Ca regulating hormones

- Introduction: effects of Ca / PO4 ions; Parathyroid: anatomy, histology, PTH; Thyroid: anatomy, histology, Calcitonin; Kidney: Vit D. Overview of Ca regulation: bone, kidney, and GI tract as effectors of Ca regulating hormones.

- PTH: structure, receptor, secretion, effect of Ca / Vit D metabolites / other factors, effects

- Calcitonin: structure, biological actions, effect on osteoclasts and bone reabsorption

- Vit D: production and metabolism, absorption, transport and excretion, biological actions

- Diseases: hypoPTH, low Ca tetany, hyperPTH, kidney stones, rickets, osteoporosis. Case study (e.g. hypocalciuric hypercalcemia)

Introduction

For each hormone, the student should know:
1. Its cell of origin
2. Its chemical nature, including
   a. Distinctive features of its chemical composition
   b. Biosynthesis
   c. Whether it circulates free or bound to plasma proteins
   d. How it is degraded and removed from the body
3. Its principal physiological actions
   a. At the whole body level
   b. At the tissue level
   c. At the cellular level
   d. At the molecular level
   e. Consequences of inadequate or excess secretion
4. What signals or perturbations in the internal or external environment evoke or suppress its secretion
   a. How those signals are transmitted
   b. How that secretion is controlled
   c. What factors modulate the secretory response
   d. How rapidly the hormone acts
   e. How long it acts
   f. What factors modulate its action
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• Introduction
  • Ca is required for Na permeability in nerves, Ach release at NMJ, excitation - contraction coupling in muscles (e.g., low ECF-Ca and tetany)
  • Ca serves as intracellular signal for some hormones (e.g., Epinephrine on stroke volume)
  • Ca is needed for some enzymes' effect, for the secretion of proteins, for blood clotting to occur (e.g., EDTA)
  • Ca is a constituent of bone (Ca storage depot)
  • PO4 functions as part of intracellular buffer systems
  • PO4 is an important constituent of macromolecules such as nucleic acids, phospholipids, metabolic intermediates, and phosphoproteins
  • PO4 is a constituent of bone (PO4 storage depot)

Why do blood Ca and PO4 levels are regulated ???
What endocrine signals control all these calcium fluxes???

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          • Pathologies

PTH and Vit.D increase blood Ca while Calcitonin decreases it

[Diagram showing calcium balance in a typical adult]
The Ca sensor is a seven transmembrane domain receptor with its large amino terminal domain in the extracellular side of the plasma membrane. Potential glycosylation sites are located in the extracellular domain. Potential PKC phosphorylation sites are in the intracellular domain. Hypercalcemia decreases cAMP and PTH release from parathyroid, while hypocalcemia increases both cAMP and PTH release. Teophylline and cAMP stimulate PTH release. Examples of pathologies: pseudo hypoparathyroidism type Ia (alpha subunit of Gs) and familial hypocalciuria hypercalcemia (Ca receptor).

Increased plasma calcium concentrations regulate calcium reabsorption in the thick ascending limb of Henle’s loop. In this portion of the nephron, calcium passes through the cell walls of the tubules driven by a positive luminal voltage. The calcium receptor signals through the guanosine nucleotide binding protein Gq to activate PLC (phospholipase C) and form DAG (diacylglycerol), which activates PKC (protein kinase C). Back diffusion of potassium through renal outer medullary potassium channels (ROMK) is inhibited, which decreases the positive potential of luminal fluid and limits reabsorption of sodium and chloride. The receptor also signals through Gi, thus inhibits adenylyl cyclase (AC) and reduces any cyclic AMP dependent stimulation of the sodium/potassium/2 chloride cotransporter (PKA, a protein kinase A).
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Drawing of a section through a human parathyroid gland showing small chief cells and larger oxyphil cells. The cells are arranged in cords surrounded by loose connective tissue.

PTH is only made in the parathyroid gland and is essential for Ca homeostasis.

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A. Posttranslational metabolism of PTH. The leader sequence (-31 to -6) is removed cotranslationally in the endoplasmic reticulum. The hexapeptide -6 to 1 is removed in the Golgi during packaging of the peptide. C-terminal fragments are generated in the secretory granules just prior to or during secretion. B. The known biologically active portion of PTH, the epitopes required for detection and assay of the intact hormone. Detection antibodies that recognize sequences downstream from the amino terminal tripeptide cannot distinguish between the intact active hormone and its truncated antagonist.
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Effects of PTH on the principal cells in the distal nephron. PTH stimulates insertion of epithelial calcium channels in the luminal membrane and calcium extrusion mechanisms in the basolateral membrane. Gs = the stimulatory G protein; AC = adenylyl cyclase; cAMP = cyclic adenosine monophosphate; PKA = protein kinase A.
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**Effects of PTH on proximal tubule cells.** Phosphorylation of NERF (sodium hydrogen exchange regulatory factor) releases PT (sodium phosphate cotransporter) from anchoring sites in the membrane. PTs migrate in the plane of the membrane to clathrin-coated pits, where they are internalized and transferred to lysosomes and degraded. PTH also stimulates the expression and activation of the enzyme (P450 1α-hydroxylase) that converts 25-0H2D3 to 1,25(OH)2D3, the active form of vitamin D.

G

S

E

GS = G subunit of the stimulatory G protein; AC = adenylyl cyclase; cAMP = cyclic adenosine monophosphate; PKA = protein kinase A; CREB = cyclic AMP response element binding protein.

**PTH** is made in the parathyroid only (84 aa). It is essential for Ca homeostasis

**PTH** acts directly on the skeleton and kidneys

**PTH** is the product of a single copy gene (pre-pro-PTH)

**PTH** gene is subject to strong repressor activity in all cells but parathyroids

**PTH** gene transcription is negatively regulated by ECF-Ca and by active Vit. D

**cis** elements in **PTH** gene include Ca response element (CaRE), Vit. D response element (VDRE), and a cAMP response element (CRE)

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As Ca plasma content rises, PTH secretion decreases.

PTH increases plasma Ca concentration.

A thick ground section of the tibia illustrating cortical compact bone and the lattice of trabeculae of cancellous bone.

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PTH stimulates osteoclastic activity and Calcitonin inhibits it.
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Cross-section through a bony trabecula. The pale blue area indicates mineralized matrix.

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**PTH stimulates osteoclastic activity and Calcitonin inhibits it**

A) Local osteolytic hypercalcemia secondary to leukemia
B) Hypercalcemia of malignancy 2nd to squamous cell carcinoma
C) Hyperparathyroidism. Note the abundant osteoclasts (large arrows), osteoblasts (small arrows) and osteoids

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A hand radiograph in primary hyperparathyroidism. Note the subperiosteal erosions, which are more prominent along the radial border of the phalanges.

Regulation of PTH secretion. (-) = decrease; (+) = increase.
The mechanism of action elicited by PTH involves AC and PLC.
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Calcitonin

- Calcitonin is synthesized (32 aa peptide) by parafollicular or C cells of the thyroid gland
- its primary action is to inhibit bone resorption by inhibiting osteoclast lysosomal activity
- its gene encodes multiple mRNA (CGRP) whose peptides (α and β) cause arterial vasodilation. CGRP is widely distributed in central & peripheral nervous system, heart, lungs, thyroid, & GI
- the main stimuli for Calcitonin secretion are an elevated serum Ca and the GI hormone gastrin
- its mechanism of action is through cAMP / PKA

Photomicrograph showing the relationship of calcitonin secreting parafollicular cells to follicles in the thyroid gland of a rat. Arrows point to parafollicular cells. The colloid-filled thyroid follicle is surround by cuboidal epithelial cells.

Overall regulation of calcium balance by PTH

The mechanism of action elicited by calcitonin involves AC and cAMP
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The mechanism of action elicited by calcitonin involves AC and cAMP
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Vit. D is activated in the kidney by the action of PTH
Overall regulation of calcium balance by PTH, calcitonin, and 1,25(OH)2D3. Solid green arrows indicate stimulation; dashed arrows represent inhibition.

Vit.D is activated in the kidney by the action of PTH.
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Vit.D activation is inhibited in the kidney by PO4 and in the parathyroid by Ca on PTH

The mechanism of action of Vit.D is at the genomic level
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The mechanism of action of Vit.D is at the genomic level

Overdosing with vitD might be lethal causing hypercalcemia and soft tissue / vascular calcification
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Radiographic appearance of osteoporosis in humans

Changes in bone mass with age

Radiographic appearance of osteoporosis in humans
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Radiographic appearance of osteoporosis in humans

A model for the general control of bone turnover
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Examples of calcium-related endocrine pathologies

Osteomalacia (rickets) caused by simple nutritional Vit. D deficiency resulting from impaired mineralization of newly formed bone. Osteomalacia is the result of a lack of Vit. D, impairment of Vit. D metabolism, or lack of Ca or P at the mineralizing site. Before growth plate closure the same condition is referred as rickets and is characterized by failure of calcification of cartilage at the growth plate.

Osteomalacia (rickets) caused by hypophosphatemia. is also known as “phosphate diabetes” or Vit. D resistant rickets. Is associated with growth retardation and bowing deformities of the legs. Patients have normal serum Ca with low P content due to increase urine P excretion (phosphate depletion resulting from renal tubular dysfunction).
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Paget’s disease is characterized by marked focal increase in bone resorption and bone formation resulting in disorder bone architecture (e.g. bowing of the femur, bone destruction and soft tissue swelling). Viral origin ??

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