Metabolisme calsium & Iodium

Dr.dr. Joko Wahyu Wibowo, MKes

Physiological Importance of Calcium

- Ca salts in bone provide structural integrity of the skeleton.
- Ca is the most abundant mineral in the body.
- The amount of Ca is balance among intake, storage, and excretion.
- This balance is controlled by transfer of Ca among 3 organs: intestine, bone, kidneys.
- Ca ions in extracellular and cellular fluids is essential to normal function of a host of biochemical processes
  - Neuoromuscular excitability and signal transduction
  - Blood coagulation
  - Hormonal secretion
  - Enzymatic regulation
  - Neuron excitation

Calcium metabolism

- 99% of total body calcium in the bone .
- 1% in ICF ,ECF ,& cell membranes .
- Calcium weight is 400mg/kg in infant & 950mg/kg in adult .
- The 1% can be divided in 3 components :

1) 50% ionized . 2) 40% bound to protein .

3)10% complex w/anions{citrate,phosphate,..

Intake of Calcium

- About 1000 mg of Ca is ingested per day.
- About 200 mg of this is absorbed into the body.
- Absorption occurs in the small intestine, and requires vitamin D (stay tuned....)

Storage of Calcium

- The primary site of storage is our bones (about 1000 grams).
- Some calcium is stored within cells (endoplasmic reticulum and mitochondria).
- Bone is produced by osteoblast cells which produce collagen, which is then mineralized by calcium and phosphate (hydroxyapatite).
- Bone is remineralized (broken down) by osteoclasts, which secrete acid, causing the release of calcium and phosphate into the bloodstream.
- There is constant exchange of calcium between bone and blood.

Excretion of Calcium

- The major site of Ca excretion in the body is the kidneys.
- The rate of Ca loss and reabsorption at the kidney can be regulated.
- Regulation of absorption, storage, and excretion of Ca results in maintenance of calcium homeostasis.

Regulation of Intracellular [Calcium]

- Control of cellular Ca homeostasis is as carefully maintained as in extracellular fluids
- $[Ca^{2+}]_{cyt}$ is approximately $1/1000^{th}$ of extracellular concentration
- Stored in mitochondria and ER
- "pump-leak" transport systems control $[Ca^{2+}]_{cyt}$
  - Calcium leaks into cytosolic compartment and is actively pumped into storage sites in organelles to shift it away from cytosolic pools.

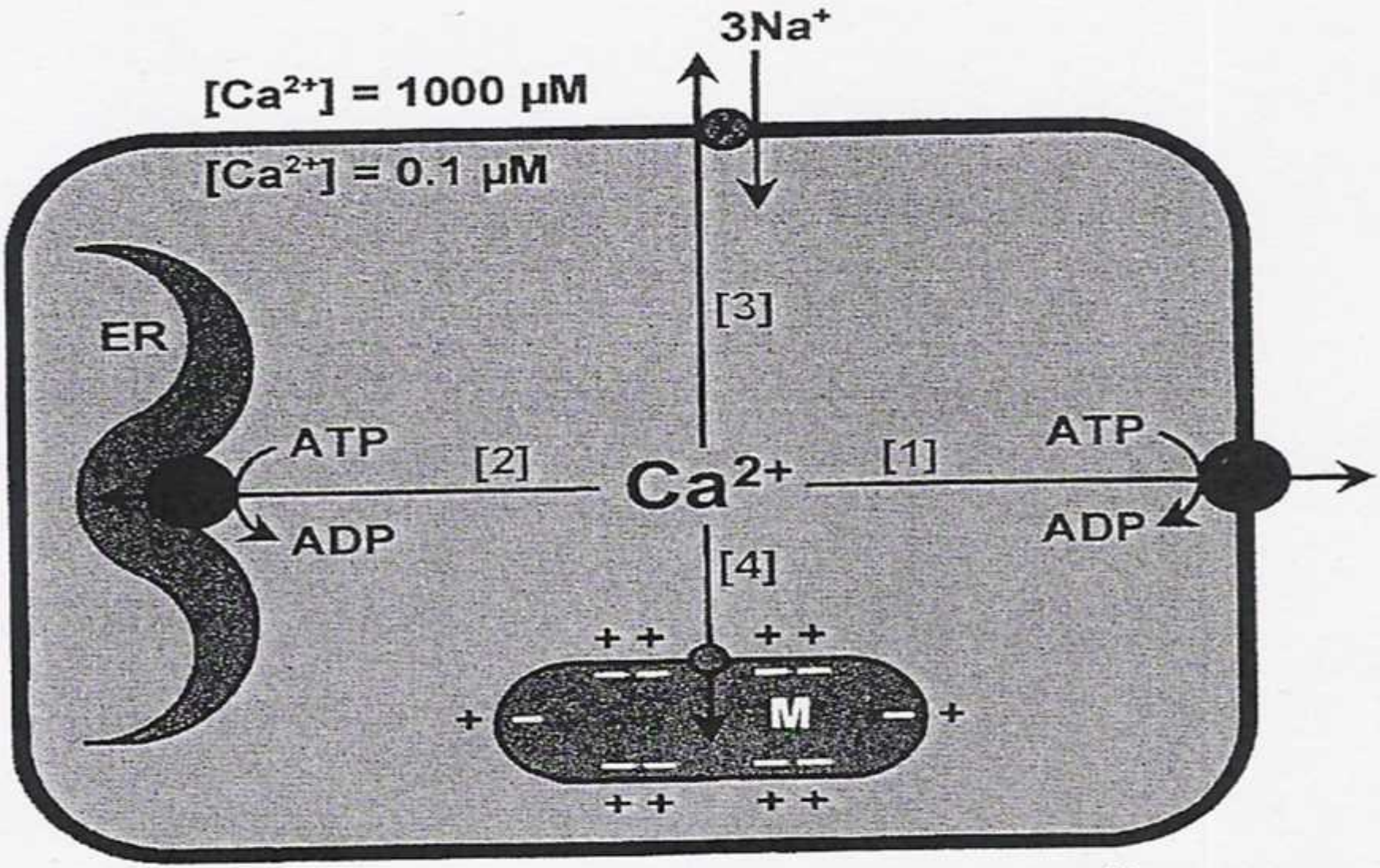


Figure 3-14. Four mechanisms for the elimination of Ca^{2+} from the cytoplasm: Ca^{2+}-ATPase-mediated pumping into (1) the extracellular space as well as (2) the endoplasmic reticulum (ER) and ion-gradient–driven transport into (3) the extracellular space (by the Ca^{2+}/Na^{+} exchanger) as well as (4) the mitochondria (M; by the Ca^{2+} uniporter).

Extracellular Calcium

- When extracellular calcium falls below normal, the nervous system becomes progressively more excitable because of increase permeability of neuronal membranes to sodium.
- Hyperexcitability causes tetanic contractions
  - Hypercalcemic tetany $[Ca^{2+}]_{cyt}$

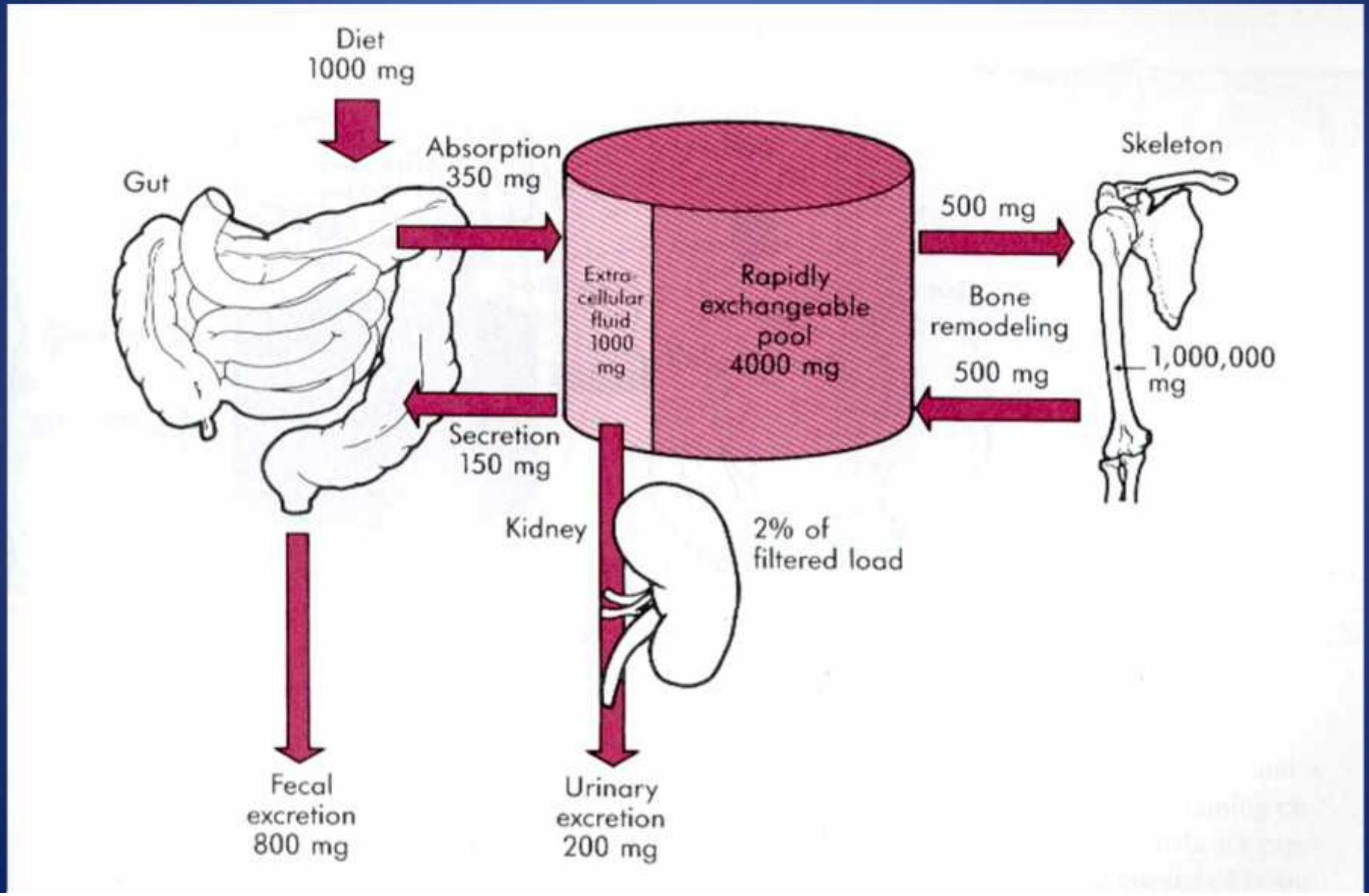
Extracellular Calcium

- Three definable fractions of calcium in serum:
  - Ionized calcium 50%
  - Protein-bound calcium 40%
    - 90% bound to albumin
    - Remainder bound to globulins
  - Calcium complexed to serum constituents 10%
    - Citrate and phosphate

Extracellular Calcium

- Binding of calcium to albumin is pH dependent
- Acute alkalosis increases calcium binding to protein and decreases ionized calcium
- Patients who develop acute respiratory alkalosis have increased neural excitability and are prone to seizures due to low ionized calcium in the extracellular fluid which results in increased permeability to sodium ions

Calcium Turnover



Calcium in Blood and Bone

- Ca^{2+} normally ranges from 8.5-10 mg/dL in the plasma.
- The active free ionized Ca^{2+} is only about 48% 46% is bound to protein in a non-diffusible state while 6% is complexed to salt.
- Only free, ionized Ca^{2+} is biologically active.

Hypocalcemia

- Causes of hypocalcemia
  - Specific causes in neonates

I. Early neonatal hypocalcemia:(within 48-72 hour of birth)

Causes: 1- prematurity: poor intake, decrease response to Vit. D, increase calcitonin, decrease albumin.

2- birth asphyxia: delayed introduction to feed, increase calcitonin, increased endogenous PO4 load, alkali therapy.

3- infant of diabetic mother: functional parahypothyroidism induced by Mg defficiency has predominant role

Specific causes in neonates (cont.)

4- IUGR: interruption Ca delivery across placenta, prematurity, asphyxia.

- Serum Ca correlate directly to gestational age.

Specific causes in neonates (cont.)

II. Late neonatal hypocalcemia: happen from 5 days of birth, may appear till 6 weeks of age.

- Causes:

1. Exogenous PO4 load, most common due to high PO4 content in formula, or cows milk and decreased in GFR contribute also.
2. Mg deficiency.
3. Transient hypoparathyroidism
4. Hypoparathyroidism due to other causes: (idiopathic, congenital, maternal hyperparathyroidism, hypomagnesemia)

- Hypoparathyroidism:

1. DiGeorge syndrome: aplasia or hypoplasia of parathyroid gland.

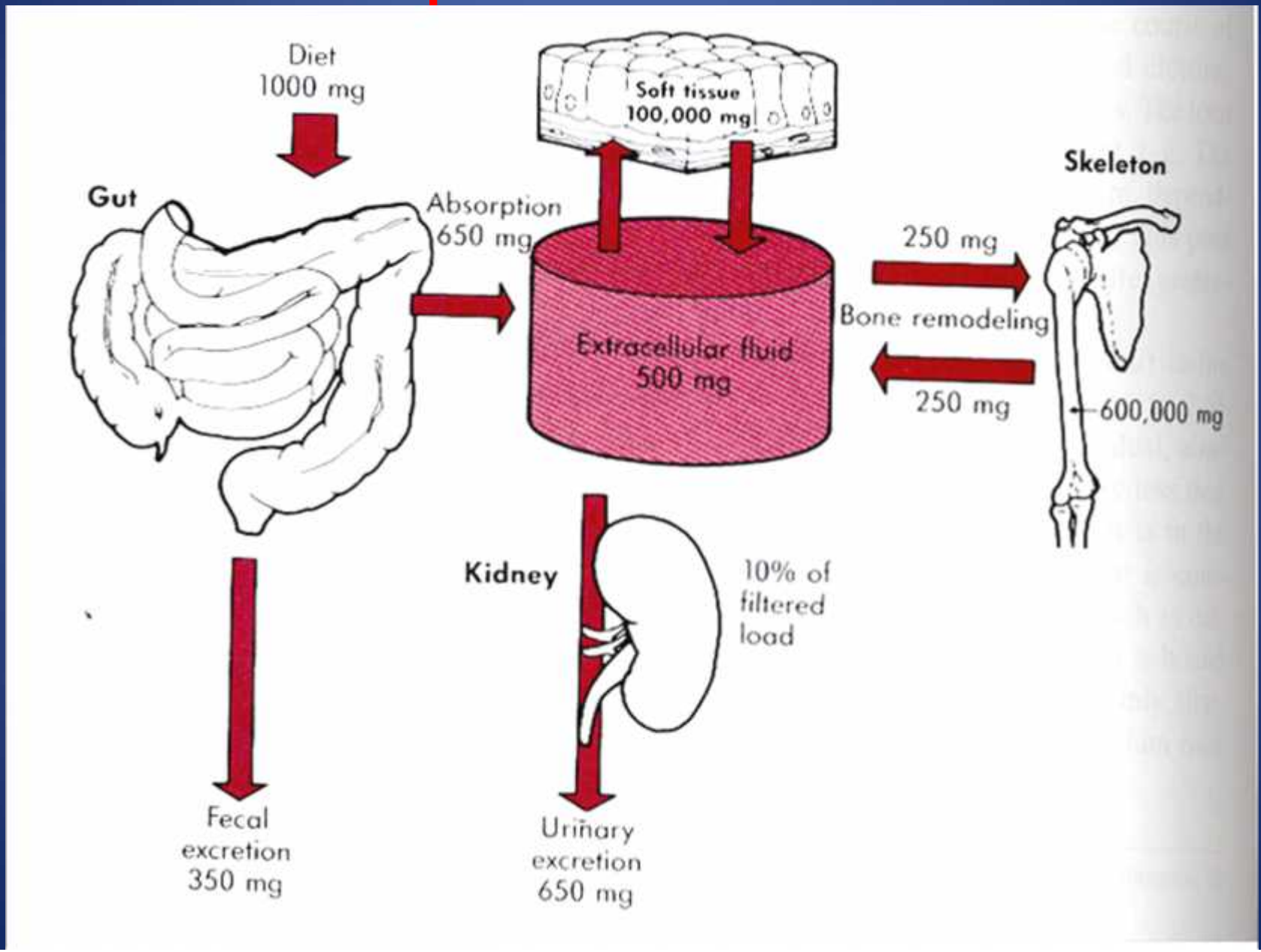
   associated with different anomalies including cardiac and facial anomaly mainly and also VATER and CHARGE associations.
2. X-linked hypoparathyroidism (absent of the gland that affect boys and appeared with the first 6 months of age.
3. AR hypoparathyroidism with dymorphic features: mutation of parathyroid hormone gene.
4. HDR syndrome: AD consist from (nerve deafness, renal dysplasia, and hypoparathyroidism)

5. Autoimmune polyglandular syndrome type I: AR, due to mutation in autoimmune regulator gene

Consist from (hypoparathyroidism, addisson disease, mucocutaneous candidiasis).

6. Calcium sensor receptor gene mutation.

Phosphate Turnover



Phosphorous in Blood and Bone

- PO_4 normal plasma concentration is 3.0-4.5 mg/dL. 87% is diffusible, with 35% complexed to different ions and 52% ionized.
- 13% is in a non-diffusible protein bound state. 85-90% is found in bone.
- The rest is in ATP, cAMP, and proteins

Control of Bone Formation and Resorption

- Bone resorption of Ca^{2+} by two mechanims: osteocytic osteolysis is a rapid and transient effect and osteoclasitc resorption which is slow and sustained.
- Both are stimulated by PTH. $CaPO_4$ precipitates out of solution id its solubility is exceeded. The solubility is defined by the equilibrium equation: Ksp = $[Ca^{2+}]_3[PO_4^{3-}]_2$.
- In the absence of hormonal regulation plasma Ca^{2+} is maintained at 6-7 mg/dL by this equilibrium.

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.

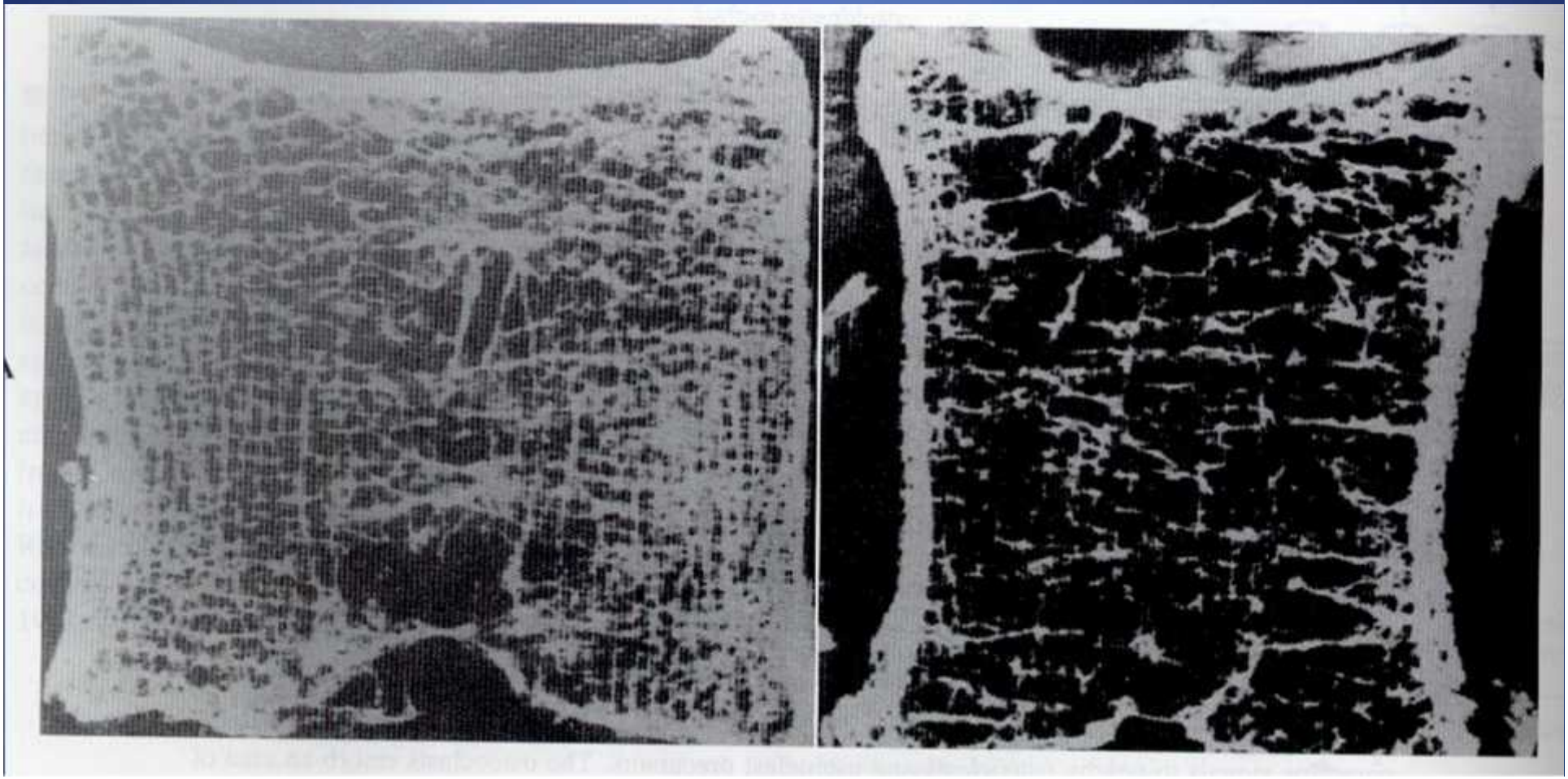


Table 48-1 Major effects of various hormones on bone

Bone formation	*Bone resorption*
Stimulated by	**Stimulated by**
Growth hormone (constant)	Parathyroid hormone (constant)
Insulin-like growth factors	Vitamin D
Insulin	Cortisol
Estrogen	Thyroid hormone
Androgen	Prostaglandins
Vitamin D (mineralization)	Interleukin-1
Transforming growth factor-β	Interleukin-6
Skeletal growth factor	Tumor necrosis factor α
Bone-derived growth factor	Tumor necrosis factor β
Platelet-derived growth factor	
Calcitonin	
Parathyroid hormone (intermittent)	
Inhibited by	**Inhibited by**
Cortisol	Estrogen
	Androgen
	Calcitonin
	Transforming growth factor-β
	γ-Interferon
	Nitric oxide

Hormonal Control of Bones

Hormonal Control of Ca^{2+}

- Three principal hormones regulate Ca^{2+} and three organs that function in Ca^{2+} homeostasis.
- **Parathyroid hormone (PTH)**, **1,25-dihydroxy Vitamin D3 (Vitamin D3)**, and **Calcitonin**, regulate Ca^{2+} resorption, reabsorption, absorption and excretion from the bone, kidney and intestine. In addition, many other hormones effect bone formation and resorption.

Table 48-3 Target genes of vitamin D

Gene	*Transcription*
Vitamin D receptor	Increased
Calcium-binding proteins	Increased
(calbindins)	Increased
Calcium pump	Increased
Osteocalcin	Increased
Alkaline phosphatase	Increased
24-Hydroxylase	Increased
Parathyroid hormone	Decreased
1-Hydroxylase	Decreased
Collagen	Decreased
Interleukin-2	Decreased
γ-Interferon	Decreased

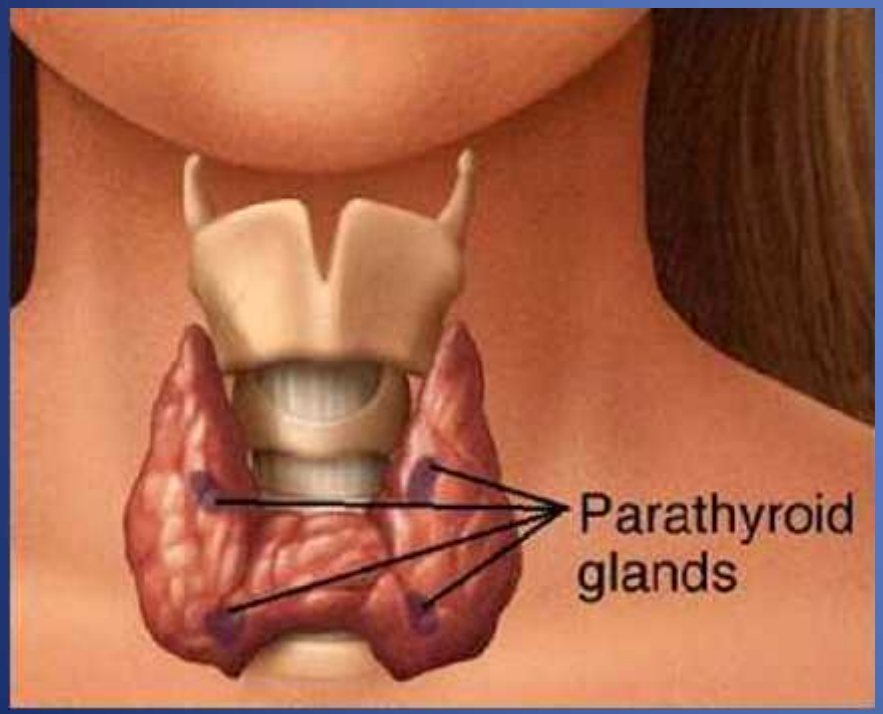
Vitamin D promotes intestinal calcium absorption

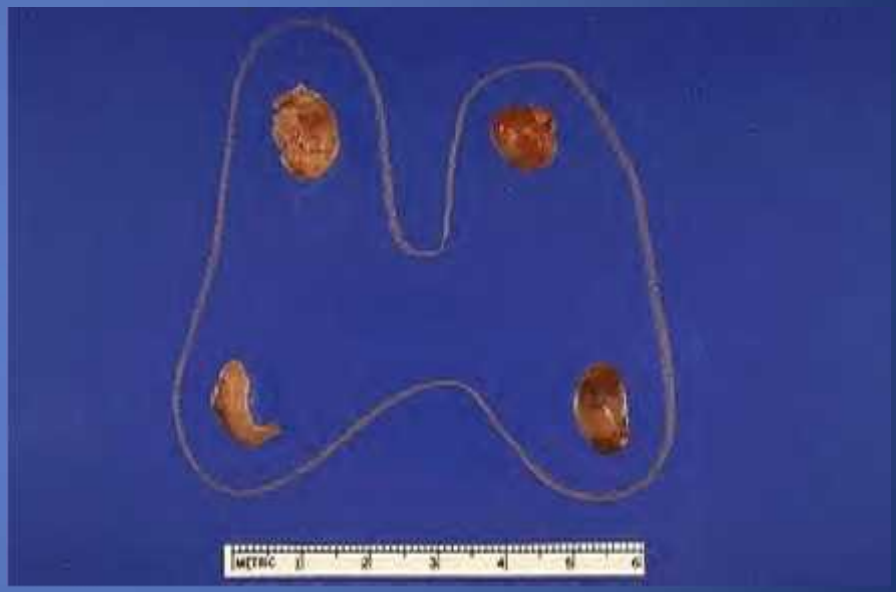
- Vitamin D acts via steroid hormone like receptor to increase transcriptional and translational activity
- One gene product is calcium-binding protein (CaBP)
- CaBP facilitates calcium uptake by intestinal cells

Parathyroid Hormone

- PTH is synthesized and secreted by the parathyroid gland which lie posterior to the thyroid glands.
- The blood supply to the parathyroid glands is from the thyroid arteries.
- The Chief Cells in the parathyroid gland are the principal site of PTH synthesis.
- It is THE MAJOR of Ca homeostasis in humans.

Parathyroid Glands





Regulation of PTH

- The dominant regulator of PTH is plasma Ca^{2+}.
- Secretion of PTH is inversely related to [Ca^{2+}].
- Maximum secretion of PTH occurs at plasma Ca^{2+} below 3.5 mg/dL.
- At Ca^{2+} above 5.5 mg/dL, PTH secretion is maximally inhibited.

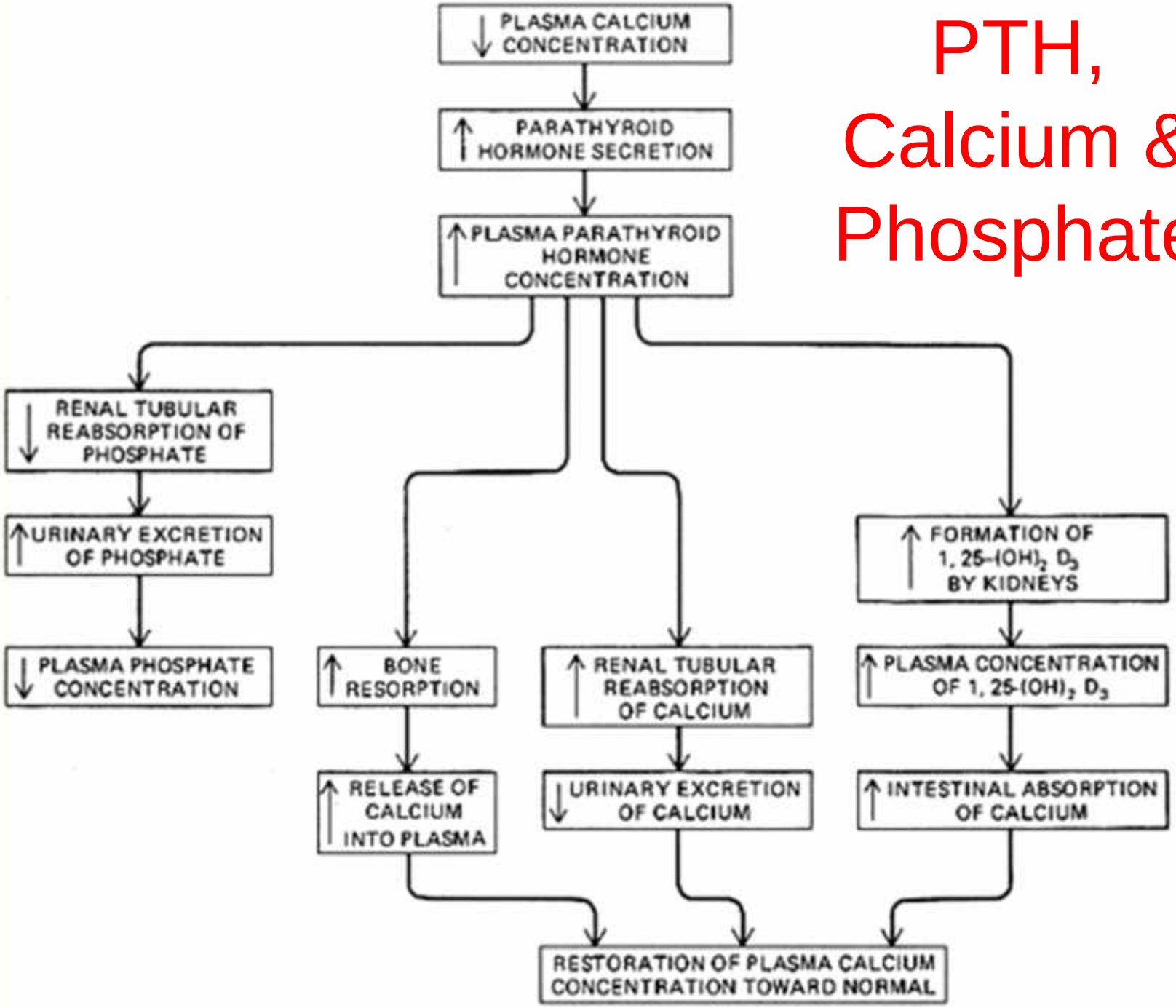
Regulation of PTH

- When Ca^{2+} falls, cAMP rises and PTH is secreted.
- 1,25-$(OH)_2$-D inhibits PTH gene expression, providing another level of feedback control of PTH.
- Despite close connection between Ca^{2+} and PO_4, no direct control of PTH is exerted by phosphate levels.

PTH action

- The overall action of PTH is to increase plasma Ca^{2+} levels and decrease plasma phosphate levels.
- PTH acts directly on the bones to stimulate Ca^{2+} resorption and kidney to stimulate Ca^{2+} reabsorption in the distal tubule of the kidney and to inhibit reabosorptioin of phosphate (thereby stimulating its excretion).
- PTH also acts indirectly on intestine by stimulating 1,25-$(OH)_2$-D synthesis.

PTH, Calcium & Phosphate



Calcitonin

- Calcitonin acts to decrease plasma Ca^{2+} levels.
- While PTH and vitamin D act to increase plasma Ca^{2+}-- only calcitonin causes a decrease in plasma Ca^{2+}.
- Calcitonin is synthesized and secreted by the parafollicular cells of the thyroid gland.
- They are distinct from thyroid follicular cells by their large size, pale cytoplasm, and small secretory granules.

Calcitonin

- The target cell for calcitonin is the osteoclast.
- Calcitonin acts via increased cAMP concentrations to inhibit osteoclast motility and cell shape and inactivates them.
- The major effect of calcitonin administration is a rapid fall in Ca^{2+} caused by inhibition of bone resorption.

Calcitonin

- Role of calcitonin in normal Ca^{2+} control is not understood—may be more important in control of bone remodeling.
- Used clinically in treatment of hypercalcelmia and in certain bone diseases in which sustained reduction of osteoclastic resorption is therapeutically advantageous.
- Chronic excess of calcitonin does not produce hypocalcemia and removal of parafollicular cells does not cause hypercalcemia. PTH and Vitamin D3 regulation dominate.
- May be more important in regulating bone remodeling than in Ca^{2+} homeostasis.

Influences of Growth Hormone

- Normal GH levels are required for skeletal growth.
- GH increases intestinal calcium absorption and renal phosphate resorption.
- Insufficient GH prevents normal bone production.
- Excessive GH results in bone abnormalities (acceleration of bone formation AND resorption).

Effects of Glucocorticoids

- Normal levels of glucocorticoids (cortisol) are necessary for skeletal growth.
- Excess glucocorticoid levels decrease renal calcium reabsorption, interfere with intestinal calcium absorption, and stimulate PTH secretion.
- High glucocorticoid levels also interfere with growth hormone production and action, and gonadal steroid production.
- Net Result: rapid osteoporosis (bone loss).

Influence of Thyroid Hormones

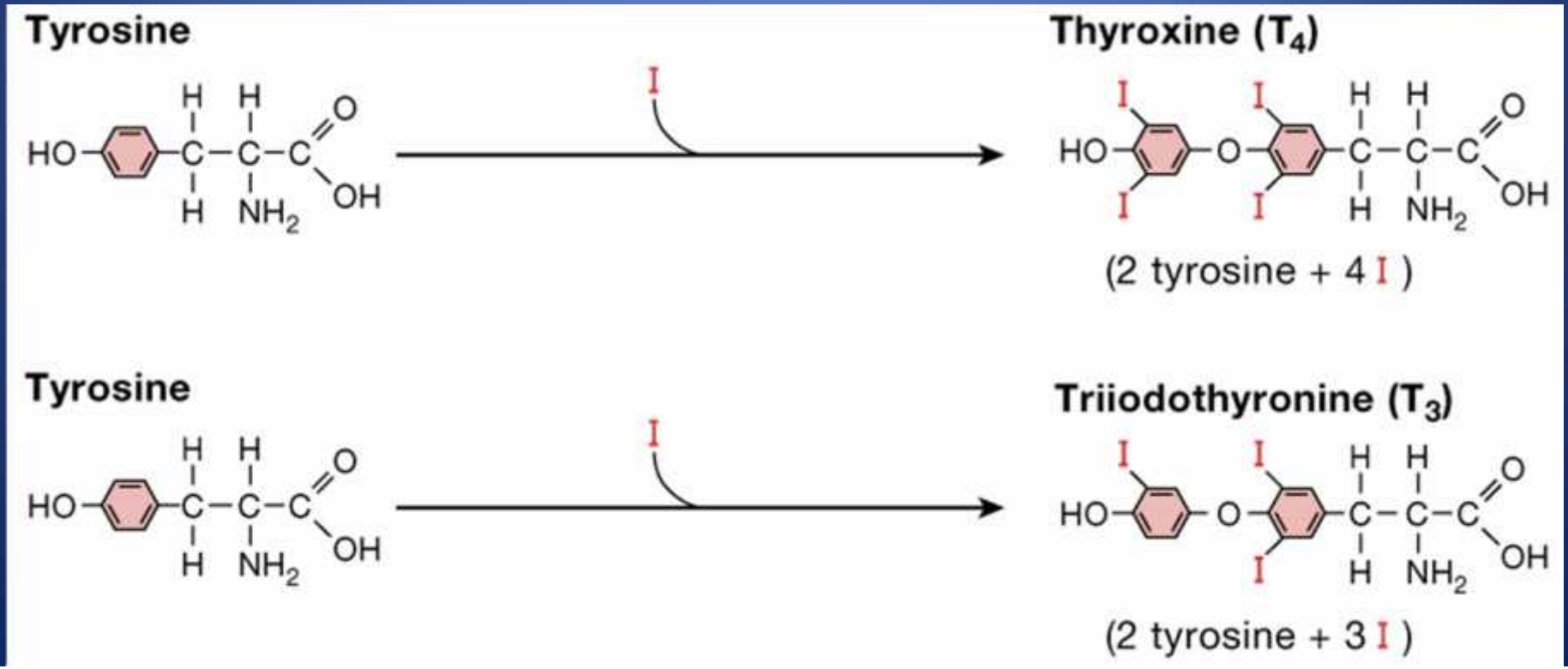
- Thyroid hormones are important in skeletal growth during infancy and childhood (direct effects on osteoblasts).
- Hypothyroidism leads to decreased bone growth.
- Hyperthyroidism can lead to increased bone loss, suppression of PTH, decreased vitamin D metabolism, decreased calcium absorption. Leads to osteoporosis.

Effects of Diet

- Increasing dietary intake of Ca may prevent osteoporosis in postmenopausal women.
- Excessive Na intake in diet can impair renal Ca reabsorption, resulting in lower blood Ca and increased PTH release. Normally, PTH results in increased absorption of Ca from the GI tract (via vitamin D). But in aging women, vitamin D production decreases, so Ca isn't absorbed, and PTH instead causes increased bone loss.
- High protein diet may cause loss of Ca from bone, due to acidic environment resulting from protein metabolism and decreased reabsorption at the kidney.

Thyroid Hormones

- There are two biologically active thyroid hormones:
  - tetraiodothyronine (T4; usually called thyroxine)
  - triiodothyronine (T3)
- Derived from modification of tyrosine.

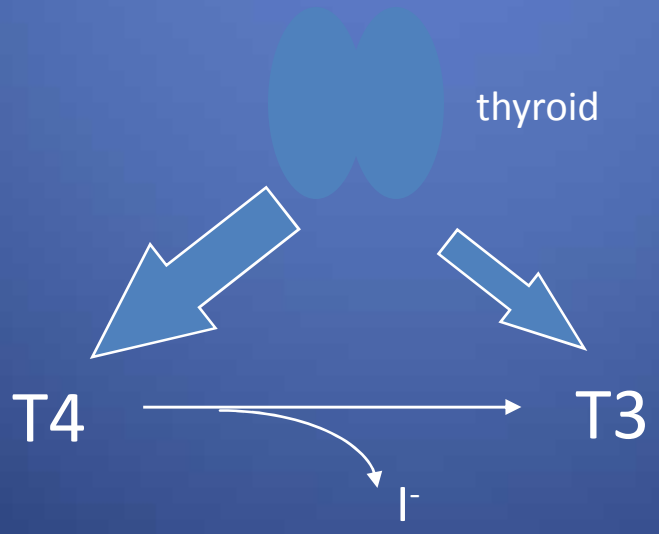


Why is Iodine Important in Thyroid Hormone Production?

- Thyroid hormones are unique biological molecules in that they incorporate iodine in their structure.
- Thus, adequate iodine intake (diet, water) is required for normal thyroid hormone production.
- Major sources of iodine:
  - iodized salt
  - iodated bread
  - dairy products
  - shellfish
- Minimum requirement: 75 micrograms/day
- US intake: 200 - 500 micrograms/day

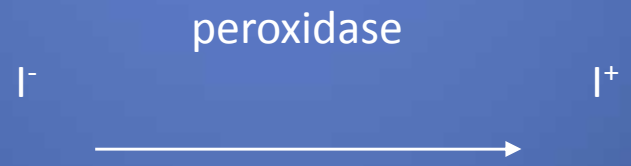
Differences between T4 and T3

- The thyroid secretes about 80 microg of T4, but only 5 microg of T3 per day.
- However, T3 has a much greater biological activity (about 10 X) than T4.
- An additional 25 microg/day of T3 is produced by peripheral monodeiodination of T4 (stay tuned….).



Iodine Metabolism

- Dietary iodine is absorbed in the GI tract, then taken up by the thyroid gland (or removed from the body by the kidneys).
- The transport of iodide into follicular cells is dependent upon a Na^+/I^- cotransport system.
- Iodide taken up by the thyroid gland is oxidized by peroxide in the lumen of the follicle:



- Oxidized iodine can then be used in production of thyroid hormones.

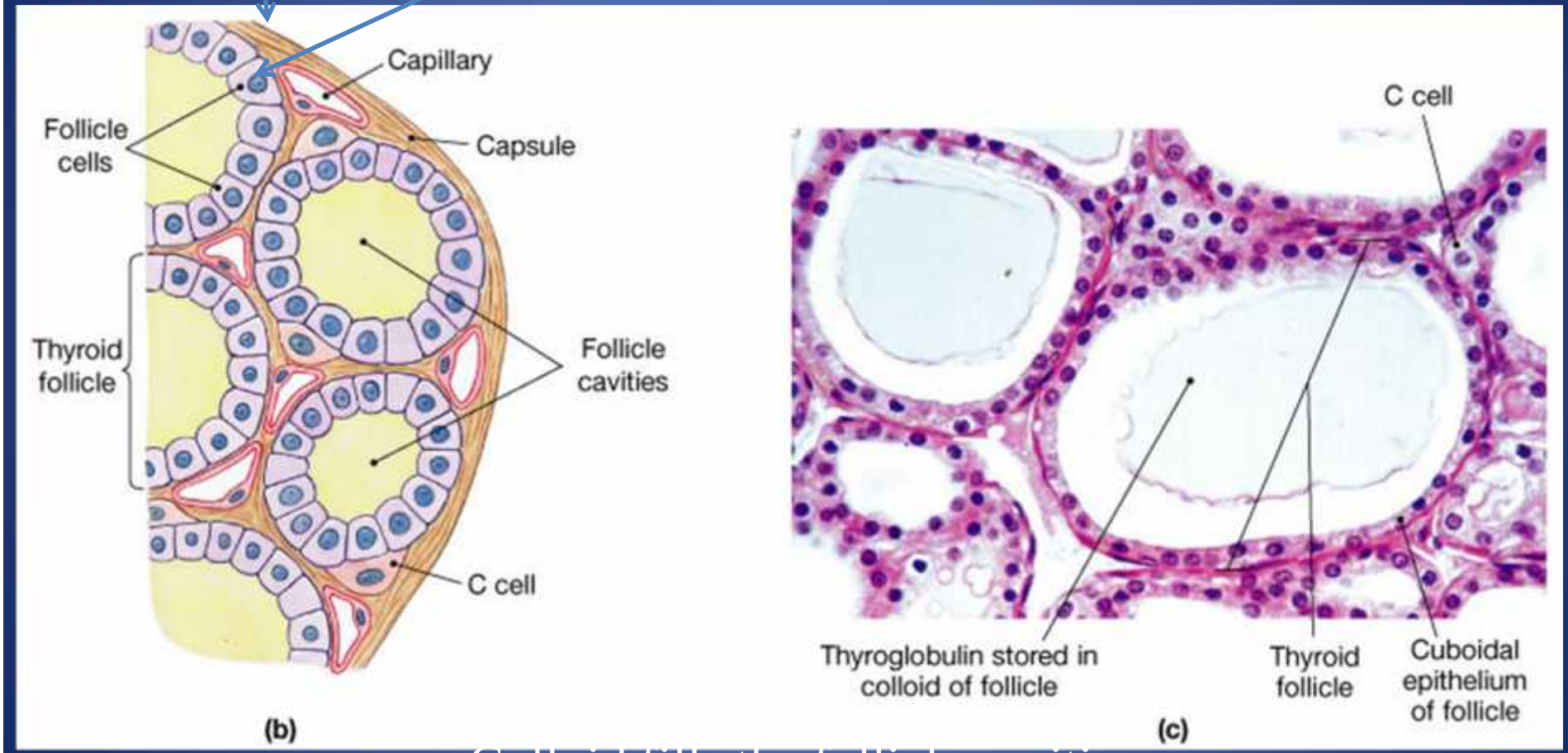
The Next Step: Production of Thyroglobulin

- Pituitary produces TSH, which binds to follicle cell receptors.
- The follicle cells of the thyroid produce thyroglobulin.
- Thyroglobulin is a very large glycoprotein.
- Thyroglobulin is released into the colloid space, where it's tyrosine residues are iodinated by I^+.
- This results in tyrosine residues which have one or two iodines attached (monoiodotyrosine or diiodotyrosine).

The Thyroid Gland – Histology

Gland is composed of hollow spheres, called colloid follicles.

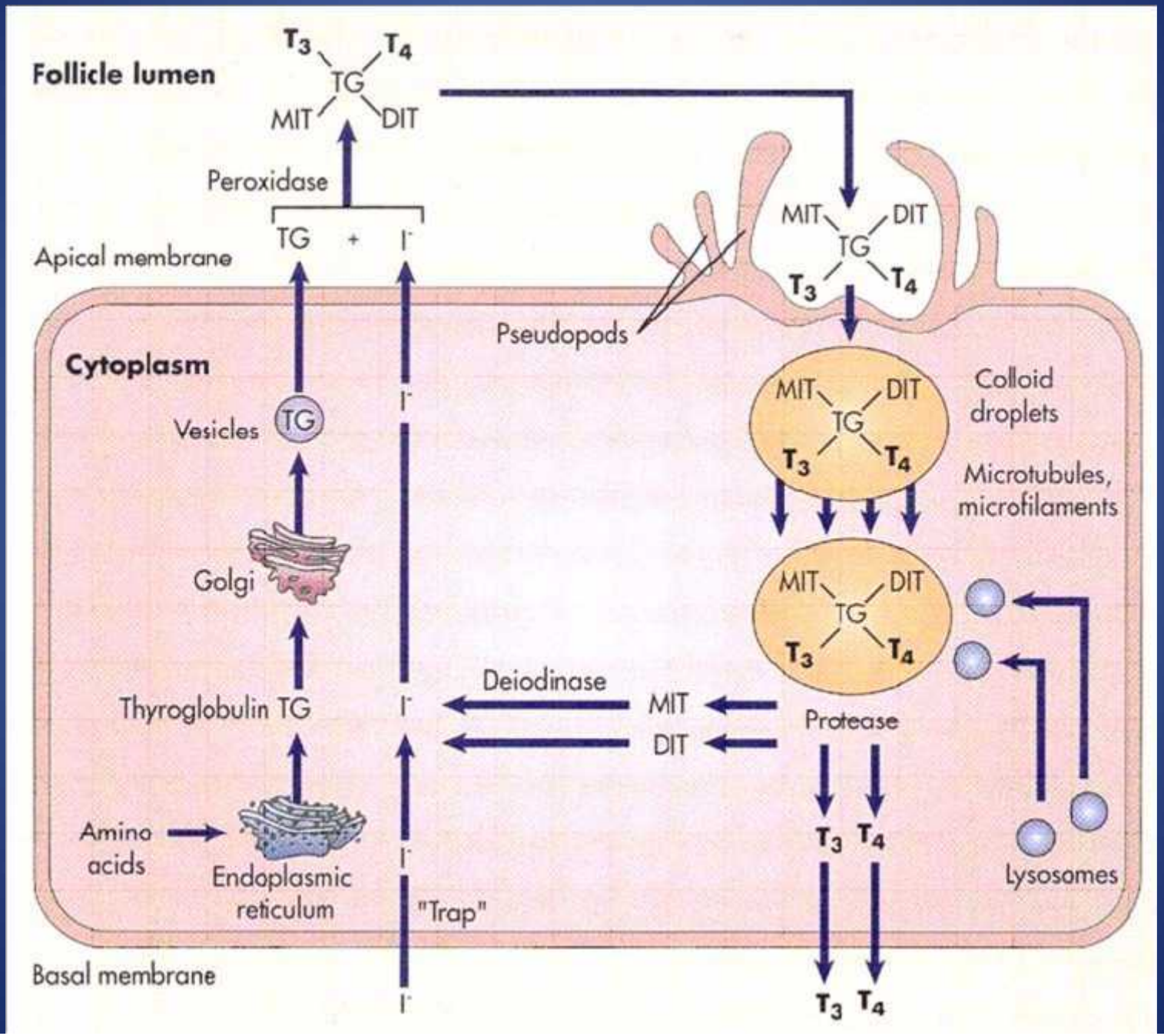
Squamous epithelial cells, cuboidal cells (follicle cells)



Colloid fills the follicle cavities

Follicle cells produce thyroglobulin ---- I → TH

Thyroid Hormone Synthesis



Transport of Thyroid Hormones

- Thyroid hormones are not very soluble in water (but are lipid-soluble).
- Thus, they are found in the circulation associated with binding proteins:

  - Thyroid Hormone-Binding Globulin (~70% of hormone)

  - Pre-albumin (transthyretin), (~15%)

  - Albumin (~15%)
- Less than 1% of thyroid hormone is found free in the circulation.
- Only free and albumin-bound thyroid hormone is biologically available to tissues.

Conversion of T4 to T3

- T3 has much greater biological activity than T4.
- A large amount of T4 (25%) is converted to T3 in peripheral tissues.
- This conversion takes place mainly in the liver and kidneys. The T3 formed is then released to the blood stream.
- In addition to T3, an equal amount of “reverse T3” may also be formed. This has no biological activity.

One Major Advantage of this System

- The thyroid gland is capable of storing many weeks worth of thyroid hormone (coupled to thyroglobulin).

- If no iodine is available for this period, thyroid hormone secretion will be maintained.

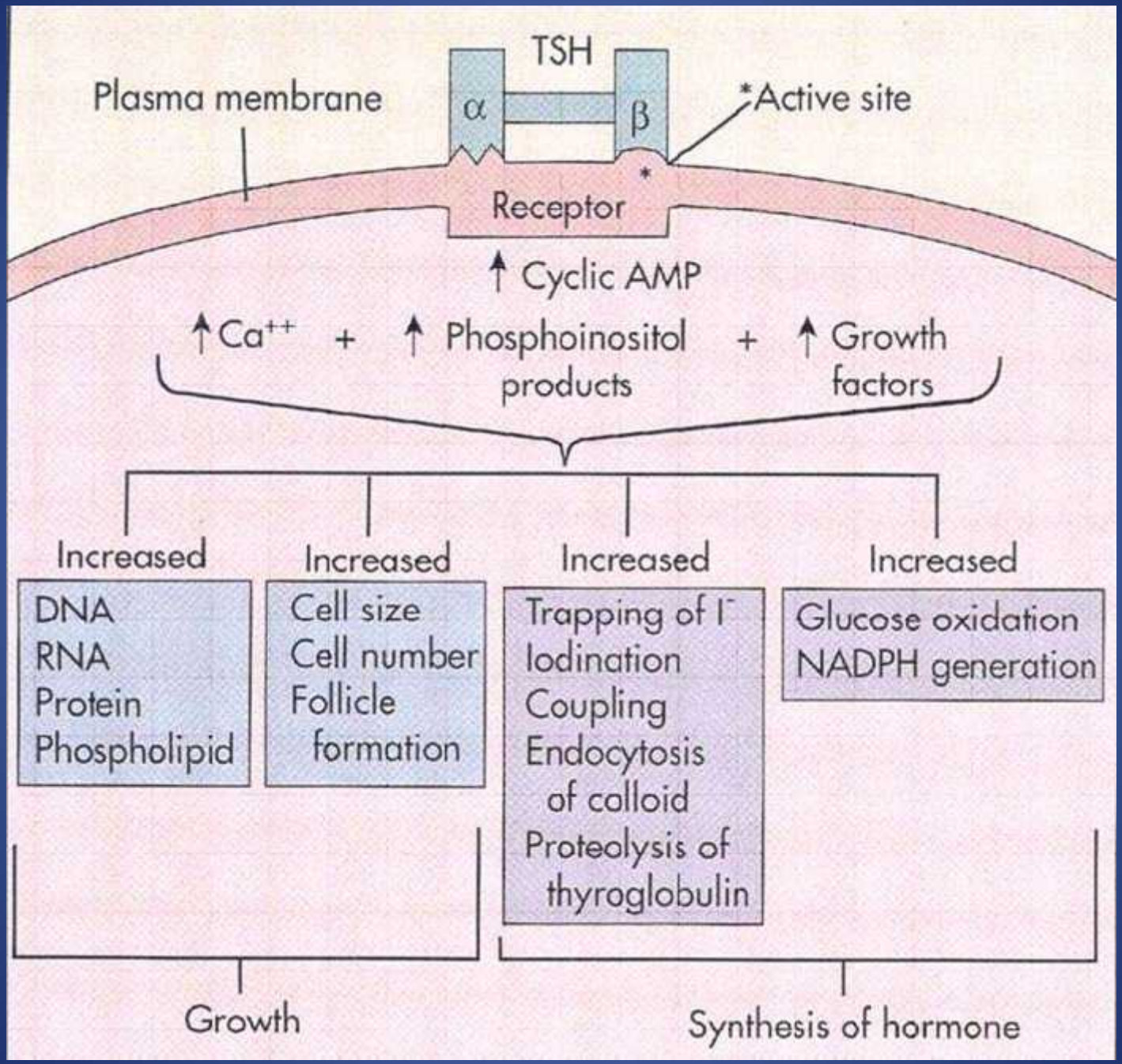
Autoregulation of Thyroid Hormone Production

- The rate of iodine uptake and incorporation into thyroglobulin is influenced by the amount of iodide available:

  - low iodide levels increase iodine transport into follicular cells

  - high iodide levels decrease iodine transport into follicular cells

Thus, there is negative feedback regulation of iodide transport by iodide.


TSH
Plasma membrane
α
β
*Active site
*
Receptor
↑ Cyclic AMP
↑ Ca++ + ↑ Phosphoinositol products + ↑ Growth factors
Increased
DNA
RNA
Protein
Phospholipid
Increased
Cell size
Cell number
Follicle formation
Increased
Trapping of I-
Iodination
Coupling
Endocytosis of colloid
Proteolysis of thyroglobulin
Increased
Glucose oxidation
NADPH generation
Growth
Synthesis of hormone

Other Factors Regulating Thyroid Hormone Levels

- Diet: a high carbohydrate diet increases T3 levels, resulting in increased metabolic rate (diet-induced thermogenesis).
- Low carbohydrate diets decrease T3 levels, resulting in decreased metabolic rate.
- Cold Stress: increases T3 levels in other animals, but not in humans.
- Other stresses: increased or decreased?
- Any condition that increases body energy requirements (*e.g.*, pregnancy, prolonged cold) stimulates hypothalamus → TRH → TSH (Pit)

Actions of Thyroid Hormone

- Required for GH and prolactin production and secretion
- Required for GH action
- Increases intestinal glucose reabsorption (glucose transporter)
- Increases mitochondrial oxidative phosphorylation (ATP production)
- Increases activity of adrenal medulla (sympathetic; glucose production)
- Induces enzyme synthesis
- Result: stimulation of growth of tissues and increased metabolic rate. Increased heat production (calorigenic effect)

Effects of Thyroid Hormone on Nutrient Sources

- Effects on protein synthesis and degradation:

  -increased protein synthesis at low thyroid hormone levels (low metabolic rate; growth)

  -increased protein degradation at high thyroid hormone levels (high metabolic rate; energy)

- Effects on carbohydrates:

  -low doses of thyroid hormone increase glycogen synthesis (low metabolic rate; storage of energy)

  - high doses increase glycogen breakdown (high metabolic rate; glucose production)

More on Receptor Coactivators and Corepressors

- When not bound to hormone, the thyroid hormone receptor binds to target DNA (TRE on 5' flanking region). It is associated with **corepressor proteins** that cause DNA to be tightly wound and inhibit transcription.
- Binding of hormone causes a conformational change, resulting in loss of corepressor binding and association with **coactivator** proteins, which loosen DNA structure and stimulate transcription.

Expression and Regulation of Thyroid Hormone Receptors

- Thyroid hormone receptors are found in many tissues of the body, but not in adult brain, spleen, testes, uterus, and thyroid gland itself.
- Thyroid hormone inhibits thyroid hormone receptor expression (TRE on THR genes).

One Major Target Gene of T3: The Na^+/K^+ ATPase Pump

- Pumps sodium and potassium across cell membranes to maintain resting membrane potential
- Activity of the Na^+/K^+ pump uses up energy, in the form of ATP
- About 1/3rd of all ATP in the body is used by the Na^+/K^+ ATPase
- T3 increases the synthesis of Na^+/K^+ pumps, markedly increasing ATP consumption.
- T3 also acts on mitochondria to increase ATP synthesis
- The resulting increased metabolic rate increases thermogenesis (heat production).

Effects Thyroid Hormones in Growth and Tissue Development

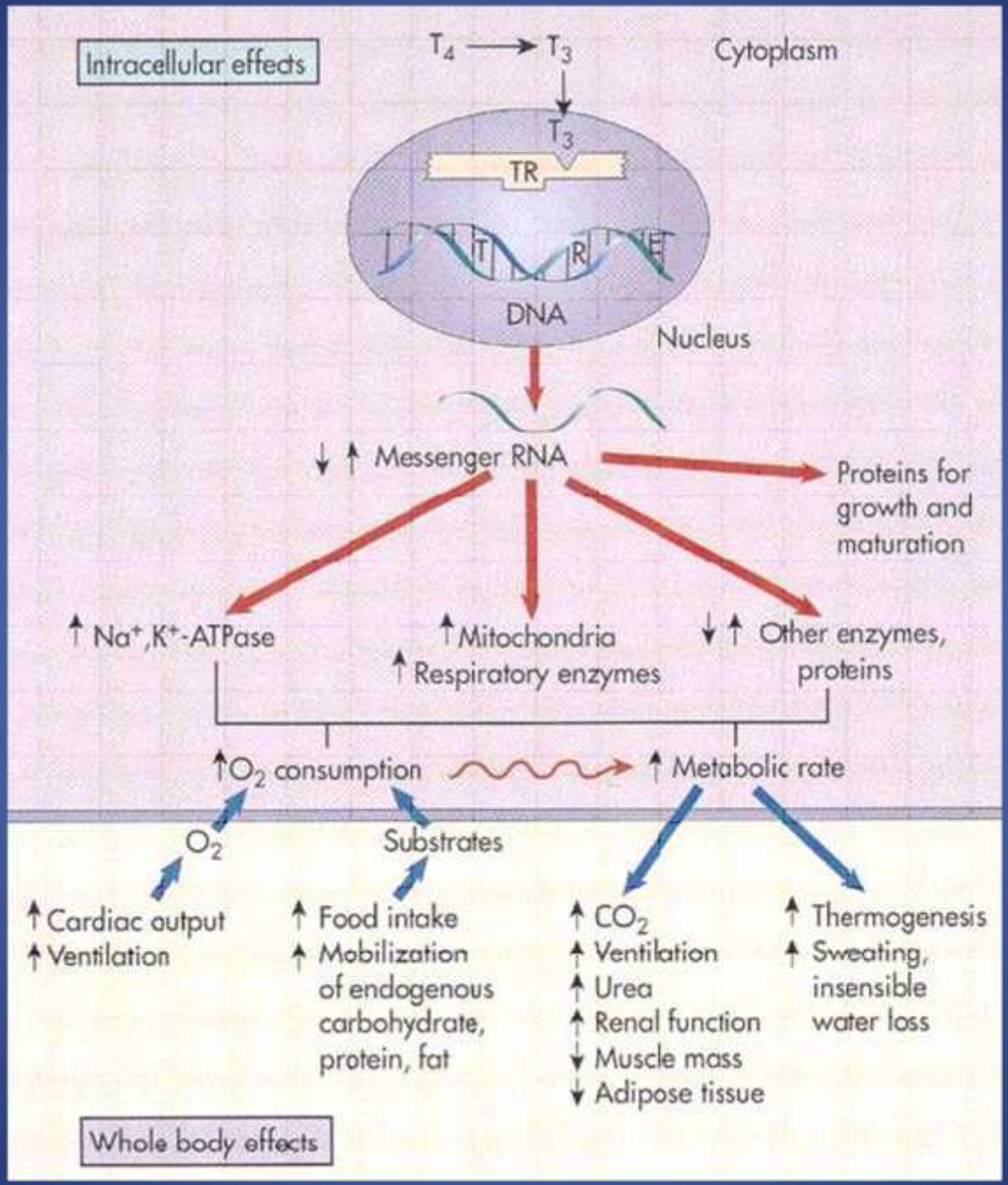
- Increase growth and maturation of bone
- Increase tooth development and eruption
- Increase growth and maturation of epidermis,hair follicles and nails
- Increase rate and force of skeletal muscle contraction
- Inhibits synthesis and increases degradation of mucopolysaccharides in subcutaneous tissue

Effects of Thyroid Hormones on the Nervous System

- Critical for normal CNS neuronal development
- Enhances wakefulness and alertness
- Enhances memory and learning capacity
- Required for normal emotional tone
- Increase speed and amplitude of peripheral nerve reflexes

Effects of Thyroid Hormones on the Reproductive System

- Required for normal follicular development and ovulation in the female
- Required for the normal maintenance of pregnancy
- Required for normal spermatogenesis in the male


Intracellular effects
$T_4 \rightarrow T_3$
Cytoplasm
T_3
TR
DNA
Nucleus
↓ ↑ Messenger RNA
Proteins for growth and maturation
↑ Na^+, K^+-ATPase
↑ Mitochondria
↑ Respiratory enzymes
↓ ↑ Other enzymes, proteins
↑ O_2 consumption
↑ Metabolic rate
O_2
Substrates
↑ Cardiac output
↑ Ventilation
↑ Food intake
↑ Mobilization of endogenous carbohydrate, protein, fat
↑ CO_2
↑ Ventilation
↑ Urea
↑ Renal function
↓ Muscle mass
↓ Adipose tissue
↑ Thermogenesis
↑ Sweating, insensible water loss
Whole body effects

Thyroid Hormone Deficiency: Hypothyroidism

- Early onset: delayed/incomplete physical and mental development
- Later onset (youth): Impaired physical growth
- Adult onset (myxedema) : gradual changes occur. Tiredness, lethargy, decreased metabolic rate, slowing of mental function and motor activity, cold intolerance, weight gain, goiter, hair loss, dry skin. Eventually may result in coma.
- Many causes (insufficient iodine, lack of thyroid gland, lack of hormone receptors, lack of TH binding globulin….)

How is Hypothyroidism Related to Goiter?

- During iodine deficiency, thyroid hormone production decreases.
- This results in increased TSH release (less negative feedback).
- TSH acts on thyroid, increasing blood flow, and stimulating follicular cells and increasing colloid production.

Iodine deficiency and the foetus

- Brain development fast between 3-5 months pregnancy and from third trimester till end of second year
- Maternal T4 essential for first 24 weeks
- Foetal T4 starts at 24 weeks
- 30% cord blood is of maternal origin

Iodine and the neonate

- Perinatal mortality
- Infant mortality
- Low birth weight
- Brain development needs T4
- Iodine deficiency mental retardation, retarded motor development.
- General IQ decrease of 15 Points

Iodine deficiency and adults

- Lack of energy
- apathy, slow brains
- goitre and mechanical complications
- Nodular thyroid
- hyperthyroidism
- Pregnancy and cretinism

TERIMA KASIH

WASSALAM.....