Drugs affecting the hypothalamic – pituitary axis

Regina Demlová, FÚ LF MU

✓ The hypothalamo-pituitary axis is the unit formed by the **hypothalamus** and **pituitary gland**, which exerts control over many parts of the endocrine system.

✓ the nervous system regulates the endocrine system and endocrine activity modulates the activity of the CNS.

✓Hormones (peptides) – receptors – muscles, bones, fat tissue

A/ membrane R → AC – catalyze the conversion of ATP to cAMP and pyrophosphate - a regulatory signal via specific cAMP-binding proteins, either transcription factors or other enzymes (e.g., cAMP-dependent kinases).

B/ cytosolic receptor → translocation to the nucleus in a form capable of interacting with the DNA.

Controlling the hypothalamic-pituitary-target organ axis :

important factor ***Negative feedback***

the action of hypothalamic hormones may be inhibited :

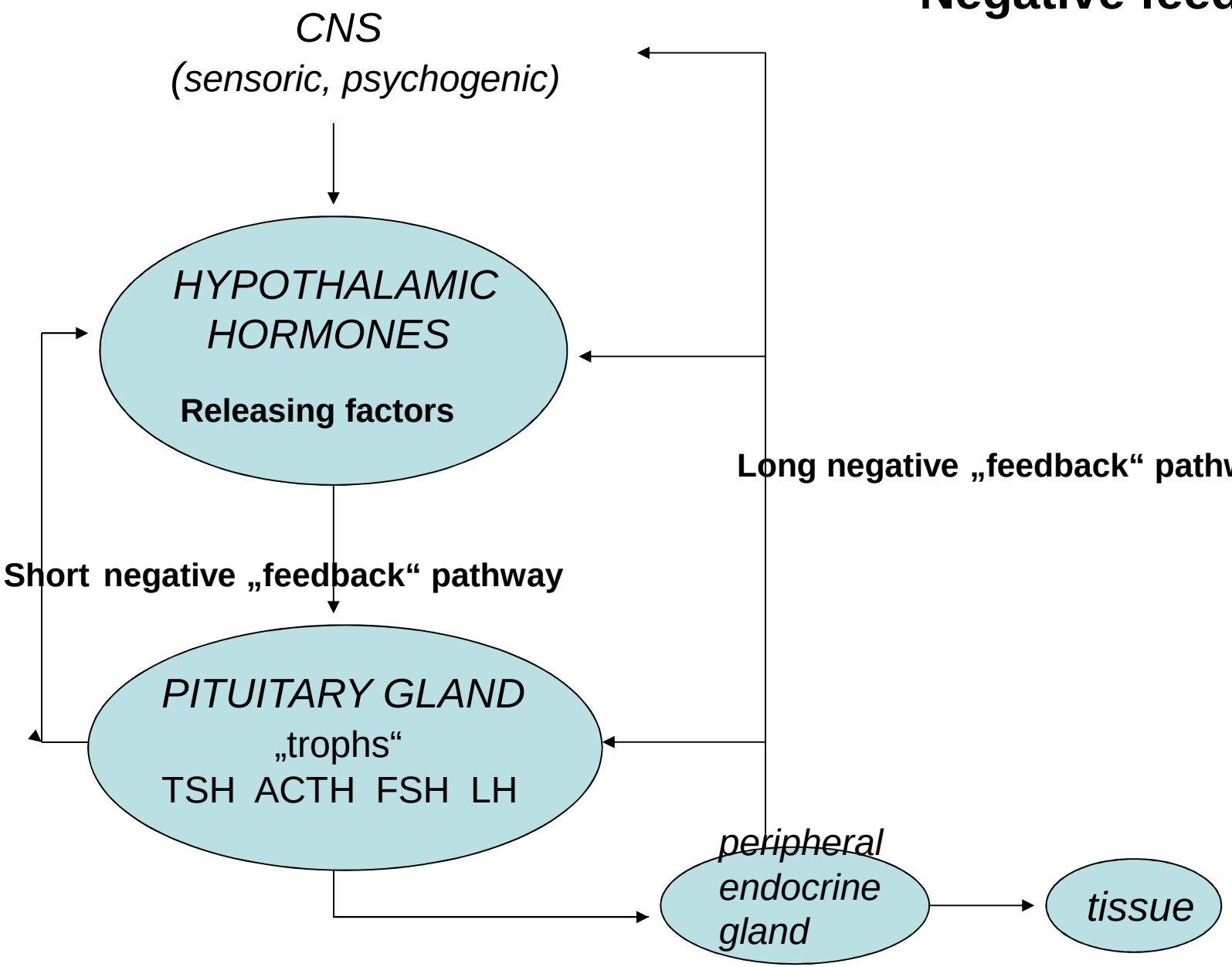
A/ by long feedback patway from the target gland hormone or

B/ by short feedback pathway from the pituitary hormone.

There may also be direct feedback from the target gland hormone to the pituitary gland.

Input is also received at the hypothalamus from higher brain centres

Negative feedback



Endocrinopathy

- any disease due to disorder of the endocrine system

A. the hypothalamic-pituitary-target organ axis

- Peripheral - primary - arise at the level of peripheral endocrine.glands
  central - secondary - arise at the level of regulation - adenohypophysis,
  central - tertiary - hypothalamus

B. tissue - defect of conversion to an active metabolite, absence of tissue receptors (PK, PD)

Syndromes: hyperfunctional
hypofunctional

Etiology of endocrinopathy:

genetic defects

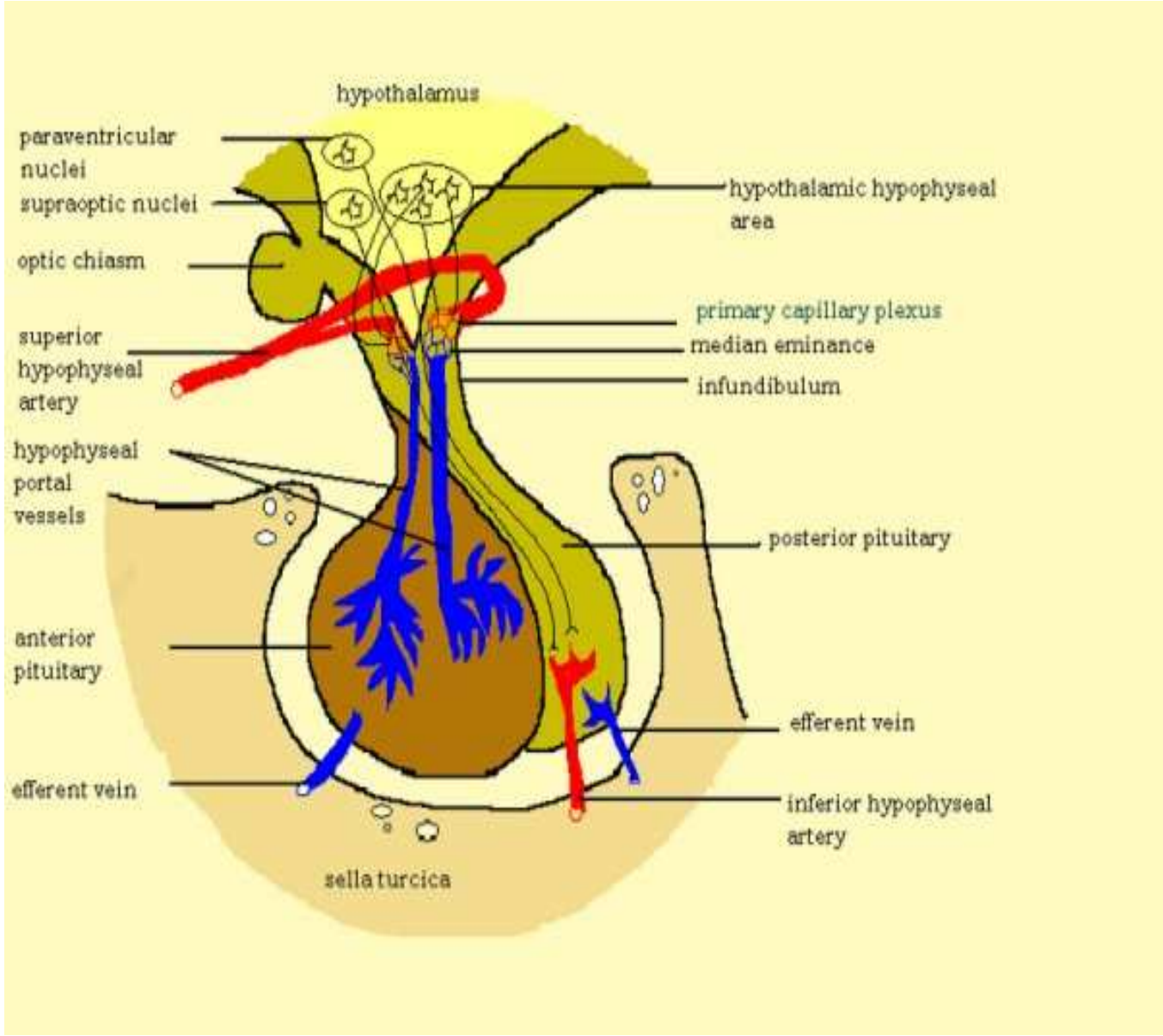
tumors - adenoma (usually hyperfunctional syndrome)

neuroendocrine tumors

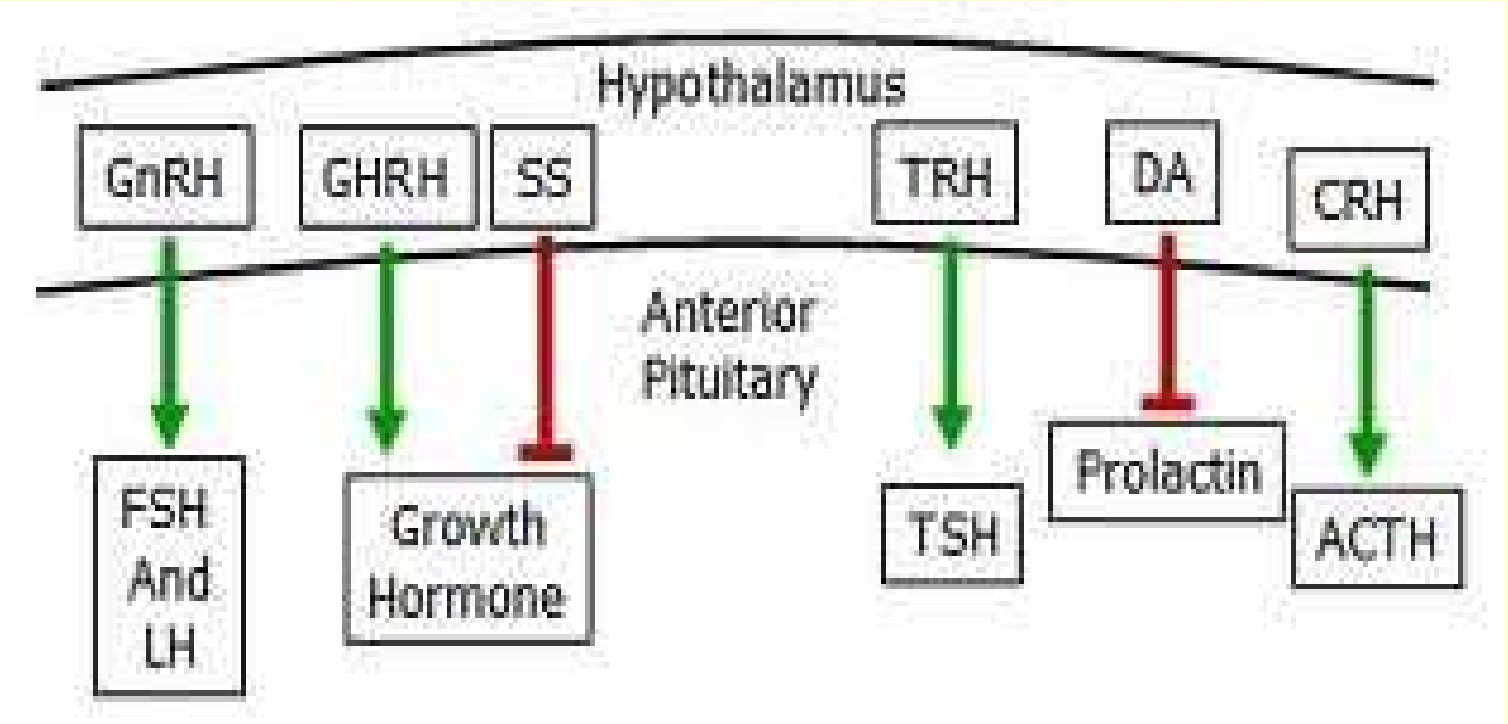
inflammation

ischaemia,

surgery, radiotherapy, accidents


hypothalamus
paraventricular nuclei
supraoptic nuclei
optic chiasm
superior hypophyseal artery
hypophyseal portal vessels
anterior pituitary
efferent vein
hypothalamic hypophyseal area
primary capillary plexus
median eminance
infundibulum
posterior pituitary
efferent vein
inferior hypophyseal artery
sella turcica

Releasing or inhibiting hormones (- liberines, - statines)



Growth hormone-releasing factor (GHRF, somatorelin)

- Peptide, 44 amino-acid residues
- The effect of GHRF is selective for GH in the anterior pituitary gland
- An analogue, **sermorelin**, used as **diagnostic test** for growth hormone secretion (i.v., s.c., intranasally)

Growth hormone-inhibiting factor (somatostatin)

- Peptide, 14 amino-acid residues, inhibits the release of GH
- Pancreatic D-cells, IGF-1 in the liver stimulates the production
- *Inhibits the release of thyroid-stimulating hormone (TSH)*

Growth hormone-inhibiting factor (somatostatin)

Gastrointestinal system

- Somatostatin suppresses the release of gastrointestinal hormones:
  - Gastrin
  - Cholecystokinin (CCK)
  - Secretin
  - Vasoactive intestinal peptide (VIP)
  - Gastric inhibitory polypeptide (GIP)
- suppresses the release of pancreatic hormones

Analogue of somatostatin

octreotide (SANDOSTATIN s.c., SANDOSTATIN LAR i.m.)

Indication:

- The FDA has approved the usage of *octreotide acetate* as an injectable depot formulation for the treatment of

✓ acromegaly, gigantism

✓ diarrhea and flushing episodes associated with carcinoid syndrome

✓ diarrhea in patients with vasoactive intestinal - secreting tumors (VIPoam)

Analogue of somatostatin

lanreotide (SOMATULINE PR s.c., AUTOGEL s.c.)

- similar therapeutic indication

✓ acromegaly, gigantism

✓ diarrhea and flushing episodes associated with carcinoid syndrome and neuroendocrine tumors

Thyrotrophin-releasing hormone (TRH)

- Tripeptide horme
- Releases TSH from the anterior pituitary
- Synthetic analogue **protirelin** – diagnostic purposes (thyroid disorders – hypo- or hyper-thyreoidism)

Corticotrophin-releasing hormone (CRH)

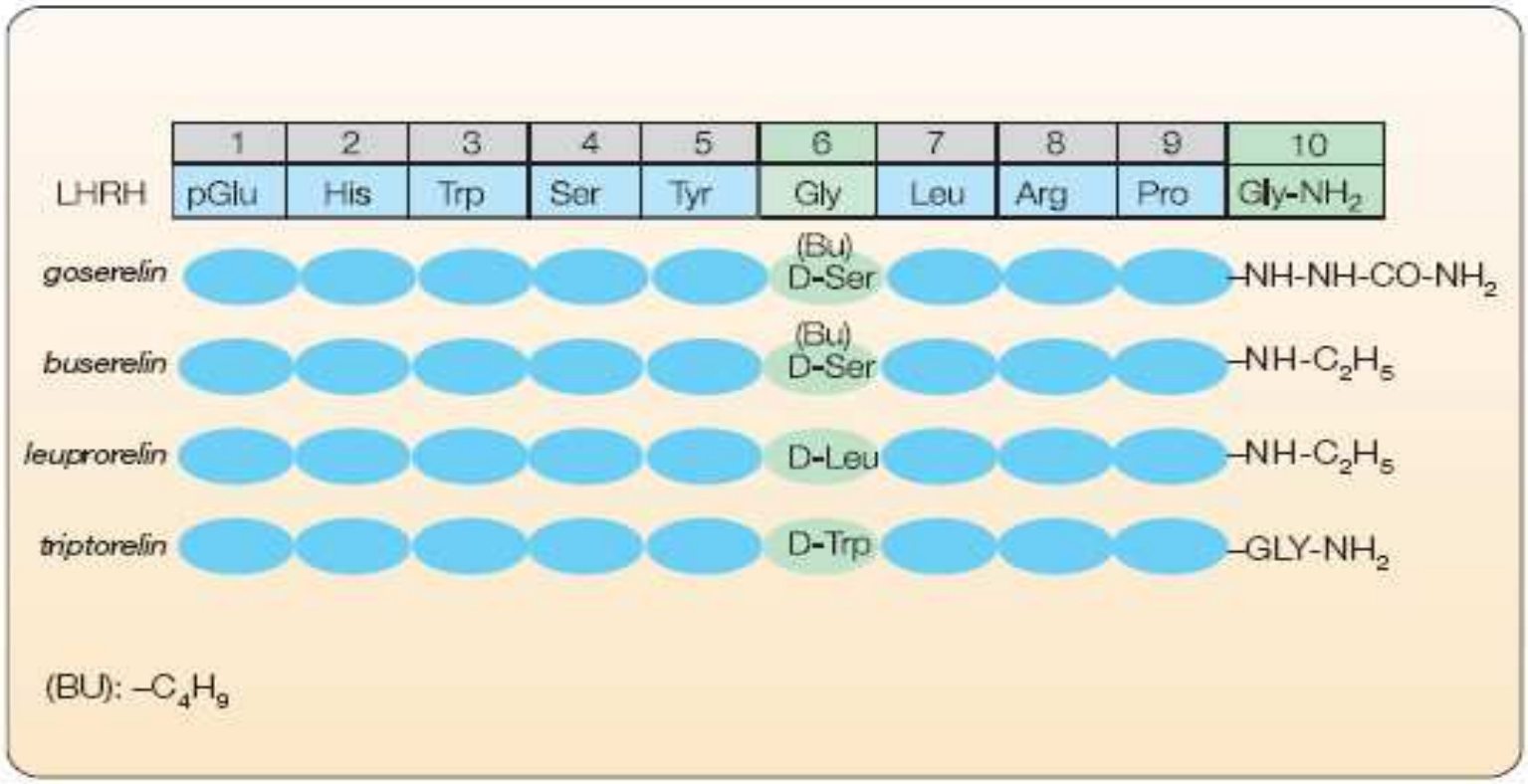
- Peptide, 44 amino-acid residues
- Releases ACTH and ß-endorphin from the anterior pituitary
- Synthetic analogue **corticorelin** – to test the ability of the pituitary to secrete ACTH

Gonadotrophin-releasing hormone(GnRH, LHRH)

- Decapeptide that releases both follicle-stimulating hormone and luteinising hormone (FSH, LH)
- Synthetic form is gonadorelin, given in pulsatile fashion stimulates gonadotrophin release from the anterior pituitary
- Dg. or therapy (LHRH analogues)

Analogues of GnRH/LHRH

- Synthetised by Nobel laureate Andrew Schelly (1971)
- Similar structure, 200-times more potent than endogenous GnRH/LHRH



Obr. 2 *Struktura LHRH a jeho syntetických analog*

Analogues of GnRH/LHRH (agonists)

- activate the GnRH receptor resulting in increased secretion of FSH and LH

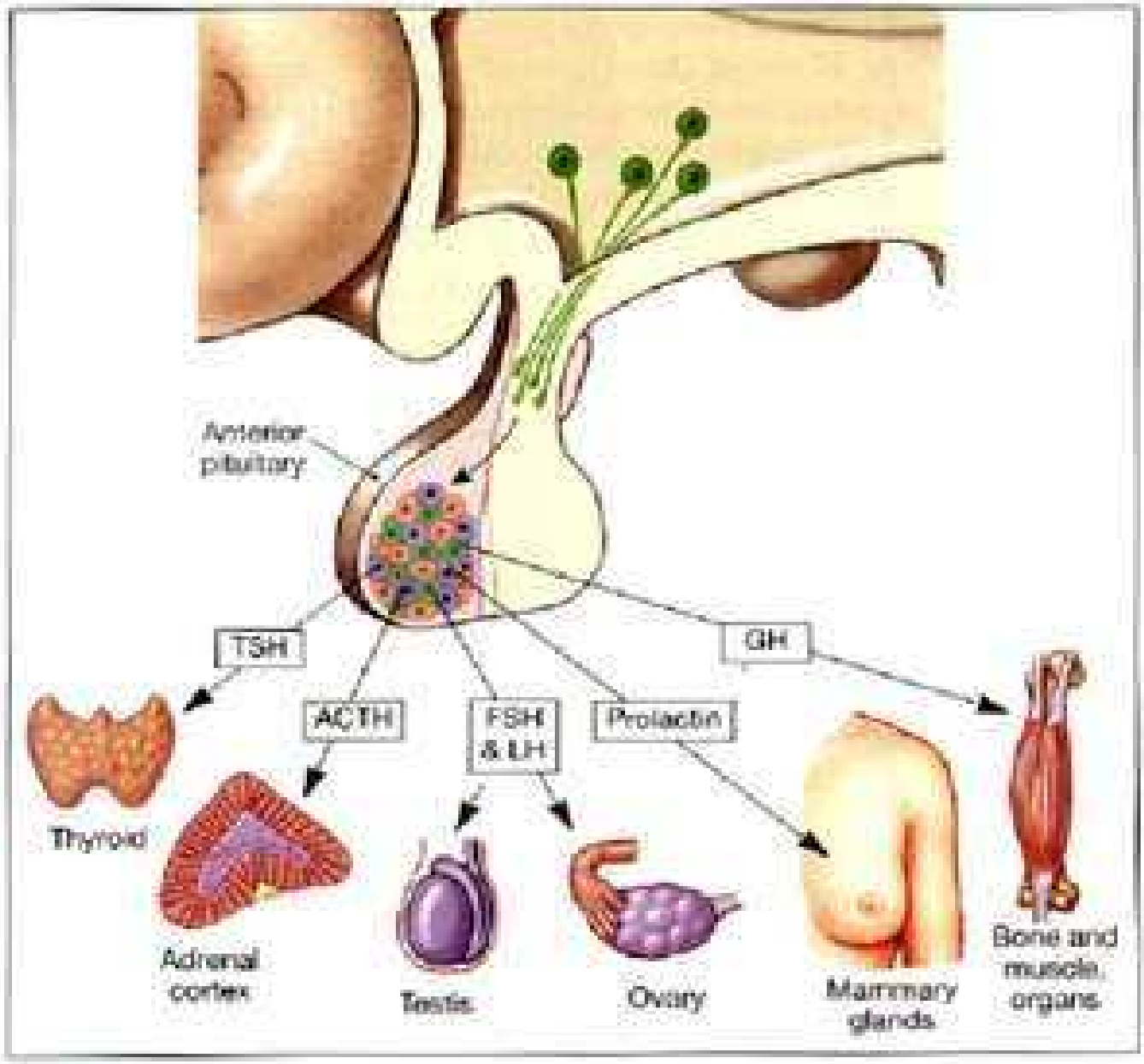
- Initially it was thought that agonists could be used as potent and prolonged stimulators of pituitary gonadotropin release, but after their initial stimulating action – termed a “flare” effect - eventually caused a paradoxical and sustained drop in gonadotropin secretion - this “downregulation” and can be observed after about 10 days

- Are given to cause gonadal suppression in various sex-hormone-dependent conditions….

Goserelin (ZOLADEX Depot)

Indication:

- Prostatic carcinoma
- Adjuvant therapy of breast cancer
- Endometriosis
- Large uterine fibroids (myoma)


Anterior pituitary
TSH
ACTH
FSH & LH
Prolactin
GH
Thyroid
Adrenal cortex
Testis
Ovary
Mammary glands
Bone and muscle organs

PITUITARY GLAND

✓Hyperfunction = ***hyperpituitarismu***s – partial, 1 - 2 hormones (STH)

✓Hypofunction = ***hypopituitarismus*** - panhypopituitarismus

Sheehan syndrome – postpartum

Growth hormone (GH, STH)

191-amino acid, synthesized, stored, and secreted by somatotropic cells within the lateral wings of the anterior pituitary gland

.

- Somatotropic cells in the anterior pituitary gland then synthesize and secrete GH in a pulsatile manner, in response to these stimuli by the hypothalamus.

- A number of factors are known to affect GH secretion, such as age, gender, diet, exercise, stress, and other hormones.

Growth hormone (GH, STH)

- Effects of growth hormone on the tissues of the body can generally be described as anabolic (building up).

- **Direct** effects by binding to receptors on target cells, where it activates the MAPK/ERK pathway - stimulates division and multiplication of chondrocytes of cartilage.

- **Indirect** - GH also stimulates the production of insulin-like growth factor 1 (IGF-1, formerly known as somatomedin C)

- IGF-1 has growth-stimulating effects on a wide variety of tissues. Increases calcium retention, and strengthens and increases the mineralization of bone

- Increases muscle, promotes lipolysis, increases protein synthesis
- Promotes gluconeogenesis in the liver

Growth hormone (GH, STH)

Somatropin and its agonists

- **H01AC01: Somatropin (GENOTROPIN 16, 36 m.j.) */**
- H01AC02: Somatrem
- H01AC03: Mekasermin
- H01AC04: Sermorelin
- H01AC05: Mekasermin rinfabát
- H01AC06: Tesamorelin

*/ Somatropinum (INN) produced in *Escherichia coli* cells by recombinant DNA technology

Indication of somatropin

- Children
- Growth disturbance due to insufficient secretion of growth hormone (growth hormone deficiency, GHD) and growth disturbance associated with Turner syndrome or chronic renal insufficiency.
- Prader-Willi syndrome (PWS), for improvement of growth and body composition. The diagnosis of PWS should be confirmed by appropriate genetic testing.

- Adults
- Replacement therapy in adults with pronounced growth hormone deficiency.

Method of administration, contraindications (CI)

- The dosage and administration schedule should be individualized.
- The injection should be given subcutaneously and the site varied to prevent lipoatrophy.

CI:

- Somatropin must not be used when there is any evidence of activity of a tumour. Intracranial tumours must be inactive and antitumour therapy must be completed prior to starting growth hormone therapy. Treatment should be discontinued if there is evidence of tumour growth
- GENOTROPIN should not be used for growth promotion in children with closed epiphyses.
- Patients with acute critical illness suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions should not be treated with GENOTROPIN

Adrenocorticotropic hormone , corticotropin (ACTH)

- is a polypeptide tropic hormone, often produced in response to biological stress
- Its principal effects are increased production and release of corticosteroids. A deficiency of ACTH is a cause of secondary adrenal insufficiency and an excess of it is a cause of Cushing's syndrome

- ACTH is synthesized from pre-pro-opiomelanocortin (pre-POMC)

(MSH, ß-lipotropin a , ß-endorphin)

- Synthetic analog t**etracosactid**

Tetracosactid (SYNACTHEN)

As a diagnostic test for the investigation of adrenocortical insufficiency.

Adults

- only as a single intramuscular or intravenous dose; it is not to be used for repeated therapeutic administration.
- *The 30-minute Synacthen diagnostic test*
- This test is based on measurement of the plasma cortisol concentration immediately before and exactly 30 minutes after an intramuscular or intravenous injection of 250mcg (1ml) Synacthen.

Use in children

- An intravenous dose of 250mcg/1.73 m^2 body surface area has been suggested. Thus for children aged 5-7 years, approximately half the adult dose will be adequate. For more accurate dosing of other ages, standard body surface area tables should be consulted.

Thyrotropin (thyroid-stimulating hormone - TSH)

- TSH is a glycoprotein and consists of two subunits, the *alpha* and the *beta* subunit.

- The α (*alpha*) subunit is nearly identical to that of human chorionic gonadotropin (hCG), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) - responsible for stimulation of adenylate cyclase (92-amino acid sequence)

- The β (*beta*) subunit is unique to TSH, and therefore determines its receptor specificity. The β chain has a 118-amino acid sequence.

- It is secreted throughout life but particularly reaches high levels during the periods of rapid growth and development.

Thyrotropin (thyroid-stimulating hormone - TSH)

- Only diagnostic purposes
- TSH concentrations are measured as part of a thyroid function test in patients suspected of having an excess (hyperthyroidism) or deficiency (hypothyroidism) of thyroid hormones.
- Interpretation of the results depends on both the TSH and T_4 concentrations (measurement of T_3 may also be useful)

Gonadotropins (FSH, LH, hCG)

- This is a family of proteins, which include the mammalian hormones
- Follicle-stimulating hormone (FSH)
- Luteinizing hormone(LH)
- placental chorionic gonadotropins hCG

These hormones are central to the complex endocrine system that regulates normal growth, sexual development, and reproductive function.

LH and FSH are secreted by the anterior pituitary gland, while hCG and eCG are secreted by the placenta

- There are various preparations of gonadotropins for therapeutic use, mainly as fertility medication (recombinant)

Prolaktin

- Peptide hormon
- It stimulates the mammary glands to produce milk (lactation)
- Therapeutic use : Prolactin inhibitors (dopamine agonists, which effectively treat hyperprolactinemia)

Prolactin inhibitors

- **Lisurid** (ergolin derivate, D2 dopamin agonist)
- **Tergurid** (D2 dopamin agonist-antagonist)
- **Cabergolin** (D2 dopamin agonist – slow release)
- **Bromocriptin**

*Bromocriptin (*MEDOCRIPTINE tbl.) - indication:

- **Inhibition of lactation for medical reasons**
- The inhibition or suppression of puerperal lactation where medically indicated such as after intrapartum loss or neonatal death.

- **Hyperprolactinaemia**
- The treatment of hyperprolactinaemia in men and women with hypogonadism and/or galactorrhoea.

.

- **Prolactinomas**
- To reduce tumour size, particularly in those at risk of optic nerve compression.

- Maximum dose : 30 mg p.o.

The posterior pituitary

- consists mainly of neuronal projections (axons) extending from the nuclei of the hypothalamus. These axons release peptide hormones into the capillaries of the hypophyseal circulation.

Vasopressin or antidiuretic hormone (**ADH**) –

indirect effect - stimulates water retention, distal tubulus

direct pressoric effect - raises blood pressure by contracting arterioles

Oxytocin - Uterine contractions; lactation

ADH, vasopressin

Kidney

- 1. Increasing the water permeability of distal tubule, allowing water reabsorption and excretion of more concentrated urine - V2 receptors, which are G protein-coupled receptors on the basolateral plasma membrane of the epithelial cells, which activates adenylyl cyclases III - convert ATP into cAMP

Cardiovascular system

- Vasopressin increases peripheral vascular resistance (vasoconstriction) and thus increases arterial blood pressure. V1 receptors – phospholipasis C/IP3..

CNS modulator

- implicated in memory formation, including delayed reflexes, image, short- and long-term memory, though the mechanism remains unknown

ADH, vasopressin – synthetic analogues

Desmopresin (MINIRIN) is used in conditions featuring low vasopressin secretion, as well as for control of bleeding (in some forms of von Willebrand disease and in mild haemophilia A)

Terlipresin (REMESTYP) is used as vasoconstrictors in certain conditions (gynecology, urology…. use of vasopressin analogues for esophageal varices commenced in 1970)

- *i.v. 2 mg every 4 hours, max 48 h.*

Oxytocin

- In lactating (breastfeeding) mothers, oxytocin acts at the mammar glands, causing milk to be 'let down' into subareolar sinuses
- Uterine contraction: Important for cervical dilation before birth, oxytocin causes contractions during the second and third stages of labor.
- Oxytocin is also thought to modulate inflammation by decreasing certain cytokines.
- Synthetic oxytocin - trade names **Pitocin and Syntocinon**
- **i.v., i.m., s.c.**

Bone homeostasis

Bone cell types

- There are three types of bone cells:
- **Osteoblasts** are the differentiated bone forming cells and secrete bone matrix on which Ca^{++} and PO precipitate.
- **Osteocytes**, the mature bone cells are enclosed in bone matrix.
- **Osteoclasts** is a large multinucleated cell derived from monocytes whose function is to resorb bone. Inorganic bone is composed of hydroxyapatite and organic matrix is composed primarily of collagen.

Bone formation

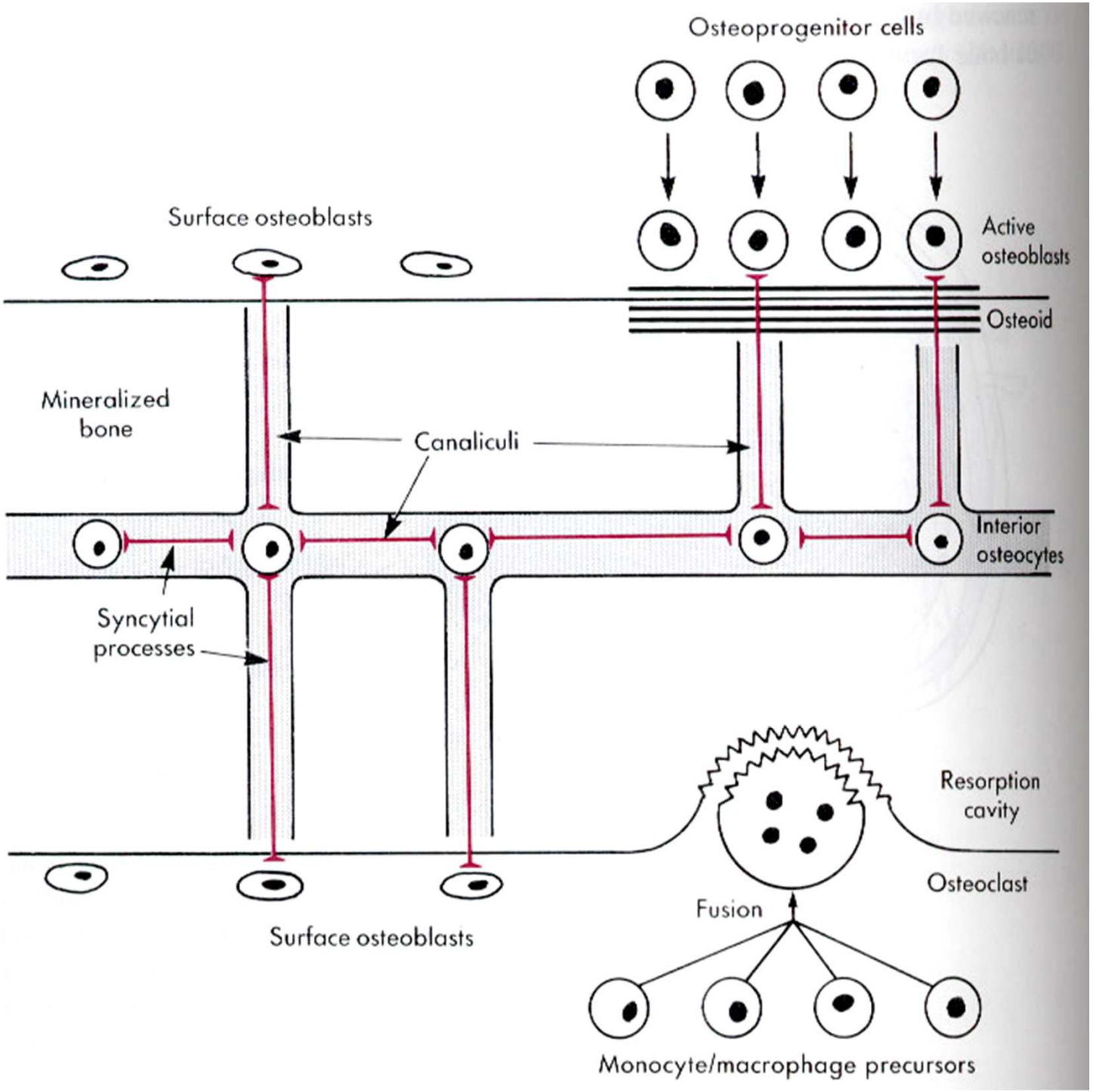
- Active **osteoblasts** synthesize and extrude collagen
- Collagen fibrils form arrays of an organic matrix called the **osteoid**.
- Calcium phosphate is deposited in the osteoid and becomes mineralized
- Mineralization is combination of $CaP0_4$, OH^-, and $H_3CO_3^-$ hydroxyapatite.

Mineralization

- Requires adequate Calcium and phosphate
- Dependent on Vitamin D
- Alkaline phosphatase and osteocalcin play roles in bone formation
- Their plasma levels are indicators of osteoblast activity.

Canaliculi

- Within each bone unit is a minute fluid-containing channel called the **canaliculi**.
- Canaliculi traverse the mineralized bone.
- Interior osteocytes remain connected to surface cells via syncytial cell processes.
- This process permits transfer of calcium from enormous surface area of the interior to extracellular fluid.


Osteoprogenitor cells
Surface osteoblasts
Active osteoblasts
Osteoid
Mineralized bone
Canaliculi
Interior osteocytes
Syncytial processes
Resorption cavity
Osteoclast
Fusion
Surface osteoblasts
Monocyte/macrophage precursors

Bones cells

Calcium, bones and osteoporosis

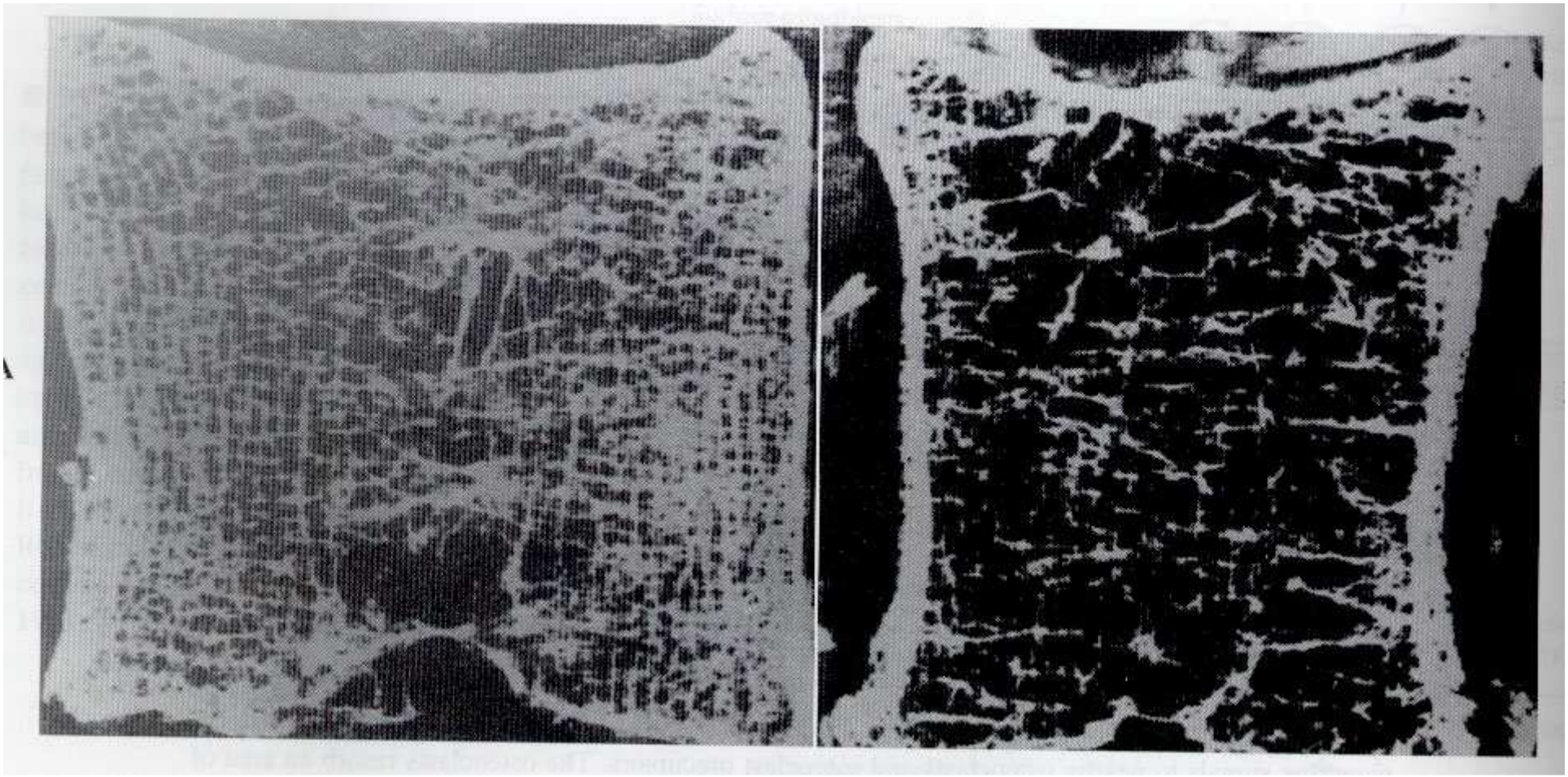
- The total bone mass of humans peaks at 25-35 years of age.
- Men have more bone mass than women.
- A gradual decline occurs in both genders with aging, but women undergo an accelerated loss of bone due to increased resorption during perimenopause.
- Bone resorption exceeds formation.

Calcium, bones and osteoporosis

- Reduced bone density and mass: **osteoporosis**
- Susceptibility to fracture.
- Earlier in life for women than men but eventually both genders succumb**.**
- Reduced risk:
  - **Calcium in the diet**
  - **habitual exercise**
  - **avoidance of smoking and alcohol intake**
  - **avoid drinking carbonated soft drinks**

Vertebrae of 40- vs. 92-year-old women

Note the marked loss of trabeculae with preservation of cortex.



Hormonal control of Ca2+

- Three principal hormones regulate Ca^{++} and three organs that function in Ca^{++} homeostasis.

- **Parathyroid hormone (PTH)**, **1,25-dihydroxy Vitamin D3 (Vitamin D3)**, and **Calcitonin**, regulate Ca^{++}

- resorption, reabsorption, absorption and excretion from **the bone, kidney and intestine**. In addition, many other hormones effect bone formation and resorption.

PARATHYROID GLANDS

PARATHORMON - is secreted by the cells of the parathyroid glands as a polypeptide containing 84 amino acids.

- It acts to increase the concentration of calcium (Ca^{2+}) in the blood
- by acting upon the parathyroid hormone 1 receptor (high levels in bone and kidney) and the parathyroid hormone 2 receptor (high levels in the central nervous system, pancreas, testis, and placenta)
- Naturall PTH half-life is approximately 4 minutes

Effects:

BONE - It enhances the release of calcium from the bones circulation

INTESTINE - via kidney It enhances the absorption of calcium in the intestine by increasing the production of activated vitamin D.

KIDNEY - enhances active reabsorption of calcium and magnesium from distal tubules, also decreases the reabsorption of phosphate

PARAFOLLICULAR CELLS

- **CALCITONIN -** a 32-amino acid linear polypeptide hormone, purified in 1962 by Copp and Cheney

Lowers blood Ca^{2+} levels in three ways:

- Inhibits Ca^{2+} absorption by the i**ntestines**
- Inhibits osteoclast activity in **bones**
- Inhibits renal tubular cell reabsorption of Ca^{2+} allowing it to be secreted in the urine

- The calcitonin receptor, found on osteoclasts and in kidney and regions of the brain, is a G protein-coupled receptor

Calcitonin - treatment

I

- **Salmon calcitonin (MIACALCIC)** is therapeutically used for the treatment of:

- Postmenopausal osteoporosis
- Hypercalcaemia
- Paget's disease
- Bone metastases
- Phantom limb pain

- Miacalcic 200 IU Nasal Spray, solution.
- Miacalcic® 400 IU/2ml Solution for Injection and Infusion.

…vitamin D…

History

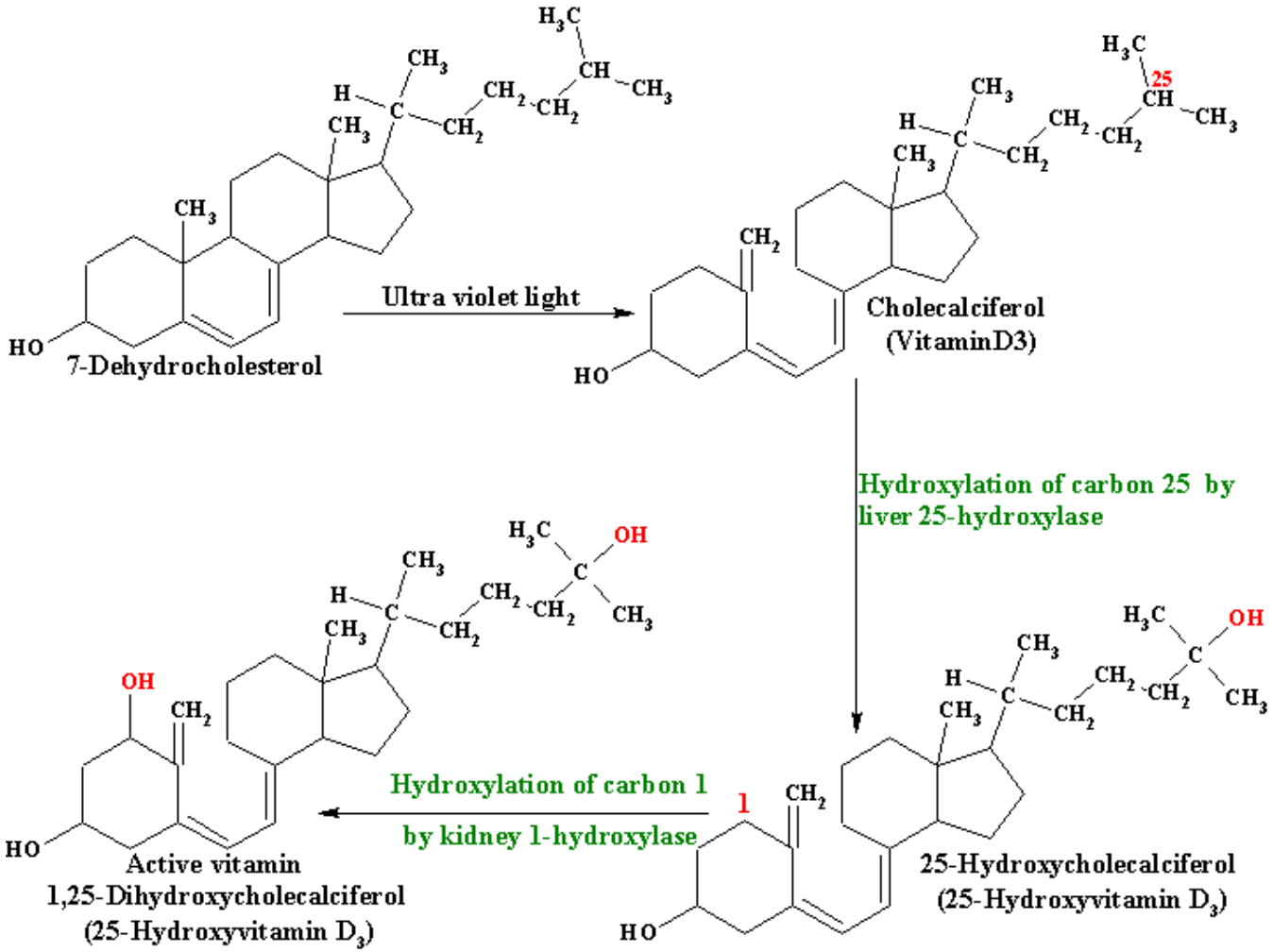
1920/1921 - British doctor Edward Mellanby (1884-1955) noticed dogs that were fed cod liver oil did not develop rickets and concluded vitamin A, or a closely associated factor, could prevent the disease…..

In 1923, it was established that when 7-dehydrocholesterol is irradiated with light, a form of a fat-soluble vitamin is produced (now known as D_3).

…biology…

- is a group of fat-soluble vitamines
- in humans, vitamin D can be ingested as cholecalciferol (vitamin D_3) or ergocalciferol (vitamin D_2)
- can also be synthesize from cholesterol, when sun exposure is adequate (hence its nickname, the "sunshine vitamin").

biosynthesis



- **Calcitriol mediates its biological effects by binding to the vitamin receptor (VDR)**

- **The binding of calcitriol to the VDR allows the VDR to act as a transcription factor that modulates the gene expression of transport proteins (such calbindin), which are involved in calcium absorption in the intestine.**

- **VDR activation in the intestine, bone, kidney, and parathyroid gland cells leads to the maintenance of calcium and phosphorus levels in the blood and to the maintenance of bone content**

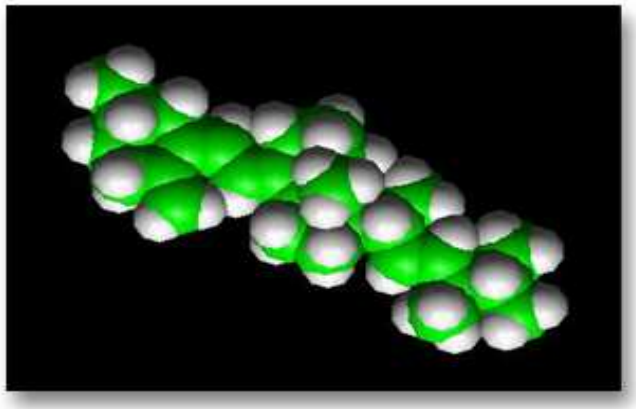
One of the most important roles of vitamin D is to maintain skeletal calcium balance by promoting……

- **calcium absorption in the intestines**
- **bone resorption by increasing osteoclast number**

Vitamin D deficiency can result in lower bone mineral density and an increased risk of reduced bone density (osteoporosis) or bone fracture

- **The VDR is known to be involved in cell proliferation and differentiation - anticancer effects (anti VEGF) ?**

Vitamin D also affects the immune system, and VDRs are expressed in several white blood cells, including monocytes and activated T and B cells



Vitamin D molecule

Vitamin D and prevention of breast cancer.

Welsh J. Acta Pharmacol Sin. 2007 Sep;28(9):1373-82.

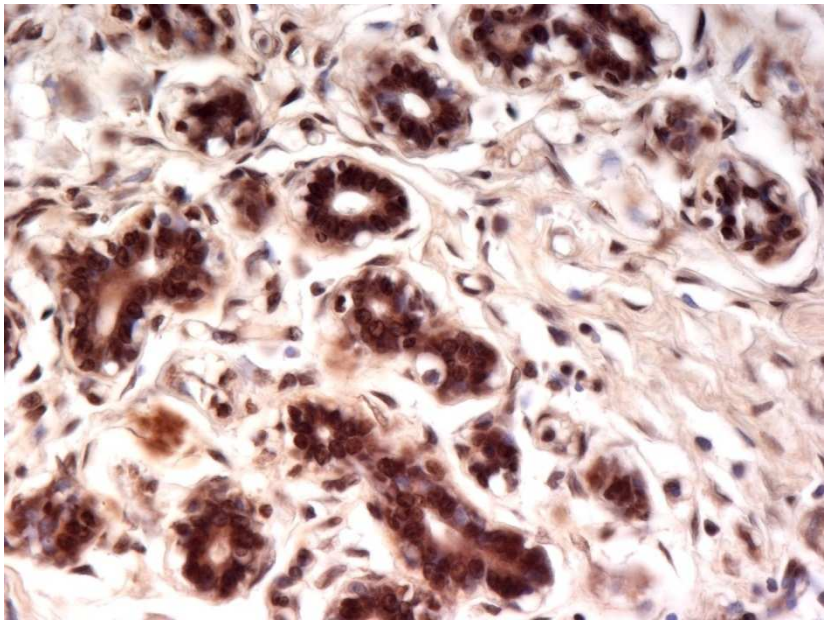
…in vitro studies have demonstrated that the VDR ligand, 1,25-dihydroxyvitamin D3 exerts negative growth regulatory effects on mammary epithelial cells that contribute to maintenance of the differentiated phenotype.

Vitamin D regulates the phenotype of human breast cancer cells.

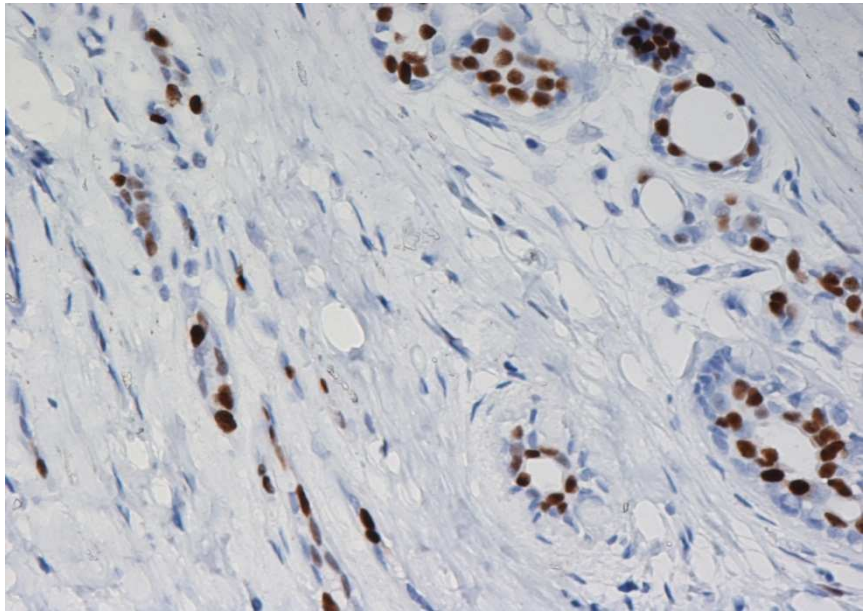
Pendás-Franco N, et al. Differentiation. 2007 Mar;75(3):193-207. Epub 2006 Dec 11

…1,25(OH)(2)D(3) profoundly affects the phenotype of breast cancer cells, and suggest that it reverts the myoepithelial features associated with more aggressive forms and poor prognosis in human breast cancer.

VDR expresion:breast Ca



breast cancer, 400x, VDR positivity in epithel and stroma, not corresponding to ER positivity pattern



Identical specimen stained for ER, only luminal cells stain positive

1. Osteoporosis

- an increased risk of fracture
- In osteoporosis, the bone mineral density (BMD) is reduced, defined by the WHO as a bone mineral density of 2.5 standard deviations or more

- The form of osteoporosis most common in women after menopause is referred to as **primary type 1 or postmenopausal osteoporosis.**

- **Primary type 2 osteoporosis** or senile osteoporosis occurs after age 75 and is seen in both females and males at a ratio of 2:1.

…prevention, treatment …

- Life style, nutrition, exercise, HRT after menopause, Ca, vitamin D

- **Bisphosphonates** Inhibit the body from breaking down bone (a process called resorption)

- **Selective estrogen receptor modulators** (called SERMS or estrogen analogs) Mimic estrogens in some tissues and antiestrogens in others; cause the body to retain the bone it has by working like estrogen, but without some unwanted side effects Raloxifene (Evista, postmenopause)

- **Calcitonin** (Miacalcin Nasal Spray), not very effective for postmenopause prevention; also can relieve bone pain due to osteoporosis-induced fracture.,

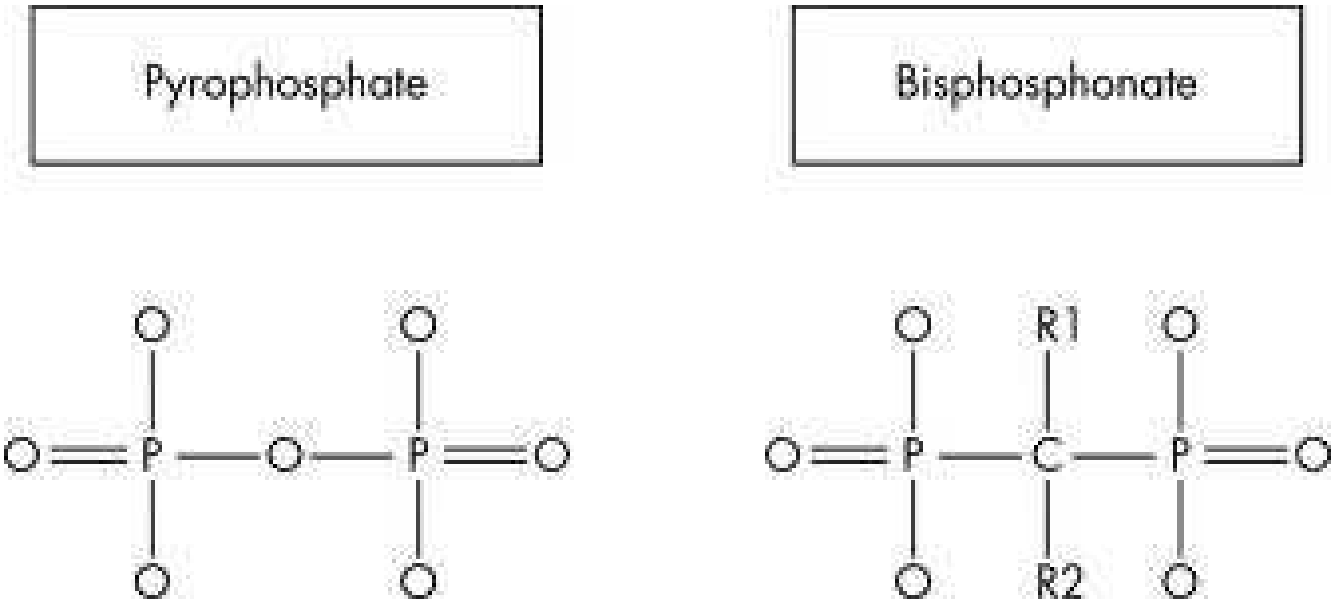
Bisphosphonates

Bisphosphonates

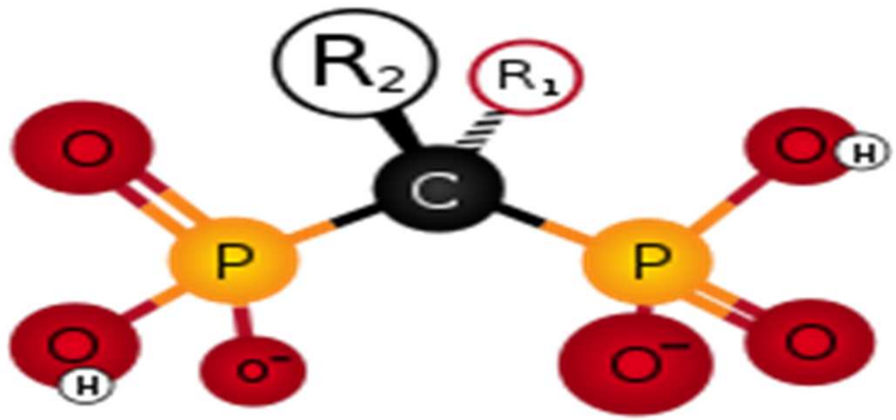
- They are similar in structure to pyrophosphate.

The two PO_3 (phosphonate) groups covalently linked to carbon

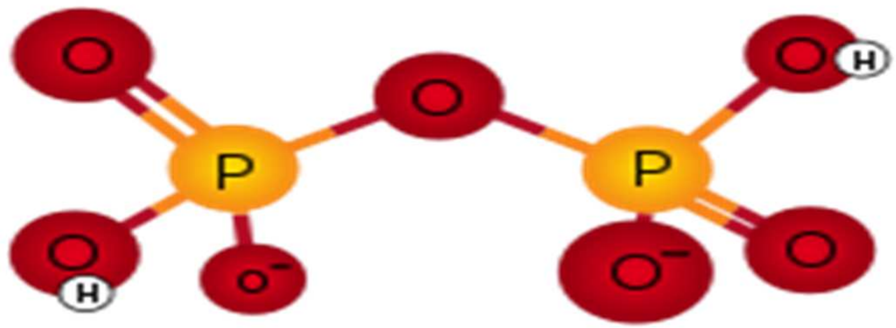
(P-C-P)



Bisphosphonates



Bisphosphonate

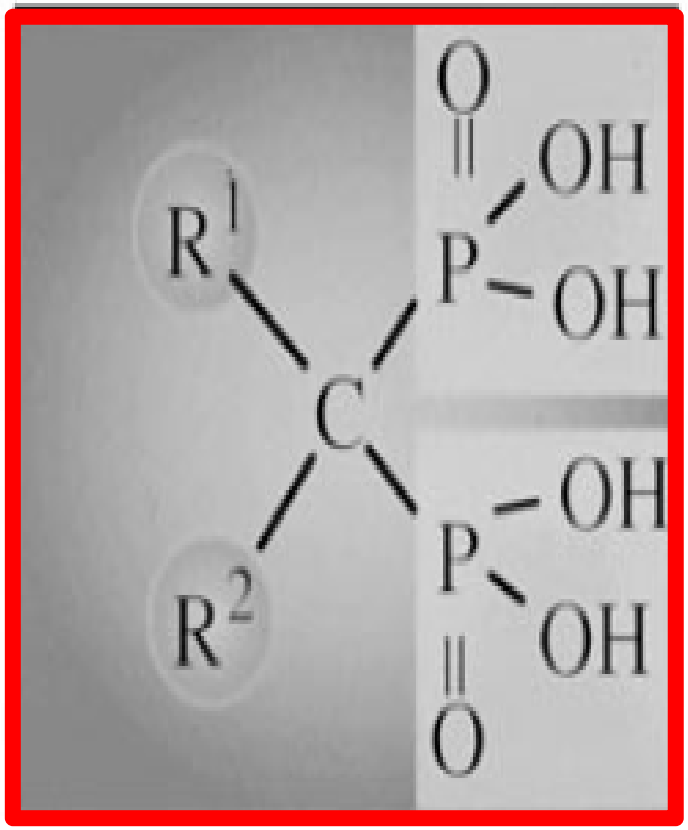


Pyrophosphate

Pediatrics 2007;119;S150-S162

When R^1 is an OH group, binding to bone is enhanced

R^2 site determines anti-resorptive potency biochemically, including effects on binding to hydroxyapatite



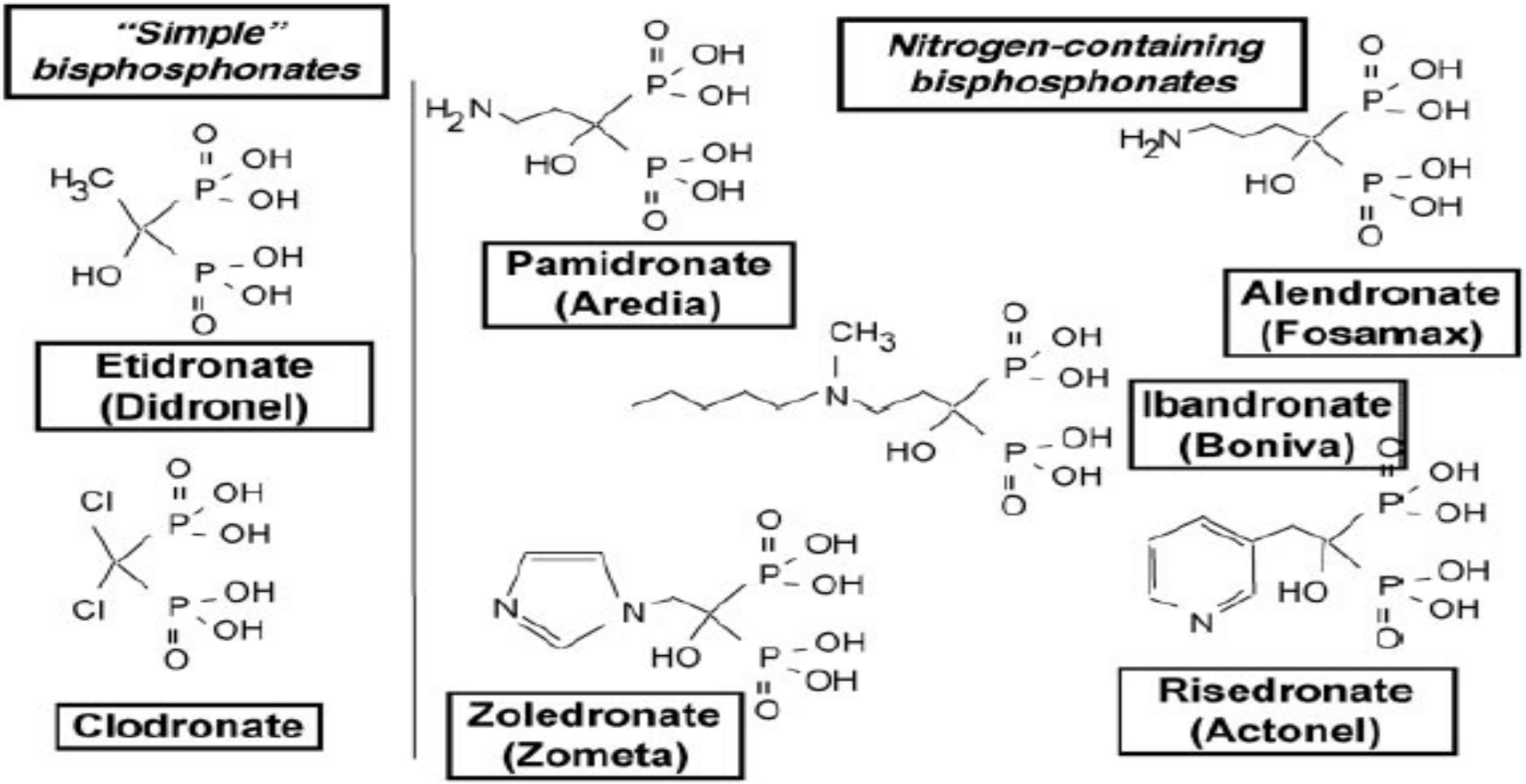
Both phosphonate groups act as a "bone hook" and are essential for both binding to hydroxyapatite and biochemical mechanism of action

Bisphosphonates: Mode of Action and Pharmacology

R. Graham G. Russell, MD, PhD

Pediatrics 2007;119;S150-S162

nitrogen containing BP are considered to be most effective



Mechanism of action of BP

binding to the hydroxyapatite crystals at the bone surface

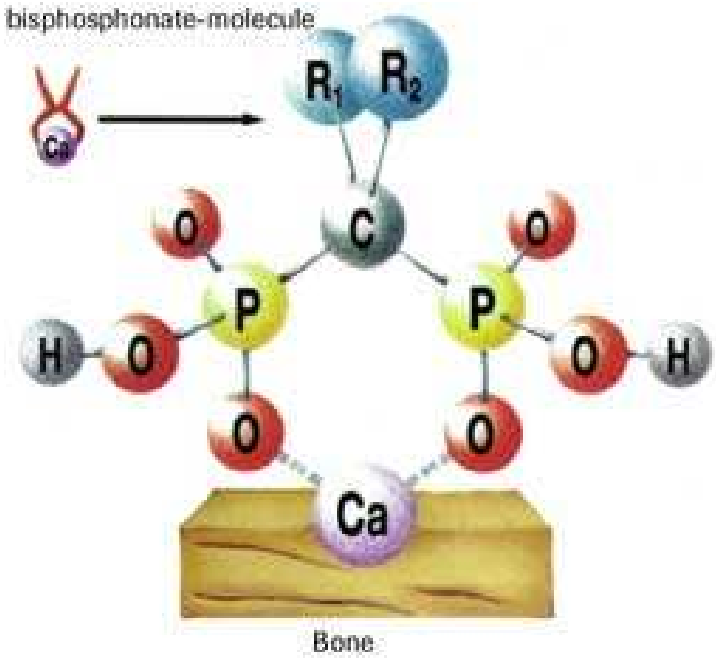
- preferentially binds to hydroxyapatite in the area of osteoclasts and penetrates into them

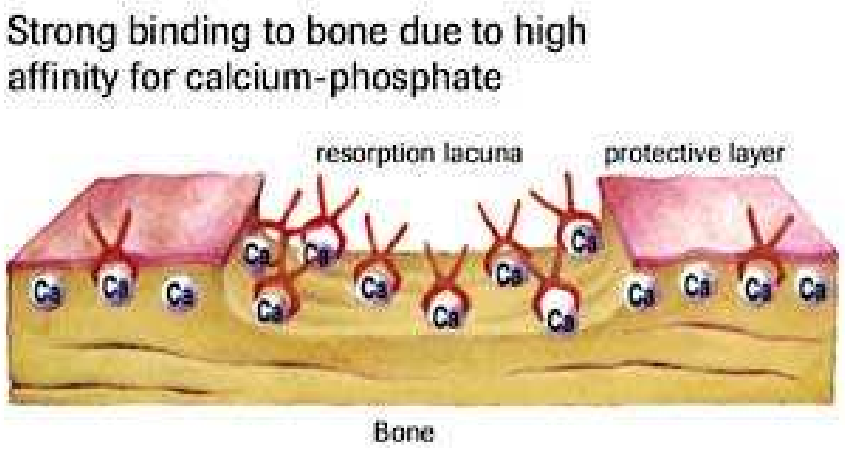
the final result is

inhibition of bone resorption

Horák, Remedia, 4/2006

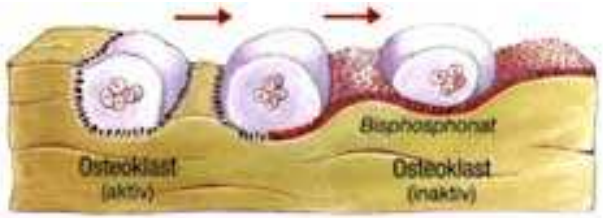
Binding BP to bone



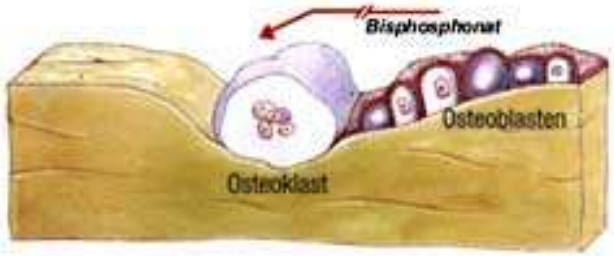


Hydroxyapatit : Ca10(PO4)6OH2

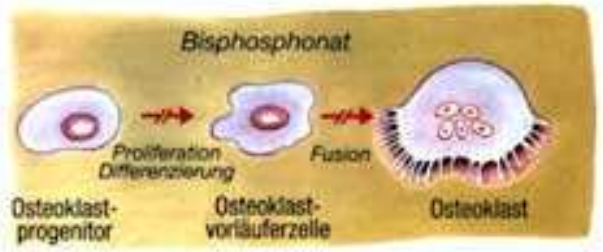
Inhibition of osteoclasts



1. Direct inhibition of osteoclasts when they take up bisphosphonate present on bone.



2. Indirect inhibition of osteokclasts via reduction of osteoclast- stimulating activity of osteoblasts.



3. Reduction of number of osteoclasts by influence on their recruitment or life-span.

1st generation of BP

- Non-*N*-containing bisphosphonates:

- Etidronate (Didronel) — 1 (potency relative to that of etidronate)
- Clodronate (Bonefos, Lodronate) — 10

They are metabolised in the cell to compounds that replace the terminal pyrophosphate moiety of ATP, forming a nonfunctional molecule that competes with adenosine triphosphate (ATP) in the cellular energy metabolism.

The osteoclast initiates apoptosis, leading to an overall decrease in the breakdown of bone.

2nd generation of BP

- *N*-containing bisphosphonates:

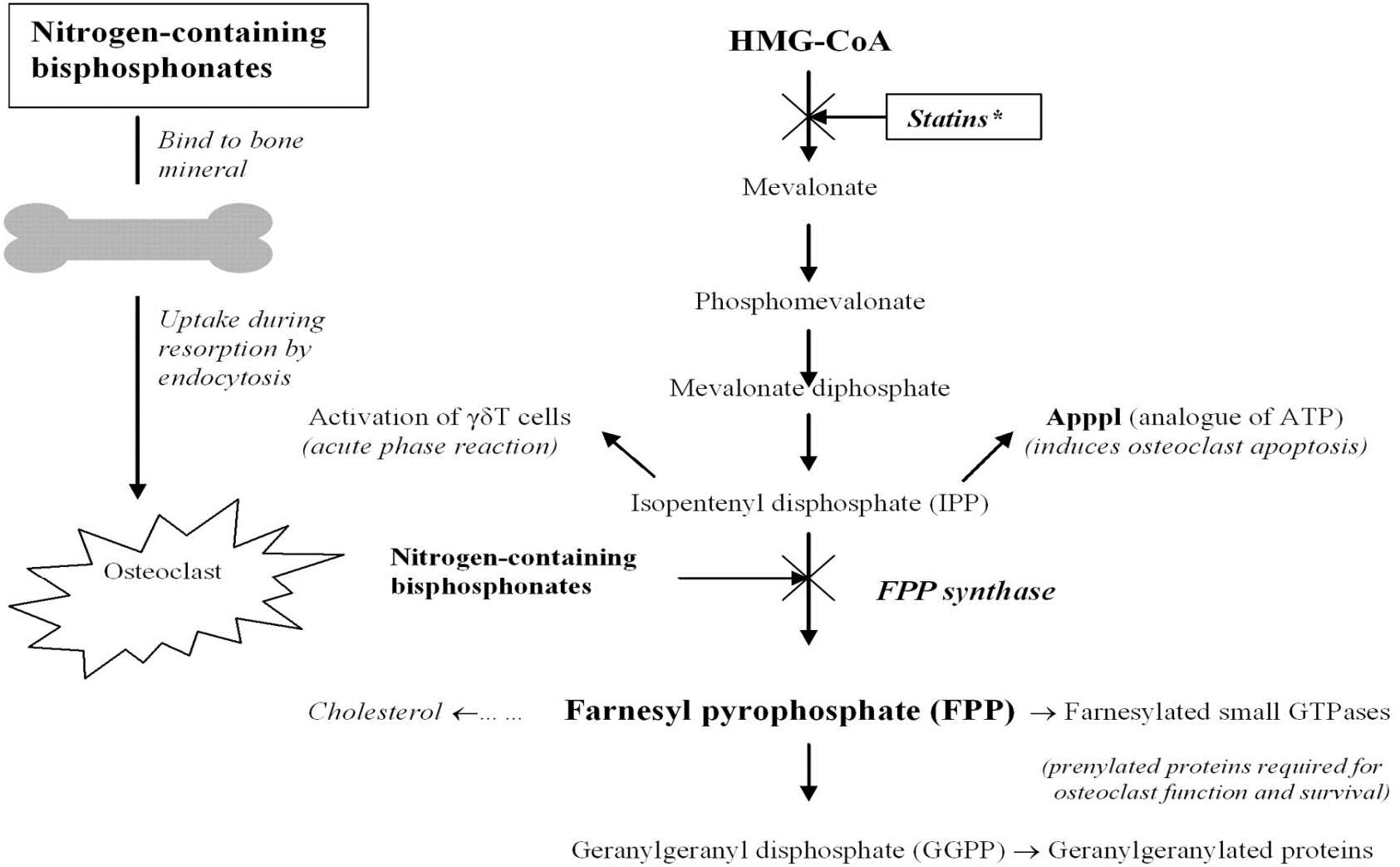
- Pamidronate (APD, Aredia) — 100
- Alendronate (Fosamax) — 500
- Ibandronate (Boniva) — 1000
- Risedronate (Actonel) — 2000
- Zoledronate (Zometa, Aclasta) — 10000

MoA: 2nd generation of BP

- Nitrogenous BP act on bone metabolism by binding and blocking the enzyme farnesyl diphosphate synthase (FPPS) in the HMG-CoA reductase pathway (also known as the mevalonate pathway)

- Disruption of the HMG CoA-reductase pathway at the level of FPPS prevents the formation of two metabolites (farnesiol and geranylgeraniol) that are essential for connecting some small proteins to the cell membrane. This phenomenon is known as prenylation

Diagram showing the action of nitrogen-containing bisphosphonates on inhibiting FPP synthase, preventing the synthesis of FPP and GGPP (both required for protein prenylation) and leading to accumulation of IPP. * Statin therapy (HMG CoA reductase inhibitors...



Toussaint N D et al. CJASN 2009;4:221-233

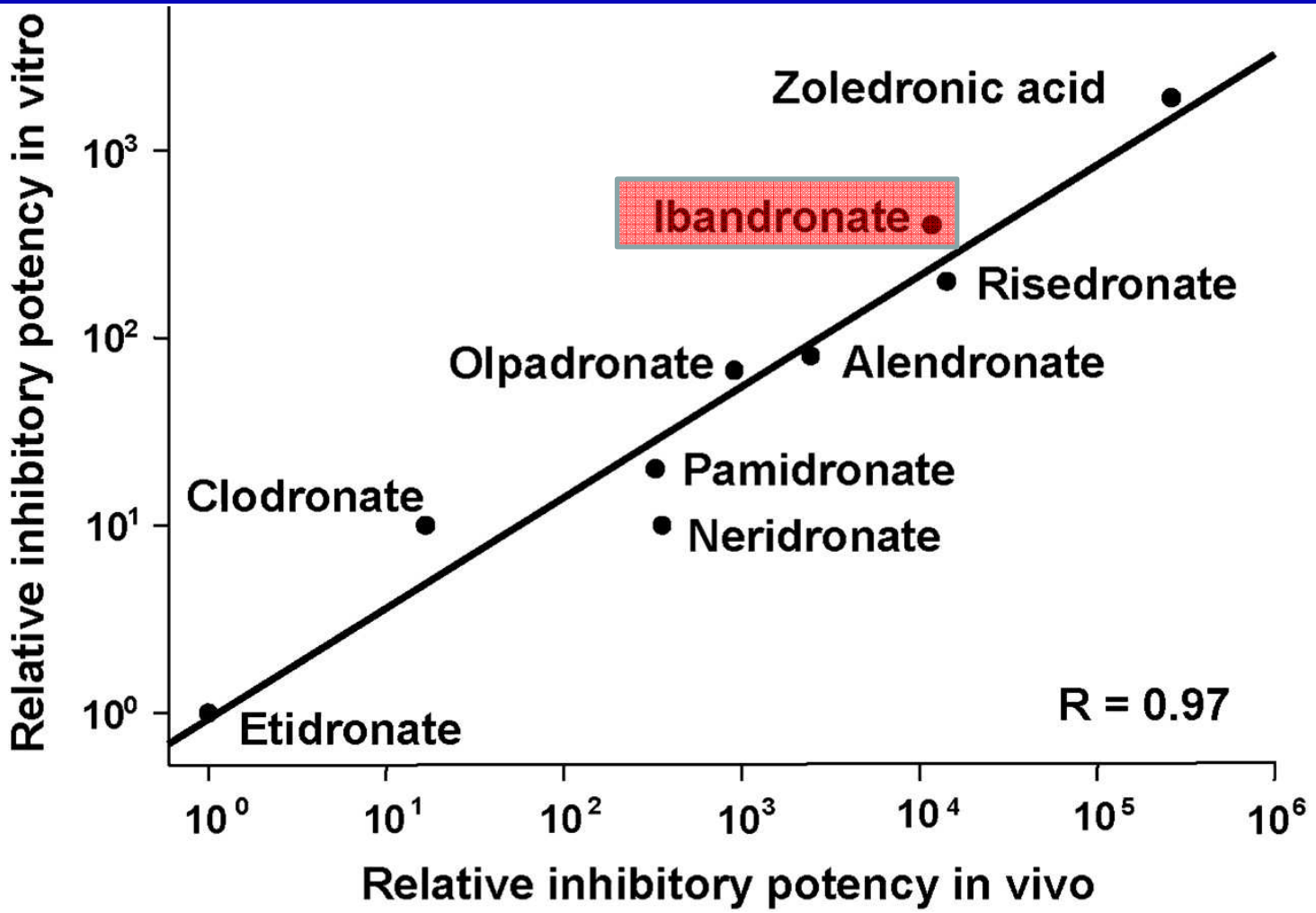
1st and 2nd generation of BP

Summary:

- Incorporated into cytotoxic ATP analogs (etidronate)
  - Affect cellular activity

- Interfere with the mevalonate pathway (nitrogen-containing BPs)
  - Cause apoptosis

Inhibitory potency



Aapro M et al. Ann Oncol 2007;annonc.mdm442

Annals of Oncology

Bisphosphonates - history

- 1865 - used for industrial purposes such as preventing precipitation calcium-carbonates in the textile and oil industry and in agriculture.

- 20th century
  - evidence of inhibition of bone resorption
  - therapy hypercalcemia, Paget's disease and osteoporosis
  - reducing the morbidity associated with bone metastases of breast cancer, prostate cancer and multiple myeloma.

Bisphosphonates - indications

- Treatment of osteoclastmediated bone loss due to osteoporosis
- Paget disease of bone
- malignancies metastatic to bone, multiple myeloma, and hypercalcemia of malignancy
- commonly prescribed for prevention and treatment of a variety of other skeletal conditions, such as low bone density and osteogenesis imperfecta.

Treatment goals in oncology

prevention SRE
(pathological fractures, spinal cord compression with neurological symptoms)
need for bone surgery
need for palliative radiotherapy of bone)

Prevention of malignant hypercalcemia

QoL improvement, pain control

The incidence of skeletal metastases in various types of cancers

– Myeloma	70–95%
– Prostatic Ca	65–75%
– Breast Ca	65–75%
– NSCLC	30–40%

Complications:

– Bone pain	50–90%
– Patholgical fractures	10–40%
– Hypercalcemia	10–20%

Coleman RE. Cancer Treat Rev 2001;27:165–76
Diel I. Semin Oncol 2001;28:78–80

PK of BF

- 50-70% of intravenously administered bisphosphonates bind primarily to the bone

  are excreted in the urine in unchanged form
  oral form - 99% is excreted in the faeces

  a big part of bisphosphonate that binds to bone, is within a few days again released into the circulation and excreted from the body via the kidneys

Adverse effects

- Intravenous bisphosphonates can give fever and flu-like symptoms after the first infusion, which is thought to occur because of their potential to activate human T cells

- Nephrotoxicity (rare)

Adverse effects

- Bisphosphonates, when administered intravenously for the treatment of cancer, have been associated with osteonecrosis of the jaw (ONJ), with the mandible twice as frequently affected as the maxilla and most cases occurring following high-dose intravenous administration used for some cancer patients.

Osteonecrosis of the jaw