Parathyroid hormone secretion and action

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INTRODUCTION

- Parathyroid hormone (PTH) is one of the two major hormones ***modulating calcium and phosphate homeostasis***, the other being calcitriol (1,25-dihydroxyvitamin D) [1].
- The minute-to-minute regulation of serum calcium is exclusively regulated through PTH(8.5-10.5mg/dl), maintaining the concentration of this cation within a narrow range, through stimulation of renal tubular calcium reabsorption and bone resorption [2,3]. On a more chronic basis, PTH also stimulates the conversion of calcidiol (25-hydroxyvitamin D) to calcitriol in renal tubular cells, thereby stimulating intestinal calcium absorption.

- PTH secretion is regulated by serum ionized calcium acting via an exquisitely sensitive **calcium-sensing receptor (CaSR)** on the surface of parathyroid cells [4].
- The receptor has a long **amino terminus**, seven **transmembrane segments**, and a shorter intracellular **carboxyl terminus.**

PTH synthesis and degradation

- PTH is synthesized as a 115- amino acid polypeptide called pre-pro-PTH, which is cleaved within parathyroid cells at the N-terminal portion first to pro-PTH (90 amino acids) and then to PTH (84 amino acids). The latter is the major storage, secreted, and biologically active form of the hormone.

- In addition to **intact PTH**, some **inactive carboxyl-terminal** fragments and small amounts of **active amino-terminal** fragments of PTH are present in the parathyroid glands.
- During **hypocalcemia**, intracellular degradation of PTH decreases, and mostly PTH 1-84 is secreted; in comparison, during **hypercalcemia** mostly biologically inactive carboxyl-terminal fragments of PTH are secreted.

- Under **normocalcemic** conditions, PTH 1-84 constitutes **20** percent of total circulating PTH molecules. This proportion increases to **33** percent under **hypocalcemic** conditions, and decreases to **4** percent in the presence of **hypercalcemia** .

- Once secreted, PTH is rapidly cleared from plasma through uptake principally by the liver and kidney, where PTH 1-84 is cleaved into amino- and carboxyl-terminal fragments that are then cleared by the kidney.

- Intact PTH has a plasma half-life of two to four minutes. In comparison, the **C-terminal fragments**, which are cleared principally by the kidney, **have half-lives that are 5 to 10 times greater**. As a result, circulating immunoreactive PTH in normal subjects comprises:
- Intact PTH — 5 to 30 percent
- C-terminal fragments — 70 to 95 percent
- N-terminal fragments — a small percentage

PTH receptors

- PTH, in its various molecular forms, acts by binding to and activating one of several types of PTH receptors recognized to date [6]. The classical PTH/PTHrP receptor, otherwise known as PTH1R, was cloned in 1991 [8]. This receptor is heavily expressed in bone and kidney, and is also present in other tissues such as breast, skin, heart, blood vessels, pancreas, and others that are not regarded as classical PTH target tissues [6]. ***The PTH1R binds intact PTH and biologically active N-terminal hormone fragments of PTH, such as PTH 1-34.*** It recognizes both PTH and PTH-related protein (PTHrP) due to the substantial degree of homology in the N-terminal parts of these two moieties.

- Subsequently, a closely related receptor was isolated, named the PTH2 receptor (PTH2R), which selectively binds PTH but not PTHrP [6].
- It is heavily expressed in the ***central nervous system, cardiovascular and gastrointestinal systems, as well as lung and testes***, and may be involved in the perception of pain.

- Increasing evidence points to the presence of novel PTH receptors (C-PTHRs) with specificity for the carboxyl-terminal region of PTH, a portion of the hormone that was previously thought to be biologically inert but has now been shown to possess hypocalcemic activity. The C-PTHRs are present in various tissues but are most heavily expressed in bone.

- Activation of the PTH1R activates multiple cellular signaling pathways including cAMP, the PLC pathway, PKC, and release of intracellular calcium stores [6,11-13].
- The details of how these intracellular signal transduction pathways ultimately stimulate bone resorption, renal tubular calcium reabsorption, or hydroxylation of calcidiol ***remain to be fully elucidated.***

Calcium-PTH interactions

- Extracellular calcium ions regulate numerous biological processes, including intracellular signaling for
- secretion of many hormones,
- muscle contraction, and
- the coagulation cascade. It is therefore important that serum ionized calcium concentrations be maintained within a very narrow range.

- In normal subjects, a decrease in serum ionized calcium of as little as 0.1 mg/dL (0.025 mmol/L) results in a large increase in serum PTH concentration within minutes; conversely, an equally small increase in serum ionized calcium rapidly lowers the serum PTH concentration.

The PTH response to hypocalcemia has the following temporal profile :

- **Seconds to minutes** — **exocytosis** of PTH from secretory vesicles into the extracellular fluid.
- **Minutes to one hour** — reduction in the intracellular **degradation** of PTH.
- **Hours to days** — increase in PTH **gene expression** as a result of stabilization of PTH mRNA [17] (also stimulated by low serum calcitriol concentrations, owing to increased transcription of the PTH gene).
- **Days to weeks** — **proliferation** of parathyroid cells (also stimulated by low serum calcitriol concentrations).

ACTIONS OF PTH

- The classical effects of PTH on calcium and phosphate homeostasis, ***namely elevation of serum calcium, phosphaturia, and calcitriol synthesis***, are mediated through the **PTH/PTHrP receptor**, a G-coupled receptor that is mostly expressed in *bone and kidney*, but is also present in fetal tissue and growth plate chondrocytes [38].
- Loss-of-function mutations of the PTH/PTHrP receptor result in **severe skeletal dysplasia** (***Blomstrand chondrodysplasia***), as well as severe abnormalities in **breast and tooth** development.

Skeletal actions of PTH

- The ***immediate*** effect of PTH is to mobilize calcium from skeletal stores that are readily available and in equilibrium with the extracellular fluid.
- ***Later***, PTH stimulates release of calcium (and also phosphate) by activation of bone resorption.

- The prevailing view has been that osteoblasts, but not osteoclasts, express PTH receptors [6]. Thus, osteoclast formation requires an interaction with cells of the osteoblastic lineage, which may depend upon cell-cell contact and regulators of osteoclast formation such as RANK (the receptor activator of nuclear factor kappaB), osteoprotegerin, and RANK ligand (RANKL) [42]. PTH increases osteoclast activity and number ***indirectly*** through effects on RANKL and osteoprotegerin .

- The net effect of PTH on bone varies according to the severity and chronicity of the PTH excess, ranging from **osteopenia to osteitis fibrosa cystica**. ***Trabecular bone*** volume seems to be preserved at the expense of **cortical** bone [44,45].
- Furthermore, while chronic hyperparathyroidism results in bone resorption, *intermittent administration of PTH stimulates bone formation more than bone resorption*. Thus, administration of PTH subcutaneously once daily results in substantial increments in bone mineral density and a decrease in the risk of both vertebral and non-vertebral fractures in patients with osteoporosis.

Renal actions of PTH

- **Reabsorption of calcium** — Filtered calcium is reabsorbed along much of the nephron. Most filtered calcium is reabsorbed passively in the proximal tubule down the favorable electrochemical gradients created by sodium and water reabsorption. In contrast, calcium transport is actively regulated in the distal nephron according to the needs of the organism.
- **Reabsorption of phosphate** — PTH inhibits mostly proximal but also distal tubular reabsorption of phosphorus. This effect is primarily mediated by decreased activity, internalization, and degradation of the sodium-phosphate cotransporter in the luminal membrane of the proximal tubules.
- **Synthesis of calcitriol** — PTH stimulates the synthesis of 1-alpha hydroxylase in the proximal tubules and thus conversion of calcidiol to calcitriol.

TABLE 353-1 Classification of Causes of Hypercalcemia

I. Parathyroid-Related

A. Primary hyperparathyroidism

1. Adenoma(s)
2. Multiple endocrine neoplasia
3. Carcinoma

B. Lithium therapy

C. Familial hypocalciuric hypercalcemia

II.Malignancy-Related

A. Solid tumor with metastases (breast)

B. Solid tumor with humoral mediation of hypercalcemia (lung, kidney)

C. Hematologic malignancies (multiple myeloma, lymphoma,leukemia)

III. Vitamin D-Related

A. Vitamin D intoxication

B. ↑ 1,25(OH)2D; sarcoidosis and other granulomatous diseases

C. Idiopathic hypercalcemia of infancy

IV. Associated with High Bone Turnover

A. Hyperthyroidism

B. Immobilization

C. Thiazides

D. Vitamin A intoxication

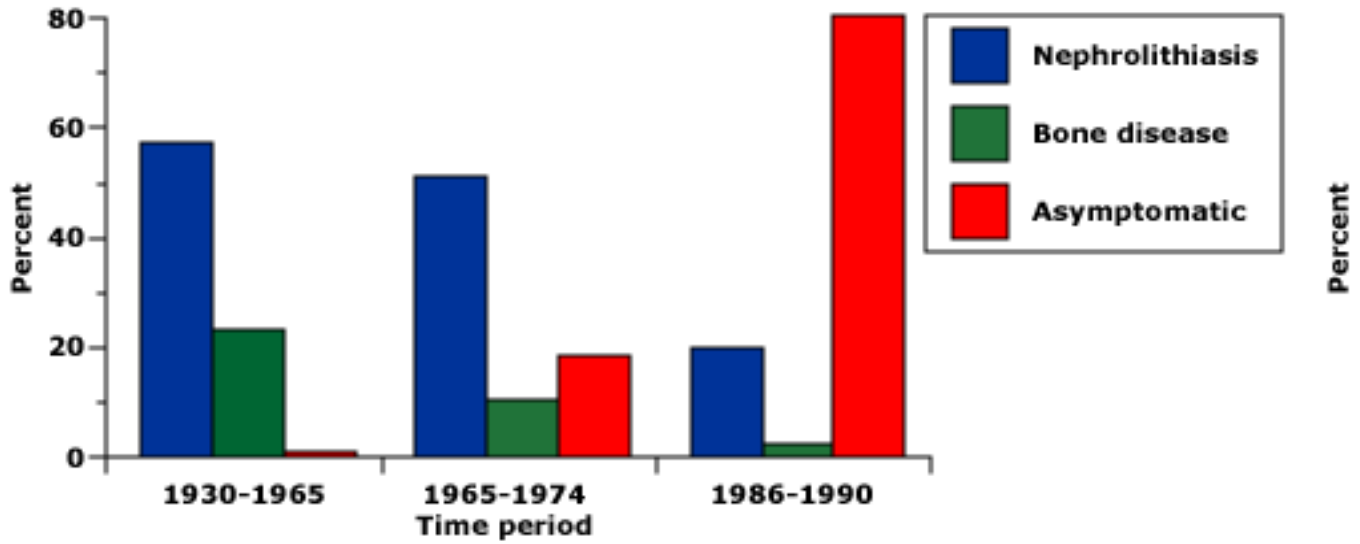
V. Associated with Renal Failure

A. Severe secondary hyperparathyroidism

B. Aluminum intoxication

C. Milk-alkali syndrome

Changing presentation of primary hyperparathyroidism



Different patterns of presentation of primary hyperparathyroidism in three different time periods. The latest survey shows that 80 percent of patients are asymptomatic and discovered incidentally on routine blood screening; bone disease (osteitis fibrosa cystica), on the other hand, has virtually disappeared as a presenting symptom. Bone disease was assessed by x-rays and bone densitometry; patients with skeletal involvement by bone density measurement were not included.

Data from: Cope O, N Engl J Med 1966; 274:1174; Heath H III, et al, N Engl J Med 1980; 302:189; and Silverberg SJ, et al, Am J Med 1990; 89:327.

- The most common clinical presentation of primary hyperparathyroidism (PHPT) in western populations is asymptomatic hypercalcemia detected by routine biochemical screening.
- The classical symptoms and signs of PHPT, such as osteopenia, subperiosteal bone resorption, osteitis fibrosa cystica, nephrocalcinosis and nephrolithiasis, are due to prolonged excessive PTH secretion and hypercalcemia. Although osteitis fibrosa cystica is rarely seen in the United States and Europe, it is still prevalent in ***developing countries***. The geographical differences in the clinical manifestations of PHPT may be explained, at least in part, by the greater prevalence of ***vitamin D deficiency*** in some countries.
- ***Neurobehavioral and cognitive complaints*** may be more prevalent in patients with PHPT than in the general population. However, the nonspecific nature of these symptoms makes it difficult to ascribe a particular complaint to PHPT in a given patient.

TABLE 353-5 Functional Classification of Hypocalcemia
(Excluding Neonatal Conditions)

PTH Absent

Hereditary hypoparathyroidism

Acquired hypoparathyroidism

Hypomagnesemia

PTH ineffective

Chronic renal failure

Active vitamin D lacking

↓*Dietary intake or sunlight*

Intestinal malabsorption

Defective metabolism:

Anticonvulsant therapy

Vitamin D-dependent rickets type I

Active vitamin D ineffective

Vitamin D-dependent rickets type II

Pseudohypoparathyroidism

PTH Overwhelmed

Severe, acute hyperphosphatemia

Tumor lysis

Acute renal failure

Rhabdomyolysis

Osteitis fibrosa after parathyroidectomy

Hungry bone syndrome

Clin manif hypocalcemia

Clinical manifestations of hypocalcemia

Acute
Neuromuscular irritability (Tetany)
Paresthesias (peri-oral, extremities)
Muscle twitching
Carpopedal spasm
Trousseau's sign
Chvostek's sign
Seizures
Laryngospasm
Bronchospasm
Cardiac
Prolonged QT interval
Hypotension
Heart failure
Arrhythmia
Papilledema
Chronic
Ectopic calcification (basal ganglia)
Extrapyramidal signs
Parkinsonism
Dementia
Subcapsular cataracts
Abnormal dentition
Dry skin