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HORMONAL CONTROL OF CALCIUM HOMEOSTASIS, CHEMISTRY AND CONTROL OF SECRETION OF PARATHORMONE, CALCIUM AND VITAMIN -D

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chemistry and control of secretion of parathormone, calcium and vitamin -D

Secretion of parathyroid hormone is determined chiefly by serum ionized calcium concentration through negative feedback. Parathyroid cells express calcium-sensing receptors on the cell surface. PTH is secreted when [Ca2+] is decreased (calcitonin is secreted when serum calcium levels are elevated).

. PTH raises blood calcium by resorbing bone, conserving urinary calcium, and activating vitamin D in order to increase intestinal calcium absorption. Blood calcium, in turn, decreases PTH secretion. The PTH-calcium homeostatic loop acts

to maintain a constant level of blood calcium in the face of varying dietary and skeletal demands. This physiologically appealing story remains a powerful organizing principle for understanding parathyroid function, but has been modified by important observations in the last few years.

1. The characterization of parathyroid hormone-related protein (PTHrP) has introduced important new ideas: this predominantly paracrine factor shares receptors with PTH; the structure and sequence of PTHrP is only beginning to lead to greater understanding of PTH structure.

2. The parathyroid cell is regulated not only by calcium but also by 1,25(OH)2D3 ·

3. The PTH receptor shares striking homology with receptors for calcitonin and secretin; together these receptors begin to define a new subfamily of G protein-linked receptors.

4. Parathyroid hormone not only activates adenylate cyclase in cells, but also activates phospholipase C. The precise roles of these and other candidate pathways of PTH action remain unclear.

5. In bone, PTH can stimulate trabecular bone formation at the same time that it stimulates cortical bone resorption.

These new observations are all still imperfectly understood but suggest complicated levels of regulation and roles for PTH that substantially expand the classical model. In this chapter, the actions of PTH at the tissue level will first be summarized. Then, the biosynthesis and secretion of PTH by the parathyroid cell will be discussed. An analysis of PTH chemistry and structure will then be followed by new information about PTH receptors and the second messengers responsible for initiating the cell's responses to PTH. A. Physiologic Actions Recognition of the physiologic effects of PTH originally derived from observations in humans and animals with hypoparathyroidism and in patients with severe primary hyperparathyroidism. In hyperparathyroidism, in particular, progressive osteopenia, hypercalcemia, hypophosphatemia, hypercalciuria, and kidney stones had implicated bone, kidney, and possibly

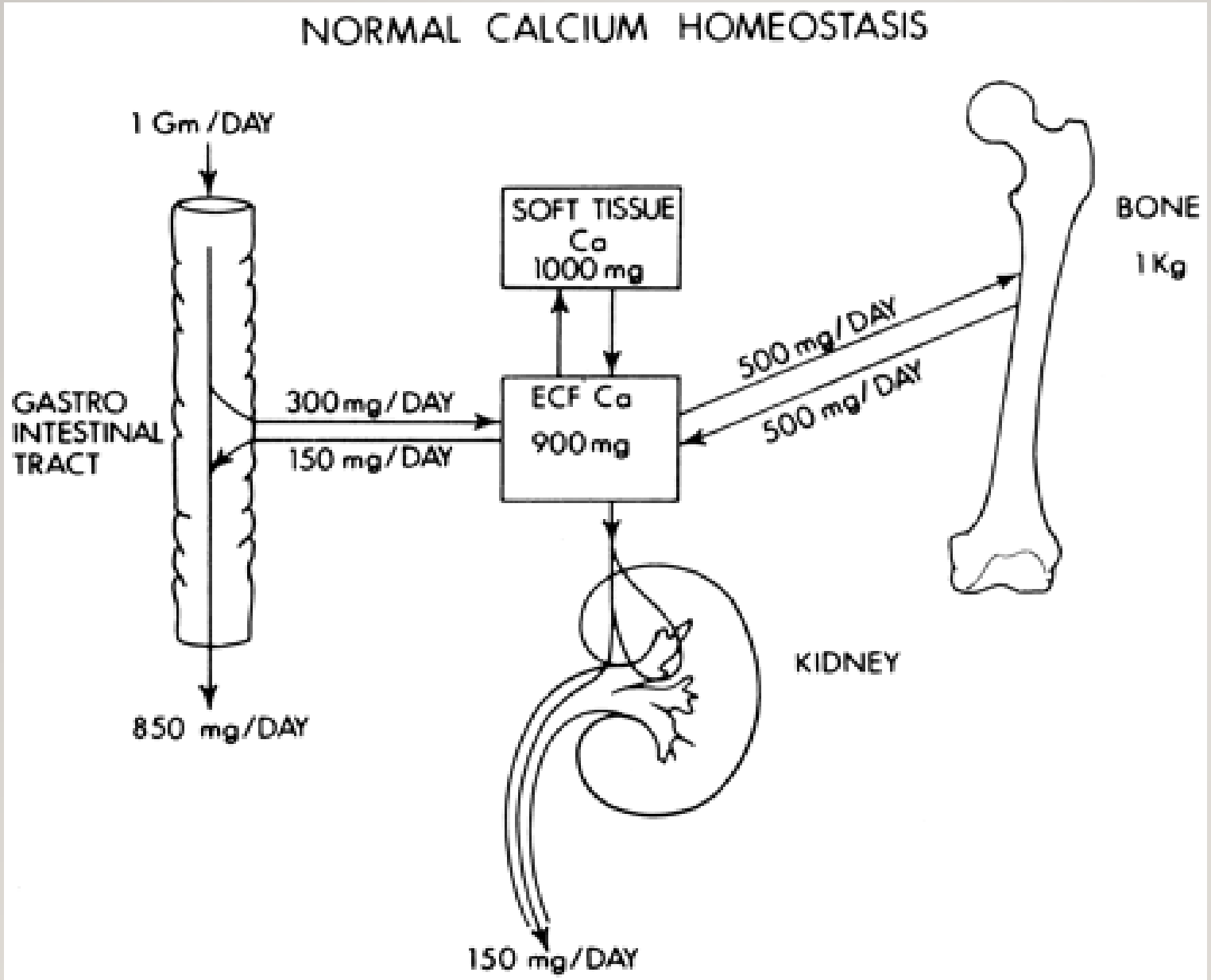
intestine as the major putative target tissues of the hormone. The roles of these tissues as mediators of PTH action were subsequently borne out by an enormous volume of scientific investigation. Thus, although stimulation of intestinal calcium absorption is now thought to occur mainly indirectly, via enhanced renal synthesis of 1,25(OH)zD3 , alterations in cellular activities of bone and kidney are now understood to be the principal mechanisms whereby PTH maintains mineral-ion and skeletal hemeostasis.

I. **Actions in Bone:Numerous** studies in vivo and in vitro have confirmed that sustained exposure to PTH, particularly at high concentrations, leads to activation and recruitment of osteoclasts, accelerated bone resorption, and subsequent net bone loss. These changes are accompanied by activation of osteoclastic membrane proton pumps, local release of acid hydrolases, release of calcium, phosphate,

and degraded matrix components into blood, and a variety of other responses that are not specific to PTH but rather constitute the generic response of osteoclasts to a variety of different bone-resorbing agents. Other, more rapid responses to PTH precede evidence of osteoclastic bone resorption and may be of particular importance for the minute-to-minute regulation of blood calcium. Thus, administration of PTH is followed within minutes by a transient decrease in blood calcium, due at least in part to uptake by bone cells (PARSONS and ROBINSON 1971). This is succeeded by an increased mobilization of calcium from bone. This calcium may be derived from a pool distinct from the mineralized matrix phase; release may be mediated by(nonosteoclastic) osteocytes distributed along the endosteum of bon

Control of Calcium Homeostasis

The extracellular fluid (or plasma) calcium concentration is tightly controlled by a complex homeostatic mechanism involving fluxes of calcium between the extracellular fluid (ECF)1 and the kidney, bone, and gut. These fluxes are carefully regulated by three major hormones: parathyroid hormone (PTH), calcitonin, and 1,25-dihydroxyvitamin . Important cellular functions are dependent on the maintenance of the extracellular calcium concentration within a narrow range . Disturbances of this tightly regulated homeostatic system leads to disorders of calcium metabolism that have predictable effects, which can be ascribed to effects on these cellular functions.



Calcium homeostasis in a healthy adult over 24 h

The approximate fluxes of calcium into and out of the ECF that occur during each 24-h period are shown in Fig. 1 . Usually, bone mineral accretion equals skeletal mineral resorption, and calcium content in the urine approximates that of net intestinal absorption. An average Western diet provides a calcium intake of ~1 g of elemental calcium per day. Typically, ~30% (300 mg) is absorbed, the majority across the small intestine and a small percentage in the colon . Because gut secretion of calcium is relatively constant at 150 mg per day, the net calcium absorption is ~150 mg per day for a healthy adult in normal calcium balance. Calcium absorbed from the gut enters the blood and is filtered by the kidney. The majority of filtered calcium (>98%) is reabsorbed in the proximal renal tubules; thus, only 150 mg per day is excreted in healthy individuals .

The skeleton is the major body storage site for calcium. A healthy adult contains ~1–1.3 kg of calcium, and 99% of this is in the form of hydroxyapatite in the skeleton . The remaining 1% is contained in the ECF and soft tissues. Additionally, <1% of the skeletal content of calcium is in bone fluid and exchanges freely with the ECF.

Although the hormonal control of calcium fluxes is central to understanding of normal calcium homeostasis, Parfitt and co-workers have also emphasized the importance of physico-chemical exchanges of calcium between the bone fluid and the ECF. The bone fluid is rich in calcium because it is in equilibrium with the mineral phase of bone at the bone surface. The exchanges between the bone fluid and the ECF may be important in determining the set point (mean concentration of serum calcium at steady state) and error correction (by which serum calcium is returned to the set point and corrected by oscillations in the ionized calcium concentrations about this mean). The relative importance of this exchange mechanism has been underappreciated.

Hormonal Effects on Calcium Homeostasis

Blood ionized calcium concentrations are remarkably stable in healthy individuals because of the homeostatic system involving the actions of the three calciotropic hormones on the target organs of bone, gut, and kidney, and possibly also on fluxes between the bone canalicular fluid and the ECF mentioned above. Normal calcium homeostasis is primarily dependent on the interactions of PTH, 1, and calcitonin on these organs to maintain the ionized calcium concentration within a very narrow range. Other factors also influence calcium fluxes, although current evidence suggests that only these three hormones are under negative feedback control.

The biological actions of PTH include (a) stimulation of osteoclastic bone resorption and release of calcium and phosphate from bone, (b) stimulation of calcium reabsorption and inhibition of phosphate reabsorption from the renal tubules, and (c) stimulation of renal production of 1,, which increases intestinal absorption of calcium and phosphate. The amino-terminal end of the PTH molecule binds to the PTH receptor to elicit these biologic responses. The PTH receptor has recently been cloned and found to be a member of the large family of receptors that contain a seven transmembrane-spanning domain and work through activation of G-proteins .

pth and pth-related peptide

PTH is an 84-amino acid peptide that is synthesized by the chief cells of the parathyroid gland. Secretion of PTH is highly dependent on the ionized calcium concentration and represents a simple negative feedback loop. The serum PTH concentration decreases as the serum calcium concentration increases, although PTH secretion is not entirely suppressible

The biological actions of PTH include (a) stimulation of osteoclastic bone resorption and release of calcium and phosphate from bone, (b) stimulation of calcium reabsorption and inhibition of phosphate reabsorption from the renal tubules, and (c) stimulation of renal production of 1,25(OH)2D3, which increases intestinal absorption of calcium and phosphate. The amino-terminal end of the PTH molecule binds to the PTH receptor to elicit these biologic responses. The PTH receptor has recently been cloned and found to be a member of the large family of receptors that contain a seven transmembrane-spanning domain and work through activation of G-proteins

The physiological role of the PTH-rP remains unclear. It probably has no regulatory effect on calcium homeostasis under physiological conditions. It is produced in healthy skin cells as well as in amniotic cells, and it may have effects on epithelial cell replication and on smooth muscle contraction during labor

Calcitonin: Calcitonin is a 32-amino acid peptide that is synthesized and secreted by the parafollicular cells of the thyroid gland. The ionized calcium concentration is the most important regulator of calcitonin secretion . Increases in ionized calcium produce an increase in calcitonin secretion, and conversely, a fall in the ambient calcium concentration inhibits calcitonin secretion. Gastrointestinal peptide hormones, gastrin in particular, are potent calcitonin secretogogues. This likely is responsible for increased calcitonin secretion after meals, but the physiologic relevance of this observation remains unclear. Pentagastrin, a gastrin analog, is used as a provocative stimulus to determine the capacity of a patient to secrete calcitonin

Defenses against Hypercalcemia and Hypocalcemia

1. The usual physiologic defenses against hypercalcemia and hypocalcemia are listed in Table 1. The majority of these defense mechanisms are mediated through the hormonal actions of PTH and 1,25(OH)2D3
2. Defenses against hypocalcemia and hypercalcemia.
3. Protection against decreased plasma calcium (e.g., caused by dietary or hormonal deficiency)
4. Glomerular filtration: filtered load of calcium decreases
5. Calciotropic hormones (PTH, 1,25(OH)2D3, and calcitonin)
6. Effects on bone and kidney: hypocalcemia stimulates PTH release, which increases plasma calcium by effects on renal tubules and osteoclasts

7.Effects on gut (adaptation): increased fractional absorption of dietary calcium, mediated by 1,25(OH)2D3 8.Protection against increases in plasma calcium (caused by bone destruction or large dietary calcium load)

8.Glomerular filtration: filtered load of calcium increases Calciotropic hormones

9.PTH; but no further decrease in secretion if plasma calcium >2.9 mmol/L (11.5 mg/dL)

10.Calcitonin; but no long-term efficacy

11.1,25(OH)2D3; but gut effects are slow and limited

A fall in ionized calcium concentration is immediately sensed by the parathyroid glands, which respond with an increase in PTH secretion. PTH increases osteoclastic bone resorption, releasing calcium and phosphate from bone into the ECF. PTH also causes increased renal tubular reabsorption of calcium as well as inhibition of phosphate reabsorption. PTH stimulates synthesis of 1,25(OH)2D3, which further increases absorption of calcium and phosphate from the gut. If these mechanisms are intact, the extracellular calcium concentrations should return to normal.

In the converse situation, a rise in ionized calcium concentration causes a decrease in PTH secretion from the parathyroid glands. Thus, renal tubular calcium reabsorption and osteoclastic bone resorption are decreased. Synthesis of 1,25(OH)2D3 is also decreased, which in turn decreases absorption of dietary calcium and phosphate. Thus, a healthy individual responds to increases in ionized calcium with an increase in renal calcium excretion and a decrease in intestinal absorption of calcium.

In general, these hormonal responses are more effective in protecting against hypocalcemia than hypercalcemia. Perturbations in these mechanisms as exemplified by excessive increases in bone resorption, deficiencies or excesses of PTH or 1,25(OH)2D3, and defects in renal capacity to handle calcium and phosphate will lead to either hypercalcemia or hypocalcemia.

THANK YOU