Calcium balance

Importance of calcium

- in vertebrates plays double role:
  - in the form of inorganic salts (hydroxyapatite) builds up the internal frame (skeleton)
  - found in the extracellular space in soluble form
- calcium metabolism is strictly regulated as its appropriate level is indispensable in many physiological processes
  - sets the threshold of voltage-dependent Na^+-channels – low Ca^{++} level: increased excitability, spontaneous contractions, tetanus
  - exocytosis – synapses, gland cells
  - action potentials in the heart and smooth muscles
  - muscle contraction
  - hemostasis (blood clotting)
- half of the Ca^{++} in the blood is bound to proteins, part of the rest is bound to anions, free, ionized concentration is: 1,1-1,2 mmol/l
- during alkalosis (e.g. hyperventilation) – more negative charges on proteins – increased binding of Ca^{++} to proteins – Ca^{++} level decreases - increased excitability of neurons and muscles

Calcium metabolism

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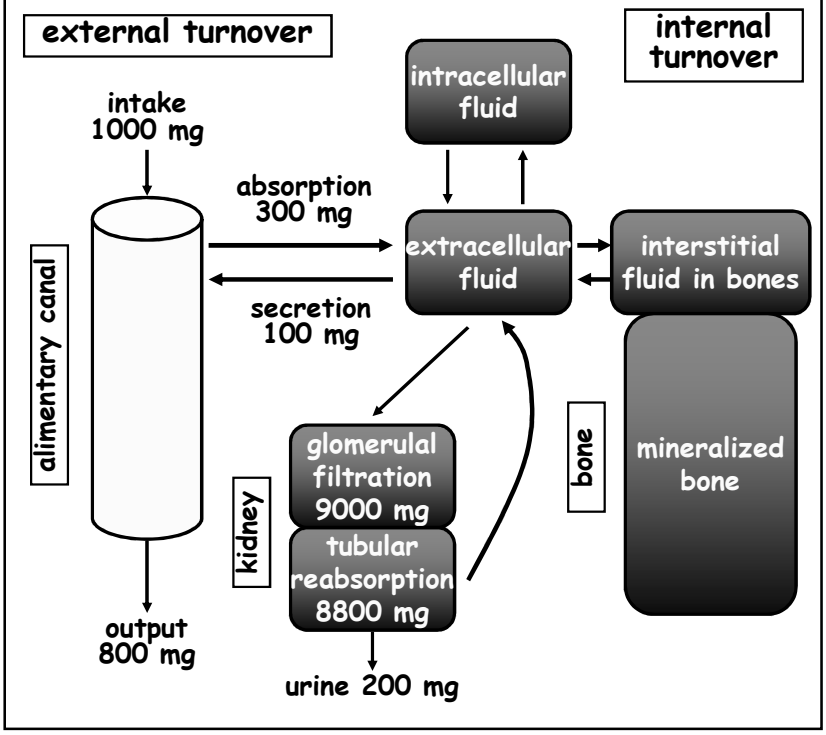

Bone tissue

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- our body contains about 1-2 kg calcium, of this 99% in bones
- remodeling is continuous in bones, it can restore diminished plasma level if necessary
- remodeling is regulated by several hormones: parathyroid hormone, calcitriol (vitamin D), calcitonin, androgens (estrogens), glucocorticoids
- osteoprogenitor – osteoblast – matrix synthesis (collagen, etc. fibers) – osteoid tissue
- osteoblasts surrounded by the matrix become osteocytes; keeping contact with each other through thin processes
- the next step is mineralization or calcification a – hydroxyapatite precipitates on the fibers
- precipitation is induced by an increase of phosphate concentration – phosphatase and pyrophosphatase activity of osteoblasts release phosphate from organic and inorganic phosphates

Remodeling of the bone

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- osteoclasts are giant, multinucleated macrophages
- they are activated by paracrine factors released by the osteoblasts and other local influences (TNF, IL-1, etc.)
- secretion of H^+-ions and hydrolyzing enzymes – dissolution of the hydroxyapatite and the matrix
- remodeling goes according the "brick wall model" - triggering effect is unknown
- osteoclasts bore cavities into the bone (7-10 days), osteoblasts synthesize the matrix, then mineralization follows
- in young people rebuilding is 100%, later not: osteoporosis
- androgens facilitate, glucocorticoids inhibit rebuilding
- matrix contains cytokines freed during dissolution of the bone – they inhibit this process and facilitate rebuilding

Parathyroid hormone (PTH)

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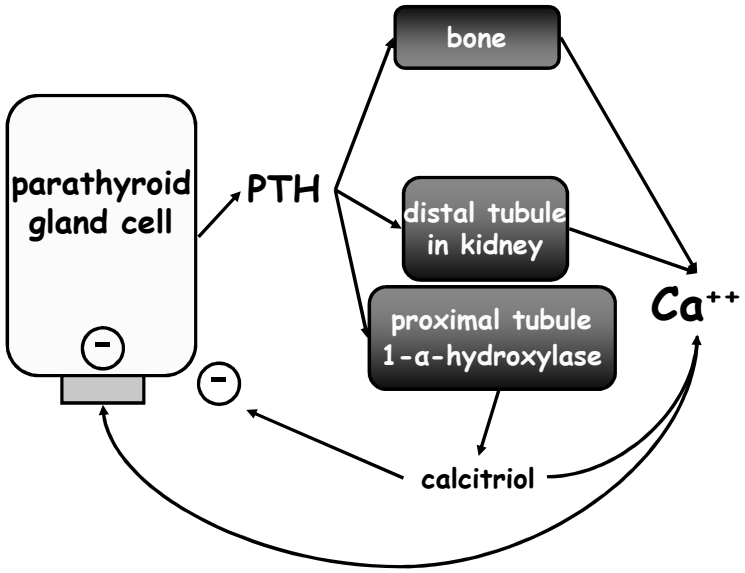
- in humans produced by 4 parathyroid glands (40 mg each) located in the thyroid gland
- deletion of the thyroid gland – death in humans, in some species auxiliary parathyroid glands
- cells here and in many other tissues also produce PTH-related-peptide – paracrine role
- pre-pro-PTH (115) – pro-PTH (90) – PTH (84)
- production is regulated by the Ca^{++} level in the blood through negative feedback (fast)
- very sensitive between 1-1,3 mmol/l, higher or lower levels cause no additional change
- Ca^{++} level is detected by G-protein associated 7TM receptors – low level – cAMP synthesis – PTH release
- another, slower element of the regulation is calcitriol (vitamin D)

Regulation of PTH production



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Effects of parathyroid hormone

- its main effect is to increase the Ca^{++} level in the blood
- acts mainly on the kidneys and the bones
- kidney
  - Ca^{++} reabsorption increases in distal tubules
  - P-reabsorption decreases in the proximal tubules
  - 1-a-hydroxylase activity is facilitated in proximal tubules
- bone
  - Ca^{++} permeability of osteocyte processes forming a barrier between the capillaries and the interstitial fluid increases (2-3 hours)
  - osteoblasts activate osteoclasts (they have no PTH receptor) through paracrine mediation (after 12 hours)
  - immature osteoclasts differentiate into maturate osteoclasts
- high PTH level: osteolysis, low level: tetanus

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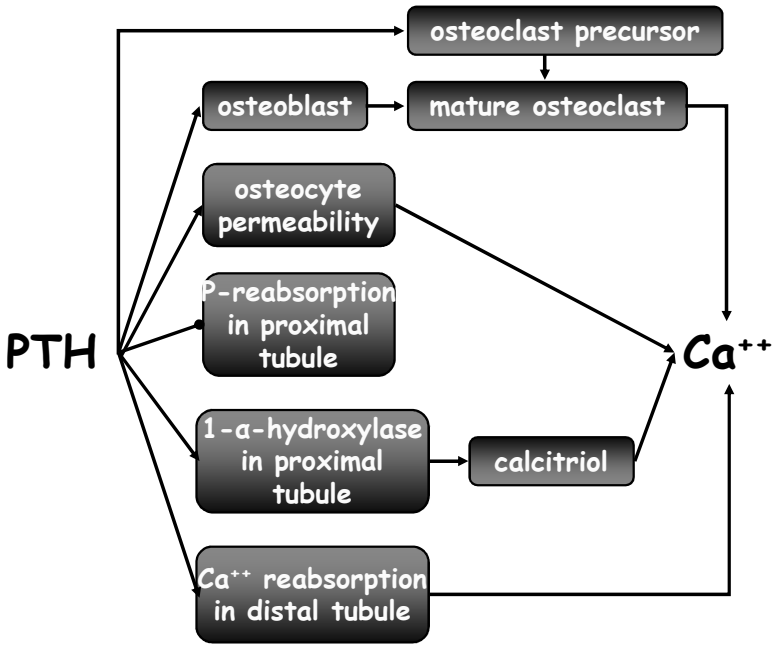
Parathyroid hormone effects



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Calcitriol (vitamin D)

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- vitamin D is known in two forms:
  - ergocalciferol, D_2 – uptake with food
  - cholecalciferol, D_3 – uptake with food (cod liver oil), or produced in the skin from 7-dehydrocolesterol under the influence of UV irradiation (sunshine)
- vitamin D is only missing, if there is no uptake with food and there is no sunshine either
- calciferols are inactive – they are transformed in an unregulated way (possibility of overdosing) in the liver to 25-OH-calciferol, which has weak activity
- additional OH at position 1 in the kidney in a regulated way – calcitriol
- regulation:
  - negative feedback at 3 points
  - alternate hydroxylase binding OH to position 24, rendering the molecule inactive

Effects of calcitriol

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- calcitriol effects can be grouped in 3 categories:
  - increase of blood Ca^{++} level
  - effects on bones and other tissues
  - inhibition of its own production and that of PTH
- increase of Ca^{++} level mainly through facilitating reabsorption from the alimentary canal – in addition, weak facilitation of active transport in the renal distal tubules
- in the bones it effects osteoblasts and immature osteoclasts, similarly to PTH
  - influences mineralization of osteoid tissue
  - in high concentration stimulates osteoclasts through factors released by osteoblasts
  - facilitates the maturation of immature osteoclasts
- lymphocytes and monocytes posses calcitriol receptors – modulation of immune functions

Calcitriol effects

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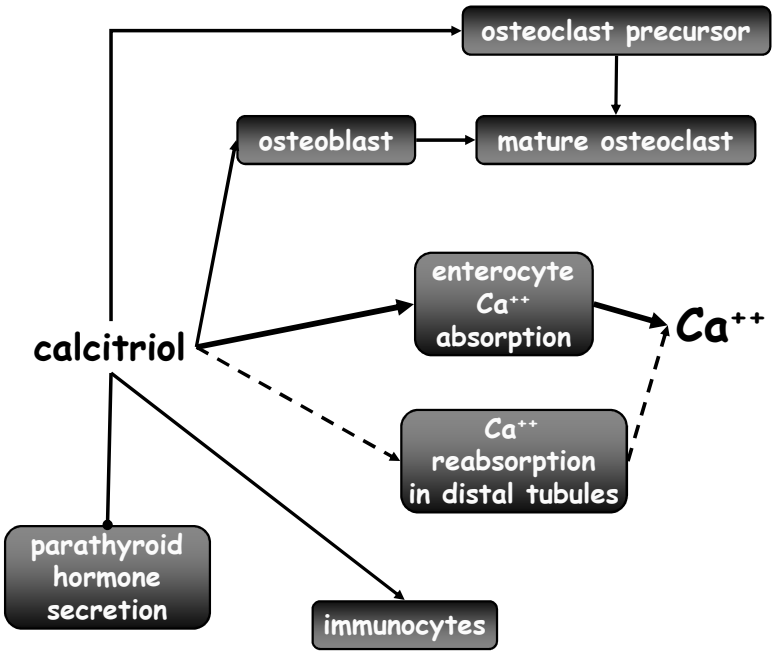

Calcitonin

- gene is present in various cells – alternate splicing – different products:
  - in C-cells distributed diffusely in the thyroid gland – calcitonin precursor
  - in nerve cells and other cells „calcitonin-gene-related-peptide", CGRP – acting as transmitter
- precursor (124) – calcitonin (32)
- production regulated directly by blood Ca^{++} level through G-protein associated 7TM receptor – higher level – increased cAMP synthesis – increased calcitonin secretion
- calcitonin acts on 7TM receptors, activating several G-protein pathways – cAMP increase, protein kinase C activation
- osteoclast inactivation - decreased Ca^{++} level
- in addition, decreased Ca^{++} reabsorption, increased excretion in the kidney