancy (HHM) and local osteolysis. Patients with HHM account approximately for 75% - 80% of patient with hypercalcemia associated with malignancy.

In HHM, calcium levels are not increased due to excess of PTH. The cause is in secretion of humoral factors mimicking PTH action, usually associated with secretion of PTHrP by the primary tumor, or more commonly its metastases. After being secreted by tumors, PTHrP circulates and acts on its target tissues (bone and kidney) as an endocrine hormone causing hypercalcemia.

PTH is usually suppressed due to elevated serum calcium concentrations. Besides hypercalcemia, PTHrP like PTH causes hypophosphatemia and increases urinary cyclic AMP. However, when compared with patients with primary hyperparathyroidism, patients with PTHrP-induced hypercalcemia do not have the raised concentrations of 1,25-dihydroxyvitamin D, see Table 2.

A variety of other mechanisms lead to hypercalcemia associated with malignancy. These include:

-Osteolytic activity within bony metastases (breast cancer, multiple myeloma, haematological malignancies)

-Impaired renal function due to a tumor or its treatment

-Release of calcemic cytokines by non-osteolytic bone metastases

-Ectopic 1-alpha hydroxylase activity in tumor tissues

Table 2: Humoral hypercalcemia of malignancy and primary hyperparathyroidism – biochemical findings

	HHM caused by secretion of PTHrP	Primary hyperparathyroidism
PTH	**low**	**high**
PTHrP	**high**	**low**
calcium	high	high
phosphorus	low	low
1,25-dihydroxyvitamin D	**normal**	**high**
cAMP (urinary)	high	high

References

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