الجمهوريــة الجزائريــة الديمقراطيــة الشعبيــة
وزارة التعليـم العالـي والبحـث العلمـي
جامعة محمد بوضياف بالمسيلـــة
كليـــة العلـــوم
رقم:432/ك ع/2025

جامعة محمد بوضياف المسيلة
Université Mohamed Boudiaf M'sila

المسيـــلة في: 2025/09/30

شهادة موافقة علمية على مطبوعة بيداغوجية

للأستاذة بن الشيخ دليلة - أستاذ محاضر أ -

يشهد رئيس المجلس العلمي لكلية العلوم بجامعة محمد بوضياف بالمسيلة، أنه بعد الإطـــلاع علـى تقاريـــر الخبـــــرة الواردة من طرف الخبـــراء من صف الأستاذيـــة:

- السيدة: **بيسات صغيرة أستاذ محاضر أ بجامعة المسيلة.**
- السيد ة: **بوعزيز أمال أستاذ التعليم العالي بجامعة سطيف1**

والمعينيـن من طرف المجلس العلمي لكلية العلوم في الاجتماع المنعقد في دورته العادية يوم2025/06/11 لإجـراء الخبـرة للمطبوعـة البيداغوجيـة الخاصة بالأستاذ ة: **بن الشيخ دليلة** - أستاذ محاضر- أ- بقسم الميكروبيولوجيا والكيمياء الحيوية والمتعلقة بخبرة للمطبوعـة البيداغوجيـة للمـــادة المعنونة بـ: « **Biochemistry** » والمقررة في برنامج التكوين :لطلبة الطب L2 المفتوح بملحقة الطب كلية العلوم

تـــمت الموافقـــة عليه شكـــلا ومضمونـــا.

رئيس المجلس العلمي لكلية العلوم

بعزيز حكيم

People's Democratic Republic of Algeria

Ministry of Higher Education and Scientific Research

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Course Handout

Level:Medical 2nd year

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2024-2025

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Preface

This handout is primarily intended for students in the health sciences, trainees in medical or paramedical fields, and anyone seeking to deepen their understanding of the biochemical foundations of human physiology. Its main objective is to provide a clear, structured overview of key elements essential to homeostasis and the prevention of various diseases.

The document is organized around fundamental topics: **uric acid**, **renal function**, **hormones**, **vitamins**, and **trace elements**. Each chapter explores the physiological role, regulatory mechanisms, and potential imbalances associated with these essential components of the human body.

Uric acid, a final product of purine metabolism, can lead to conditions such as gout or kidney stones when elevated. Monitoring uric acid levels plays a critical role in diagnosing and managing metabolic disorders. **Renal function** is central to maintaining fluid and electrolyte balance and waste elimination. Tests such as the glomerular filtration rate (GFR) and serum creatinine are key to identifying early signs of kidney dysfunction. **Hormones** serve as chemical messengers regulating a wide range of functions, including growth, metabolism, mood, and reproduction. Hormonal imbalances can have significant consequences, making their assessment and regulation essential to maintaining health.

Vitamins, though required in small amounts, are crucial for biochemical processes such as energy production, tissue repair, and immune function. Both deficiency and excess can have harmful effects, underlining the need for balanced intake. **Trace elements** like iron, zinc, copper, and selenium are required in minute quantities but are vital for enzymatic reactions, immune defense, and cellular health. Their balance, like that of hormones and vitamins, is essential for proper physiological function.

This handout emphasizes the **core knowledge** required to understand the biological roles of these elements, their clinical relevance, and the laboratory tests used to evaluate them. It is written in a pedagogical style, with accessible explanations, physiological summaries, and links to practical medical applications.

We hope this resource will help you grasp these fundamental concepts and effectively apply them in your academic or professional journey.

General Introduction

Biochemistry serves as a foundational pillar in clinical medicine, offering crucial insights into the molecular mechanisms underlying health and disease. In clinical practice, it plays a central role in diagnosing, monitoring, and managing a wide spectrum of conditions. Major areas of clinical biochemistry include renal function, hormonal balance, and the assessment of trace elements and vitamins, each contributing essential information for maintaining physiological equilibrium and guiding treatment strategies.

Renal function is a core focus of clinical biochemistry, as the kidneys are vital for filtering blood, regulating electrolytes, and removing waste like uric acid. Evaluating kidney health involves biomarkers such as creatinine, urea, and the glomerular filtration rate (GFR), which help detect disorders like chronic kidney disease or acute kidney injury. Timely interpretation of these markers is critical for early intervention and preserving kidney function.

Endocrinology, another major domain, investigates hormone-related processes that regulate metabolism, growth, and reproduction. Biochemical tests measuring hormones such as insulin, cortisol, and thyroid hormones reveal imbalances that may lead to conditions like diabetes, thyroid dysfunction, or reproductive disorders. These assessments are essential for diagnosis, treatment planning, and monitoring therapeutic outcomes in endocrine diseases.

Trace elements and vitamins are micronutrients required in small amounts but are indispensable for enzymatic activity, immune function, and cellular health. Deficiencies or excesses—detected through biochemical assays—can lead to conditions like anemia, osteoporosis, or neurological issues. Monitoring and managing these nutrient levels ensure proper bodily function and support overall well-being, highlighting their critical role in preventive and therapeutic care.

I. Renal Function

Introduction

The kidneys are crucial organs that are essential to preserving the body's equilibrium and general health. Located in the lower back, The kidneys are in charge of controlling fluid and electrolyte balance, filtering blood, and eliminating waste, and ensuring the proper excretion of metabolic byproducts. Renal function refers to the ability of the kidneys to perform these critical tasks, which are fundamental to sustaining life and supporting a wide range of physiological processes.

The primary function of the kidneys involves filtering approximately 180 liters of blood each day to remove waste substances like urea, creatinine, and excess ions such as potassium and sodium. The kidney's functional units, the nephrons, are where this filtration process takes place. Through a series of filtration, reabsorption, and secretion processes, the kidneys regulate the composition of blood, maintain optimal fluid balance, and control blood pressure. The kidneys also contribute to the synthesis of hormones including renin, which lowers blood pressure, and erythropoietin, which promotes the formation of red blood cells.

The assessment of renal function is crucial in diagnosing and managing kidney-related conditions such as acute kidney injury (AKI), chronic kidney disease (CKD), and electrolyte imbalances. Clinically, renal function is often evaluated through blood tests and urine tests that measure key biomarkers, including blood urea nitrogen (BUN), serum creatinine, electrolyte levels (e.g., sodium, potassium), and glomerular filtration rate (GFR). These tests aid in assessing kidney function, identifying kidney damage early, and tracking the development of renal disease.

Impaired renal function can result in a number of issues, including as metabolic acidosis, fluid retention, electrolyte abnormalities, and the buildup of toxins in the blood. The kidneys can no longer efficiently filter waste when renal failure occurs, necessitating interventions such as dialysis or kidney transplantation.

I. Uric acid

I.1. Definition

Uric acid (UA), or 2-6-8 trihydroxypurine, is a chemical compound with the molecular formula $C_5H_4N_4O_3$. It consists of a pyrimidine nucleus and an imidazole nucleus. It is a weak acid with a pKa of 5.75 (see Figure I.1). Depending on the pH of the surrounding medium, the balance will change to allow for the creation of the molecular form for pH < pKa or towards the ionized form for pH > pKa (see FigureI.2).

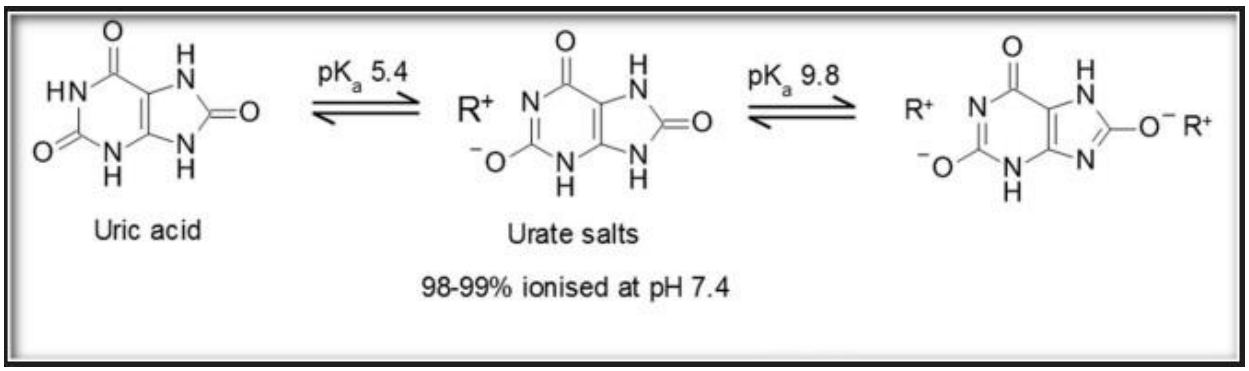


Figure I.1. Uric acid and urate conjugate bases' chemical structures.

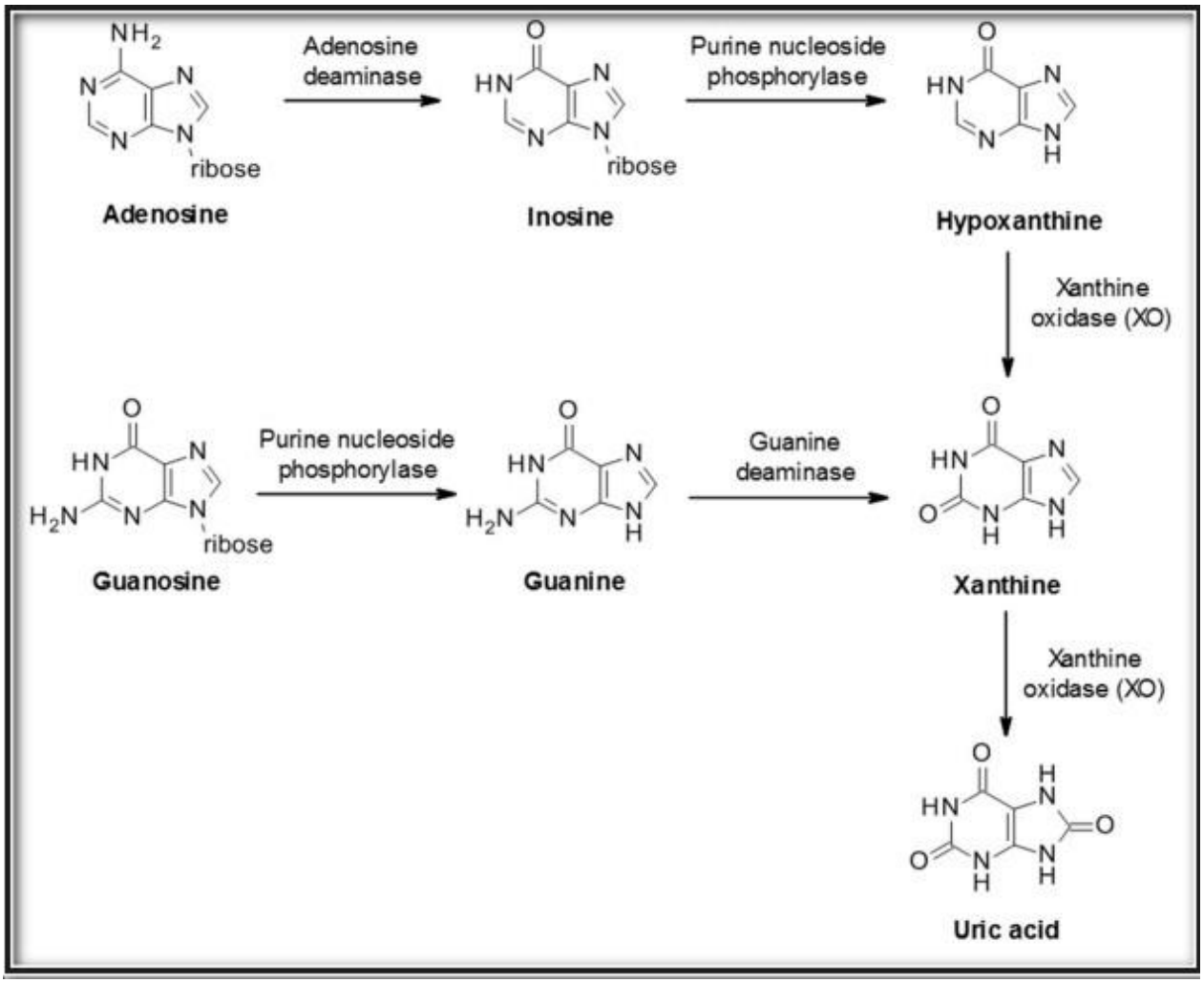


Figure I.2. Purines are used in the biosynthesis of uric acid. Uric acid is produced by catabolizing purine mononucleotides, albeit the exact mechanism varies depending on the tissue and cell.

I.2. Origins of Uric Acid

The primary byproduct of purine catabolism is uric acid. Two-thirds of purines are endogenous (from de novo purine synthesis, catabolism of cellular nucleic acids), and one-third are exogenous (coming from the catabolism of dietary nucleic acids).

2.1. De Novo Purine Synthesis

Beginning with ribose-5-phosphate (R5P), a byproduct of the pentose phosphate pathway, the majority of cells are able to carry out de novo synthesis of the purine ring. Inosine monophosphate (IMP), a metabolic junction that leads to the synthesis of adenosine monophosphate (AMP) and guanosine monophosphate (GMP), is the end product of this synthesis. Nucleic acids and other coenzymes can be synthesized using these purine nucleotides as substrates. Inosine, adenosine, and guanosine are the corresponding nucleosides that result from their breakdown and are subsequently converted into purines.

Another route for the removal of nitrogen in the form of uric acid (uricogenesis) is the synthesis of purines and the breakdown of purine nucleotides.

2.2. Catabolism of Ribonucleotides

Another source of purine base synthesis comes from the catabolism of purine ribonucleotides during cellular turnover or cell lysis. Indeed, nucleic acids are present in all cells, and their turnover (synthesis and degradation) is a continuous process. mRNAs, in particular, are rapidly synthesized and degraded. For this purpose, all cells have the enzymatic machinery required to degrade nucleic acids into nucleotides, nucleosides, and then into pyrimidines and purines. These free purines are either eliminated after being transformed into uric acid or reused to regenerate nucleotides.

Guanine, which comes either from the degradation of GMP or from the digestion of dietary nucleic acids, is transformed into xanthine, a metabolic crossroads of purine bases, by guanine deaminase.

Adenine, on the other hand, comes either from the degradation of AMP in cells where the ATP/ADP ratio is very low or from the digestion of dietary nucleic acids. As seen previously, it is metabolized into hypoxanthine by adenine deaminase, continuing its degradation towards the synthesis of uric acid.

Similarly, hypoxanthine is converted into xanthine, then into uric acid under the action of a single enzyme: xanthine oxidase. This is the first substrate that truly enters the elimination of purine bases.

2.3. Catabolism of Exogenous Purine Bases

The majority of dietary nucleic acids are ingested as nucleoproteins, whose nucleic acids are released into the intestinal tract by the action of proteolytic enzymes (see Figure I.3). Depending on the individual's diet, dietary intake can constitute a significant daily source of purines. Foods that are particularly rich in purines include meat, offal, fish, poultry, tomatoes, and alcoholic beverages, especially beer, which

contains large amounts of guanosine. This exogenous source accounts for approximately one-third of the circulating uric acid pool derived from dietary intake.

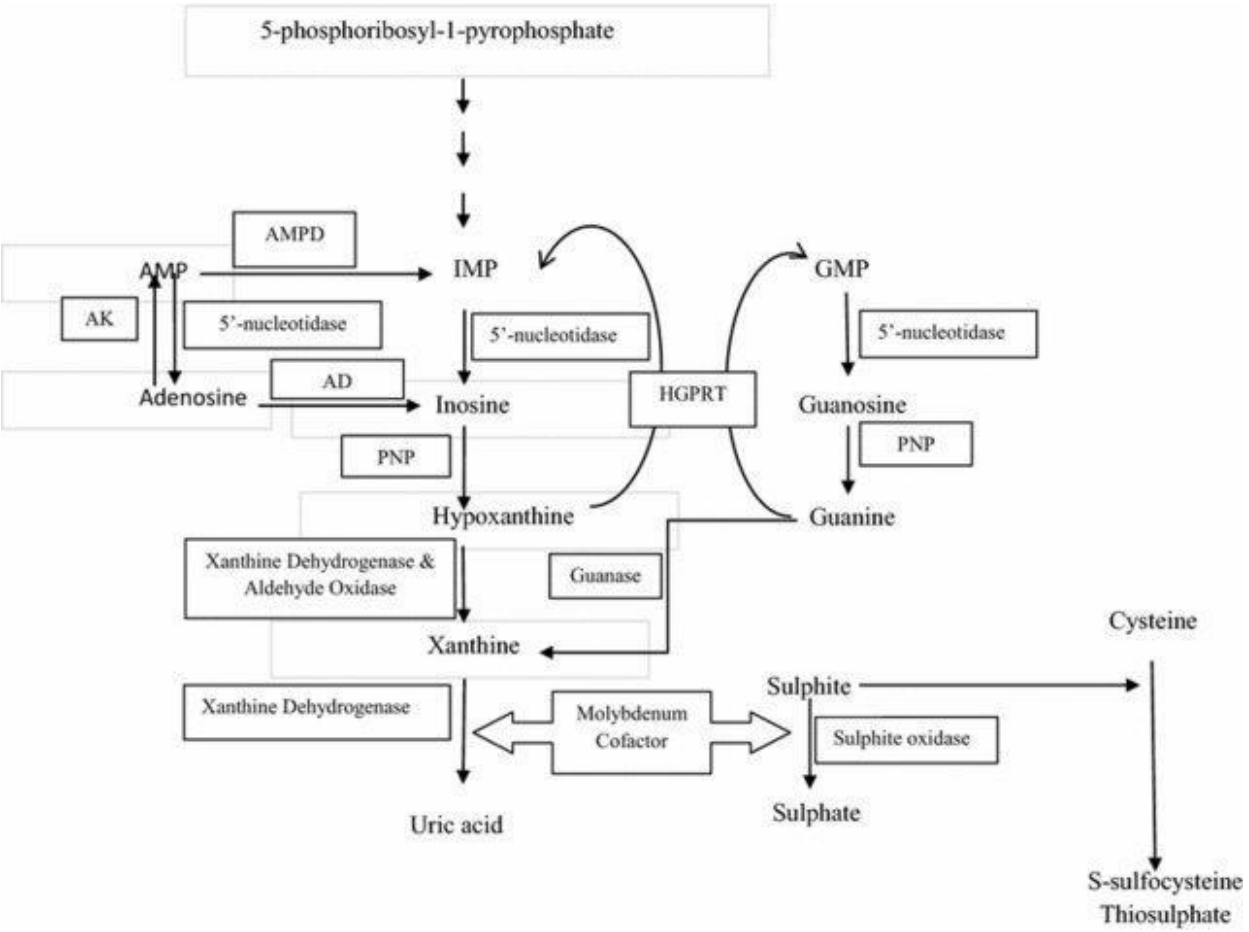


Figure.I.3. Purine metabolic pathway. AK adenosine kinase, AMPD AMP deaminase, AD adenosine deaminase, PNP purine neucleosidephosphorylase, AMP adenosine monophosphate, IMP inosine monophosphate, GMP guanosine monophosphate, and HGPRT hypoxanthine guanine phosphoribosyl transferase.

I.3. State of Uric Acid and its Distribution

Uric acid is distributed 80% in extracellular fluids and 20% in plasma. This high proportion explains why the value of the uric acid pool is directly related to the blood's uric acid level (uricemia). In plasma, uric acid is predominantly found in its free form, as urate, due to the blood pH of approximately 7.40, which

is much higher than the pKa value of uric acid (5.75). Only a small proportion of uric acid is attached to albumin and other plasma proteins (its main carrier), low-density lipoproteins (LDL), β2-globulins, etc.

Uric acid bound to proteins has a 70% greater solubility in plasma compared to its free form.

I.4. Elimination of Uric Acid

About 70% of uric acid (UA) is eliminated through the kidneys, and 30% is eliminated via the digestive tract through intestinal uricolysis carried out by intestinal bacteria.

I.4.1. Renal Elimination of Uric Acid

The glomeruli filter over 95% of uric acid. Between 98 and 100 percent of the filtered uric acid is reabsorbed in the S1 segment of the proximal convoluted tubule (PCT). About half of the uric acid that was first filtered is then secreted in the S2 segment via a tubular secretion process. Lastly, 40% of the urates that are secreted are reabsorbed in the tubule's S3 section. The urine eventually contains about 10% of the filtered uric acid (see Figure I.4).

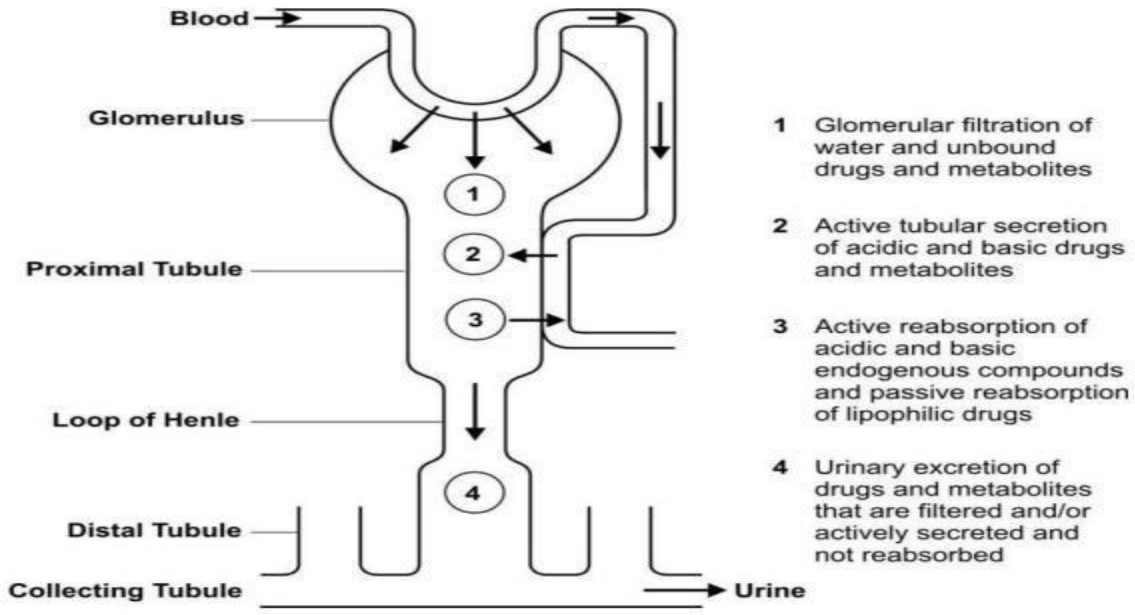


Figure.I.4. Renal Elimination of Uric Acid

I.4.2. Elimination of Uric Acid via the Digestive Tract

This occurs through digestive secretions (salivary, biliary, pancreatic, and intestinal). Under normal conditions, intestinal bacteria, equipped with uricases, completely degrade uric acid into allantoin, and even further into carbon dioxide and ammonia, which are then excreted in the feces or consumed for their own metabolism.

I.5. Biochemical Exploration

I.5.1. Sample Collection

- Fasting for 12 hours
- Blood sample: serum or plasma on lithium heparinate
- 24-hour urine, alkalinized with 10 mL of 5% sodium or potassium hydroxide
- Avoid performing the test after the intake of tea, coffee, theophylline, salicylates, or vitamin C. The first three provide uric acid to the body, while the latter two interfere with the test using phosphotungstic acid.

I.5.2. Purpose of the Test: Uric acid is a global marker for assessing renal function.

I.5.3. Normal Values

Uricemia:

- In men = 30-70 mg/L
- In women = 25-60 mg/L
- In children = 10-35 mg/L

Uricuria: 400-800 mg/24h

I.5.4. Physiological Variations

The values of uricemia vary depending on:

- **Sex:** Uricemia is generally higher in men than in women by about 20-30%. A significant increase occurs in men at puberty (while the increase is smaller in women) and in women during pre-

menopause. Indeed, estrogens have a uricosuric effect in women, which explains the increase in uric acid levels after menopause.

- **Age:** Uricemia tends to be high at birth, then decreases and stabilizes.
- **Weight:** There is a positive correlation with the weight of adults, especially for those over 80 kg.
- **Ethnicity:** There are considerable variations, genetically determined, among different ethnic groups.
- **Other factors:** diet, physical exercise, hydration status, medications, pregnancy, etc.

I.6. Pathologies Linked to Uric Acid

I.6.1. Hyperuricemia

Hyperuricemia is a uric acid excess in the serum. When the serum level is higher than 458 µmol/L (77 mg/L) in men and 405 µmol/L (68 mg/L) in women, it is deemed hyperuricemia.

I.6.1.1. Causes of Hyperuricemia

Hyperuricemia results either from an excess of production, a defect in renal elimination, or a combination of both. It can be primary (due to primary defects in purine metabolism or urinary elimination of uric acid) or secondary (due to diet, the administration of xenobiotics, or diseases that affect uric acid metabolism).

Hyperuricemia due to renal excretion defects represents 75% of hyperuricemia cases and is characterized by normal or decreased uric acid excretion (less than 2.4 mmol/24h). Any pathological variation in renal excretion can lead to an increase in sodium urate levels in the body. This condition tends to be compensated by an increase in intestinal uricolysis. The main causes of these hyperuricemias are:

- **Primary Hyperuricemia:** Specific defect in tubular secretion.
- **Secondary Hyperuricemia:**
    - **Renal insufficiency:** Reduced glomerular filtration rate (GFR).
    - **Iatrogenic causes:** Diuretics, cyclosporine, salicylates, beta-blockers, angiotensin II, anti-tuberculosis antibiotics.
    - **Competitive inhibition:** Lactic acid, alcohol, ketone bodies.

- **Other conditions:** Hypertension, obesity, hypothyroidism, sarcoidosis, hyperparathyroidism.

I.6.1.2 Complications of Hyperuricemia

The complications of hyperuricemia are related to the deposition or precipitation of uric acid. These complications include **rheumatological** (gout), **urological** (kidney stones), and **nephrological** (uric nephropathy) conditions.

I.6.1.2.1. Gout

- Formerly known as "the disease of kings," gout is a common metabolic disorder and one of the leading causes of inflammatory arthritis in men over 40 years old.
- It is the result of an excess of uric acid and local acidosis, leading to the deposition of sodium urate crystals.
- Gout initially manifests as acute attacks, particularly at the base of the big toe. The inflammatory crisis is brought on by uric acid crystals precipitating in the synovial fluid. It may later progress to a subacute phase, where inflammatory attacks may affect all large joints.
- Chronic gout is characterized by tophi, which are amorphous uric acid deposits found in areas like the extensor tendons, the ear lobes (see Figure I.5), and sometimes in the bones near joints. When this happens, gout progresses to a chronic polyarthritis.

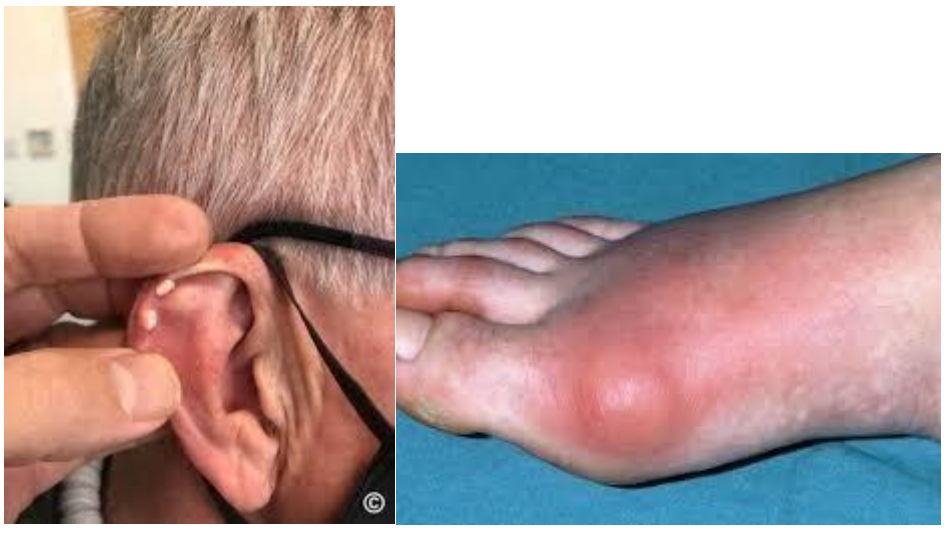


Figure I.5. Acute Gout Attack of the Big Toe, Tophus on the Ear and Elbow

I.6.1.2.2. Renal Lithiasis (Kidney Stones)

This condition occurs when uric acid stones in the renal excretory pathways, which inevitably leads to renal colic. Uric acid stones are radio-invisible, but urinary excretion (uraturia) is either high or normal and is notably accompanied by significant urinary acidity, which should be mitigated by the intake of alkaline drinks.

I.6.1.2.3. Uric Nephropathy

Uric nephropathy occurs when deposits of uric acid in the renal pyramids. It is directly linked to hyperuricemia, and any appearance of microscopic hematuria or increased blood pressure should prompt the prescription of inhibitors of uric acid synthesis, which lower uricemia before chronic renal insufficiency develops.

I.6.1.3 Treatment

a. Hygienic and Dietary Guidelines

- Limit purine-rich foods (e.g., organ meats, highly fermented cheeses, spinach, mushrooms, legumes).
- Increase milk consumption.
- Avoid alcohol.
- Stay well-hydrated.
- Stabilize body weight.

b. Pharmacological Treatments

- **Acute Gout Attack**
    - For treatment during an acute gout attack: colchicine and/or NSAIDs (Non-Steroidal Anti-Inflammatory Drugs).
- **Chronic Gout**
    - Hypouricemic treatment: Allopurinol (Zyloric), a drug used for gout, is a structural analogue of hypoxanthine that strongly prevents purines from being converted into uric acid by the enzyme xanthine oxidase (xanthine dehydrogenase).

I.6.2. Hypouricemia

Hypouricemia is defined arbitrarily as a uric acid level below 25 mg/l. Repeated measurements allow differentiation between temporary hypouricemia (which generally occurs in a specific context) and chronic hypouricemia. It is rare, and hypouricemia is usually discovered incidentally during a biological assessment. Rarely, clinical manifestations such as oxidative stress may be observed.

6.2.1 Etiologies of Hypouricemia

Hypouricemia can be caused by two distinct, but not mutually exclusive, physiopathological mechanisms:

a) Decreased Uric Acid Production

- Iatrogenic Causes: Xanthine oxidase inhibitors (e.g., allopurinol, febuxostat).
- Severe Liver Disease: Hepatocellular insufficiency.
- Xanthine Oxidase Deficiency.
- Adenosine Deaminase Deficiency.
- Nucleoside Phosphorylase Deficiency.

b) Increased Renal Clearance of Uric Acid

- Iatrogenic Causes: Uricolytic agents (e.g., pegloticase).
- Inhibition of Reabsorption: Uricosuric agents like probenecid, benzbromarone, fenofibrate, losartan, aminoglycosides, sulfamethoxazole-trimethoprim, phenylbutazone, high-dose salicylates, ascorbic acid (>4g), mannitol.
- Inhibition of Secretion: Acute infusion of amino acids (e.g., glycine), glucose, or fructose.
- Increased Excretion Fraction of Uric Acid: Conditions like Syndrome of Inappropriate ADH Secretion and Fanconi Syndrome.
- Familial Idiopathic Hypouricemia: Isolated defect in tubular transport of uric acid (both reabsorption and secretion)

II. Exploration of renal function

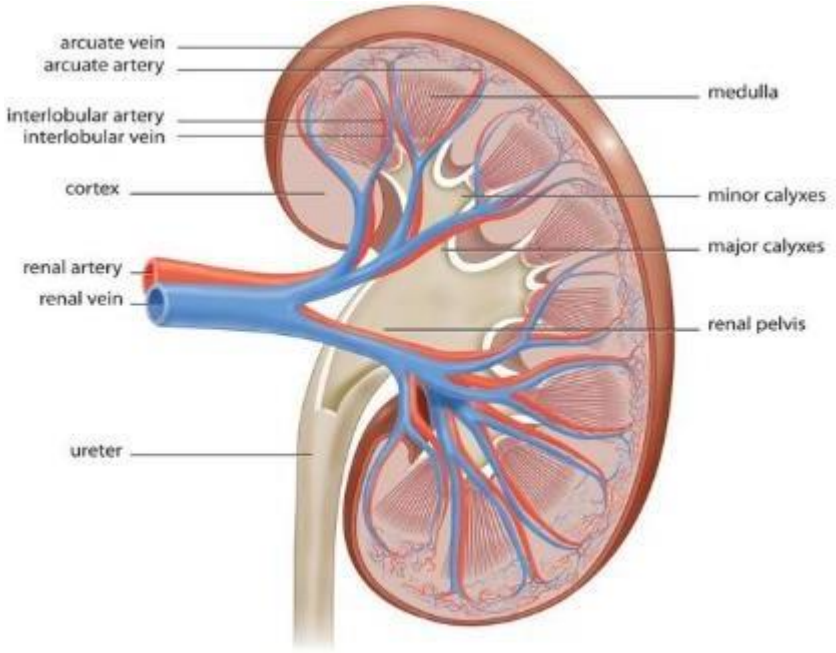
II.1. Introduction

The kidneys' essential role in preserving the internal environment's equilibrium is intimately related to that task. Urea, protons, uric acid, creatinine, bilirubin, and other metabolic byproducts are eliminated by the kidneys, along with a variety of exogenous chemicals like food additives, pharmaceuticals, and a balanced quantity of water and electrolytes. A glomerulus and a tubule make up the nephron, the kidney's functional unit. Assessing hemodynamic, glomerular, and/or tubular functioning both quantitatively and qualitatively is the goal of renal functional testing.

II.2. Anatomical Overview

The kidneys are bean-shaped organs that are situated in the lumbar area at the rear of the abdomen. Each is topped by an adrenal gland, which is functionally completely independent. The **renal hilum** consists of a renal artery and a renal vein.

• The functional unit and structural of the kidney are the **nephron** (see FigureII.1).



FigureII.1. Renal Anatomic structure

Each nephron includes:

• A **glomerulus**: the filtration unit

• A a **loop of Henle, proximal tubule**, a **collecting ductand** a **distal tubule**. These tubules are responsible for **reabsorption** and **secretion**.

II.3. Physiological Overview

The usual urine volume, around **1500 ml per 24 hours**, is the result of **glomerular filtration**, **tubular reabsorption**, and **tubular secretion**.

II.3.1. Urine Formation:

Glomerular Filtration:

- Glomerular filtration leads to the formation of a **plasma ultrafiltrate**. The filtered volume is considerable — approximately **180 liters per day**.
- All **low molecular weight molecules** (such as water, urea, glucose, electrolytes, etc.) can pass through the filtration membrane.
- Excluded from the filtration process are:
    - All **cellular** blood **elements** (e.g., white and red blood cells, platelets)
    - Molecules weighing more **than 50 kDa** (e.g., **albumin, globulins**)

Tubular Reabsorption:

• Reabsorption involves the flow of chemicals into the blood capillaries from the tubular lumen.
• Tubular reabsorption is **selective**.

• It **recovers substances essential to life** and excludes waste products.

Tubular Secretion:

Tubular secretion aims to **eliminate foreign substances** from the body, such as **medications, dyes**, etc.

II.3.2. Endocrine Functions of the Kidney:

a) Vitamin D

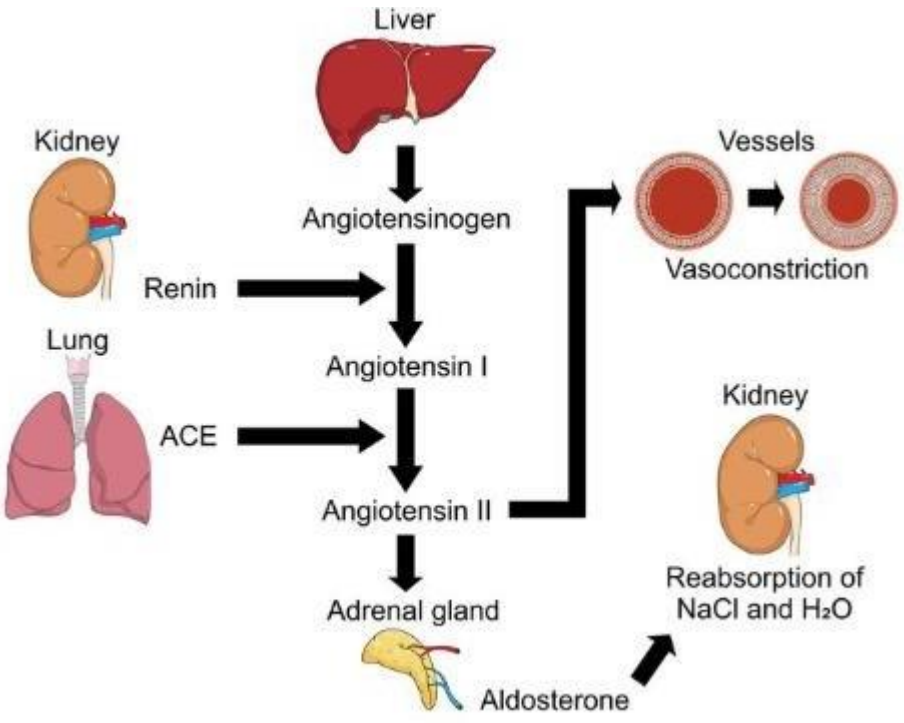
• Vitamin D and its active form of (**1,25-dihydroxyvitamin D**, or **1,25(OH)$_2$D**) is produced in the **proximal tubular cells** from its hepatic precursor, **25-hydroxyvitamin D$_3$**, under the enzyme **1α-hydroxylase** action.

b) Erythropoietin (EPO)

• EPO causes the bone marrow to produce **more red blood cells**.

c) Renin-Angiotensin-Aldosterone System (RAAS)

RAAS regulates fluid balance, blood pressure, and electrolyte homeostasis (see FigureII.2).



FigureII.2. Angiotensin system

II.3.3. Metabolic Functions

- **Elimination of nitrogenous waste products** (urea, creatinine, uric acid), as well as **drugs** and other toxins.
- **Regulation of the internal environment's balance**: including **volume**, **composition**, and **pH** of body fluids.
- **Participation in gluconeogenesis** (the production of glucose from non-carbohydrate sources).

II.4. Biochemical Assessment of Kidney Function

- The evaluation of kidney function is carried out through various **blood and urine tests**. These tests aim to assess both **glomerular** and **tubular** functions.
- A **renal work-up** includes the following parameters:
  - **Direct examination of urine** (appearance and odor)
  - **Measurement of blood and urinary urea levels**
  - **Measurement of blood and urinary creatinine levels**
  - **Estimation of the glomerular filtration rate (GFR)** by calculating **creatinine clearance**
  - **Other measurements** (e.g., **electrolyte panel**, **cystatin C**, etc.)
  - **Detection of proteinuria** (presence of proteins in the urine)

II.4.1. Direct Examination of Urine (Macroscopic Examination):

Color:

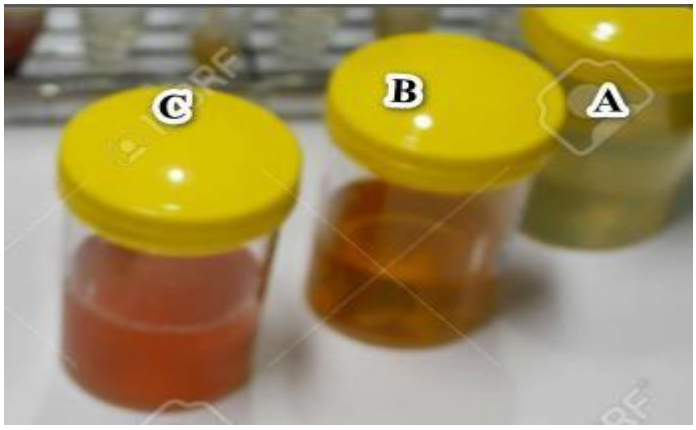
- Normal urine is **clear** with a **slightly yellowish** tint.
- **Biliary pigments** (bilirubin) may cause a darker color.
- **Red** color: could indicate **hematuria** (presence of blood), consumption of **beets**, or certain **medications**.

Odor:

- A strong odor may indicate **infection**.
- Certain **foods** can also alter the odor (e.g., asparagus).

Appearance:

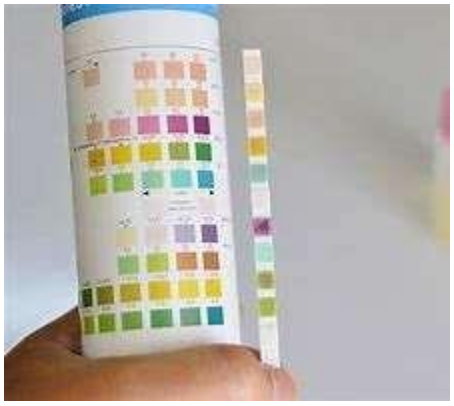
- **Cloudy** urine may suggest **bacterial infections** (see Figure II.3).



FigureII.3. Direct Examination of Urine. A: Light; B: Pink; C: Red

*The **direct appearance** (see Figure II.4) of urine is followed by the use of **test strips** (reactive strips).

*The various parameters that can currently be assessed include: **pH**, **Specific gravity (density)**, **Blood**, **Proteins**, **Ketone bodies**, **Bilirubin**, **Urobilinogen**, **Nitrites**.

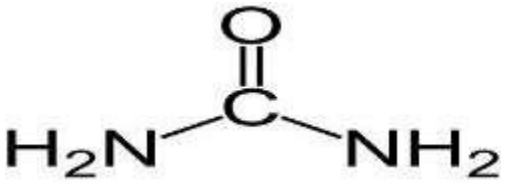


FigureII.4. Test strips

II.4.2. Urea Measurement

II.4.2.1. Metabolism

- Urea is an organic substance with the following formula: $CO(NH_2)_2$, containing two amine groups and one ketone group (see Figure II.5).
- Urea is a highly water-soluble molecule.
- It is the main form of elimination for nitrogenous waste products from protein metabolism in humans.
- The majority of ammonia (NH_3), produced in the liver by the amino acids deamination, is converted into urea (ureogenesis), utilizing CO_2 formed during the mitochondrial Krebs cycle in the liver and brain.



FigureII.5. Urea structure

II.4.2.2. Biosynthesis (Urea Cycle)

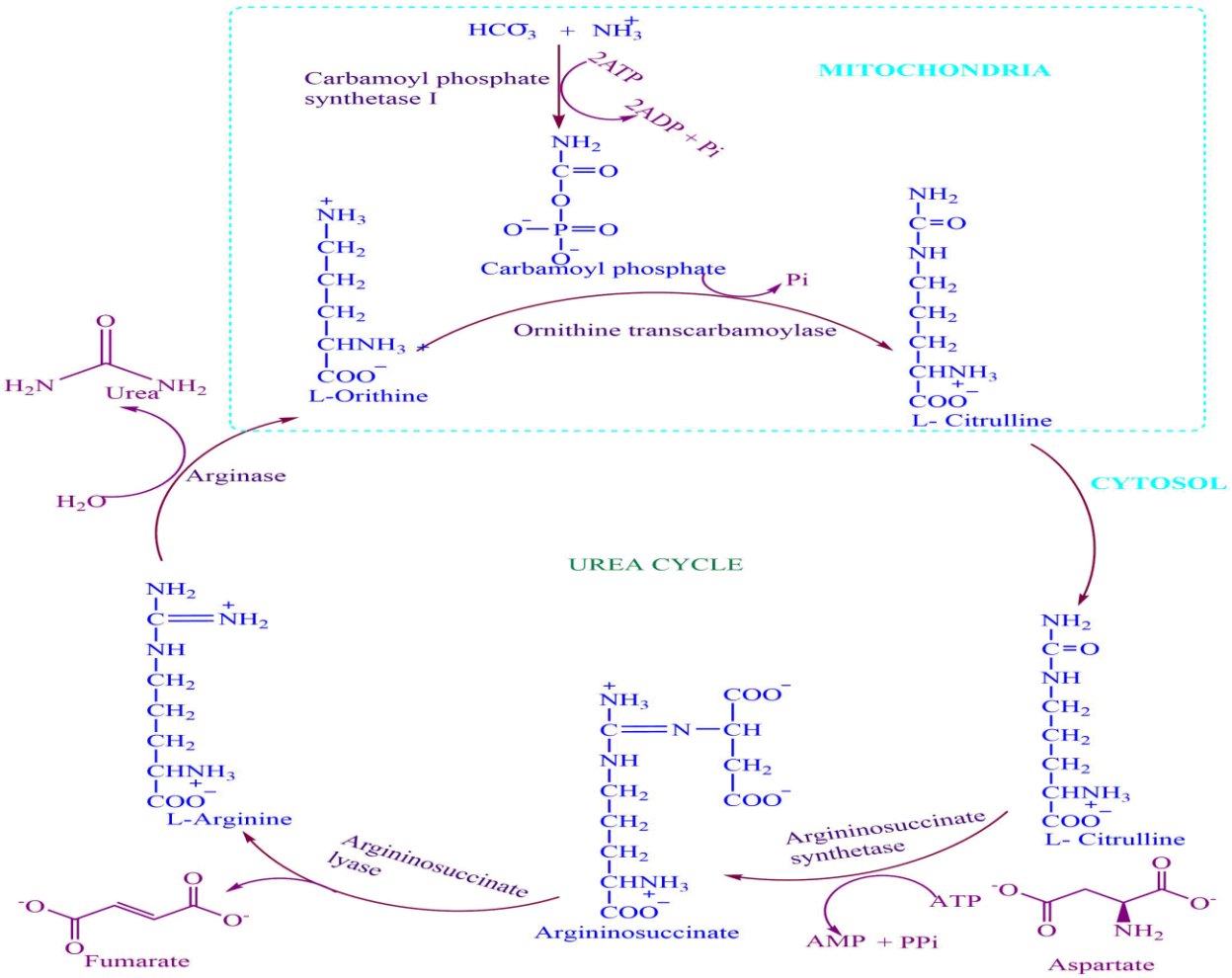
The urea cycle is a metabolic pathway in the liver that enables the body to eliminate excess nitrogen from both endogenous and exogenous sources by detoxifying ammonia into urea. The formation of one urea molecule requires two nitrogen atoms: the first is derived from NH_4^+ (ammonium), and the second is contributed by aspartate.

Two of the five reactions occur in the mitochondria, while the other three take place in the cytosol.

1. Formation of Carbamoyl Phosphate:

Carbamoyl phosphate is synthesized in an irreversible reaction from NH_4^+, CO_2, and two molecules of ATP, representing a major regulatory step in ureogenesis (see FigureII.6). This reaction is catalyzed by the

mitochondrial enzyme carbamoyl phosphate synthetase I, which is allosterically activated by N-acetylglutamate, ensuring that ureogenesis is tightly regulated according to the cell's metabolic needs.



FigureII.6. Steps of Urea cycle

2. Synthesis of Citrulline:

The first nitrogen atom enters the urea cycle when the carbamoyl group from carbamoyl phosphate (CP) is transferred to ornithine, forming citrulline in a reaction catalyzed by the mitochondrial enzyme ornithine transcarbamoylase. Citrulline is then transported from the mitochondria to the cytosol via a specific transporter to continue through the cycle.

3. Synthesis of Argininosuccinate:

The second nitrogen atom is introduced into the urea cycle through the condensation of citrulline and aspartate to form argininosuccinate, a reaction that consumes one molecule of ATP and is catalyzed by the cytosolic enzyme argininosuccinate synthetase.

4. Synthesis of Arginine:

Argininosuccinate is hydrolyzed into arginine and fumarate by the enzyme argininosuccinate lyase; the fumarate produced can enter the citric acid cycle and be converted into glucose and CO_2 through gluconeogenesis and cellular respiration.

5. Formation of Urea:

Arginine is hydrolyzed by the enzyme arginase to produce urea and ornithine; the urea is excreted, while ornithine is transported back into the mitochondria via the citrulline-ornithine transporter, allowing the urea cycle to begin anew.

Net reaction of urea cycle:

The synthesis of urea consumes **four high-energy phosphate bonds.** This process is an irreversible reaction with **a large negative** ΔG. In the formation of urea, one nitrogen atom comes from free NH_3, while the other is provided by aspartate.

$$\text{Aspartate} + NH_3 + HCO_3^- + 3ATP + H_2O \longrightarrow \text{Urea} + \text{Fumarate} + 2ADP + AMP + 2\ Pi + PPi$$

II.4.2.3. Renal Elimination

- The glomerulus freely filters urea and partially reabsorbed at the tubular level.
- The daily elimination is 20–25 g/day and is directly related to the body's water balance.

II.4.3. Sampling:

Urea can be measured in blood plasma or serum to assess uremia, and in urine as urinary urea, with uremia typically measured on fasting heparinized plasma. Sodium fluoride, which inhibits urease, must be avoided during sample collection. Samples can be stored for up to one week at +4°C or for one month at -20°C, and a 24-hour urine collection is required for accurate urinary urea assessment.

II.4.4. Assay Method

- **Diacetylmonoxime Method (DAM - Colorimetric)**

In an acidic and heated environment, DAM reacts with urea to produce a yellow coloration used for colorimetric measurement.

- **Enzymatic Method using Urease**

All enzymatic methods are based on the hydrolysis of urea by urease: **Urea + $H_2O \rightarrow CO_2 + 2\ NH_3$**

The produced **NH_3 (ammonia)** is then measured by:

  - **Colorimetry (Berthelot reaction)**
  - **Enzymatic technique (Glutamate Dehydrogenase)**

NH_3 + α-Ketoglutarate + NADPH + $H^+ \rightarrow$ Glutamate + $NADP^+$ + H_2O

II.4.5. Normal Values

- Uremia (blood urea): 0.15 – 0.45 g/L
- Urinary urea: 15 – 30 g/24h

II.4.6. Physiological Variations

- Lower levels in women; levels decrease during pregnancy
- Levels increase with a nitrogen-rich diet (e.g., high meat intake) and with age

II.4.7. Pathological Variations

- **Decreased levels** in hemodilution, enzymatic deficiency affecting hepatic ureagenesis, and liver failure
- **Increased levels**

Uremia rises in cases of extracellular dehydration and kidney failure, though **it's less specific than creatinine** due to its sensitivity to diet and hydration status. However, its increase tends to appear early and is quantitatively significant.

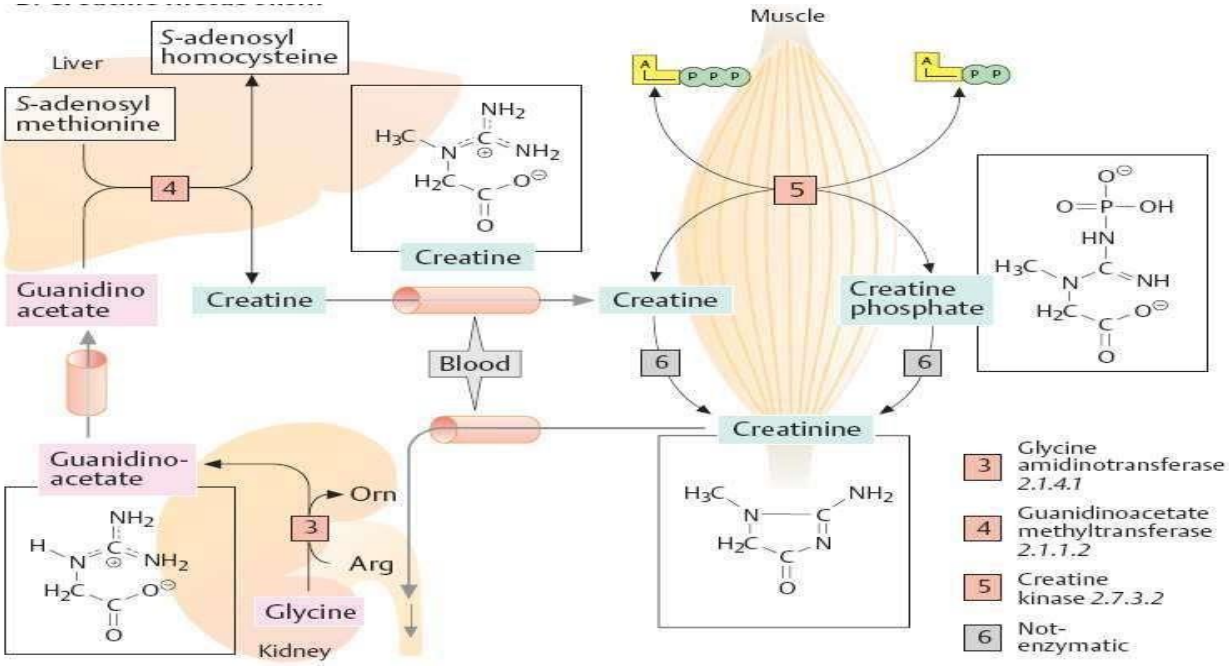
II.4.8. Creatinine Assay

II.4.8.1. Metabolism

Creatinine is the result of the impromptu dehydration of **muscle creatine**, which serves to transfer a phosphate group (as **creatine phosphate**) to ADP, thereby spontaneously producing **ATP** needed for the phosphorylation of myosin during **muscle contraction**.

Creatine is regularly produced in the **liver, kidneys, and pancreas** from **glycine and arginine**, with a final methylation step occurring in the **liver**. From there, after being released into the bloodstream, creatine is absorbed by **skeletal muscle cells** via a membrane transporter. After **dephosphorylation**, it is converted into **creatinine**, which enters the bloodstream and is ultimately excreted in the **urine**. **Creatinine is formed in two steps:**

At the renal level, guanidinoacetic acid is synthesized from glycine and arginine through the action of glycine amidinotransferase. This compound is then transported to the liver, where it is methylated into creatine by guanidinoacetate methyltransferase (see Figure II.7). The resulting creatine is released into the bloodstream and taken up by muscle cells, where it is converted by creatine kinase into creatine phosphate, a high-energy storage compound. Creatinine is formed from the non-enzymatic dehydration of creatine and serves as a metabolic waste product.



FigureII.7. Formation of Creatinine.

-Creatinine production is proportional to **muscle mass**.

-It is eliminated **exclusively by the kidneys**, without undergoing any **tubular reabsorption**.

-Its levels are **independent of hydration status and diet**.

-Creatinine clearance provides a direct indication of **kidney function**, making it the **best marker** for assessing **renal function**.

II.4.8.2. Sample Collection

- Use **heparinized plasma**, taken **fasting**, away from meals and physical activity.
- Avoid **prolonged fasting**, as it can lead to the formation of **ketone bodies**, which may interfere with the measurement.
- **24-hour urine samples** should be collected in a **plain (preservative-free) container**.

II.4.8.3. Assay Methods

a) Jaffé Colorimetric Method

- **Principle:** The strength of the yellow-orange complex that results from the reaction of creatinine with picrate in an alkaline media is proportional to the concentration of creatinine. Measurement is done at **520 nm**.
- **Interferences:** Proteins, organic acids, **ketone bodies**, **pyruvate**, **uric acid**, etc., can cause **falsely elevated results**. **Bilirubin** (BLB) can cause **false negatives**.
- **Improving specificity:** Spectrophotometric measurement in **kinetic mode** with **early reading** (between **20–120 seconds**) improves accuracy, as creatinine reacts faster with picrate than interfering substances.

a.1. Reference Values

- **Blood**
  - Men: **6 – 12 mg/L**
  - Women: **5 – 10 mg/L**
- **Urine (24h):**
  - Men: **1400 – 1700 mg/L**

a.2. Physiological Variations

- **Elderly:** Slight increase due to decreased **glomerular filtration rate (GFR)**
- **Pregnant women:** Decrease due to increased **GFR** and **hypervolemia**
- **Physical exercise:** Causes an increase in creatinine levels

a.3. Pathological Variations

- **Increased blood levels**
  - **Reduced glomerular filtration** (renal failure)
  - **Inhibition of tubular secretion** (due to diuretics, salicylates)

- **Decreased blood levels**
    - **Muscle loss** (e.g., myopathy)

b. Estimation of Glomerular Filtration Rate (GFR) by Creatinine Clearance Calculation

The precise measurement of glomerular filtration is usually performed using substances that meet the following criteria:

- The substance must filter freely through the glomerular barrier.
- Its elimination must occur exclusively through the kidneys.
- It must neither be reabsorbed nor secreted by the renal tubules.
- It must be easily measurable in both blood and urine.
- If the substance is exogenous, it should be non-toxic.

Inulin, an exogenous polysaccharide, and certain radioactive substances meet these criteria. However, these substances are not commonly used in everyday practice.

In daily practice, the glomerular filtration rate (GFR) is typically estimated by calculating the **creatinine clearance**.

b.1. Creatinine Clearance

b.1.1. Definition

A substance's clearance (Cl) is the virtual volume of plasma that is entirely free of that compound in a given amount of time, with **Normal Values: Adults (ml/min):** ≥ 90

b.1.2. Measured Clearance

- Requires a **collection of 24-hour of urine.**
- **Formula for clearance**

$$\text{Clearance} = \frac{(U \times V)}{P}$$

- **U:** Urinary creatinine concentration (mg/L)
- **V:** 24-hour urine output (mL/min)
- **P:** Plasma creatinine concentration (mg/L)

The normal value for creatinine clearance is **120 ± 20 mL/min** for a body surface area of **1.73 m²**.

The clearance must always be **corrected** for body surface area:

$$\text{Corrected Cl} = \text{Calculated Cl} \times \frac{1.73}{\text{Body Surface Area}}$$

b.1.3. Calculated Clearance (Cockcroft and Gault Formula)

[140-age(years)] * ideal weight(kg)/([creatinine(mg/dl)] *72)

For women: multiply by0.85

Clr= **120 ± 20 mL/min**

b.1.4. Simplified MDRD Formula (Modification of Diet in Renal Disease)

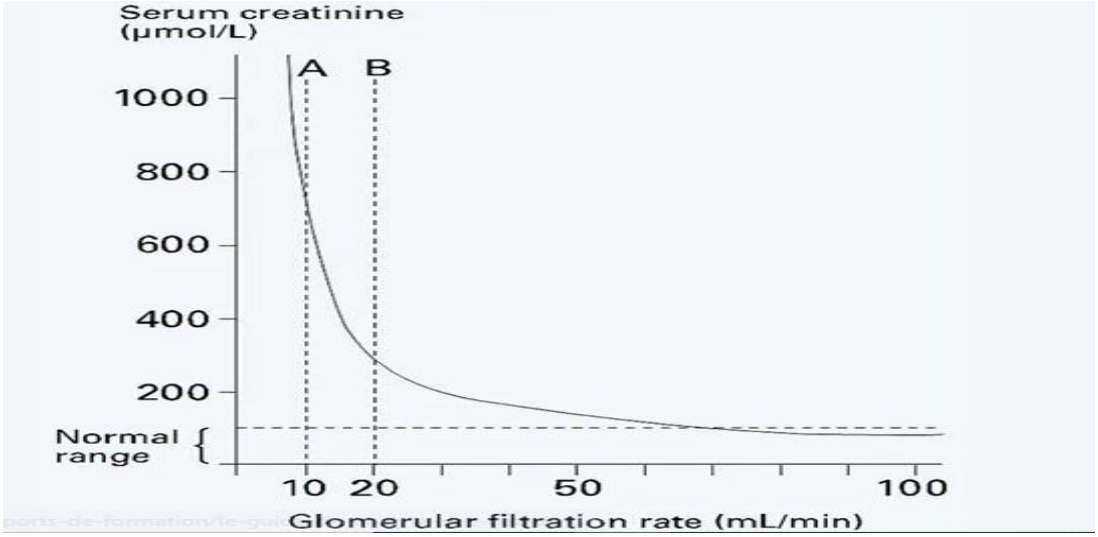
This formula is used when the **Cockcroft-Gault formula** is not applicable, often in cases where specific conditions (like weight or muscle mass) cannot be accurately assessed.

Formula:

$$\mathbf{ClCr = 175 * (creatinine * 0.0113)^{-1.154} * (age)^{-0.203} * (0.742 \text{ if female})}$$

Where:

- **ClCr** is the estimated creatinine clearance in **mL/min/1.73 m²** (see Figure II.8)
- **creatinine** is the **serum creatinine** in **µmol/L**
- **age** is the age in **years**
- The factor **0.742** is applied if the patient is female.



FigureII.8. Relationship Between **Creatinine** and **GFR:** When creatinine levels are above the normal range (represented by the **dashed horizontal line**), the value of the **glomerular filtration rate (GFR)** may have already decreased by up to **50%** of its normal value.

c. Other Assays

1. Cystatin C

- Cystatin C is a new marker used to assess kidney function.
- It is a **non-glycosylated protein** produced by all nucleated cells.
- The final urine does not include this biological signature since it is fully filtered by the glomerulus and catabolized by the proximal convoluted tubule.
- It offers several advantages, including:
    - It is **not influenced by gender, age, or muscle mass**.
    - Cystatin C seems to be more closely correlated with **glomerular filtration measurements**.
    - It is considered the most **sensitive marker** for a **reduction in GFR**.

- However, due to the **high cost** of its measurement and the **limited advantages** it offers compared to creatinine testing, creatinine remains the standard for **daily glomerular function assessment**.

2. Uric Acid

- Uric acid undergoes **renal elimination** through **glomerular filtration** and **tubular secretion**.
- **Uricemia** increases in **renal failure**, but it remains **non-specific** and **insensitive**.

3. Plasma Ionogram

- Determining **Na, K, Cl, and HCO_3 ions** is essential for assessing the **hydro-electrolyte balance**, which the kidneys are primarily responsible for maintaining.
- **Hyperkalemia** reflects the kidney's **inability to excrete potassium**.
- **Bicarbonates** provide insight into **acid-base disorders**.
- Monitoring for **renal failure**.

4. Calcium and Phosphorus Levels (Calcemia and Phosphatemia)

- In **chronic renal failure**, **phosphocalcic metabolic disorders** are common.
- Biologically, during **chronic renal failure**:
  - **Calcium levels (Calcemia)** are typically **low**.
  - **Phosphorus levels (Phosphatemia)** are **elevated**.

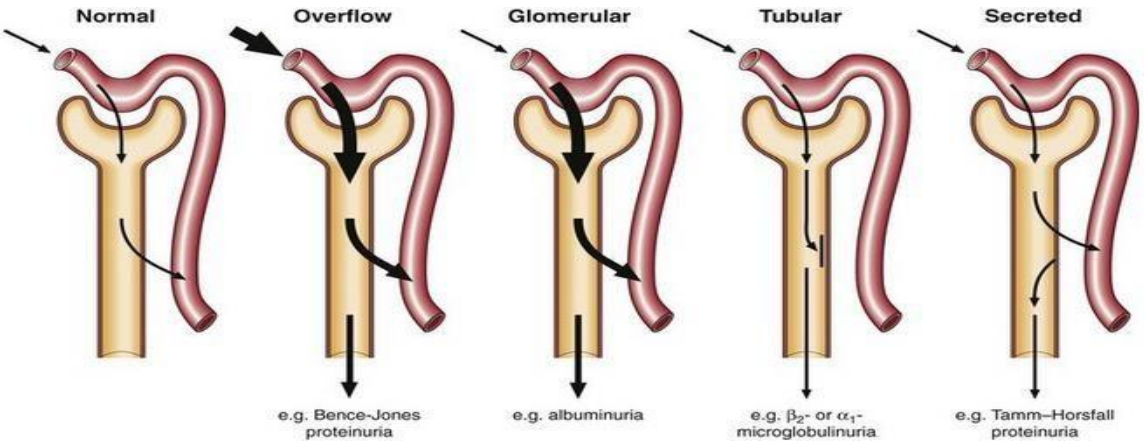
5. Proteinuria

5.1. Definition

Normal urine contains **very little protein**, usually less than **50 mg/24h**. The two main proteins are: **Albumin** (less than 20 mg), **Tamm-Horsfall protein** (less than 30 mg), secreted by the thick ascending limb of the **loop of Henle**, the rest consists of **globulins** with small molecular masses (see Figure II.9). **Proteinuria** is considered **pathological** when it exceeds **150 mg/24h** and is **persistent** which is confirmed through **quantitative measurement**. It may result from:

- **Damage to the glomerular barrier**: This is called **glomerular proteinuria**.

- **Saturation or damage to tubular reabsorption**: This is **tubular proteinuria**.
- **No structural renal alterations**: This is **overflow proteinuria** (due to low molecular weight proteins like **light chains**).

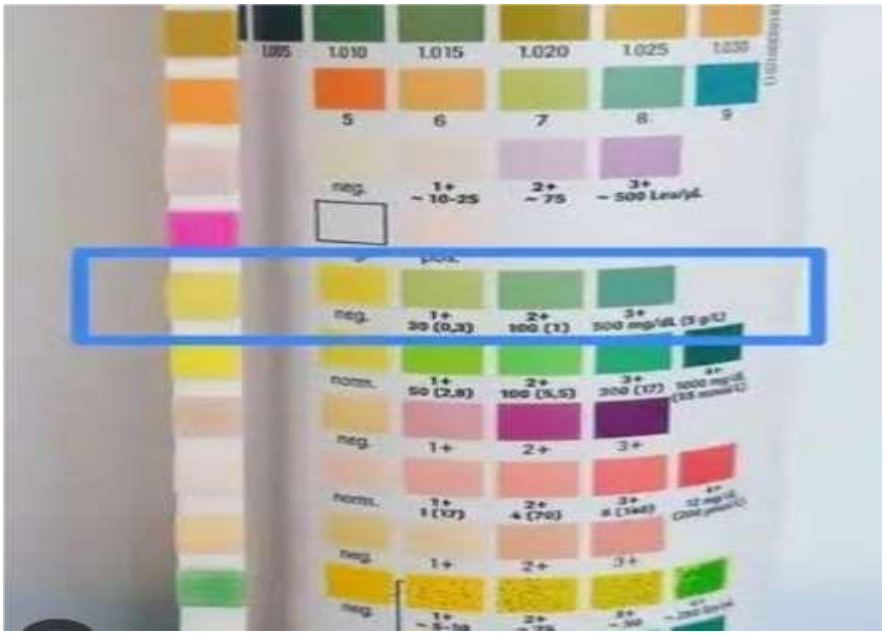


FigureII.9. Mechanism of proteinuria.

-**Screening** is done using **urine dipsticks** with a **pH indicator**.

-The **detection threshold** is **300 mg/24h**, and the test is **sensitive to albumin**, but **minimally or not at all sensitive to light chains (**see Figure II.10).

-If the test is **positive**, a **quantitative assay** must be performed.



FigureII.10. Ph indicator of Proteinuria

5.2. Proteinuria Assay

***Quantitative Assay: Pyrogallol Red Method* (+++)**

- **Pyrogallol Red (RP)** with **molybdate** forms a **red complex**, which binds to **amine groups** of proteins, creating a **blue-violet complex**.
- The protein concentration is directly correlated with the absorbance at 600 nm.

Microalbuminuria

- Microalbuminuria is the excretion of albumin in the urine between **20 and 200 µg/min**, or **30 to 300 mg/24 hours**.
- **Urinary creatinine** is measured in parallel.
- Results expressed as the **albumin/creatinine ratio** allow its use in **screening**.
- The **presence of small amounts** of albumin indicates **early glomerular damage**, and testing is recommended in **diabetic patients** if standard proteinuria is negative.

6. Pathology

6.1. Acute Kidney Injury (AKI)

Acute kidney injury is a pathological condition characterized by a **rapid deterioration** (within hours or days) of **kidney function**, often **reversible**, with the kidney unable to maintain **fluid and electrolyte homeostasis** or eliminate **nitrogenous waste** (urea and creatinine retention).

In some cases, AKI is associated with a **decrease in urine output**:

- It is termed **oliguric AKI** when the volume of urine is between **100 and 500 mL/24h**.
- It is called **anuric AKI** when the volume of urine is **less than 100 mL/day**.

a) Functional (Pre-Renal) AKI

This results from a **decreased glomerular filtration rate** due to **renal hypoperfusion**.

- **Histologically**, the kidney appears **normal**.
- It is **usually reversible** within **24 to 48 hours**.
- **Main causes:**
    - **Hypovolemia** (e.g. dehydration, hemorrhage)
    - **Heart failure**
    - **Sepsis**

Biological findings

- **Urea increased**, **creatinine slightly increased**
- **Urinary Na^+/K^+ ratio < 1**

b) Organic (Intrinsic) AKI

This type results from **destruction of the renal parenchyma**, potentially affecting all structures: **glomeruli, tubules, interstitium, or renal vessels**.

Biological findings

- Increased **urea and creatinine levels**

- **Hyperkalemia**
- In the **urinary ionogram**: **Urinary Na^+/K^+ ratio > 1**

6.2. Chronic Kidney Disease (CKD)

CKD is the result of the **progressive and irreversible destruction** of **nephron mass**.

Causes (Etiologies): Glomerular, **Vascular**, **Tubulo-interstitial**, and **Genetic**

Biological Profile

- **Normocytic normochromic anemia**
- **Azotemia** (nitrogen retention syndrome)
- **Polyuria**, often the first sign indicating progression to **chronicity**
- **Hyperphosphatemia** with **hypocalcemia**
- In **end-stage CKD**, **renal replacement therapy** becomes essential, including:

Hemodialysis, **Peritoneal dialysis**, and **Kidney transplantation**

III. Trace elements

III.1. Introduction

Trace elements and minerals are essential nutrients necessary for the body in very small quantities-typically in the range of milligrams for minerals and micrograms for trace elements-for various biological and physiological functions. Since the human body cannot synthesize most of these elements, their bioavailability relies entirely on consistent dietary intake throughout life. While necessary for health, excessive levels of these elements can be toxic and harmful. The main minerals include sodium, potassium, magnesium, and calcium.

According to the WHO, the main trace elements are: iron, copper, zinc, iodine, selenium, fluoride, cobalt, molybdenum, manganese, chromium, vanadium, tin, silicon, lithium, and nickel.

III.2. Toxicity of Trace Elements

It is possible to distinguish two types of trace elements based on the risk of deficiency:

- **Essential trace elements at risk of deficiency**: Iodine, Copper, Iron, Zinc, Chromium, Selenium, Molybdenum, (Fluoride*).
- **Essential trace elements with a low risk of deficiency**: Manganese, Vanadium, Silicon, Nickel, Tin, (Cobalt*).
- The effect of trace element intake depends on the dose.
- When a trace element is essential, both its absence and excessive intake can be lethal.

III.3. Role of Trace Elements

A. Binding to Proteins

- This is a fundamental phenomenon because, with rare exceptions, metals never appear in their free ionic form in the body.
- For example: Zinc, iron, copper, etc., which most often bind with albumin, but also with other proteins specific to the trace element in question.

B. Enzyme Cofactors

Some trace elements are essential for enzyme activity and bind to enzymes in two ways:

- **By integrating into the molecular structure of the enzyme**, forming a metalloenzyme. The bonds with the enzyme are strong and stable.
- Examples: Hemoglobin (protoporphyrin + Iron), Vitamin B12 (protoporphyrin + Cobalt), and Copper in the production of elastin and collagen.
- **As a cofactor for the enzyme**, which is indispensable for its proper function, often referred to as a "metal-activator enzyme."

C. Structure of Vitamins

- Some trace elements are part of the structure of vitamins.
- This is the case with cobalt, which is complexed within the corrin ring of Vitamin B12.

D. Hormonal Action

- Trace elements can directly influence hormonal signaling, either by participating in the molecular structure of the hormone (such as iodine in thyroid hormones), by affecting its spatial conformation (like zinc in insulin), or by acting at the hormonal receptor level.
- They can either facilitate or inhibit the recognition of the hormone by its receptor.

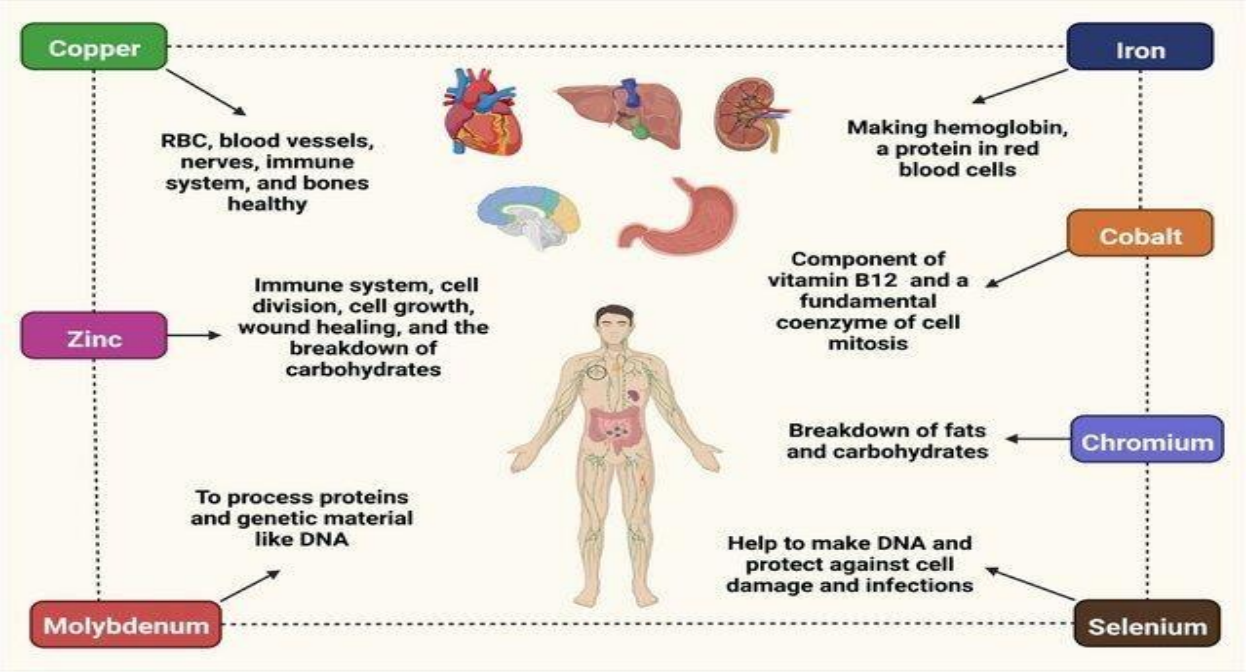
E. Defense of the Organism

- Primarily in the fight against oxygen free radicals.
- Enzymatic systems with antioxidant properties include copper and zinc superoxide dismutases (SOD), manganese SOD, catalases, and selenium-dependent glutathione peroxidases.
- All these enzymes utilize trace element cofactors—copper, zinc, manganese, and selenium—which are thus referred to as antioxidant trace elements.

F. Structural Role

- Although present in trace amounts, trace elements can strengthen the structural integrity of certain tissues:

- **Fluoride** replaces a hydroxyl (OH) group in the hydroxyapatite of bones and teeth (see Figure III.1).
- **Silicon** helps connect collagen fibers to mucopolysaccharides in connective tissues.



FigureIII.1. Role of trace elements in human health.

III.4. Metabolism of Trace Elements

The metabolism of trace elements involves their absorption, distribution, utilization, and excretion within the body.

III4.1. Absorption

- In food, a trace element can exist in the following forms:
  - **Free**: either ionized or not;
  - **Bound to small molecules**: more or less soluble;
  - **Bound to specific or non-specific proteins**.
- The absorption process occurs based on the chemical forms of the trace elements.

III.4.1.1. Simple Diffusion

- Passive process according to a concentration gradient.

III.4.1.2. Passive Transport

- Transmembrane transporters (specific or non-specific) facilitate the movement.

III.4.1.3. Active Transport

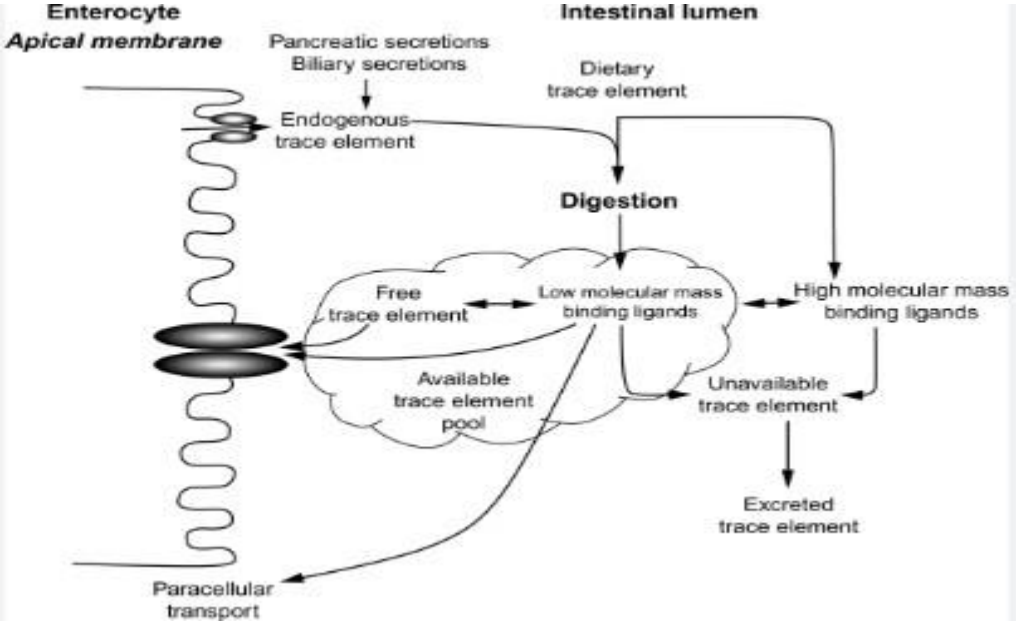
- Against a concentration gradient, involving ion pumps that consume ATP.

III.4.2. Transport

- Trace elements are rarely present in their ionic form in the bloodstream.
- They will be bound to various transporters after absorption, which will carry them to their site of action or storage. These transporters can include:
    - **Non-specific proteins**,
    - **Small molecules**, such as amino acids or vitamins,
    - **Specific transport proteins**: e.g., Transferrin (for Iron), Transcobalamin (for Cobalt), Ceruloplasmin (for Copper), etc.

III.4.3. Storage

- Trace elements are stored in various tissues (see FigureIII.2):
    - **Liver** (+++),
    - **Kidney** (++),
    - **Bone tissue** (+),
    - **Intestine** (+).
- **Storage Proteins**
    - **Specific proteins**: e.g., Ferritin,
    - **Non-specific proteins**: e.g., Metallothioneins (for Copper, Zinc, Manganese).



FigureIII.2. Metabolism of trace elements

III.4. 4.Tissue Utilization

- Metals have various destinies: They can be used or stored at the cellular level (in storage proteins); They can be metabolized, oxidized, or reduced under the influence of specific enzymes; Or they may be incorporated into enzymes.

III.4.5. Excretion

- **Liver:** via bile (primarily): Cu (Copper), Mn (Manganese), Fe (Iron), Ni (Nickel);
- **Kidneys:** via urine (mainly): Cr (Chromium), Co (Cobalt), Se (Selenium), Mo (Molybdenum), I (Iodine), and F (Fluorine);
- **Sweat (possible route):** Cr (Chromium), Fe (Iron), Cu (Copper), Zn (Zinc), and Se (Selenium),

III.5. Pathologies Related to Trace Elements

- Diseases may result from an excess or shortage of specific trace elements.
- A hereditary error (genetic mutation) affecting a gene coding for a protein involved in the metabolism of a trace element leads to a disorder, the severity of which depends on the biological role of the mutated protein.

- *Example:* A mutation affecting the ATP7B protein causes **Wilson's disease**.

III.6. Main Trace Elements

The main trace elements essential for human health include **iron,** which is essential for blood oxygen transport; zinc, which promotes wound healing and immune function; **copper,** which is involved in energy production and nervous system health; **iodine**, which is required for the creation of thyroid hormones; and **selenium,** which functions as an antioxidant and supports thyroid function; **manganese**, important for bone formation and metabolism; **fluoride**, which helps maintain dental and bone health; **chromium**, involved in glucose metabolism; and **molybdenum**, which supports enzyme function related to amino acid metabolism.

III.6.1. Metabolism of Iron

1. Introduction

Iron presents a unique paradox; it is vital for our health yet can also be harmful. It is crucial for oxygen transport, serving as a component of heme and various enzymes like catalases, cytochromes, and peroxidases, and is involved in electron transfer. However, iron can also be toxic, with Fe^{2+} playing a significant role in generating harmful oxygen free radicals.

2. Iron Distribution in the Body

An adult typically contains between 3 to 4 grams of iron, distributed across several compartments that vary in quantity.

2.1. Functional Compartment

This compartment holds about 70% of total iron (approximately 2.8 grams), mainly in the ferrous form found in heme proteins, especially hemoglobin. Small amounts are also present in myoglobin and some oxidative enzymes.

2.2. Transport Compartment

Comprising just 0.1% of total iron (4 mg), this includes non-heme or ferric iron found in plasma, bound to transferrin.

2.3. Reserve Compartment

Accounting for 25% of total iron (1 gram), this iron is stored in the mononuclear phagocyte system cells (in the liver, spleen, and bone marrow) and in hepatocytes, existing in two forms: **Ferritin**: A protein that dissolves and functions as a mobilizable reserve, and **Hemosiderin**: An insoluble protein containing a higher iron fraction, with reserves that are harder to mobilize.

3. Iron Metabolism

3.1. The Iron Cycle

The body conserves iron meticulously. The unique aspect of iron metabolism is that it functions almost in a closed loop. The iron pool is constantly being renewed; iron used in hemoglobin is retrieved after red blood cells are broken down (see Figure III.3). Daily losses are minimal, and dietary absorption is aimed at replacing physiological losses and any excessive losses.

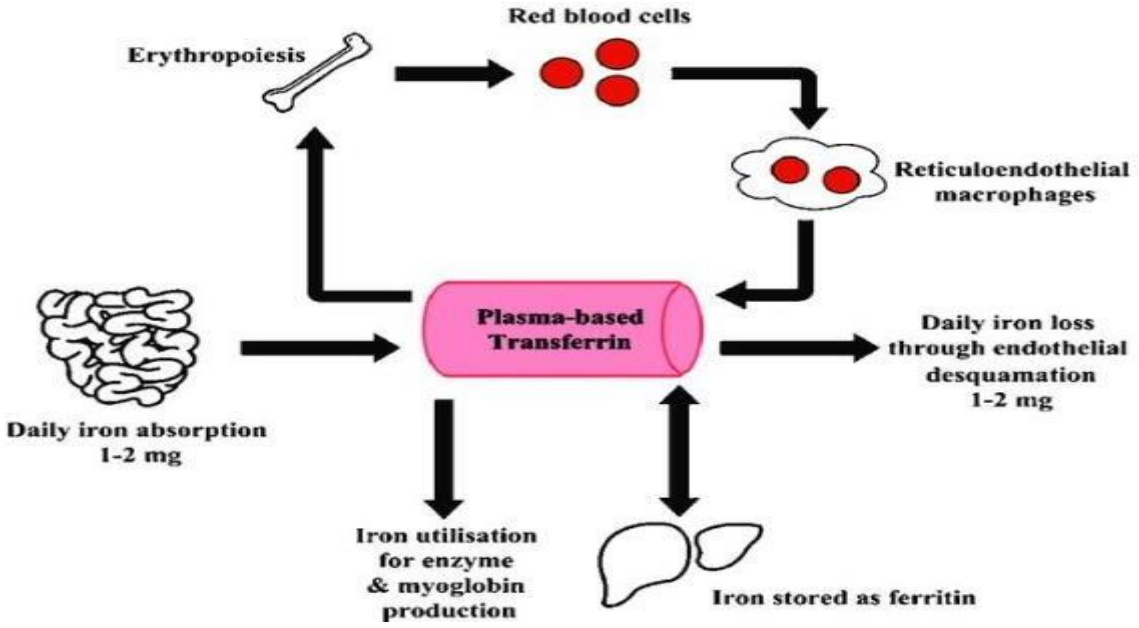


Figure III.3. Iron cycle

3.2. Intake, Requirements, and Losses

3.2.a. Losses

Every day, the body loses roughly 1 mg of iron, primarily through digestion (65% via secretion and desquamation) and 35% through skin shedding, hair loss, and urine. In women, these losses are heightened due to menstruation, pregnancy, and breastfeeding, and there is no regulatory mechanism for elimination.

3.2.b. Iron Requirements

The daily iron requirements are 1 mg for men and 2 mg for women, with increased needs during pregnancy, lactation, and in children and adolescents.

3.2.c. Iron Intake

Iron intake, provided in both heme and non-heme forms, typically meets daily needs of around 10-20 mg. Sources rich in iron include brewer's yeast, cocoa, lentils, soy, egg yolks, dried fruits, beans, spinach, and lettuce.

3.3. Iron Absorption in the Intestines

Only 5 to 10% of daily iron intake is absorbed, sufficient to replace losses. The absorption primarily occurs in the duodenum and upper jejunum, facilitated by mature enterocytes at the villi tips. Heme iron is absorbed more effectively than ferric iron.

The absorbed iron is transported to the plasma, while some remains in the enterocyte bound to ferritin and is lost during cell shedding.

a. Intraluminal Phase (Stomach, Duodenum)

- **Heme Iron:** In the pylorus, hemoglobin and myoglobin are broken down into heme and globin. The globin releases amino acids that help dissolve heme, which is then quickly absorbed.
- **Non-Heme Iron**: This type of iron needs to be solubilized by mucin and an acidic environment before it can be absorbed.

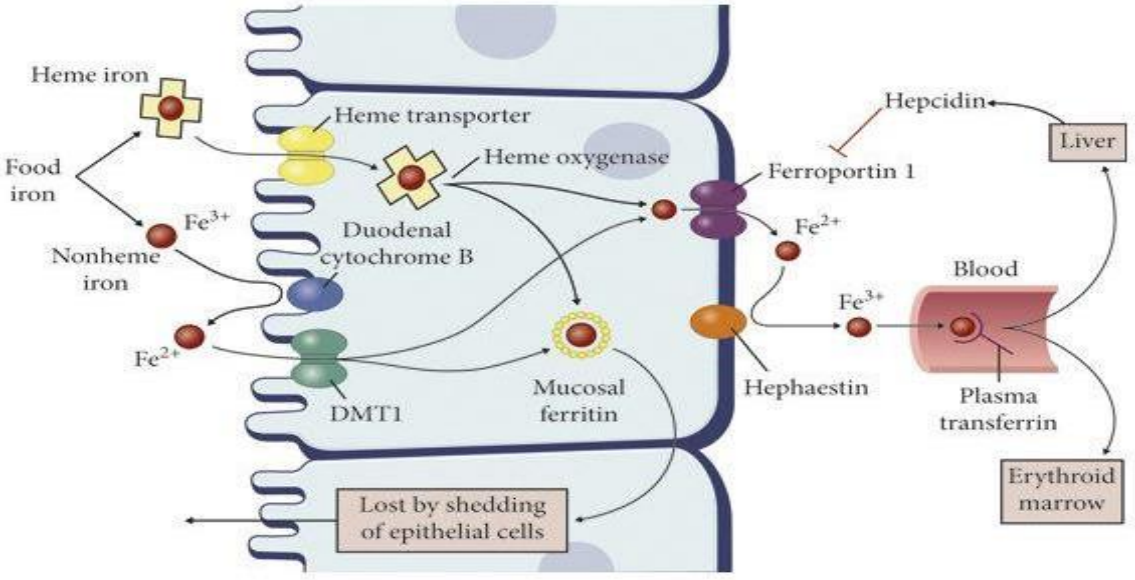
b. Incorporation into the Enterocyte

- **Heme Iron**: Heme passes through the apical side of the enterocyte via a specific transporter, HCP1. Inside the cell, it is converted by heme oxygenase to release Fe^{2+}.
- **Non-Heme Iron:** The enzyme Dcytb converts intestinal lumen ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}), which is then carried across the luminal membrane by the divalent metal transporter DMT1.

c. Basolateral Release of Iron

The movement of iron from the enterocyte to the plasma involves two key proteins:

- **Ferroportin**: The sole iron exporter, which transports Fe^{2+} from the basal side of the enterocyte into the bloodstream, regulated by hepcidin (see Figure III.4).
- **Hepcidin**: An enzyme that oxidizes Fe^{2+} to Fe^{3+}, allowing it to be carried by transferrin. Hepcidin is part of the family of copper-dependent oxidases.



FigureIII.4. Mechanisms of intestinal iron absorption.

3.4. Factors Influencing Absorption

Enhanced by:

• Increased dietary iron intake: up to 2 times (maximum)

• Heme iron: absorbed 3 to 4 times more efficiently than non-heme iron

- Heme iron absorption ≈ 20%; Non-heme iron absorption ≈ 1–4%; Consumption of vitamin C

Limited by:

• **Phytic acid**: found in whole grains and legumes (e.g., whole wheat, brown rice, fava beans, and lentils) → soaking and cooking can reduce its effect; **Oxalic acid**: present in cooked spinach, beets,

rhubarb, and cocoa; **High amounts of other minerals**: such as magnesium and calcium (found in highly mineralized water, soy, dairy products, and eggs); **Phosphate-based additives**: commonly found in meat, sausages, and cheese; **Tannins**: present in tea, cocoa, and coffee

3.5. Main Dietary Sources of Iron

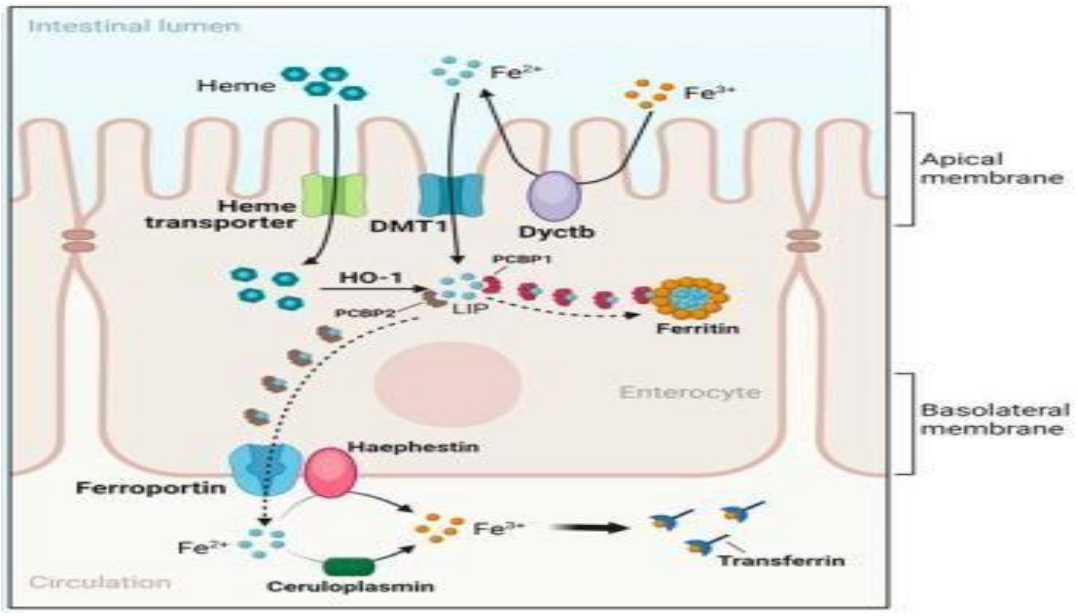
Iron is found in a variety of foods (see Table III.1), typically categorized into **heme iron sources** (from animals) and **non-heme iron sources** (mostly from plants).

Table III.1. Sources of Iron

Heme Iron Sources (better absorbed)	**Non-Heme Iron Sources (less well absorbed)**
Red meat (beef, lamb) Poultry (chicken, turkey) Liver and organ meats Fish and seafood (sardines, tuna, clams)	Legumes (lentils, chickpeas, beans) Whole grains (quinoa, brown rice, oats) Tofu and soy products Leafy green vegetables (spinach, kale) Dried fruits (apricots, raisins) Nuts and seeds (pumpkin seeds, cashews)

3.6. Iron Export from the Enterocyte at the Basolateral Side: 2 Key Proteins

- **Ferroportin:** A **membrane transporter** that allows the **export of ferrous iron (Fe^{2+})** from the enterocyte into the bloodstream (plasma). Its **expression is regulated based on the body's iron needs** (see Figure III.5).
- **Hephaestin:** A **membrane-anchored protein** with **ferroxidase activity** (part of the **copper-dependent oxidase family**). It **oxidizes Fe^{2+} to Fe^{3+}**, which is the form that can be **bound by transferrin** in the blood for transport.



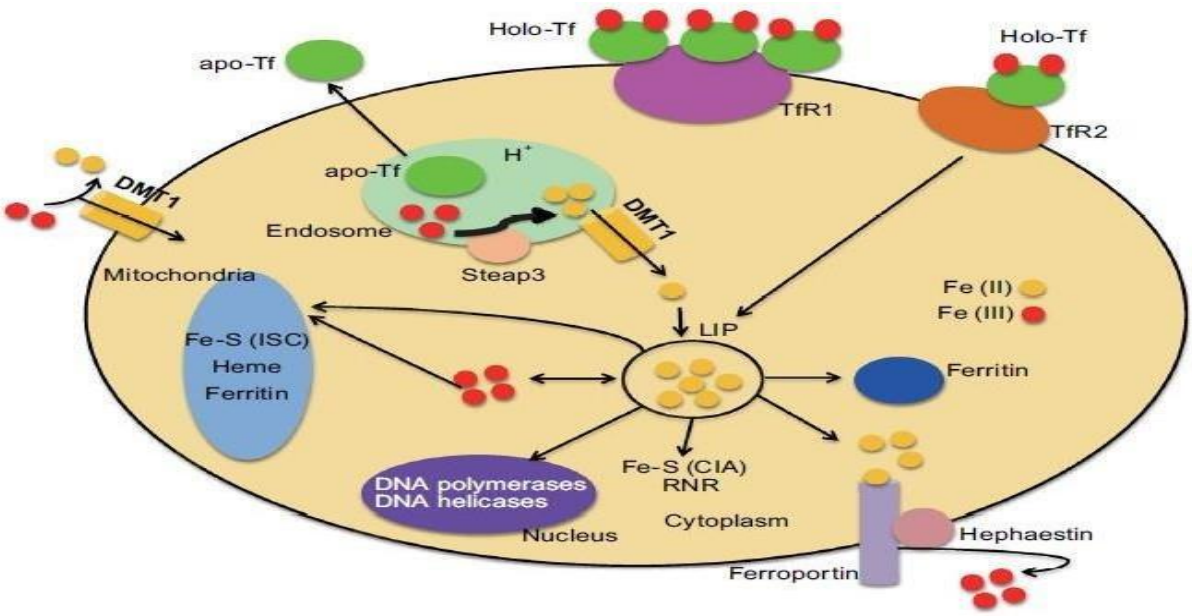
FigureIII.5. Dietary iron absorption.

3.7. Plasma Transport of Iron

Iron released from intestinal epithelial cells, hepatocytes, or macrophages is carried by **transferrin**, a glycoprotein that can bind up to two atoms of iron in the form of Fe^{3+}. Secreted actively by hepatocytes, transferrin is essential for maintaining iron solubility and distributing it throughout the body's tissues.

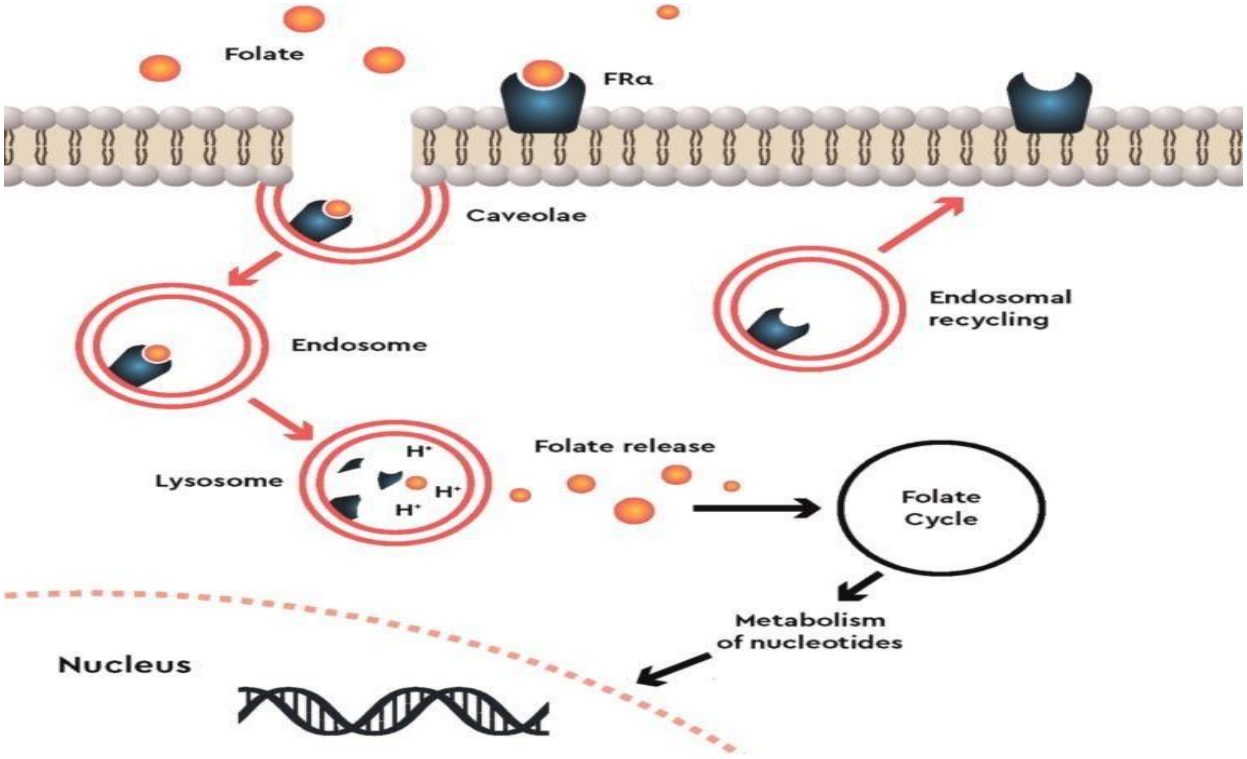
3.8. Iron Uptake via the Transferrin Receptor

Cells uptake iron which link to Transferrin through the **transferrin receptor (RTF)**, which exists in two forms (see Figure III.6):



FigureIII.6. The holoTf-TfR1 complex is endocytosed and internalized into an endosome.

- **RTF1**: A homodimeric transmembrane glycoprotein found on nearly all cell types, capable of binding two transferrin molecules.
- **RTF2**: Shares 66% structural homology with RTF1 and is primarily expressed in the liver (see Figure III.7).



FigureIII.7. Endocytosis of the TF/RTF complex.

3.9. Iron Metabolism Within Cells

a. Metabolic Use (Functional Pool)

About 75% of iron is used for synthesizing hemoglobin, while the rest is allocated for the production of other non-heme and heme proteins.

b. Iron Storage

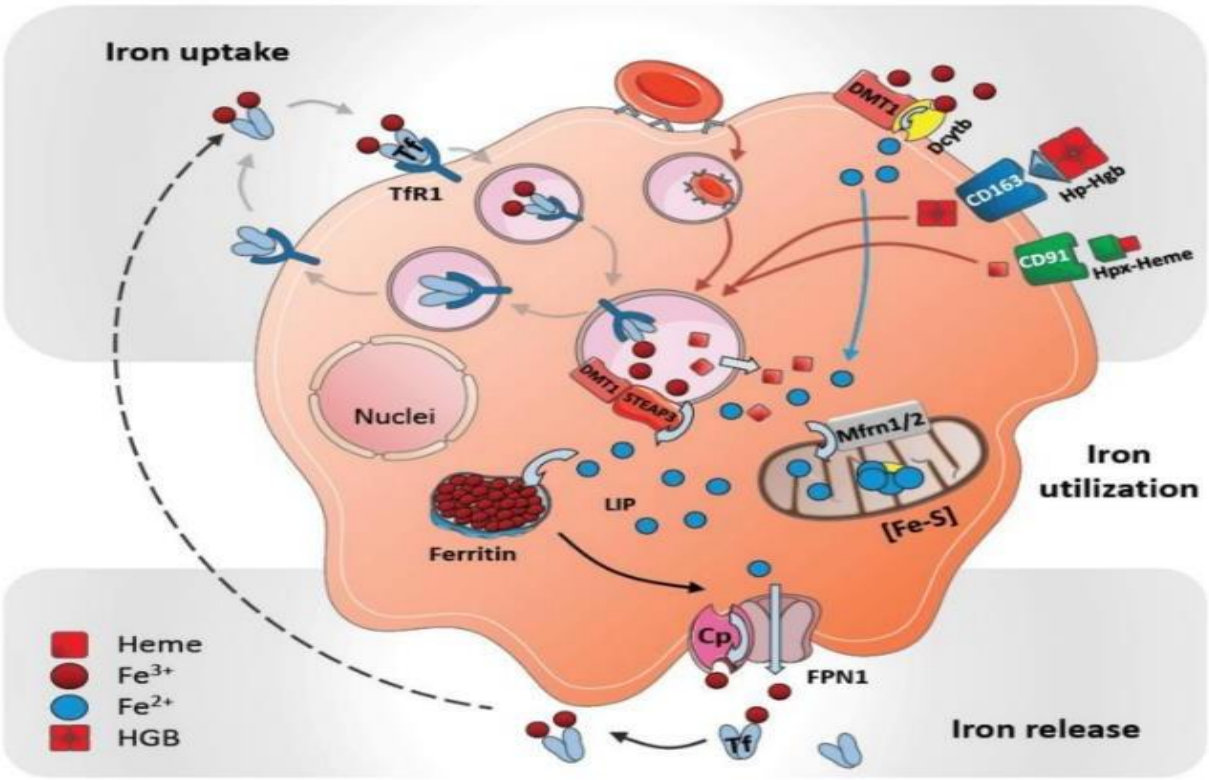
When the iron concentration in the cytoplasm increases, it is stored to avoid toxicity. The main storage sites are in the liver and spleen, primarily within two proteins: **ferritin** and **hemosiderin**.

3.10. Recycling of Heme Iron (Erythrophagocytosis)

Most of the iron used for the daily red blood cells (RBCs) production comes from the recycling of iron released by senescent RBCs: this is erythrophagocytosis.

- Senescent RBCs are phagocytized by macrophages. They are degraded, and with the help of heme oxygenase (HO), iron is released from hemoglobin. Other possible pathways for iron entry into the macrophage involve the HFE-β2m-RTf1 complex and the haptoglobin-hemoglobin complex. Hemoglobin is degraded by HO to release iron (see Figure III.8).

The iron is then either stored in ferritin or recycled. It is exported by ferroportin and then oxidized by circulating ceruloplasmin before being taken up by circulating transferrin.



FigureIII.8. Iron metabolism by macrophages.

3.11. Iron elimination

There is no iron excretion active mechanism; instead, iron is eliminated through the digestive system, skin, urine, and bile, with daily losses estimated at 1 to 2 mg.

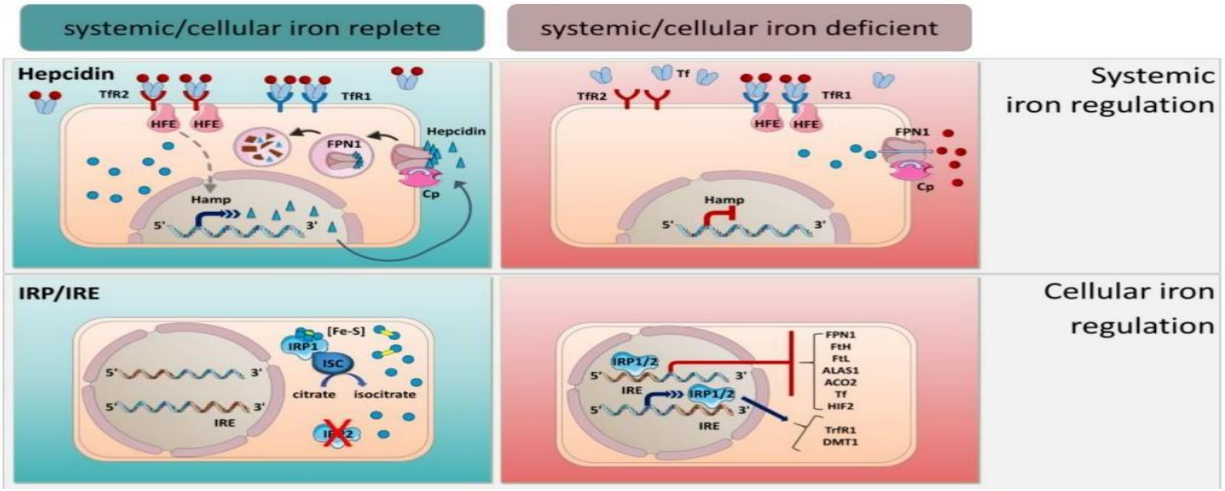
4. Iron Homeostasis maintenance

Maintaining iron homeostasis involves three main factors that influence the iron absorption in the intestines and its release from macrophages.

4.1. The role of Hepcidin

Hepcidin plays a crucial role in regulating iron homeostasis. This small peptide hormone (25 AA), produced by the liver, is known as a hypotransferrinemic hormone because it restricts both internal and external iron intake by promoting the internalization of ferroportin. It negatively regulates the absorption of intestinal iron and the recycling of heme iron by macrophages (see Figure III.9).

When the body requires more iron, hepcidin production is greatly reduced, enhancing intestinal absorption and the iron release reserves from macrophages. In contrast, during inflammatory responses, hepcidin levels typically increase, leading to decreased intestinal iron absorption and reduced recycling by macrophages.



FigureIII.9. Principal iron regulating systems. Hepcidin, the IRP/IRE, Spi-C/Bach1, and HIF/HRE regulate iron metabolism.

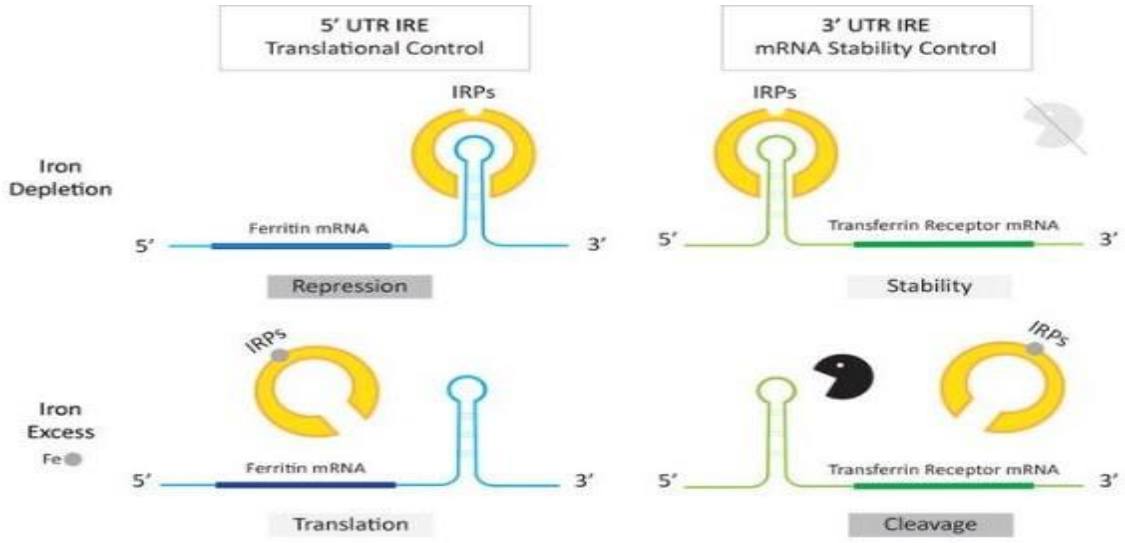
4.2. The HFE protein

HFE is an HLA class I molecule found in enterocytes and macrophages that captures iron through the transferrin/RTf1/β2-microglobulin complex. According to the crypt model, crypt cells evaluate the body's

iron status based on the saturation of circulating transferrin. This information is transmitted to the crypt cells via the complex of HFE, β2-microglobulin, and the transferrin receptor, aiding iron uptake. In response, these cells adjust dietary iron absorption in mature villous cells by altering the iron transporters expression, DMT1 and ferroportin, depending on the levels of iron in the crypt cells.

4.3. Intercellular regulation by the IRE-IRP system

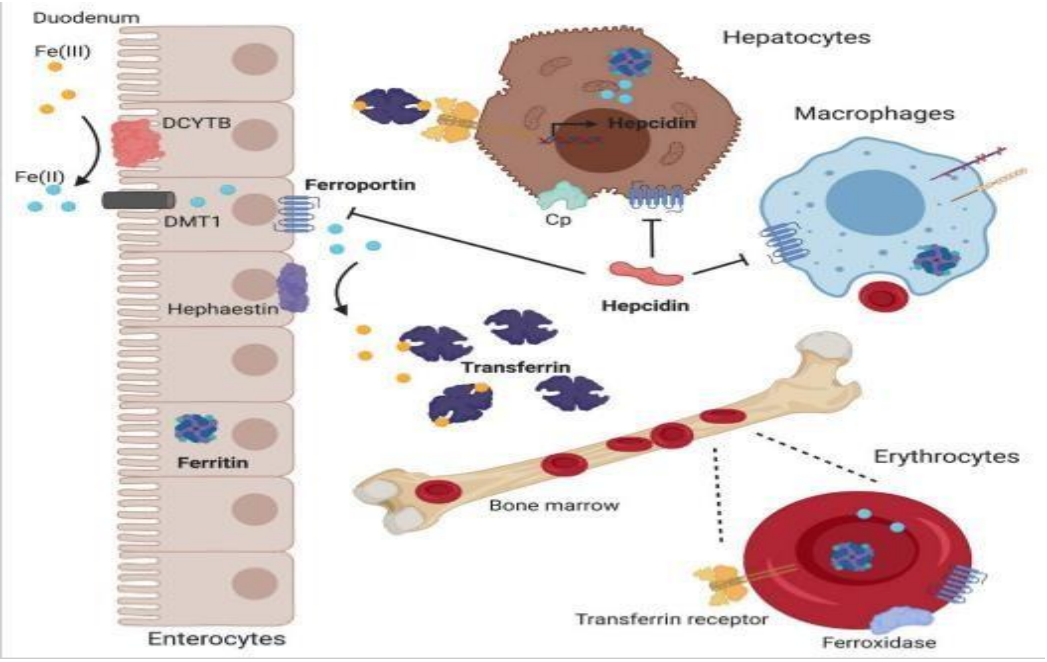
Regulating intracellular iron levels relies on controlling iron entry and storage through the IRE-IRP system. Iron intake is managed by modulating ferritin and transferrin receptor synthesis (see Figure III.10). Their mRNAs contain iron regulatory elements (IRE) in their untranslated regions, which can bind cytoplasmic iron regulatory proteins (IRP) to influence protein synthesis.



FigureIII.10. Depiction of the IRP/IRE regulatory mechanism functioning at the post-transcriptional level for two gene groups involved in iron metabolism: ferritin and transferrin receptor-1.

IRP can function as a regulatory factor or an enzyme (aconitase) relying on an iron-sulfur center's existence. When this center is present, IRP acts as aconitase; when absent, it binds to IREs, preventing ferritin mRNA translation while stabilizing transferrin receptor mRNA. When labile iron levels rise, IRP retains its iron-sulfur center and does not bind to IREs, allowing ferritin synthesis while reducing transferrin receptor levels (see Figure III.11). Conversely, during iron deficiency, IRP loses its iron-sulfur

center, binds to IREs, inhibits ferritin synthesis, and promotes the expression of transferrin receptor to enhance iron uptake and limit storage.



FigureIII.11. Key players in iron metabolism.

5. Investigation of Iron metabolism

Blood tests for iron metabolism are performed using venous samples.

5.1. Sample collection

- Use a dry or heparinized tube.
- Samples should be collected between 8 a.m. and 10 a.m. consistently for follow-up, as serum iron levels vary significantly throughout the day.
- Ensure to avoid hemolysis during collection.

5.2. Serum Iron Testing

5.2.a. Physical methods

Atomic absorption photometry is rarely utilized, despite being the gold standard.

5.2.b. Colorimetric methods

These methods follow a similar process:

- Iron (Fe3+) is released from its transport protein through acidification (using an acidic buffer).
- Fe3+ is then reduced to Fe2+ (using a reducing agent like vitamin C).
- Fe2+ reacts with a chromogen to create a colored compound, with the color intensity reflecting the iron concentration in the sample. Various chromogens, such as triazines, ferene, and ferrozine, can be used.

5.2.c. Normal ranges

- Men: 10 – 30 µmol/l
- Women: 6 – 26 µmol/l
- Children:11–24µmol/l

  Isolated serum iron measurements are not very informative due to daily fluctuations.

5.3. Transferrin measurement

The body's iron stores and circulation transferrin levels are inversely correlated.
5.3.a. Methods: Immunochemical techniques (particularly immuno-turbidimetric methods).

5.3.b. Normal ranges: 2 – 4 g/l

5.4. Total Iron binding capacity (TIBC) calculation

5.4.a. Calculation

TIBC indicates the maximum iron transport capacity of transferrin and is calculated based on transferrin levels.

CTF µmol/l = TRF (g/l) × 25

5.4.b. Normal ranges

- 200-400 µg/dl

- 50-90 µmol/l

5.5. Calculation of Transferrin Saturation Coefficient (CS)

5.5.a. Calculation

CS = (Serum Iron / TIBC) × 100

This equation expresses the transferrin saturation as a percentage, indicating how much of the total iron-binding capacity is occupied by iron

5.5.b. Normal range: 20-40%

5.6. Ferritin measurement

5.6.a. Methods

Immunochemical techniques are employed, but there is no standardized reference method.
***5.6.b. Normal values*:** Ferritin levels vary by age and sex:

- Men: 30–300 µg/l
- Women: 15–150 µg/l (before menopause)
- Women: 20–200 µg/l (after menopause)
- Children: 15–80 µg/l

5.7. Measurement of Soluble Transferrin Receptors

Soluble transferrin receptors (RsTf) are truncated versions of the membrane receptor's extracellular domain. This circulating monomeric form can still bind one transferrin molecule. The concentration of RsTf in plasma is correlated with the number of transferrin receptors and thus indicates iron status. Measuring RsTf can assess iron levels and erythropoiesis, using either ELISA (rarely) or immunoturbidimetry/nephelometry.

5.8. Others method

Prussian Blue Staining:

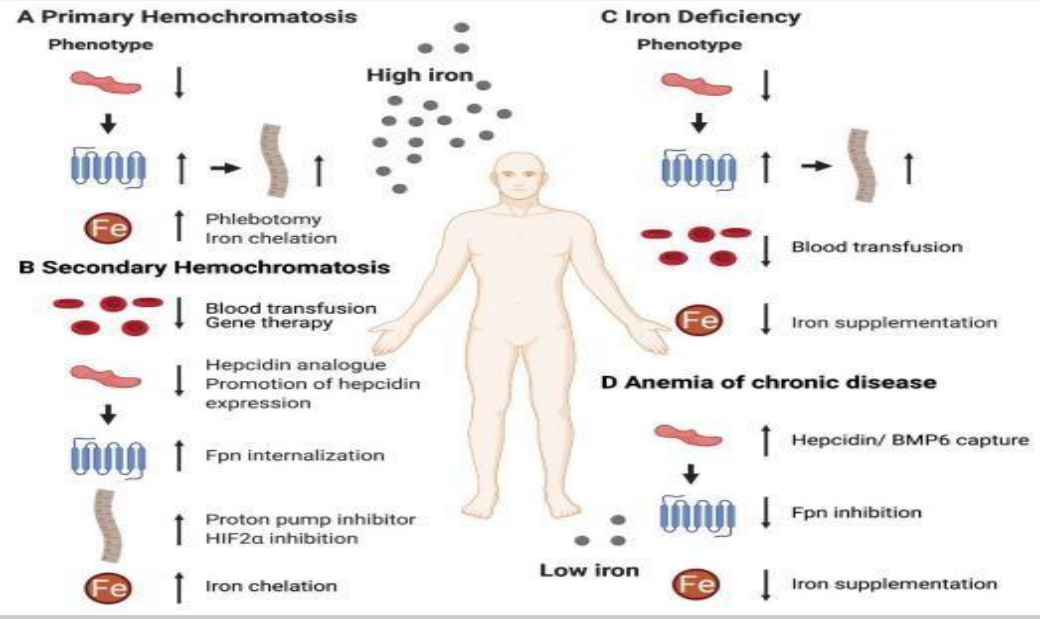
In an acidic medium and in the presence of ferric ions, potassium ferrocyanide transforms into a blue precipitate of ferricyanide called Prussian blue, which visualizes macrophagic reserves. On a bone marrow smear, this staining detects abnormal iron accumulation in erythroblasts, which are then referred to as sideroblasts. This examination is particularly useful for investigating iron incorporation disorders in older individuals, known as "myelodysplastic syndromes."

6. Pathological variations

6.1. Hereditary Hemochromatoses

6.1.a. Type I HFE Hemochromatosis: This condition has an autosomal recessive inheritance pattern and is characterized by iron overload caused by excessive iron absorption, leading to its accumulation. Several mutations can affect the HFE gene on chromosome 6:

- **C282Y Mutation**: This mutation substitutes cysteine with tyrosine at position 282, disrupting the transport of the HFE protein to the membrane and its binding to RTf1. It is the most common mutation ((see Figure III.12).
- **H63D Mutation**: This mutation involves the substitution of histidine with aspartate at position 63.



FigureIII.12. Therapeutic strategies targeting iron metabolism.

i. Natural history

- Gradual iron accumulation in the body
- Latent phase lasting 15-20 years
- Biological markers include:
  - Increased serum iron
  - Increased CS
  - Increased ferritin
- Clinical symptoms typically appear around ages 30-40 in men.

ii. Clinical symptoms

- **Skin manifestations**: Hyperpigmentation (melanodermia)
- **Liver involvement**: Hepatomegaly, mild elevation of transaminases, increased risk of hepatocellular carcinoma
- **Endocrine issues**: Diabetes, hypogonadism
- **Other complications**: Cardiac and joint problems

iii. Laboratory findings

- Elevated serum iron levels
- Increased ferritin (high sensitivity, low specificity)
- Transferrin saturation (CS) exceeding 45%
- Other findings include elevated blood glucose and transaminases
- **Molecular diagnosis**: Genetic testing to identify mutations is crucial for confirming the diagnosis.

iv. Treatment options

- Phlebotomy: Reduces iron levels through reactive erythropoiesis
- Iron chelators for cases where phlebotomy is not suitable
- Family phenotypic and genotypic assessment

6.1.b. NON-HFE Hemochromatosis type II, III, AND IV

- **Juvenile Hemochromatosis, Type II (autosomal recessive inheritance)**
  - **Type II A**: HJV gene responsible for hemojuvelin
  - **Type II B**: HAMP gene responsible for hepcidin
- **Type III Hemochromatosis (autosomal recessive)**
  - RTf2 gene
- **Type IV Hemochromatosis (autosomal dominant)**
  - Ferroportin gene

6.2. NON-Hemochromatic Iron overload

6.2.a. With normal saturation coefficient

- Dysmetabolic hepatosiderosis: Liver iron overload associated with metabolic syndrome and insulin resistance
- Hereditary aceruloplasminemia

6.2.b. With increased saturation coefficient

- **Liver conditions**: Viral hepatitis, Alcoholic hepatitis, Non-alcoholic steatohepatitis, Late-onset cutaneous porphyria, Cirrhosis, Hepatocellular carcinoma (HCC)

- **Anemia resulting from ineffective erythropoiesis**, leading to increased intestinal iron absorption:Thalassemia, Sideroblastic anemia

- **Excessive Parenteral Iron Intake**: Frequent blood transfusions, Hemodialysis combined with transfusions
- **Excessive Oral Iron Intake**

6.2. Iron deficiencies

6.2.a. Anemias

- Decreased hemoglobin levels:
  - in men, less than 13 g/dl
  - in women, less than 12 g/dl
  - in newborns, less than 14 g/dl
- Causes of diagnostic errors:
  - Pseudo-anemia due to hemodilution: An increase in the volume of plasma causes dilution of hemoglobin, seen in conditions like pregnancy, kidney failure, and heart failure.
  - Anemia masked by hemoconcentration: Occurs in cases like dehydration or extensive burns.

6.2.b. Iron defficienty anemias

i. Pathophysiology

1. **Pre-latent deficiency**: Reduction in tissue iron stores leads to lower ferritin levels.
2. **Latent deficiency**: As reserves deplete, serum iron decreases, transferrin increases, total iron-binding capacity (TIBC) rises, transferrin saturation (CS) drops, and soluble transferrin receptors (RsTf) increase.
3. **Manifest deficiency**: This affects erythropoiesis, resulting in lower hemoglobin (Hb), microcytosis (reduced mean corpuscular volume, MCV), and hypochromia (decreased mean corpuscular hemoglobin, MCH).

ii. Clinical signs

- Four main signs: Pallorm Fatiguem Rapid heartbeat (tachycardia), and Shortness of breath during exertion (dyspnea)
- Other symptoms may include: Increased breathing rate (polypnea)m Non-specific systolic murmur Low blood pressure (hypotension)m and Changes in hair and nails

iii. Laboratory tests

Common tests used in clinical practice (as per HAS recommendations):

- Measurement of serum ferritin (which is decreased)
    - Highly sensitive but not very specific (C-reactive protein tests can help identify inflammatory conditions).
    - Alternatively,
- Measurement of transferrin saturation (which is decreased) alongside serum iron (decreased) and increased TIBC.

iv. Etiologies

- **Increased Iron Loss**: Gastrointestinal or genital bleeding
- **Increased Iron Requirements**: Growth, pregnancy, blood donations
- **Decreased Iron Intake**: Inadequate dietary intake
- **Malabsorption**: Conditions like celiac disease, reduced gastric acidity, Medications (such as gastric acid suppressants)

6.2. c. Inflammatory anemias

i. Pathophysiology

Inflammatory anemia occurs during immune system activation and inflammatory states, where inflammatory mediators can:

- Inhibit erythropoiesis precursors, shorten red blood cell lifespan, and disrupt erythropoietin synthesis and function—this is the initial mechanism.

- Alter iron metabolism by sequestering iron released during hemolysis in the reticuloendothelial system (with hepcidin playing a key role). As a result, while ferritin reserves may be normal or elevated, serum iron and iron available for erythropoiesis are reduced. Inflammation directly increases ferritin synthesis.

ii. Laboratory findings

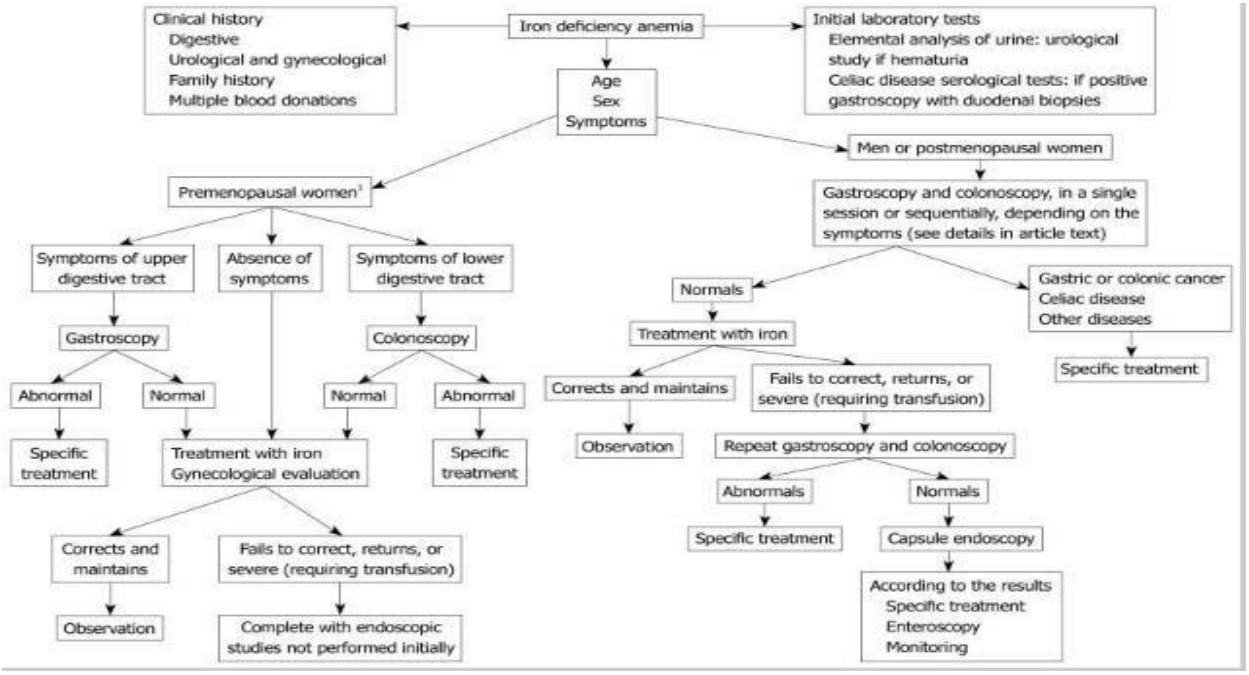
During inflammation, ferritin is no longer a reliable marker for iron status.

- Instead, transport iron markers should be used: serum iron and transferrin levels. These tests allow for the calculation of transferrin saturation (CS < 20%).
- **Iron status assessment**: Decreased serum iron, Decreased transferrin saturation, and Increased ferritin

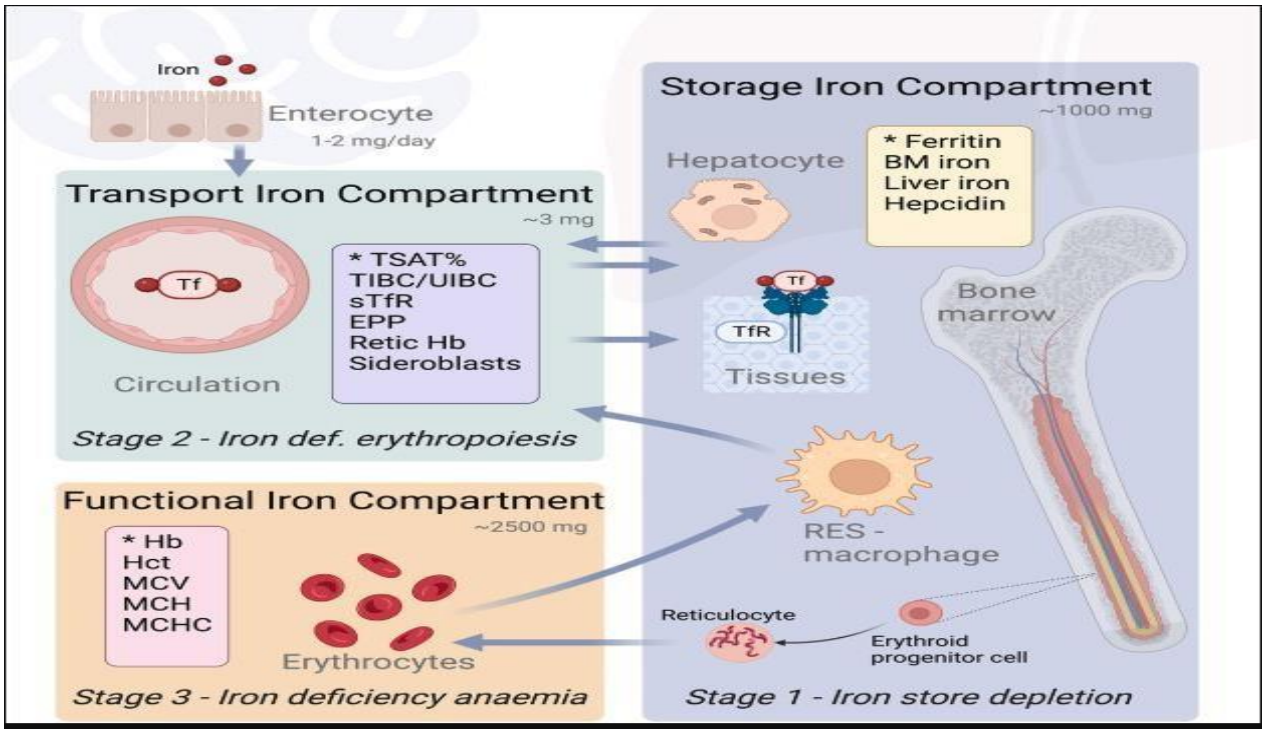
- **Biological Inflammatory Syndrome**: Increased white blood cell count (hyperleukocytosis), Elevated erythrocyte sedimentation rate (ESR), and Presence of inflammatory proteins, including C-reactive protein (CRP)

iii. Etiologies

- Inflammatory diseases, Chronic kidney disease, Chronic inflammatory bowel diseases, Cancers, Autoimmune disorders (see Figure III.13 and 14).



FigureIII.13. Etiologic diagnosis of iron deficiency anemia



FigureIII.14. The parameters for testing the body's iron compartments.

III.6.2. Metabolism of Copper

1. Introduction

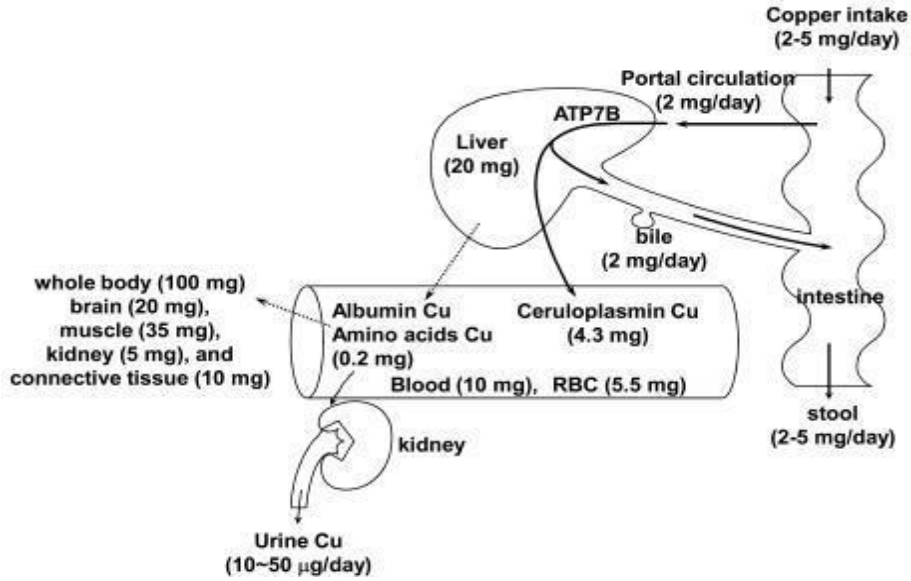
Copper is a crucial trace component obtained through diet. It is integrated with various enzymes that play roles in regulating iron metabolism, forming connective tissue, producing cellular energy, maintaining antioxidant balance, synthesizing melanin, and supporting neurological functions.

2. Copper balance in the body

Approximately 25 to 50% of dietary copper is absorbed in the stomach and duodenum. Its passage through the portal system involves the ATP7A transporter, which carries it to the liver, binding to proteins and low-molecular-weight amino acids.

2.1. Absorption

In the liver, copper is managed by a chaperone molecule called Atox1, which is a cytosolic partner of the ATP7B transporter. The ATP7B transporter is found in the liver, nervous system, and kidneys. The level of intracellular copper regulates the localization of ATP7B ((see Figure III.15). When normally phosphorylated and located in the Golgi apparatus, ATP7B incorporates copper into apoceruloplasmin to form holoceruloplasmin.



FigureIII.15. Absorption of Copper, transport and elimination

Intracellular Transport and Distribution

In hepatocytes, copper is initially taken up by the copper transporter CTR1 and then binds to cytoplasmic chaperone proteins such as ATOX1, which direct it to the Golgi apparatus. There, the protein ATP7B facilitates the transfer of copper into the Golgi network, where it binds to apoceruloplasmin to form holoceruloplasmin, the active form of ceruloplasmin. Any excess copper is stored safely in a non-toxic form bound to metallothionein.

Ceruloplasmin

Ceruloplasmin is a glycoprotein responsible for transporting over 95% of circulating copper in the blood. It exists in two forms: apoceruloplasmin (without copper) and holoceruloplasmin (copper-bound, active form). This protein plays a key role in iron metabolism by oxidizing ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}), enabling its binding to transferrin and thereby protecting tissues from iron-induced toxicity. Its ferroxidase activity is dependent on the presence of copper. Ceruloplasmin levels can increase in conditions such as pregnancy, estrogen therapy, and inflammatory syndromes, while they may decrease in cases of nephrotic syndrome and malnutrition.

Elimination

When intracellular copper levels rise, ATP7B undergoes hyperphosphorylation, leading to its relocation from the Golgi to the cytoplasm, which facilitates copper excretion into bile. Urinary elimination plays a minor role in copper clearance, with bile being the primary excretion route. Other minor excretion pathways include saliva, sweat, menstrual flow, and intestinal excretion from the bloodstream.

3. Copper pathologies

3.1. WILSON'S Disease

Wilson's disease, also known as "hepatolenticular degeneration," is a genetic condition that has an autosomal recessive inheritance pattern. It is characterized by copper toxicity due to the accumulation of free copper in tissues, primarily in the liver, brain, and around the cornea. This condition arises from mutations in the ATP7B gene located on chromosome 13, which encodes the ATP7B protein responsible for copper transport within hepatocytes.

3.1.a. Pathophysiology

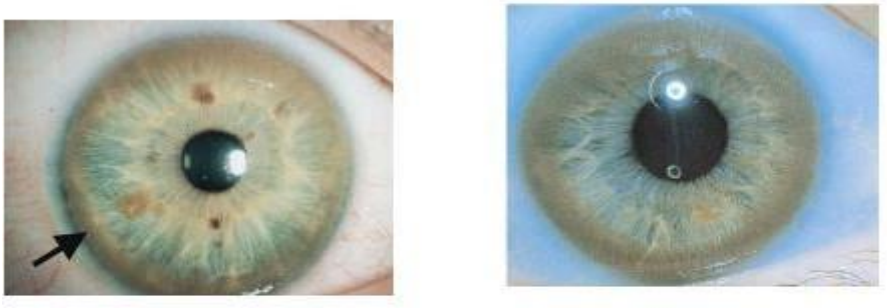
Wilson's disease is marked by a functional deficiency of ATP7B, leading to copper overload that hepatocytes cannot excrete into bile. The excess copper accumulates in the liver, both bound to metallothionein (a storage protein) and in free form. As a result, copper is not incorporated into apoceruloplasmin, causing a decrease in serum ceruloplasmin concentration.

3.1.b. Clinical presentation

The body gradually accumulates copper, initially in the liver and subsequently in other organs. Symptoms often manifest around the age of 20 and may include hepatic and/or neurological disorders. Psychiatric disturbances are also commonly observed.

3.1.c. Ophthalmological Manifestations

In about 80% of cases of Wilson's disease, ophthalmological symptoms are present, notably the Kayser-Fleischer ring (see Figure III.16). This ring is a pathognomonic sign of Wilson's disease, although its absence does not rule out the condition.



FigureIII.16. Kayser-Fleischer ring

3.1.d. Biology: Decreased serum ceruloplasmin levels, Decreased total copper levels, Increased free copper levels (free copper = total copper - copper bound to ceruloplasmin), Elevated 24-hour urinary copper excretion, increased hepatic copper levels (assessed via liver biopsy), and Molecular diagnosis involves testing for mutations in the ATP7B gene.

3.1.e. Treatment: Use for treatment: Copper-restricted diet, D-penicillamine, Zinc supplementation

3.2. MENKES Disease

An X-linked condition is Menkes disease recessive disorder characterized by a defect in intestinal copper transport due to a mutation in the ATP7A gene located on the X chromosome. It presents with intrauterine growth retardation that continues after birth, and neurological deterioration occurs progressively. Serum copper levels, urinary copper excretion, and ceruloplasmin levels are all severely decreased

III.6.3. Zinc Metabolism

The human body contains 2 to 3 grams of zinc, primarily stored as follows: about 50% in muscles, 25% in bones, and the rest in tissues such as the prostate, hair, adrenal glands, retina, and brain.

1. Daily Requirements

- **Children:** 3 to 10 mg/day
- **Adults:** 15 to 20 mg/day

Zinc serves as a catalyst for over 300 metalloactivated enzymes, including oxidoreductases, hydrolases, and lyases. Its main functions include: Synthesis of nucleic acids, Synthesis of proteins and amino acids, Metabolism of polyunsaturated fatty acids, Hormone synthesis, Immune function, and Vision

2. Role of Zinc in the Body

Zinc is essential to numerous functions within the body. It is a component of several enzymes, such as carbonic anhydrase. Zinc boosts the immune system by increasing the number of circulating T lymphocytes and activating them, giving it notable anti-infective properties. It is involved in protein metabolism structurally, making it essential for normal fetal development during pregnancy and for healthy growth in childhood and adolescence. Zinc also plays a role in insulin synthesis, hemoglobin production, and, in men, helps prevent prostate problems. It promotes better wound healing, including ulcers and burns, and helps treat skin conditions such as acne, psoriasis, herpes, and stretch marks, thanks to its anti-inflammatory and healing properties. Zinc is necessary for maintaining smell and the senses of taste and contributes to sperm production by improving both quantity and motility, thus playing a role in male fertility. It also helps stabilize genetic material and is a crucial part of the enzymes that are involved in nucleic acid synthesis. Additionally, it supports the synthesis of amino acids like cystine and methionine, which are key components of keratin in hair. As an antioxidant, zinc helps neutralize free radicals (via enzymes like superoxide dismutase), thereby slowing the aging of the eyes and skin**.**

3. Pathological Variations of Zinc

3.1. Zinc Deficiency:

Zinc deficiency can arise from several causes. It may result from insufficient dietary intake, whether through inadequate oral or parenteral nutrition. Typically, this is not an isolated zinc deficiency but rather a broader deficiency involving multiple trace elements and vitamins. Malabsorption disorders can also lead to zinc deficiency, as seen in cases following intestinal resections, Crohn's disease, celiac disease, and acrodermatitis enteropathica. Chronic alcoholism is another common cause, leading to poor intestinal absorption of zinc.

Clinical signs of deficiency include brittle, split, or stained nails, increased susceptibility to infections, stunted growth in children, reduced fertility in men, and pregnancy complications in women.

2.2. Excess Zinc:

Zinc overload is rare and usually associated with excessive supplementation. However, the body generally regulates zinc levels effectively. Increased zinc in the urine may result from supplementation or pathological loss. Elevated urinary zinc levels can happen in circumstances like cirrhosis, kidney failure, diabetes, or due to medications with chelating or hormonal properties. **Clinically**, zinc excess may present with symptoms such as difficulty walking, speech disturbances, and tremors.

4. Indications for Zinc Supplementation

Zinc supplementation is advised for:

- **Pregnant and breastfeeding women:** There is a risk of neural tube defects, low birth weight, and developmental delays.
- **Vegetarians, the elderly, and children in growth**
- **Individuals recovering from surgery, trauma, diabetes, or chronic alcoholism**
- **People taking iron or aspirin:** These can significantly inhibit zinc absorption

III.6.4. Iodine

1. Definition and Characteristics of Iodine

Iodine is a chemical element belonging to the halogen family, represented by the symbol "I" and having an atomic weight of 127 g/mol. It is relatively rare in the Earth's crust but is more commonly found in marine environments.

Iodine plays a crucial role in the body as it is primarily used in the synthesis of thyroid hormones. These hormones regulate energy of the body usage and are essential for development and growth. Since the human body cannot produce iodine, it must be obtained through dietary sources.

2. Iodine-Rich Foods

- Saltwater fish and seafood are the best natural sources of iodine.
- Iodized table salt is also a significant source, with one teaspoon containing around 380 mg of iodine.
- Pickles, marinades, and sea salt provide natural iodine as well, although in lower quantities than iodized salt.

3. Iodine Requirements

Iodine needs vary depending on age, sex, and certain physiological conditions like pregnancy. Here are the general recommendations:

- **Infants (0-6 months)**: 110 µg/day
- **Infants (7-12 months)**: 130 µg/day
- **Children (1-8 years)**: 90 µg/day
- **Children (9-13 years)**: 120 µg/day
- **Adolescents and adults (men and women)**: 150 µg/day
- **Pregnant women**: 220 µg/day
- **Breastfeeding women**: 290 µg/day

It is essential to meet these daily intake levels to ensure proper thyroid gland function and adequate production of thyroid hormones, which regulate many bodily functions, including metabolism and growth.

4. Biological Functions of Iodine

Iodine plays a crucial role in several biological functions: The production of thyroid hormones and the proper functioning of the thyroid gland, Intellectual and brain development, Growth of tissues, cells, and organs, Increasing fertility, Stimulating thermogenesis (the production of heat in the body), Regulating heart rate, and the metabolism of fats and sugars.

5. Iodine Deficiency

Iodine deficiency can lead to several health issues:

- **Goiter**: A very common condition in many countries, where the thyroid gland enlarges. While goiter can have various causes, iodine deficiency is by far the most prevalent.
- **Deficiency during pregnancy**: It can cause **cretinism**, a condition characterized by severe developmental anomalies, including mental retardation in the child.

6. Iodine Toxicity (Excessive Iodine Intake)

Consuming more than 2000 µg of iodine daily can lead to thyroid dysfunction. This is especially seen in individuals who are iodine-deficient and are then given supplementation. An overdose of iodine can have an anti-thyroid effect, which may lead to **thyrotoxicosis** (excess thyroid hormone in the body).

III.6.5. Selenium

1. Definition and Role in the Body

Selenium (chemical symbol Se) is a non-metal trace element known for its antioxidant properties. In the human body, it binds to various proteins and is mainly stored in muscle tissue.

2. Reference Values

In the general population:

- Serum selenium: 60 to 120 µg/L (0.75 to 1.51 µmol/L)
- Urinary selenium: 10 to 50 µg/24h

3. Sources

The selenium content in food depends on the soil where it is grown and its protein content. Foods rich in selenium include fish, seafood, eggs, cereals, garlic, and mushrooms. Meat, organ meats, wheat germ, brewer's yeast, nuts, and some vegetables also provide good amounts, while fruits, legumes, and dairy products contain less.

4. Biological Roles

Selenium plays several crucial roles in the body:

- It is involved in thyroid hormone metabolism through a selenium-dependent enzyme called deiodinase.
- It contributes to cardiovascular protection and stimulates the immune system.
- It helps combat cellular aging due to its antioxidant function.
- It may also reduce the toxicity of certain heavy metals like arsenic, cadmium, mercury, lead, and platinum.

5. Pathological Variations

5.1. Selenium Deficiency

Low selenium levels are seen in various conditions such as malnutrition, parenteral nutrition, malabsorption, cirrhosis, chronic kidney disease, immune deficiency, and viral infections. Extremely low levels (<0.40 µmol/L) are associated with specific diseases like Keshan disease (a cardiomyopathy) and Kashin-Beck disease (a type of osteoarthropathy).

5.2. Selenium Excess

Elevated selenium levels can occur due to supplementation or poisoning. Although selenium toxicity is rare in humans, it becomes toxic above 500 µg per day. In cases of exposure to selenium-rich fumes (e.g., in industrial settings), clinical signs of toxicity include bronchial and skin irritation, gastrointestinal issues, and a distinctive garlic-like odor on the breath and skin.

III.3. 6. Fluor

1. General Characteristics

Fluorine (symbol F) is a crucial trace component. Within the body, it is primarily found in the bones and teeth.

2. Dietary Sources

- The majority of fluorine comes from drinking water, whether bottled or tap.
- Other sources include seafood, especially shellfish and fish, which are the richest animal-based sources of fluorine, containing between 0.015 and 0.2 mg per 100 g.
- Tea is also an important source of fluorine, with one cup providing up to 1 mg.
- There is also fluoridated salt, which is mainly useful when drinking water contains very low levels of fluorine.

3. Biological Functions

- Fluorine is incorporated into the structure of bones and teeth, bonding with calcium and phosphate to form crystals called fluoroapatites. This contributes to the strength of the skeleton and helps prevent dental cavities by strengthening tooth enamel.
- Fluorine consumed during childhood becomes part of the dental enamel, making it more resistant to organic acids from food that adhere to teeth or get stuck between them. This significantly reduces the risk of cavities.
- Fluorine may also strengthen bones and help prevent the development of osteoporosis in older adults.

4. Fluorine Deficiency

- Fluorine deficiency is rare but may occur in cases of illness or after the removal of the stomach or duodenum (the beginning of the small intestine), which are the main sites for fluorine absorption.
- A lack of fluorine is a factor that can contribute to the development of dental cavities.

- However, the impact is minimal when teeth are regularly brushed, thanks to the protective effects of fluorine in toothpaste.

5. Excess Fluorine

- **Dental fluorosis** (staining or discoloration of the teeth) can occur in children who consume excessive amounts of fluorine, either from drinking water with high fluorine content or from combining fluorine supplements (drops, tablets) or fluoridated salt with drinking water that provides more than 0.3 mg of fluorine per liter.
- In adults, **skeletal fluorosis** (characterized by abnormal calcifications and bone fragility) can develop from a daily dose of 10 mg or more of fluorine over at least 10 years.
- Acute poisoning occurs when the daily dose exceeds 500 mg, resulting in symptoms such as headaches, digestive issues, and heart rhythm disturbances.

III.6.7. Lithium

1. General Characteristics

- **Symbol:** Li
- **Atomic Number:** 3
- **Element Type:** Alkali metal
- Lithium is a light, silvery-white metal that is highly reactive and flammable. It is not commonly found in its pure form in nature but rather in minerals like spodumene, lepidolite, and petalite.

2. Biological Functions

- **Mental Health:** Lithium is primarily known for its use in treating **bipolar disorder** and **depression**, where it helps stabilize mood and prevent extreme mood swings.
- **Neuroprotective Effects:** Lithium has been found to have neuroprotective properties, potentially assisting in the prevention of neurodegenerative illnesses like Parkinson's or Alzheimer's, although research is still ongoing.
- **Cell Signaling:** It influences various intracellular signaling pathways, particularly by inhibiting enzymes like **glycogen synthase kinase-3 (GSK-3)**, which plays a role in many cellular functions, including the regulation of brain function.

3. Deficiency and Toxicity

- **Deficiency:** Lithium deficiency does not have a recognized physiological role in the body, but the body does not naturally store lithium, and it must be obtained through medications when required.
- **Toxicity:** Overconsumption of lithium can result in lithium toxicity, which can cause symptoms like nausea, disorientation, tremors, and in extreme situations, kidney damage. Regular monitoring of lithium levels is crucial for individuals taking lithium for mental health purposes.

III.6.8. Manganese:

1. General Characteristics

- **Symbol:** Mn
- **Atomic Number:** 25
- **Element Type:** Transition metal
- Manganese is a hard, brittle metal commonly found in minerals like **pyrolusite**. It is not found in its pure form in nature but is a key component of various minerals.

2. Biological Functions:

- **Enzyme Activation:** Manganese is a critical cofactor for several important enzymes involved in **antioxidant defense**, **energy production**, and **bone formation**. One of the most well-known manganese-dependent enzymes is **SOD** (superoxide dismutase), which aids in scavenging dangerous free radicals.
- **Bone Health:** It plays a role in the development and maintenance of bone structure, working in conjunction with other minerals like calcium.
- **Collagen Synthesis:** Manganese is involved in the synthesis of **collagen**, a key protein in connective tissue, skin, and bones.
- **Metabolism:** It is essential for the proper functioning of enzymes involved in **carbohydrate metabolism**, **amino acid metabolism**, and the formation of various lipids.

3. Deficiency and Toxicity:

- **Deficiency:** Manganese deficiency is relatively rare but can lead to bone malformations, impaired growth, and reproductive issues. Deficiency may also affect the nervous system and cause issues with metabolism.
- **Toxicity:** High levels of manganese, particularly from environmental exposure or supplementation, can lead to **manganism**, a condition that causes neurological signs and symptoms that resemble those of Parkinson's disease, including tremors and difficulty moving.

Chronic exposure to excessive manganese, especially in occupational settings, is a known risk factor for toxicity.

IV. Vitamins

IV.1. Definition

The word "vitamin" comes from the contraction of two words:**Vital** = life; **Amine** = organic molecule. Vitamins are organic substances with a low molecular weight, devoid of energy value, that are essential for reproduction, growth, and the proper functioning of the body. The body cannot synthesize them on its own. Therefore, they must be obtained through diet, except for vitamin D1, which is synthesized by the skin, and vitamins B8 and K, which are partly synthesized by the bacterial flora in the large intestine.

Their presence is necessary for most biochemical reactions responsible for cellular life.

IV.2. Classification

Vitamins are classified divided into two classes according to how soluble they are:

- **In organic solvents (fat-soluble vitamins: A, E, D, F, K):** These vitamins are stored in the liver and adipose tissue (fat). They are not easily excreted and can accumulate in the body. When taken in excessive amounts, they can be harmful to the organism.
- **In water (water-soluble vitamins: B1, B5, B2, PP, B8, B6, B12, B9, C):** These vitamins remain in the body, and any excess is filtered and rapidly eliminated through urine.

IV.3. Metabolism

Vitamins are obtained through diet. They are absorbed, pass into the bloodstream, and reach tissues where they perform their roles before being eliminated.

In the stomach, the various forms of vitamins are released from food, and complex derivatives are broken down into free vitamins.

Absorption site

Vitamins are absorbed in the small intestine, mainly in the **duodenum** and **jejunum**: A, beta-C, E, D,K; B2, B1, B5, PP, B6, B9, B8.

Only **vitamin C** and **vitamin B12** are absorbed in the **ileum**. **Menaquinones (vitamin K2)** can be absorbed in the colon.

IV.3.1. Liposoluble vitamins

1. Vitamin A (Retinol / Beta-Carotene)

Vitamin A exists in two forms: retinol and beta-carotene.

- In the form of retinol ester in animal-based foods, it is transformed in the intestine into retinol, which is the active form of vitamin A. The most important active forms are retinal and retinoic acid.
- Provitamin A refers to certain carotenoids, with beta-carotene being the most significant. These carotenoids mostly have antioxidant properties, which vitamin A does not possess.

1.1. Physicochemical Properties

Vitamin A is soluble in fats, insoluble in water, ether, chloroform, and acetone. It is stable to heat but highly sensitive to oxidation, light, and air. Almost all (90%) of the absorbed vitamin A is stored in the liver. Provitamin A is much less fragile.

1.2. Sources

- **Vitamin A**: Cod liver oil, calf and beef liver, margarine, butter, eggs, cheese, milk.
- **Carotenoids**: Red pepper, paprika, sweet potato, carrot, apricot, spinach, watermelon, mango, lettuce, nectarine, papaya, and tomato.

1.3. Metabolism

1.3.1. Digestive Absorption

Retinol esters are hydrolyzed by lipase, in the digestive tract, releasing retinol, and its absorption is favored by lipids and bile salts. The liver is the organ responsible for storing vitamin A. Carotenoids are absorbed via passive diffusion. Beta-carotene is absorbed by epithelial cells, which then hydrolyze it into retinal. Around 80-90% of vitamin A from animal sources and 50-60% of carotenoids are absorbed.

1.3.2. Distribution

The liver releases retinol into the plasma, bound to RBP (retinol-binding protein). In target tissue cells, transporters help move retinol and retinoic acid into the nucleus. In the retina, retinal is bound to opsin, forming rhodopsin.

1.4. Roles

- **Vitamin A, Carotenoids, and Vision**: Vision depends on pigments composed of opsin protein and a derivative of vitamin A. Opsins exist in two main forms. When light acts on the "vitamin A" part, it generates a nerve impulse in the optic nerve. Thus, vitamin A deficiency causes vision problems, leading to blindness. Additionally, carotenoids help protect the lens.
- **Other Roles**: Participates in the balance and renewal of epithelial tissues, regulates sebaceous and sweat glands. Vitamin A and its derivatives (retinoic acid) can convert precancerous cells into normal cells. Beta-carotene and other carotenoids have preventive properties against cancer due to their antioxidant effects.

1.5. Deficiency

- **Vision-related**: Decreased night vision (nyctalopia), conjunctivitis, etc.
- **Other Severe Deficiency Symptoms**: Hyperkeratosis of the skin, dryness of sebaceous and sweat glands, increased susceptibility to infections, slowed growth, diarrhea, dental caries, kidney stones, reproductive issues (infertility), Embryonic Growth Disorders and Spontaneous Miscarriage

1.6. Hypervitaminosis A

The liver only eliminates vitamin A at a rate of 0.5% per day.

- **Acute Toxicity**: This occurs after a large intake of vitamin A and leads to intracranial hypertension, causing dizziness, nausea, vomiting, and sometimes hemorrhages. There may also be skin and mucous membrane peeling.
- **Chronic Toxicity**: Symptoms include headaches, hair loss, skin issues (erythema, peeling), mucosal damage (stomatitis, conjunctivitis), liver damage (cirrhosis), and bone and joint pain.
- **Pregnancy Contraindication**: Pregnant women should avoid vitamin A supplements or treatments with retinoids. Excessive vitamin A intake during pregnancy can lead to fetal malformations. Breastfeeding women and some women on oral contraceptives should not be supplemented with vitamin A.

2. Vitamin D

is a fat-soluble vitamin that plays a crucial role in maintaining overall health, particularly in bone health and immune function.

Vitamin D2 (Ergocalciferol): Exogenous, dietary, and plant-based origin.

Vitamin D3 (Cholecalciferol): Animal-based origin and endogenously produced by skin photosynthesis from 7-dehydrocholesterol.

2.1. Physicochemical Properties

Vitamin D is highly soluble in ether and chloroform, slightly soluble in oils and fats but insoluble in water.

Unlike other fat-soluble vitamins, vitamin D is not stored in the liver. The primary storage sites are adipose tissue and muscles.

2.2. Metabolism

In the liver: A first hydroxylation at carbon 25 by the enzyme 25-hydroxylase produces 25-hydroxycholecalciferol, which is inactive.

In the kidneys: A second hydroxylation at carbon 1 forms 1,25-dihydroxycholecalciferol (calcitriol), which is the active form of vitamin D.

2.3. Roles

Bone Health: Vitamin D is crucial for maintaining healthy bones. It promotes calcium absorption in the intestines and aids bone mineralization. It stimulates bone resorption and enhances mineralization at the bone and teeth level.

Kidney Function: It helps with phosphate reabsorption in the kidneys.

Other Roles:

- **Mammary Glands**: During pregnancy and breastfeeding, vitamin D increases calcium absorption in the intestines.
- **Placenta**: It controls calcium transport, contributing to fetal bone mineralization.
- **Muscle Function**: Vitamin D regulates calcium concentration for proper muscle function.

2.4. Vitamin D - Needs, Excess, and Deficiency

2.4.1. Needs

It is recommended that elderly people, those with darker skin, or those with limited sun exposure consider supplementation, as only 10% of our daily vitamin D needs come from food.

2.4.2. Excess

Vitamin D toxicity typically results from excessive intake of vitamin D or its metabolites (acute toxicity). Since vitamin D is soluble in fat, it can accumulate in the body, leading to chronic toxicity.

2.4.3. Deficiency

- **Rickets**: This condition primarily affects children between six months and two years of age, causing bone deformities, difficulty walking, and associated muscle weakness. In severe cases, hypocalcemia can lead to tetany and convulsions.
- **Osteomalacia**: Characterized by bone and muscle pain, this condition is often due to vitamin D deficiency in adults.

3. Vitamin E

The most active form of vitamin E is **d-alpha-tocopherol (Biologically Active Form)**. Vitamin E consists of a 6-chromanol core with a 16-carbon isoprenoid side chain, which is asymmetrical and allows for the existence of many isomers.

3.1. Physicochemical Properties

- It appears as a viscous oil with a paleyellow color.
- Vitamin E is insoluble in water but very soluble in fats, oils, and organic solvents (ether, acetone, chloroform, methanol, etc.).
- It is heat-stable, resistant to light and acids, but very sensitive to oxidation and bases.

3.2. Antioxidant Properties

- Vitamin E neutralizes free radicals that can accumulate in the body's fat tissues, preventing oxidative damage.

3.3. Metabolism

In the intestine, vitamin E esters are hydrolyzed to release vitamin E, which is then absorbed by enterocytes in the presence of bile salts. Once in the bloodstream, vitamin E is transported by lipoproteins, primarily LDL (low-density lipoproteins). The tissues that contain the highest concentrations of vitamin E include fat tissues, certain endocrine glands, and platelets. Additionally, vitamin E is highly concentrated in cellular membranes and mitochondria, where it is essential for preventing oxidative damage to cells.

3.4. Role

The primary role of vitamin E is its **antioxidant action**, which prevents the peroxidation of fatty acids into peroxides. This helps protect cells from oxidative damage.

3.5. Sources

Wheat germ oil, sunflower oil, almonds, hazelnuts, walnuts, pistachios, peanuts, grapes, butter, fatty fish, oranges, dried apricots, margarine.

3.6. Deficiency

In premature infants, vitamin E deficiency can lead to **hemolytic anemia** and increase the risk of retinal damage.

3.7. Uses

Vitamin E's antioxidant properties are crucial for managing oxidative stress, which plays a role in the development of cardiovascular, neurological, and cancer-related diseases, as well as in the **aging process.**

Intestinal Malabsorption: It is prescribed in digestive disorders involving lipid malabsorption and rare congenital diseases.

Certain Neurological Diseases: At high doses, it may slow the progression of certain diseases, such as Parkinson's disease.

4. Vitamin K

Vitamin K, a coagulation vitamin, includes phylloquinone (vitamin K1), vitamin K3, and vitamin K2.

4.1. Physicochemical Properties

Phylloquinone appears as a yellow oil. It is insoluble in water, poorly soluble in alcohol, and easily soluble in ether, chloroform, fats, and oils. It is slowly degraded by air oxygen and more rapidly by light. It is heat-stable but degraded by alkalis.

4.2. Sources

There are two natural sources of vitamin K: food and bacteria in the intestinal flora.

- Green vegetables contain phylloquinone (vitamin K1), and animal products contain a mix of vitamins K1 and K2.
- Foods rich in vitamin K include spinach, lettuce, Brussels sprouts, beef and veal liver, meats, and watercress.

4.3. Role

- Vitamin K acts as an anticoagulant factor or coagulation factor; four coagulation factors are vitamin K-dependent: factor VII (proconvertin), factor II (prothrombin), factor IX (hemophilia B), and factor X (Stuart).
- Vitamin K is a cofactor for a microsomal carboxylase.
- Vitamin K serves as an antidote in cases of accidental rodenticide poisoning in humans and pets.

4.4. Deficiency

- Skin, nasal, urinary, or digestive hemorrhages (hematemesis, melena). In cases of chronic neonatal disease, digestive hemorrhages may occur on the second or third day of life.
- More rarely, cerebral hemorrhages can occur with a poor prognosis (27% mortality, 47% neurological sequelae).

5. Vitamin F (Omega-3 Fatty Acids)

Omega-3 fatty acids, previously known as vitamin F, are polyunsaturated fats found in large quantities in certain fatty fish, nuts, camelina, canola, and soy. Diets that provide a high quantity of these omega-3-rich foods, such as the Mediterranean diet, are beneficial. Essential fatty acids include omega-3 and omega-6 fatty acids.

5.1. Mechanisms of Action

Omega-3 fatty acids can be transformed, through cyclooxygenase and lipoxygenase, into various molecules that serve as signaling agents, such as prostaglandins, thromboxanes, and leukotrienes. Omega-3s also act on certain ion channels, potentially reducing the risk of heart arrhythmias.

5.2. Deficiency

- Atherosclerosis, cholesterol deposits in the walls of blood vessels and tissues, thrombotic conditions (such as arthritis and phlebitis), heart attacks, certain liver and nerve disorders, and abnormal permeability of cell membranes.

IV.3.2. Water-soluble vitamins

1. Vitamin B1 (Thiamine)

Thiamine is an organic molecule composed of pyrimidine and thiazole rings connected by a methylene bridge. It is water-soluble and thermolabile, being denatured at 100°C. It is transformed in the body into thiamine pyrophosphate, the active product.

1.1. Metabolism

- **Absorption:** It occurs through active transport dependent on sodium.
- **Distribution:** About 90% of thiamine is concentrated in red blood cells, and the concentration in white blood cells is 10 times higher than in red blood cells. The heart is the organ richest in thiamine, followed by the kidneys, liver, and brain.

1.2. Role

- Thiamine diphosphate acts as a coenzyme in:
    - The decarboxylation reactions of alpha-keto acids, e.g., converting pyruvic acid to acetyl-CoA and alpha-ketoglutarate to succinyl-CoA. In thiamine deficiency, the concentration of pyruvic acid in the blood increases.
    - The transketolase reactions of sugars, which involve the exchange of two carbon groups between two sugars.

1.3. Sources

In a healthy adult, digestive absorption is about 4.5% of the ingested dose. Sources include:

- Brewer's yeast, wheat germ, meats, hazelnuts, liver, whole grain bread, fish, eggs, and potatoes.

1.4. Deficiency

Several causes of deficiency include alcoholism, insufficient intake (particularly in the elderly), exclusive parenteral nutrition, and consumption of foods containing "anti-thiamine" factors (e.g., tea and certain fish). Thiamine deficiency manifests as:

- **General signs:** Fatigue, anorexia, weight loss.
- **Cardiac signs:** Myocardial damage, heart failure.
- **Neurological signs:** Paresthesia, hypoesthesia, muscle wasting, calf pain upon pressure, decreased reflexes, irritability, memory issues, difficulty concentrating.
  In severe deficiency, encephalopathies can occur, presenting as psychosis with disorientation and amnesia, nystagmus, confusion, and balance problems. These encephalopathies are considered a form of **beriberi**.

Beriberi

Beriberi is a severe disease that was once widespread, especially in impoverished populations in Asia living primarily on rice. There are many classifications of clinical forms of beriberi (**Sec Beriberi, Infantile Beriberi, wet Beriberi)**:

- **Wet Beriberi:** The patient experiences edema (pitting) in the legs, sometimes in the scrotum, face, and trunk. Symptoms include palpitations, chest pain, occasionally dyspnea (shortness of breath), and a rapid, often irregular pulse. The neck veins become distended and visible with pulsations. The heart increases in size. Routine testing for albumin in the urine is advised, as its absence helps in diagnosis.

2. Vitamin B2 (Riboflavin)

2.1. Structure

The production of flavine mononucleotide (FMN) and flavine adenine dinucleotide (FAD) depends on riboflavin. It is crucial for turning basic foods—such as proteins, lipids, and carbohydrates—into energy. It also contributes to the metabolism of muscle regeneration.

2.2. Physicochemical Properties

- Riboflavin is heat-resistant, resistant to freezing, and can withstand salting but is degraded by ultraviolet (UV) light.
- The main source is milk.
- It is weakly soluble in water and works alongside magnesium (Mg^{2+}) to activate vitamins B6 and B3.

2.3. Role

As a coenzyme in the form of FAD and FMN, riboflavin plays a role in redox reactions. Additionally, it has antioxidant functions and participates in regenerating glutathione, the body's major detoxifying agent.

2.4. Requirements

Riboflavin is abundant in the diet, and daily needs are typically met.

Sources

- Brewer's yeast, lamb, veal, and beef liver, yogurt, whole milk, and whole cereals.

2.5. Deficiency

The clinical signs of riboflavin deficiency are usually mild in humans and include:

- Skin and mucous membrane lesions: seborrheic dermatitis on the face and around the nose, chapped lips, fissured corners of the mouth, purple tongue.
- Ocular lesions: tearing, conjunctivitis.

3. Vitamin B5 (Pantothenic acid)

Also known as pantheon, royal jelly is the most natural source richest in vitamin B5. It is a precursor and a component of coenzyme A.

3.1. Physicochemical Properties

- It is only obtained through diet.
- It is sensitive to heat in aqueous solution.
- Pantothenic acid is found in nature in large quantities and is abundant in the liver, kidneys, brain, and heart.

3.2. Role

Vitamin B5 promotes the growth and resilience of the skin and mucous membranes (prevents issues related to hair, nails, and skin), is necessary for the metabolism of carbohydrates, lipids, and proteins, and participates in the synthesis of certain hormones. It is also involved in the development and functioning of the central nervous system.

3.3. Sources

Brewer's yeast, calf and beef liver, egg yolk, peanuts, whole rice.

3.4. Deficiency

Extremely rare, usually associated with severe malnutrition and multiple deficiencies.

3.5. Uses

It helps relieve rheumatoid arthritis, reduces the severity of skin reactions caused by allergen exposure (such as pollen or dust), and stimulates fertility.

4. Vitamin B6 (Pyridoxine)

4.1. Structure

It gives rise to pyridoxal phosphate (PLP), a coenzyme that acts as a prosthetic group.

4.2. Physicochemical Properties

Vitamin B6 is resistant to heat, acids, and oxidation, but is destroyed by alkalis and light. It is water-soluble and is found mainly in the liver, followed by the brain, plasma, and red blood cells.

4.3. Role

Through pyridoxal phosphate, it is engaged in the metabolism of amino acids (from proteins): transamination, racemization, decarboxylation. It plays a role in the formation of antibodies, hemoglobin synthesis, and neurotransmitter production (dopamine, norepinephrine, serotonin, GABA).

4.4. Sources

Wheat germ, baker's yeast, wheat bran, sardines, calf and beef liver, lentils, banana, avocado, Brussels sprouts, oatmeal.

4.5. Deficiency

Mood disorders, depressive tendencies, neurasthenia, skin and mucosal lesions, weakened immune response. Sometimes hematological signs like microcytic hypochromic anemia are observed. **In children:** convulsive seizures, anemia, vomiting, abdominal pain.

4.6. Uses

Recommended for chronic alcoholics, people undergoing hemodialysis, pregnant and breastfeeding women, women taking oral contraceptives, undernourished elderly individuals, and athletes.

5. Vitamin B8 (Biotin)

Also known as vitamin H, it is a coenzyme involved in the metabolism of fatty acids, carbohydrates, and amino acids, as well as the synthesis of vitamins B9 and B12.

5.1. Physicochemical Properties

Vitamin B8 is soluble in water and alkaline solutions but only slightly soluble in acidic environments or organic solutions. It is heat-stable and stable in aqueous solution, slightly sensitive to oxidation, and destroyed by UV light.

It is primarily found in the liver, kidneys, brain, and adrenal glands.

5.2. Role

It acts as a coenzyme for carboxylases (in the Krebs cycle). It is involved in energy production from glucose and amino acids and in fatty acid synthesis.

5.3. Sources

Sheep and calf liver, brewer's yeast, eggs, oatmeal, avocado, beans, banana, strawberry, tomato, wholemeal bread.

5.4. Deficiency

Deficiency states are rare in humans. Biotin is commonly prescribed to slow down hair loss and for brittle nails.

6. Vitamin B9 (Folic acid)

Vitamin B9, also known as folic acid or folates.

6.1. Physicochemical properties

It is a group of compounds synthesized by plants and microorganisms. It is destroyed by heat and oxidation, and is mostly stored in the liver. Its absorption is improved by zinc. A portion is also synthesized by intestinal bacteria.

6.2. Metabolism

- **Digestive absorption:** Folates are the main dietary source. In the digestive tract, they are first released from proteins by digestive proteases, then hydrolyzed. Folic acid absorption is largely energy-dependent, relying on sodium and glucose.
- **Tissue distribution:** Red blood cells contain folates. Cerebrospinal fluid contains about three times more folates than plasma. The liver is the richest in folates, holding about half of the body's stores.
- **Excretion:** Urinary excretion is low due to tubular reabsorption. There is also biliary excretion, but it is limited by the presence of an enterohepatic cycle.

6.3. Role

Folic acid is a precursor of numerous coenzymes involved in the production of blood cells (red and white), cell reproduction, and central nervous system function (synthesis of neurotransmitters). Reduced folates (tetrahydrofolic acid) are involved in the synthesis of a pyrimidine base (deoxythymidine), purine bases, and the transformation of homocysteine into methionine.

6.4. Sources

Yeast, chicken, beef or veal liver, chicken meat, wheat germ, fresh spinach, fennel, Camembert cheese, tomato, lettuce, broccoli, oats, banana, tuna, carrot.

6.5. Deficiency

Folic acid deficiency manifests through blood disorders, various neurological issues, and digestive problems. In pregnant women, it increases the risk of miscarriage or malformations. Deficiency in folic acid and vitamin B12 causes hyperhomocysteinemia, which leads to vascular damage and increases cardiovascular risk.

6.6. Increased needs

Seen in pregnant women, premature infants, newborns, patients under anticonvulsant treatment, and chronic alcoholics.

6.7. Use

Low-dose folic acid supplementation may reduce cardiovascular events linked to moderate hyperhomocysteinemia.

7. Vitamin B12

7.1. Structure

Vitamin B12 is a macromolecule composed of four pyrrole rings forming a tetrapyrrolic nucleus, at the center of which lies a cobalt atom. This cobalt can exist in different oxidation states: trivalent, divalent, or monovalent.

7.2. Physicochemical Properties

Vitamin B12 contains cobalt ions (hence the name "cobalamin"). It is light-sensitive, destroyed by heat in acidic or basic environments, resistant to oxidation, highly soluble in water, but poorly soluble in alcohol and organic solvents.

7.3. Metabolism

- **Intestinal Absorption:** It comes from the diet and is also synthesized by certain microorganisms. Dietary B12 is released by cooking, gastric acidity, and pepsin. In the stomach and intestine, it binds to *intrinsic factor (IF)* synthesized by the parietal cells of the gastric mucosa, allowing its specific absorption in the intestine.
- **Tissue Distribution:**
    - In the blood: B12 is bound to transport proteins called *transcobalamins*.
    - In tissues: The liver stores over 60% of total body vitamin B12. Neurons, especially in the brain, also contain B12.
- **Elimination:** It is excreted in bile, urine, various secretions, and through cellular desquamation. An *enterohepatic cycle* helps conserve it.

7.4. Role

Vitamin B12 is a cofactor in two types of enzymatic reactions:

- *Isomerization*

- *Transmethylation*

These reactions are crucial for: DNA replication, Hematopoiesis, Nervous system integrity, and Immune system effectiveness

7.5. Sources

Beef, lamb, veal, and poultry liver, beef and veal kidneys, sardines, fresh cheese, salmon, tuna.

7.6. Deficiency

Main causes are either insufficient dietary intake or poor digestive absorption due to lack of intrinsic factor. Clinical signs include: Neurological damage, Skin and mucous membrane lesions

7.7. Use

Of the various B12 forms, *cyanocobalamin* and *hydroxocobalamin* are the only ones used therapeutically.

8. Vitamin C

8.1. Structure

Vitamin C includes L-ascorbic acid and its salts (sodium and calcium ascorbates).

8.2. Physicochemical Properties

It is water-soluble, less soluble in alcohol, and insoluble in ether or chloroform. It is extremely sensitive to oxygen in the air, high temperatures, pasteurization, and to metals like iron and copper.

8.3. Role

As a potent antioxidant, vitamin C is essential for shielding cells from oxidative damage. It stimulates the synthesis and maintenance of collagen, essential for skin, blood vessels, and connective tissues, and supports the production of neurotransmitters such as norepinephrine. It is vital for immune defense, enhances the absorption of dietary iron, helps reduce allergic reactions by lowering histamine levels in the blood, and reduces the toxicity of heavy metals like lead, nickel, and cadmium by promoting their elimination from the body.

8.4. Sources

Cherries, coriander, red and green peppers, lemon, orange, and grapefruit juice, parsley, paprika, kiwi, fennel, papaya, cauliflower, Brussels sprouts, and broccoli.

8.5. Deficiency

Acute deficiency symptoms include fatigue, joint and bone pain, and anemia. If left untreated, it leads to **scurvy**.

SCURVY

One of the oldest known diseases, scurvy was once a major cause of death. It begins with fatigue and progresses to swelling in the arms and legs, followed by bleeding from the nose and gums and subcutaneous bruising. Teeth may loosen and fall out. Unable to stand, patients die within weeks from exhaustion or respiratory infections.

8.6. Uses

Vitamin C is administered in both nutritional and pharmacological doses to stimulate the immune system, combat fatigue, treat acute viral infections (such as flu, chickenpox, shingles, mumps, herpes, and mononucleosis), promote collagen synthesis, and aid in the healing of traumatic or surgical wounds, pressure sores, frostbite, and gum issues.

9. Vitamin PP (Vitamin B3)

9.1. Definition

Vitamin PP includes **nicotinic acid (niacin)** and **nicotinamide**, collectively known as **vitamin B3**.

9.2. Physicochemical Properties

Vitamin B3 is primarily synthesized in the human body from **tryptophan**, with a smaller proportion obtained through diet. It is mainly stored in the **liver** and is **stable to heat, light, oxidation, and alkaline conditions**, while being **soluble in water and alcohol**.

9.3. Role

- Precursor of **NAD** and **NADP**, essential coenzymes in cellular **energy metabolism**
- Promotes **peripheral vasodilation**
- Contributes to the **repair of damaged DNA**

9.4. Sources

Brewer's and baker's yeast, liver (lamb, veal, beef), peanuts, paprika, tuna, salmon, sardines, rice, and whole-grain bread.

9.5. Deficiency

- **Moderate:** Loss of appetite, fatigue, headaches, dizziness, mood changes, and decreased sense of humor
- **Severe (Pellagra):** Caused by niacin and tryptophan deficiency, especially in corn-based diets

Pellagra

A condition marked by the **three Ds**: **dermatitis, dementia, and diarrhea**. Common historically in malnourished populations relying heavily on **maize**. If untreated, it can lead to death.

1. Dermatitis:

Dermatitis typically affects areas exposed to sunlight, such as the face, neck, hands, forearms, and legs. It presents as hyperpigmented areas that become dry, scaly, and eventually cracked. The skin becomes shiny, thin, and depigmented. The tongue and other oral mucous membranes are often painful and red.

2. Diarrhea:

Diarrhea and abdominal pain and are common symptoms due to lesions in the digestive tract, similar to those found in the mouth.

3. Dementia:

Neurological involvement manifests in a variety of symptoms, with the most common being irritability, memory loss, anxiety, and insomnia. These issues can progress to deme

V. Hormones

V.1. Introduction

The endocrine system's glands create chemical messengers called **hormones.** They reach organs and tissues via the bloodstream, where they control a variety of body processes. These functions include development and growth, metabolism, mood, reproductive processes, and the body's response to stress or injury.

V.2. Growth hormone GH

V.2.1. Physiological Overview of the Hypothalamic-Pituitary Axis

The **pituitary gland** is composed of two parts:

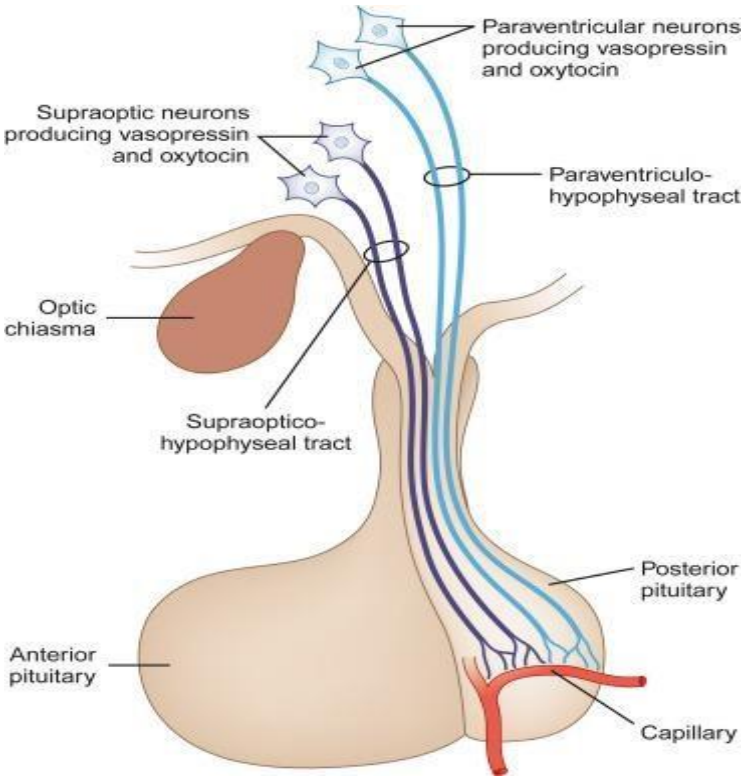
- the **anterior pituitary** (*adenohypophysis*), and
- the **posterior pituitary** (*neurohypophysis*).

Although closely connected anatomically, they have **different embryological origins** and **distinct functions**.

The **pituitary gland** is located at the base of the brain and is in close relationship with the **hypothalamus**, which plays a crucial role in regulating pituitary functions.

Hormone secretion by the **anterior pituitary** is regulated by **hypothalamic hormones (**see Figure V.1**)**, which reach the pituitary via the **hypophyseal portal blood system**.

The **posterior pituitary** secretes two hormones: **vasopressin** (also known as ADH) and **oxytocin**. These two hormones are **synthesized in the hypothalamus** and transported to the posterior pituitary by **axonal migration**.



FigureV.1. Anatomy of the neurohypophysis.

V.2.2. Definition of Growth Hormone

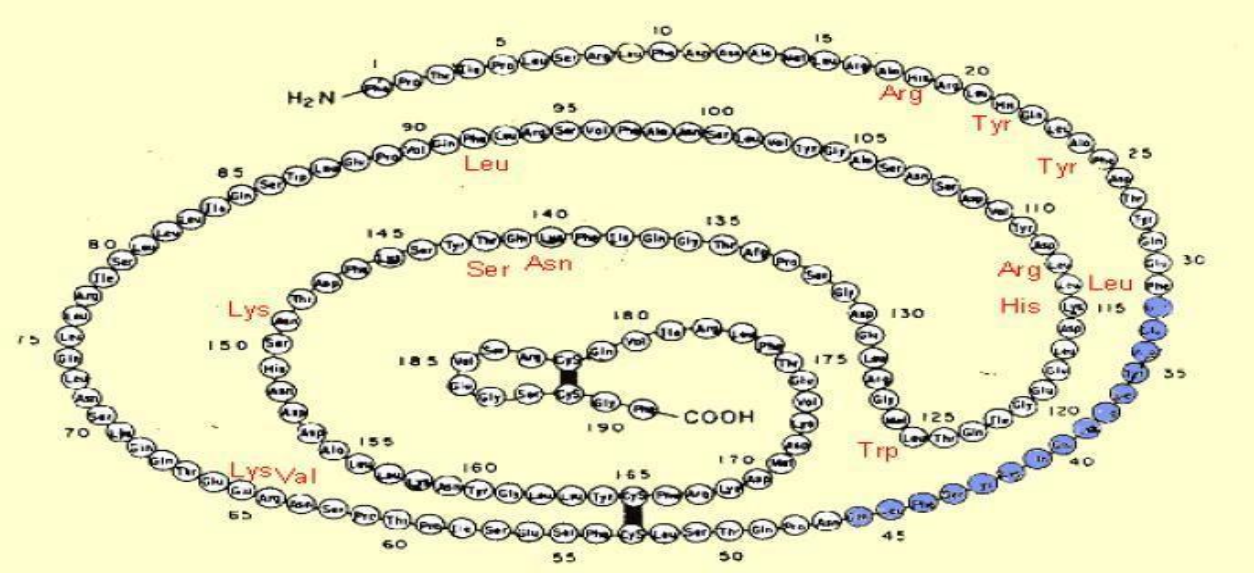
Growth hormone in humans, also known as **GH (Growth Hormone)**, **somatotrophin**, **somatotropin**, or **somatropin**, a polypeptide hormone that is released by **somatotrope cells** in the **anterior pituitary gland**. It **stimulates the reproduction and growth of cells** in humans and other vertebrates. Several disorders are associated with this hormone:

- **Dwarfism** (in cases of **GH deficiency**)
- **Gigantism** and **acromegaly** (in cases of **GH excess**)

V.2.3. Structure and Gene of Growth Hormone

The expression of growth hormone is controlled by **two genes**, **GH1** and **GH2**, both located on **human chromosome 17(**see Figure V.2**)**. There are several forms of GH:

- The **major form** (75–85%) of human GH is a **polypeptide of 191 amino acids**, with **two disulfide bridges** between **Cys53–Cys165** and **Cys182–Cys89**.
- A **minor form** (~5–10%) is a **176-amino-acid polypeptide** (about **20 kDa**), derived from the **same gene** as the 22 kDa GH.
- A portion of these molecules (~10%) form **dimers**:
    - **Homodimers** (22-22 or 20-20)
    - **Heterodimers** (20-22)
    - These dimers can be **covalently linked** (via disulfide bonds) or **non-covalently associated**.



FigureV.2. The primary structure of the 22 kDa GH: the sequence from amino acids 32 to 46 is deleted in the 20 kDa GH

V.2.3. Secretion of Growth Hormone (GH)

GH is secreted in a **pulsatile manner**, following a **circadian rhythm**. It is **mostly secreted during sleep** and about **3 hours after a meal**. It is a **protein hormone** that **circulates primarily bound to GHBP** (*Growth Hormone Binding Protein*):

- **Free form**: half-life of about **30 minutes**
- **Bound form (to GHBP)**: half-life of about **10 to 12 hours**

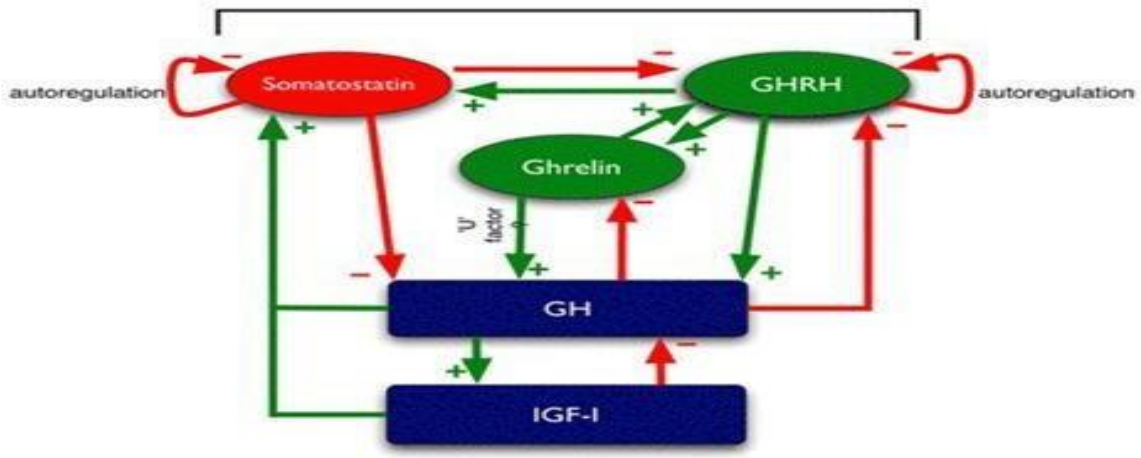
V2.4. Regulation of GH Secretion

Three levels are involved in the GH axis:

1. **Hypothalamus**, which acts through **three molecules**:
   a. **Two stimulatory factors**:
      - **GH-RH** (*Growth Hormone-Releasing Hormone*, also called **somatoliberin**)
      - **TRH** (*Thyrotropin-Releasing Hormone*)

   b. **One inhibitory factor**:
      - **SS14** (*Somatostatin*, also called **GHIF – *Growth Hormone-Inhibiting Factor*)*
2. **Anterior pituitary** (*adenohypophysis*): secretes GH
3. **Liver**: secretes **IGF-1** (*Insulin-like Growth Factor 1*, also called **somatomedin**)

GH is part of an **integrated regulatory system** (see Figure V.3**)** involving **both positive and negative feedback mechanisms**, with participation from the **central nervous system** and **peripheral tissues**.



FigureV.3. Regulation of GH secretion**.**

V.2.5. Other Factors Modulating GH Secretion

- **Positive effectors**: Thyroid hormones, Cortisol, Protein-rich meals, Hypoglycemia, Physical exercise, and Sleep
- **Negative effectors**: Obesity, Glucocorticoids

V.2.6. Growth Hormone Receptor (GHR)

Like most **peptide hormones**, growth hormone (GH) exerts its effects by binding to a **specific receptor** on the **cell surface**, belonging to the **cytokine receptor superfamily**.

The **human GH receptor** consists of: An **extracellular domain** that binds GH, A **single transmembrane domain**, and A **cytoplasmic domain**

The GHR **does not have intrinsic enzymatic activity**, but it is **constitutively associated** at the intracellular level with **tyrosine kinases**, primarily **JAK-2** (Janus Kinase 2).

The **liver** expresses the **highest levels of GHR**, although it is also expressed in **various other tissues** to differing degrees.

V.2.7.1. Mechanism of Action

One GH molecule binds to the **extracellular domains of two GHR molecules**, triggering their **homodimerization**.

This binding is **sequential**:

1. GH first binds to one GHR via a **high-affinity site**.
2. Then it binds to a **second GHR** via a **lower-affinity site**, stabilizing the complex.

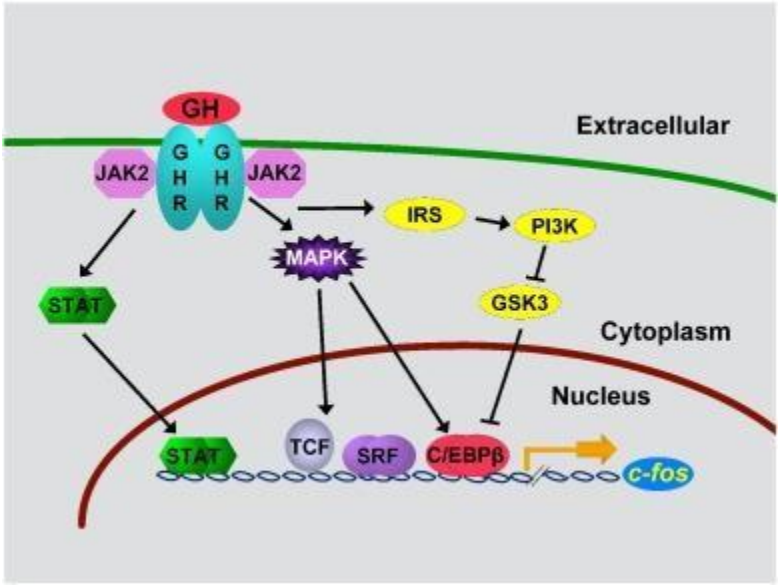
This **homodimerization** activates **JAK-2**, which **phosphorylates tyrosines** in the intracellular domain of the GHR. These phosphorylated tyrosines become **docking sites** for various signaling molecules.

V.2.7.2. Main Signaling Pathways Activated

1. **STAT Pathway** (*Signal Transducers and Activators of Transcription*): **Primary pathway** for **growth-related effects**, STAT proteins act as **transcription factors**, inducing genes like **IGF-1** (*Insulin-like Growth Factor 1*)

2. **Ras/MAPK Pathway** (*Mitogen-Activated Protein Kinase*): Involved in regulating **gene expression**, particularly those controlling **cell proliferation**
3. **PI3K Pathway** (*Phosphoinositide-3 Kinase*): Mediates many of GH's **metabolic effects (**see Figure V.4**)**

SOCS proteins (*Suppressors of Cytokine Signaling*) and the **tyrosine phosphatase Shp2** play **major roles in the negative regulation** of GHR activation.



FigureV.4. Signal Transduction Pathways Downstream of the Growth Hormone Receptor (GHR)**.**

V.2.8. Activities of Growth Hormone (GH)

GH acts directly or indirectly through IGF-1 (Insulin-like Growth Factor 1).

GH is an anabolic hormone, meaning it promotes the synthesis of molecules in the body. It has a similar effect to insulin on protein and amino acid metabolism but has an antagonistic effect to insulin on carbohydrate and lipid metabolism.

Effects of GH

- **Proteins:** Promotes protein synthesis.
- **Carbohydrates:** Promotes glycogenolysis (breakdown of glycogen into glucose).
- **Lipids:** Increases lipolysis (breakdown of fats into fatty acids and glycerol).

IGF-1 (Somatomedin C)

- **Secretion:** IGF-1 is secreted by the liver and tissues that respond to GH.
- **Structure:** It shares 50% structural homology with insulin, giving it similar effects.
- **Action:** IGF-1 has a hypoglycemic effect, lowering blood glucose levels.

GH also has the following effects

1. **Growth**
2. **Increased Phosphate Reabsorption:** GH increases tubular reabsorption of phosphate in the kidneys.

V.3. The Prolactin Axis

V.3.1. Introduction

Prolactin is a pituitary hormone, known for its role in triggering lactation. Its measurement in serum is part of the routine hormonal assessment performed in both men and women in response to various disorders.

V.3.2. Structure and Origin of Prolactin

The hormone prolactin is a polypeptide made up of 199 amino acids and shares 60% homology with Growth Hormone (GH). It is primarily synthesized by the lactotroph cells of the anterior pituitary and is secreted in pulsatile bursts.

There are several circulating forms of prolactin:

- **Monomeric prolactin**: The most biologically active form.
- **Big prolactin**: A mixture of dimers and trimers of glycosylated prolactin.
- **Big-big prolactin (macroprolactin)**: Composed of prolactin bound to IgG (immunoglobulin G).

V.3.3. Levels of the Prolactin Axis

This involves three levels:

1. **Hypothalamic level**: The hypothalamus secretes:
    - **An activator**: Thyrotropin-releasing hormone (TRH).
    - **Three inhibitors**: Dopamine, somatostatin, and GAP (Gonadotropin-releasing hormone Associated Peptide).
2. **Pituitary level**: Prolactin is released by the lactotroph cells of the anterior pituitary.
3. **Tissue level**: Prolactin acts on tissues such as the ovaries, mammary glands, and testes.

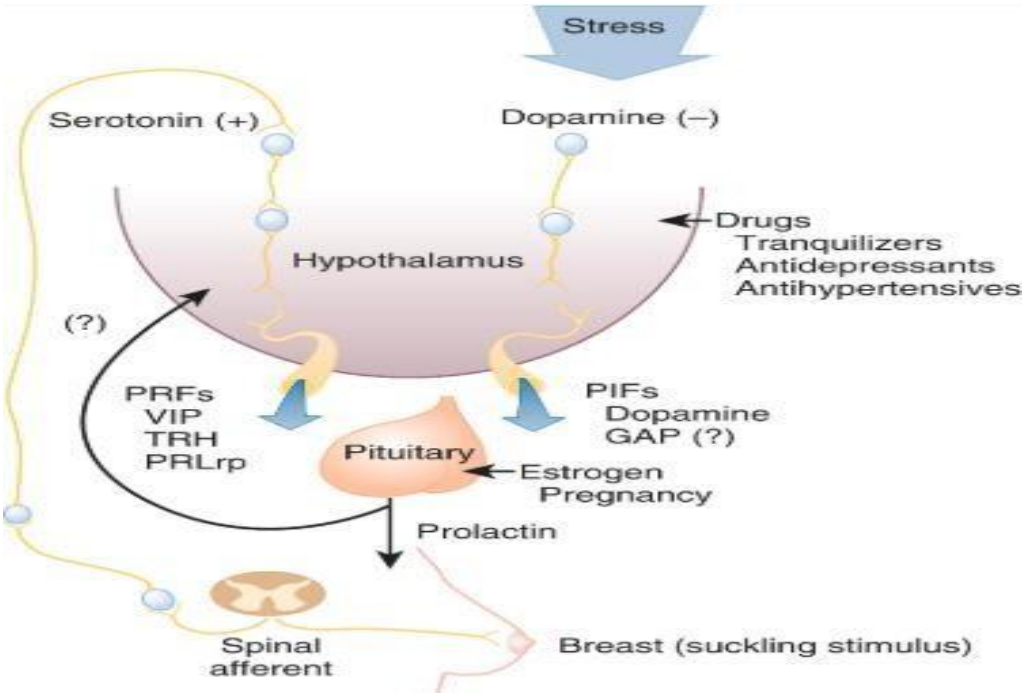
V.3.4. Regulation of Prolactin Secretion: The biosynthesis and secretion of prolactin are controlled by both central factors (from the hypothalamus) and peripheral factors (such as the gonads and thyroid).

1. Hypothalamic regulation is achieved through:

- **Inhibitory factors**: Dopamine (PIF), GABA, somatostatin, and GAP (gonadotropin-releasing hormone associated peptide).
- **Stimulating factors**: TRH (Thyrotropin-Releasing Hormone), VIP (Vasoactive Intestinal Peptide), Serotonin.
- **Autoregulation**: There is a feedback mechanism where prolactin regulates its own secretion.

2. Peripheral Regulation

- **Estradiol, progesterone, and testosterone**: These hormones play a stimulating role in prolactin secretion (see Figure V.5).
- **Thyroid hormones**: Have an inhibitory effect, acting through two mechanisms:
  - **Negative feedback** exerted by thyroid hormones on TRH.
  - **Stimulating effect** exerted by thyroid hormones on dopamine.



FigureV.5. Regulation of Prolactin Secretion

V.3.5. Prolactin Secretion Rhythm

Like most pituitary hormones, prolactin is released in a pulsatile manner. In addition, there is a circadian rhythm to prolactin secretion. In humans, prolactin levels rise during sleep (30 minutes to 1 hour after falling asleep). One to two hours after waking up, prolactin levels are at their lowest.

Stress, physical exercise, and hypoglycemia can cause physiological elevations in circulating prolactin levels.

V.3.6. Prolactin Secretion in Physiological Conditions

- **At puberty**: Prolactin levels increase in females, while they remain relatively stable in males.
- **During the menstrual cycle**: Prolactin levels are slightly elevated in contrast to the follicular phase during the luteal phase.
- **During pregnancy**: Prolactin levels rise starting from the first trimester. This increase parallels that of estrogen levels and is accompanied by significant changes in lactotrope cells.

V.3.7. Influence of Pharmacological Factors on Prolactin Secretion

Numerous substances used in daily clinical practice affect prolactin secretion.

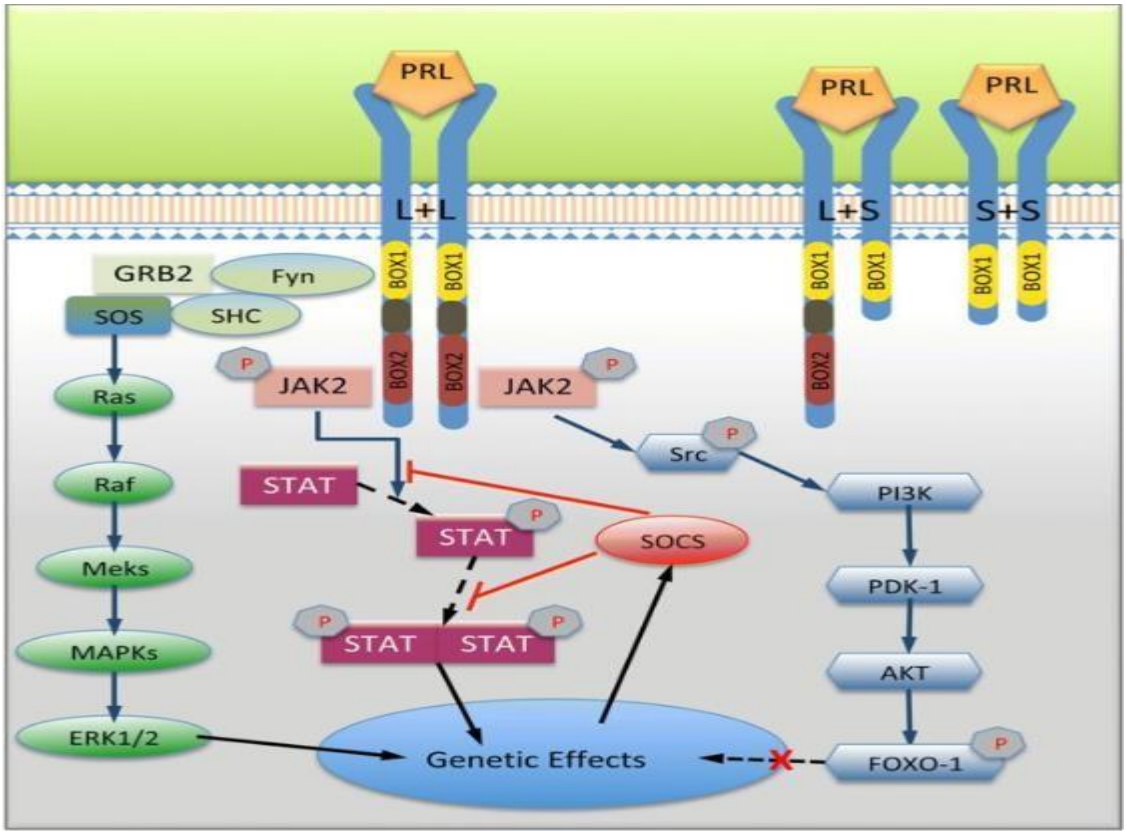
- **Substances that increase prolactin secretion**: These substances work by reducing dopamine levels: Psychotropic drugs, Antihypertensive drugs (e.g., verapamil, α-methyl dopa), H2-antagonists (e.g., cimetidine, ranitidine), Antiemetics (e.g., metoclopramide, domperidone)
- **Substances that inhibit prolactin secretion**: These are dopamine agonists: Ergot derivatives significantly reduce prolactin secretion (e.g., ergocamine, ergocryptine, bromocriptine)

V.3.8. Mode of Action of Prolactin

The mode of action of prolactin is similar to that of growth hormone (GH). The prolactin receptor also recognizes GH (see Figure V.6).

Prolactin binds to membrane receptors that are particularly found on cells in the mammary glands, ovaries, testicles, and uterus.

Binding of prolactin to its receptor triggers several phosphorylation cascades, beginning with the phosphorylation of tyrosine kinase proteins (JAK2). Eventually, the phosphorylation of MAPK and STATs leads to the stimulation of transcription in the nucleus.



FigureV.6. Main Intracellular Signaling Pathways Activated by the Prolactin Receptor

V.3.9. Biological Actions of Prolactin

- ***Milk Production***
- **Effects on the Ovaries and Testicles: At low doses**: Prolactin stimulates the synthesis of **estradiol** (a form of estrogen) in women and **testosterone** in men. **At high doses**: Prolactin inhibits the synthesis of **estradiol** and **testosterone**.

V.4. Thyroid Function

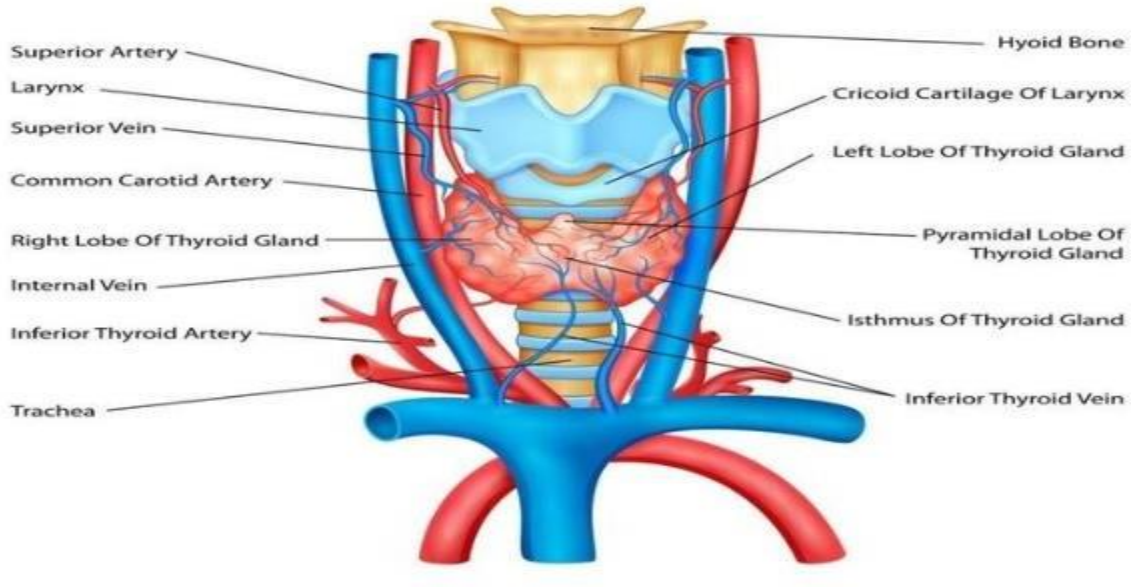
V.4.1. Introduction

The largest human endocrine gland is the thyroid. The follicular cells iodinate the tyrosine residues of thyroglobulin to form the thyroid hormones thyroxine (T4) and triiodothyronine (T3), which are then stored in the colloid. These hormones contribute to the fine regulation of cellular metabolism. They exert their functions through specific receptors of the nuclear receptor class.

V.4.2. General Information

V.4.2.1. The Thyroid

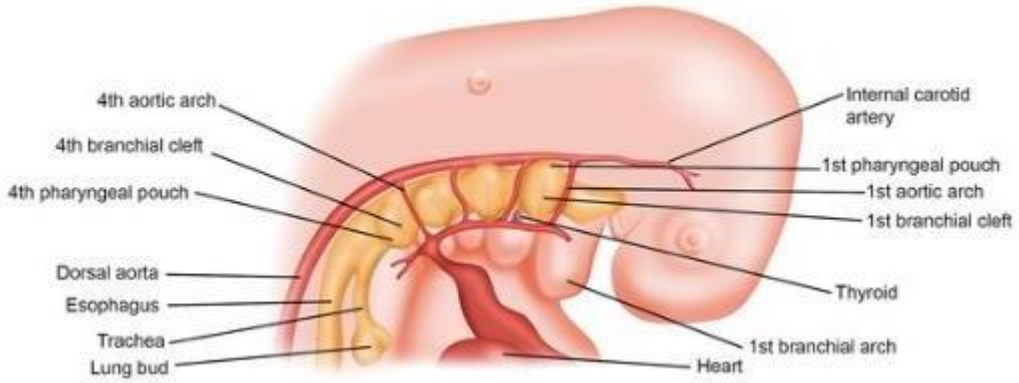
The thyroid is an endocrine gland that synthesizes and releases thyroid hormones, thyroxine (T4) and triiodothyronine (T3), into the bloodstream. The thyroid is located at the base of the neck and has a butterfly shape, with its wings surrounding the trachea. The four parathyroid glands, each a few millimeters in diameter, are found on the thyroid's posterior surface. The thyroid measures approximately 6 centimeters in height and 6 to 8 centimeters in length (see Figure V.7), making it the human body's largest endocrine gland. It is a highly vascularized structure, supplied by **two** main **arteries** and **three** main **veins**.



FigureV.7. Anatomy of Thyroid gland

V.4.2.2. Embryonic origin

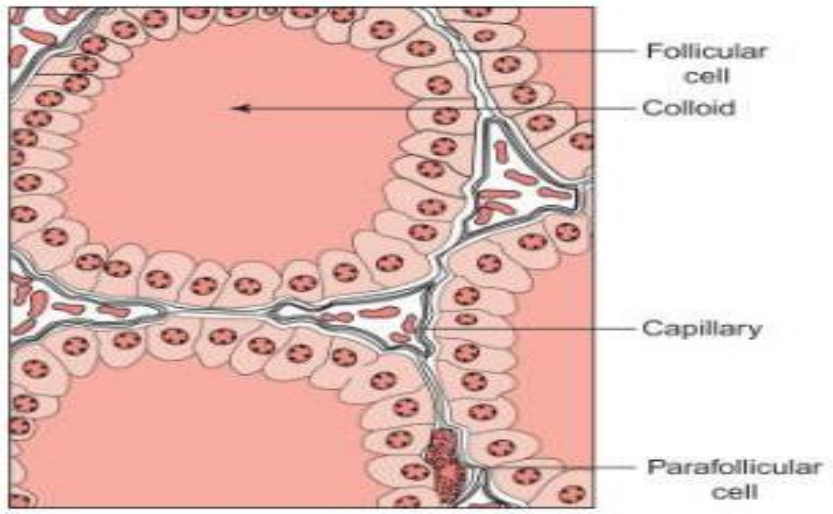
Endoderm of the floor of the pharynx that migrates to the cervical region via the thyroglossal duct (see Figure V.8): final position is the anterior surface of the trachea and the thyroid cartilage. **Migration anomaly:** ectopic thyroid tissue is common.



FigureV.8. Embryological development of thyroid gland

V.4.2.3. Histology

Secretory follicles consist of simple epithelium (thyrocytes: polarized cells) resting on a basement membrane and enclosing a cavity containing colloid. Presence of parafollicular cells (see Figure V.9): C cells (calcitonin-producing).



FigureV.9. The histological structure of thyroid gland

V.4.3. Thyroid hormone metabolism

V.4.3.1. Structure of thyroid hormones

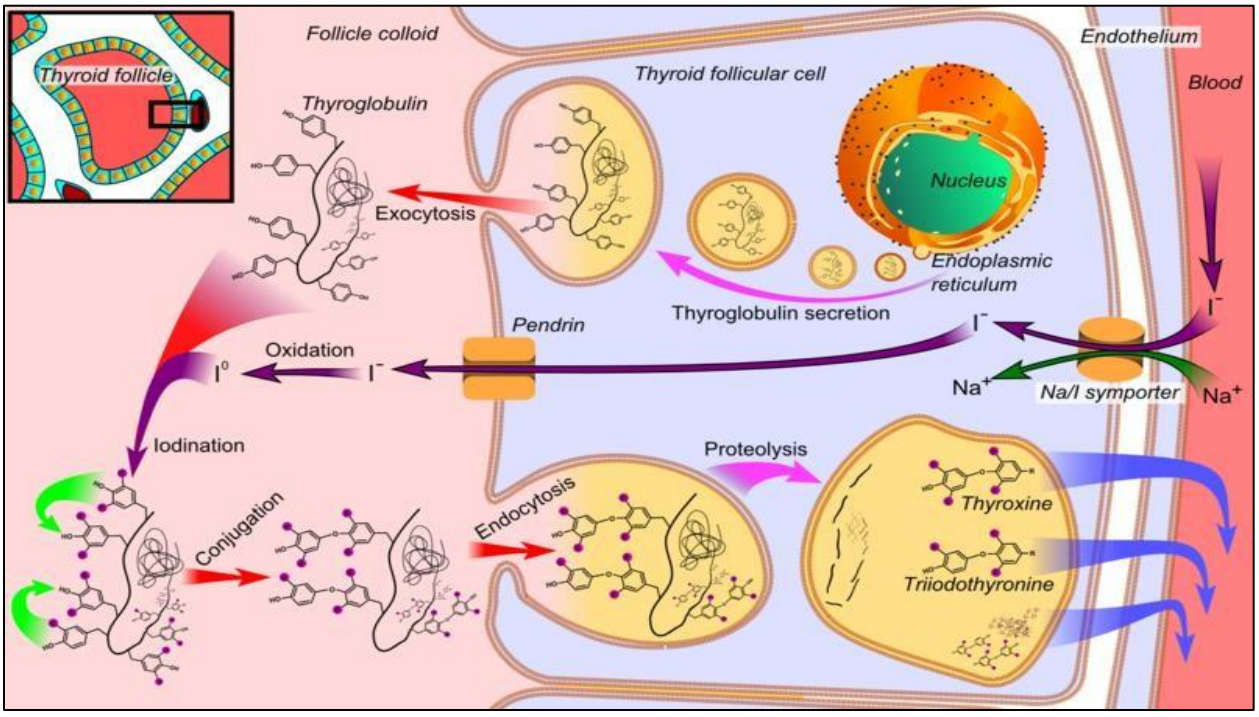
Thyronine, which is made up of two aromatic rings connected by an ether bridge, is the same chemical structure found in thyroid hormones. The quantity and location of iodine atoms in the hormones vary from one another.

V.4.3.2. Synthesis of thyroid hormones

2.1. Thyroglobulin

a) Structure: It is a glycoprotein. It is a very large dimeric molecule (molecular weight = 660,000), with each monomer containing 2,750 amino acids. Iodine attaches to the tyrosyl residues.

b) Synthesis: Thyroglobulin is synthesized by the successive assembly of amino acids along ribosomes of the endoplasmic reticulum (see Figure V.10). Thyroid cells actively take up amino acids. The addition of carbohydrate residues occurs at the final stage of synthesis in the Golgi apparatus. Iodination of tyrosines takes place after the thyroglobulin molecule is assembled.



FigureV.10. Synthesis of thyroid hormones

2.2 – Iodine

a. Intestinal absorption

Iodine enters the body mainly through digestion (daily dietary intake of 50 to 100 µg). It is absorbed in the small intestine in the form of iodide (I^-). After absorption, iodide diffuses into the plasma and extracellular fluids, reaching equilibrium approximately 4 hours after ingestion.

Plasma clearance of iodide is carried out by the thyroid and the kidneys:

- **Thyroid clearance:** 15–20 mL/min
- **Renal clearance:** 30–40 mL/min

b. Cellular uptake

Iodide uptake by the thyroid cell is linked to sodium co-transport for crossing the basal membrane, and to the presence of two types of anion channels for its passage into the colloid. Iodide uptake is **stimulated by TSH** and **inhibited by bromine** and anions such as **thiocyanate (SCN^-), perchlorate (ClO_4^-),** and **pertechnetate**. There is **self-regulation by iodine itself**: the poorer the gland is in iodine, the stronger and more prolonged the uptake—and vice versa.

c) Organification of iodine

The transformation of dietary inorganic iodine, once taken up by the thyroid, into organic iodine immediately usable for hormone synthesis depends on a **thyroid peroxidase** enzyme.

$2\ I^- \rightarrow I_2$

This is a **membrane-bound specific enzyme** that recognizes three substrates: **iodine, thyroglobulin, and H_2O_2**, which enhances its activity.

TSH increases the rate of iodine **organification.**

2.3. Binding of iodine to the tyrosyl groups of thyroglobulin

The oxidized iodine can bind to the tyrosyl residues of thyroglobulin (Tg), giving rise to the precursors of thyroid hormones: **mono-iodotyrosine (MIT)** and **di-iodotyrosine (DIT)**Iodination of Tg occurs at the **apical pole** of the thyrocytes (see Figure V.11), in the **colloid substance**.

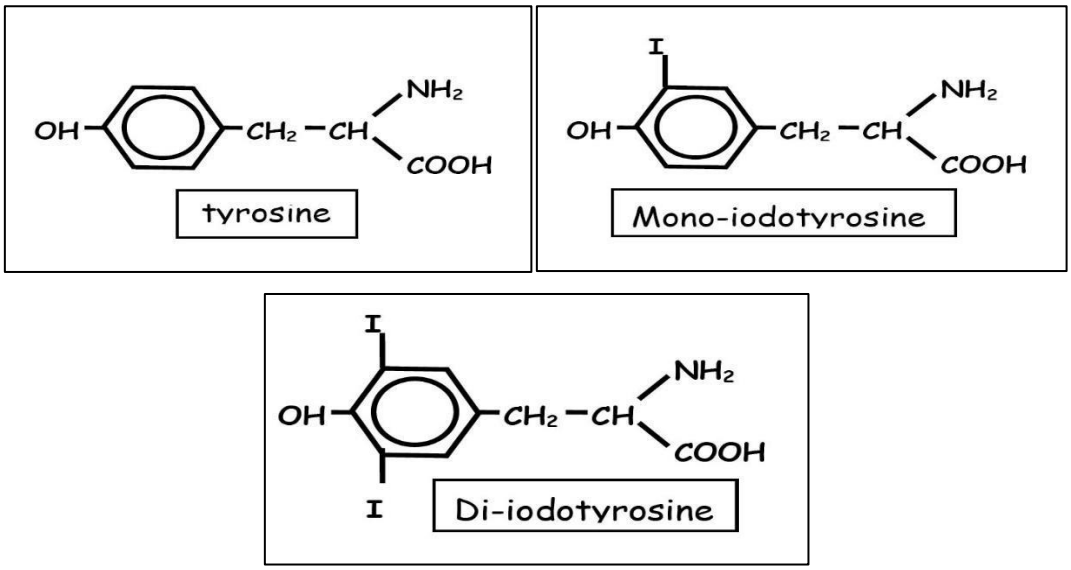


Figure.V.11. Tyrosine, mono and di-iodotyrosine structure

2.4. Coupling and Storage

One MIT (mono-iodotyrosine) residue and one DIT (di-iodotyrosine) residue combine to form **T3**, while two DIT residues combine to form **T4**. **Thyroid peroxidase** also plays a role in the coupling of these precursors.

2.5. Release

Thyroglobulin enters the epithelial cell by **microendocytosis**, where proteolytic enzymes hydrolyze it, producing the thyroid hormones T3 and T4, which are then released into the plasma. The **MIT** and **DIT** residues, released by hydrolysis of thyroglobulin, are largely **deiodinated** within the epithelial cell, and the iodide is recovered for new hormone synthesis.

Some of the **T3** released by the thyrocytes is derived from the conversion of **T4 to T3** under the influence of **5'-deiodinase**. All circulating **T4** comes from thyroid production (see Figure V.12), while most of the **T3** is produced from the peripheral conversion of T4 to T3 by **tissue deiodinases**.

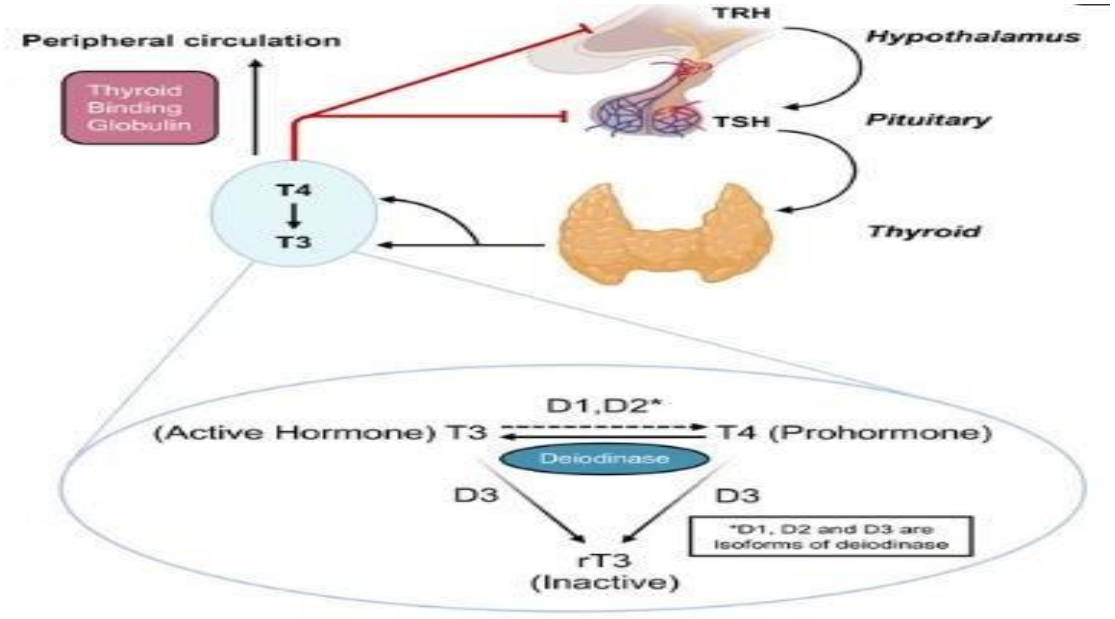


Figure.V.12. Origin of thyroiodin hormone

2.6. Plasma Transport

T4 and T3 circulate in the blood in two forms in equilibrium: one is free, and the other is bound to transport proteins.

In a euthyroid individual, only **0.02% of T4** is free, with the rest bound as follows:

- **75-80% to thyroxine-binding globulin (TBG)**
- **15-20% to prealbumin or transthyretin (TTR)**
- **5-10% to albumin.**

Similarly, only **0.3% of T3** is free, with the rest bound as follows:

- **75-80% to TBG**
- **10% to TTR**
- **10% to albumin.**

2.7. Distribution and Catabolism

Peripheral deiodination is carried out by enzymes called **5'-deiodinases**, which convert **T4 into T3**, and exist in two types:

- **Type 1 5'-deiodinase** is found in the **liver, kidney, thyroid**, and many other peripheral tissues. Its activity is **strongly influenced by nutritional status**.
- **Type 2 5'-deiodinase** is present in the **central nervous system, pituitary gland, and thyroid**. Its activity **increases in hypothyroidism** to ensure sufficient active hormone for the CNS.

V.4.4. Regulation of Thyroid Hormone Synthesis

V.4.4.1. The Thyrotropic Axis

The **hypothalamus** secretes **TRH (thyrotropin-releasing hormone)**, which acts on the **anterior pituitary**, stimulating it to secrete **TSH (thyroid-stimulating hormone)**.

TSH acts at **multiple** levels**:** It **controls and stimulates** the various steps of hormone synthesis: Iodine uptake, Iodination of thyroglobulin, Pinocytosis, Hydrolysis of thyroglobulin, and Hormone secretion

- It **maintains the thyrocyte phenotype** by regulating the expression and synthesis of: Thyroglobulin, Iodide pumps, and Thyroid peroxidase
- TSH is also a **growth factor for the thyroid gland**.

Thyroid hormones exert negative feedback on their own secretion by inhibiting both TRH and TSH release.

V.4.4.2. Thyroid Autoregulation

Thyroid autoregulation refers to temporary mechanisms that allow:

- A blockade of iodination and hormone secretion in cases of iodine excess (known as the Wolff-Chaikoff effect)
- Increased sensitivity of thyrocytes to TSH in cases of iodine deficiency
- Additionally, iodine uptake is stronger and more prolonged when the gland is iodine-deficient, and weaker when iodine stores are sufficient or excessive.

V.4.5. Mechanisms of Action of Thyroid Hormones

V.4.5.1. Extranuclear Sites of Action

- **Membrane-level actions:** Facilitate cellular metabolism by potentiating adrenergic receptors and ion pumps**,** Enhance the transport of energy substrates, such as glucose and amino acids
- **Mitochondrial actions:** Increase thermogenesis and oxygen consumption (VO_2), contributing to higher metabolic rate

V.4.5.2. Nuclear Sites of Action

- T3 binds to a cytosolic, nucleus-targeting receptor
- The T3–receptor complex enters the nucleus and regulates gene expression, leading to the synthesis of specific proteins that mediate the hormone's biological effects

Thyroid hormone receptors are encoded by **two genes:**

- **TRα (**located on **chromosome 11)**
- **TRβ (**located on **chromosome 14)**

V.4.6. Biological Effects of Thyroid Hormones

6.1. Growth and Skeletal Development

- **During the fetal period**, thyroid hormones are **not essential for growth**, but they are **crucial for bone differentiation and maturation**.
    - Their absence leads to **delayed appearance of epiphyseal ossification centers**, resulting in a **dysgenic (abnormal) skeletal appearance**.
- **In the postnatal period**, thyroid hormones become **essential for growth** and continue to regulate **bone maturation and differentiation**.
- **Growth hormone (GH)** promotes **chondrogenesis** (cartilage formation) and **cartilage growth**, while **thyroid hormones** enable **maturation and ossification** of that cartilage.
- Thyroid hormones also **stimulate GH secretion** and **enhance the effects of IGF-1** (insulin-like growth factor 1).

- **Childhood hypothyroidism** leads to **disproportionate dwarfism** (*dysharmonious dwarfism*).
- In **adults**, **hyperthyroidism** is associated with an **increased risk of osteoporosis**, due to accelerated bone turnover.

6.2. Effects on the Central Nervous System

- **Thyroid hormones play a crucial role**, especially during the **first months of life**.
- **Deficiency during this critical period** can result in **severe mental retardation**, known as **cretinism**.
- **Excess thyroid hormones** can also be harmful, as they **accelerate neuronal differentiation** at the expense of **neural cell proliferation**, potentially disrupting proper brain development.
- In **adults**, thyroid hormones continue to influence CNS function:
    - **Hypothyroidism** can cause **slowed mental function** and **drowsiness**
    - **Hyperthyroidism** is often associated with **excitability**, **nervousness**, and **irritability**

6.3. Metabolic Effects

a) Basal Metabolism: Thyroid hormones **increase thermogenesis** and **oxygen consumption (VO_2)**, contributing to a higher basal metabolic rate (BMR).

b) Carbohydrate Metabolism: Thyroid hormones are **hyperglycemic**

c) Lipid Metabolism: Thyroid hormones **increase cholesterol synthesis** but also enhance its **hepatic degradation**, leading to an overall **reduction in blood cholesterol levels**.

d) Protein Metabolism: Thyroid hormones **stimulate protein synthesis**, but they also have a **catabolic effect**

e) Water and Mineral Metabolism: Thyroid hormones **increase glomerular filtration** and **renal blood flow**. Therefore, **hypothyroidism** can lead to **edema** due to reduced kidney function.

6.4. Tissue Effects

- **Cardiac Effects**: Thyroid hormones exert a **positive chronotropic** (increased heart rate) and **positive inotropic** (increased contractility) effect on the heart.

- **Muscular Effects**: Thyroid hormones regulate **muscle contraction** and **creatine metabolism**.
- **Digestive System**: Thyroid hormones **promote intestinal transit**, enhancing gut motility.
- **Hematopoiesis and Iron Metabolism**: Thyroid hormones are involved in the regulation of **hematopoiesis** (blood cell production) and **iron metabolism**.

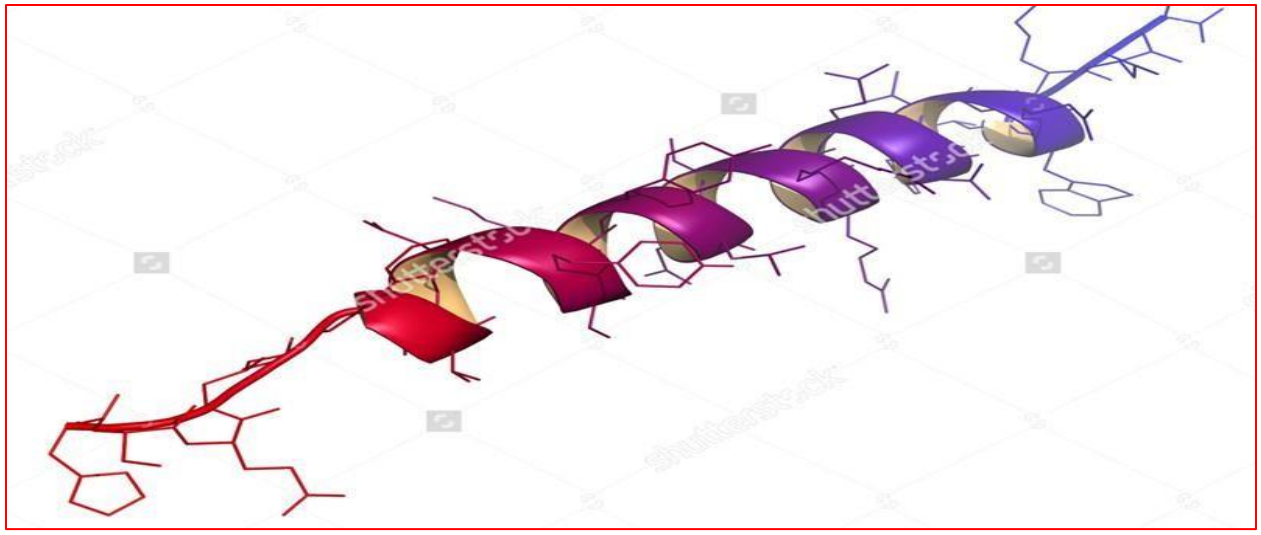
V.5. Glucagon

V.5.1. Introduction

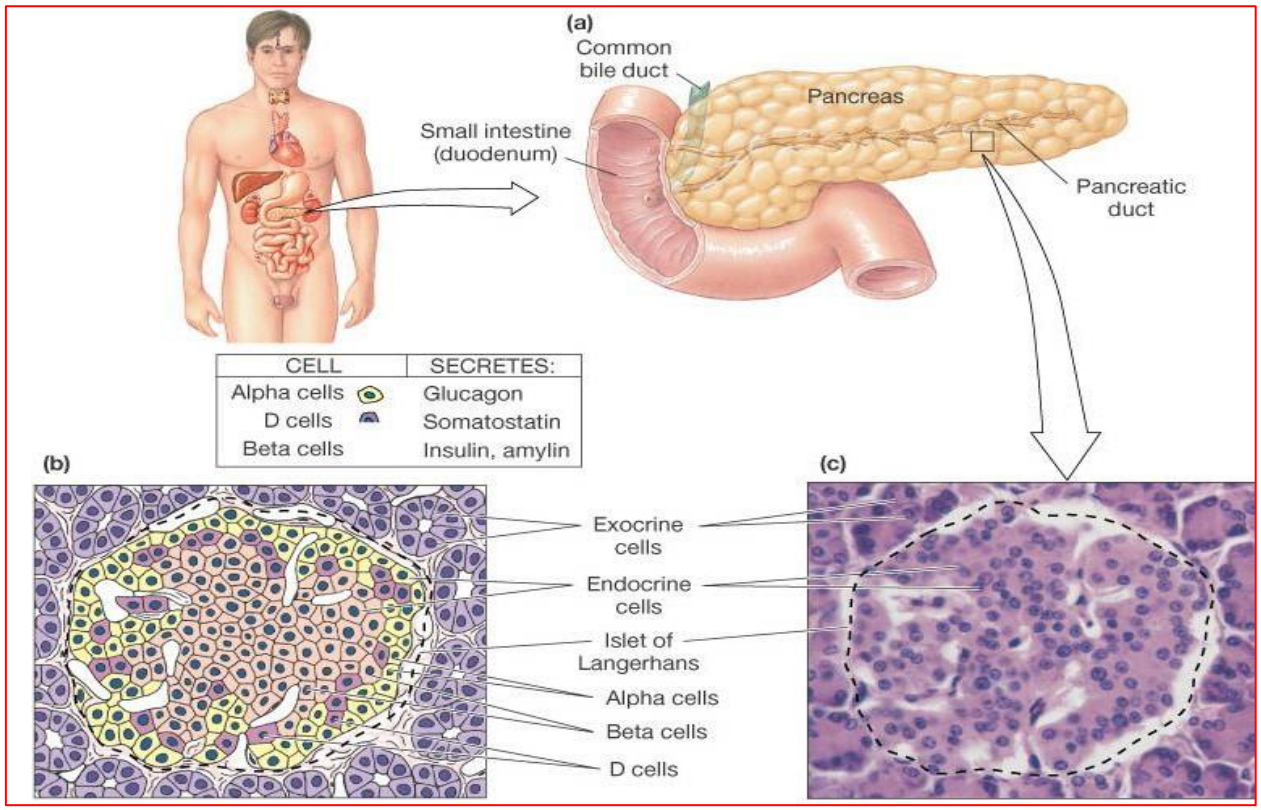
The homeostasis of intermediate metabolism is finely regulated by hormones synthesized by various endocrine glands. These hormones are secreted into the bloodstream and act on their specific target organs via dedicated receptors. The pancreas is a gland with both endocrine and exocrine functions, playing a key role in metabolic regulation through the secretion of insulin and glucagon. These hormones contribute to the control of carbohydrate, protein, and lipid metabolism.

V.5.2. Structure and metabolism

Glucagon is a polypeptide hormone with a molecular weight of 3.5 kDa made up of 29 amino acids (see Figure V.13). It exists as a single-stranded chain containing one α-helix and no disulfide bonds. It is secreted by the α cells of the pancreatic islets of Langerhans (see Figure V.14) and circulates in the blood in an unbound form. Glucagon has a short half-life of approximately 6 minutes (ranging from 5 to 9 minutes). Its levels are measured using immunoassay techniques, and normal fasting plasma concentrations range from 10 to 150 pg/ml.



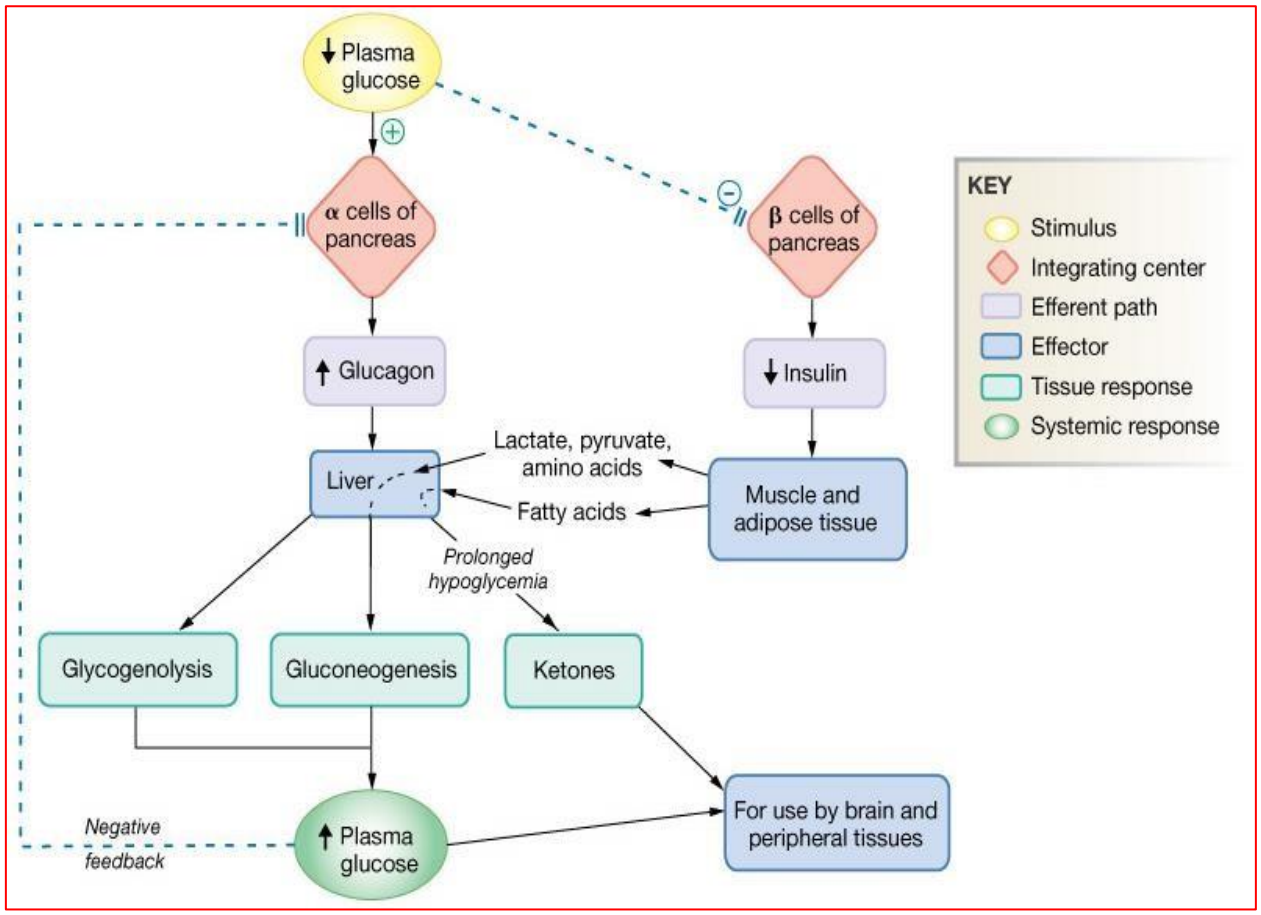
FigureV.13. Structure of Glucagon hormone



FigureV.14. Pancreas structure

V.5.3. Regulation of blood sugar

The pancreatic alpha cells recognize low blood glucose levels, such as during fasting or in between meals, and release the hormone glucagon into the bloodstream. As glucagon enters the liver, it promotes gluconeogenesis, which produces glucose from non-carbohydrate sources, and glycogenolysis, which breaks down stored glycogen into glucose. Consequently, glucose is released into the bloodstream, restoring normal blood sugar levels (see Figure V.15). This rise in glucose then inhibits further glucagon secretion through a negative feedback mechanism, helping maintain glucose homeostasis.



FigureV.15. Regulation of blood sugar by secretion of glucagon hormone.

V.5.4. Biosynthesis

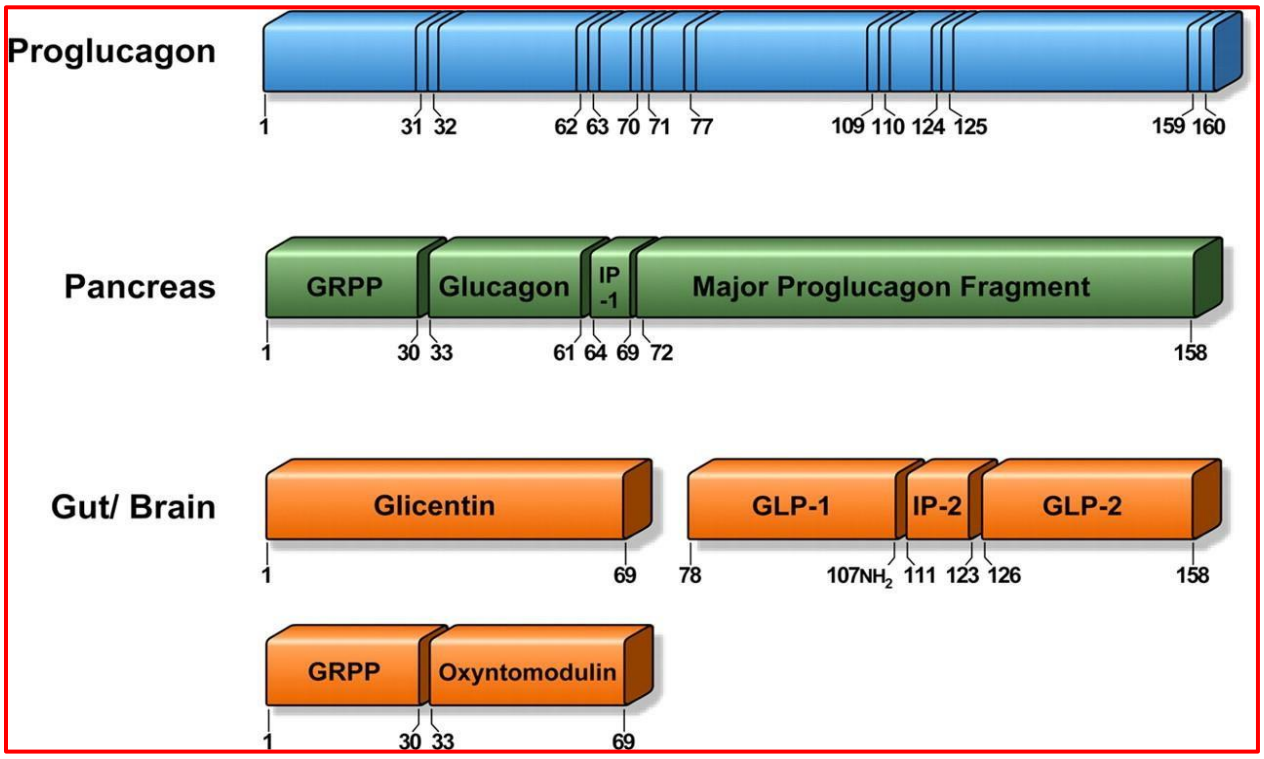
The messenger RNA encoding proglucagon produces a long peptide of 160 amino acids, which undergoes organ-specific cleavage by **prohormone convertases** (PC). In the pancreas, **PC2** processes proglucagon into several products (see Figure V.16):

-**major proglucagon fragment (MPGF)**, a large inactive peptide (residues 72–158 of proglucagon);

-**GRPP**, a polypeptide related to glicentin and inactive (residues 1–30);

- **glucagon** (residues 33–61);

-and **IP1** (residues 64–69).



FigureV.16. Different Proglucagon

V.5.5. Catabolism of Glucagon

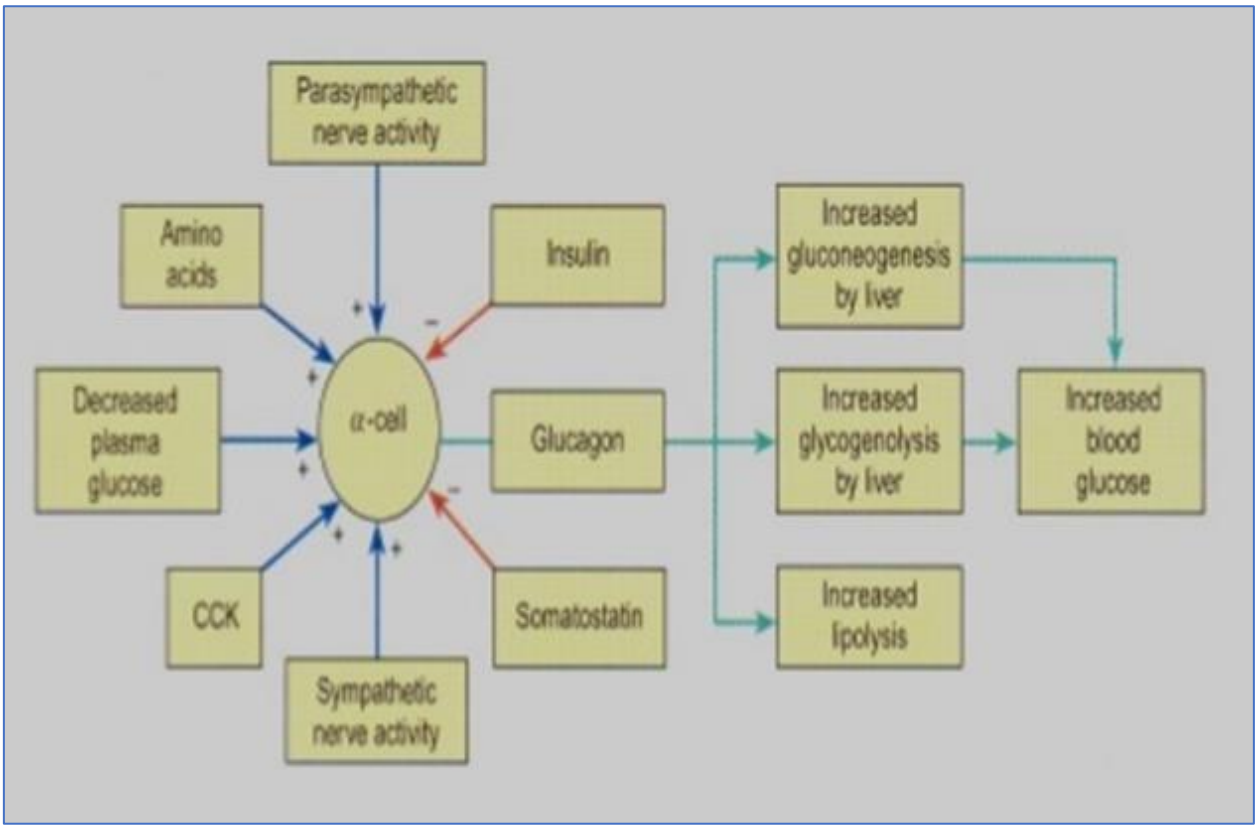
The catabolism of glucagon primarily occurs in hepatocytes, where the hormone-receptor complex is internalized and degraded. The remaining glucagon molecules are broken down by proteolysis in renal tubular cells. Renal or hepatic insufficiency, as well as prolonged biliary obstruction, can extend the half-life of glucagon.

V.5.6. Regulation

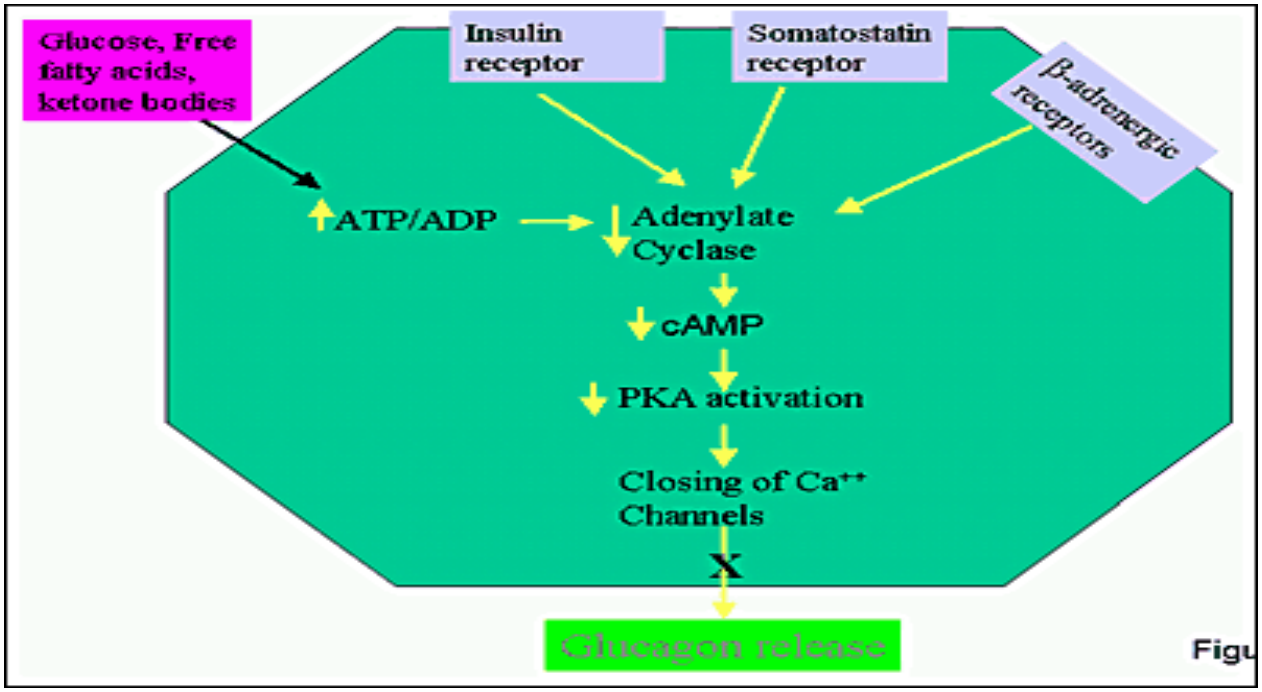
a. Stimulation: Hypoglycemia, β-adrenergic stimulation, Vagal stimulation (see Figure V.17), Protein-rich meal (asparagine, alanine, glycine)

b. Inhibition: Hyperglycemia, Free fatty acids, Postprandial state

Insulin inhibits glucagon secretion and also suppresses glucagon gene expression, thereby reducing its biosynthesis. Somatostatin inhibits both glucagon and insulin secretion (see Figure V.18).



FigureV.17. Regulation of Glucagon secretion



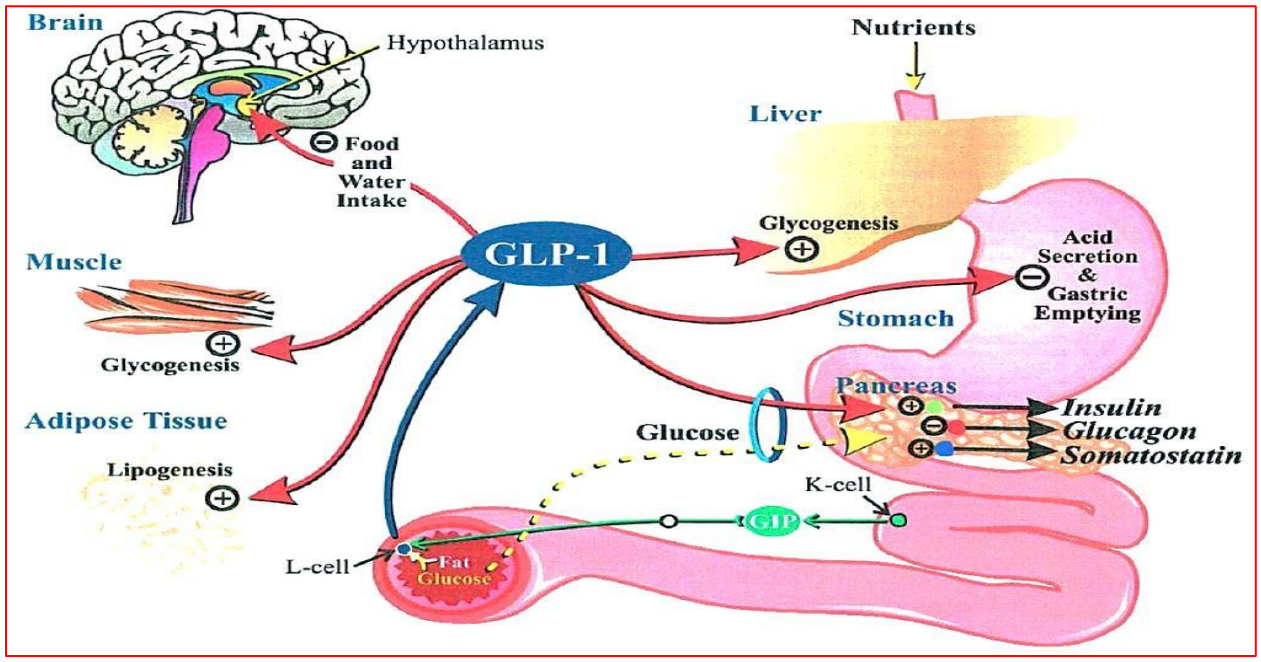
FigureV.18. Inhibition of Glucagon secretion

c. Incretins

Definition

Incretins are peptides produced by cells in the digestive tract in the presence of glucose (see Figure V.19).

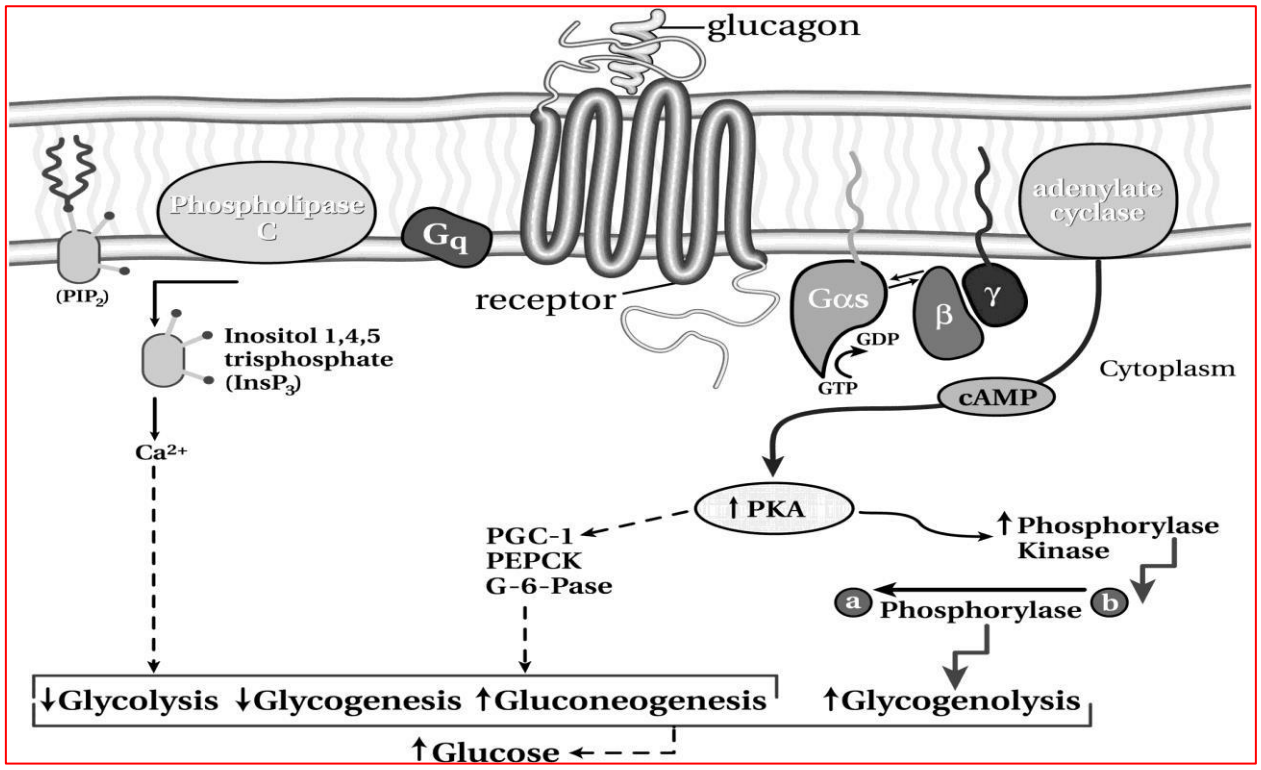
- **GLP-1 (Glucagon-Like Peptide 1)** is secreted by L cells in the enteroendocrine system, located in the distal ileum and colon.
- **GIP (Glucose-dependent Insulinotropic Peptide)** is synthesized by K cells in the enteroendocrine system, located in the duodenum and ileum.



FigureV.19. Factors influence the Regulation of Glucagon secretion.

V.5.7. Mode of action of glucagon

The hormone glucagon, which is released when blood glucose levels are low, mainly raises blood sugar levels via acting on the liver. It attaches itself to hepatocytes' G-protein coupled receptors, triggering adenylyl cyclase and raising cAMP (see Figure V.20), which triggers protein kinase A (PKA). As a result, gluconeogenesis—the production of glucose from non-carbohydrate sources—and glycogenolysis—the breakdown of glycogen—are stimulated, while simultaneously inhibiting glycolysis and glycogenesis.



FigureV.20. Mode action of Glucagon

V.5.8. Physiological role of Glucagon

8.1. Carbohydrate metabolism

Glucagon increases hepatic glycogenolysis by activating glycogen phosphorylase, it inhibits glycogenesis by phosphorylating the enzyme glycogen synthase, converting it into glycogen synthase kinase. It inhibits glycolysis by inhibiting 1-phosphofructokinase, and stimulates gluconeogenesis by activating fructose-1,6-bisphosphatase.

8.2. Lipid metabolism

Glucagon inhibits the enzymes involved in lipogenesis and stimulates lipolysis. It stimulates β-oxidation by increasing the concentration of CAT1 enzymes (acylcarnitine transferase 1) and it stimulates ketogenesis by activating HMG-CoA synthase.

8.3. Protein metabolism

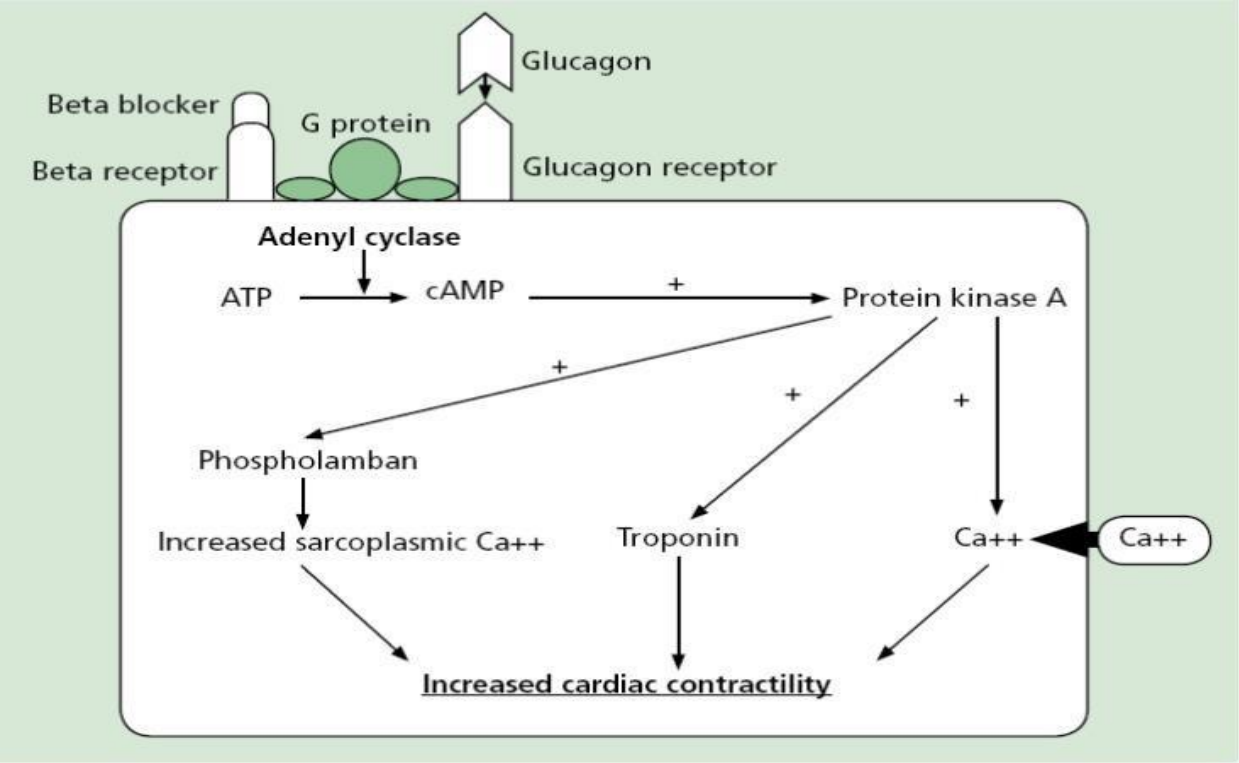
Glucagon lowers the plasma concentration of amino acids by increasing their hepatic uptake and their use in gluconeogenesis.

8.4. Effects on the kidneys

Increases urinary excretion of phosphates and Na+, Increases glomerular filtration rate (GFR).

8.5. Effects on the heart

Positive inotropic effect: Opens calcium channels through phosphorylation, leading to calcium influx, Calcium binds to troponin C, causing the interpenetration of actin and myosin filaments (muscle contraction), The strength of cardiac contractions depends on the degree of calcium channel phosphorylation, and **Positive chronotropic effect (**see Figure V.21**).**

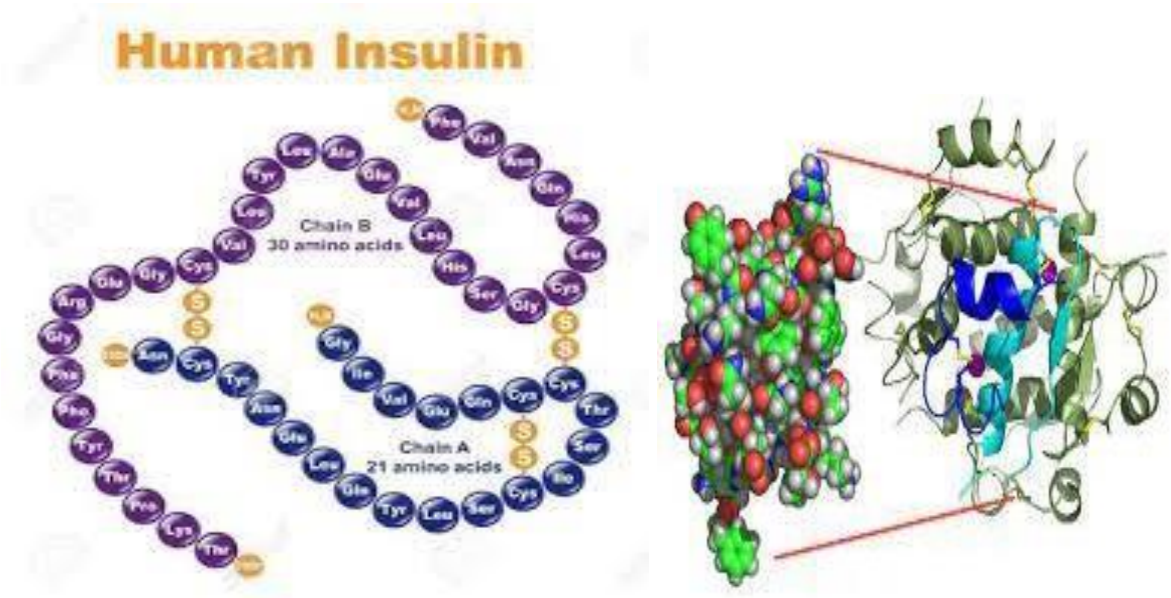


FigureV.21. Fundamental mechanism of glucagon's action in cardiac muscle cells.

V.6. Insulin

V.6.1. Introduction

Insulin is truly a "first-in-class" hormone: it was the first hormonal protein to be discovered (in 1922), the first protein to be sequenced, the first to be chemically synthesized (see Figure V.22), and the first to be identified as being derived from a prohormone.



FigureV.22. Structure of Human Insulin

An A chain with 21 amino acids and a B chain with 30 amino acids make up the heterodimeric hormone insulin, which is connected by two interchain disulfide links. There is also one intrachain disulfide bond in the A chain. Insulin is the only hormone with a hypoglycemic effect.

V.6.2. Insulin Metabolism

2.1. Synthesis

The beta (β) cells of the endocrine pancreatic islets of Langerhans produce insulin. A precursor molecule known as preproinsulin is created when the human insulin gene is transcriptionally active. After that, preproinsulin is changed into proinsulin (86 amino acids), which has the 51 amino acid chains that make up insulin as well as the C-peptide (31 amino acids) that connects the A and B chains. When zinc is present,

proinsulin molecules in the endoplasmic reticulum form hexamers. Inside these vesicles, proinsulin is cleaved by specific enzymes that remove the C-peptide, forming mature insulin. The hormonal content of these vesicles is only released from the beta cell in response to an appropriate stimulus.

2.2. Insulin Secretion

① Blood glucose passes through capillaries into the interstitial fluid that bathes the β-cells of the islets of Langerhans.

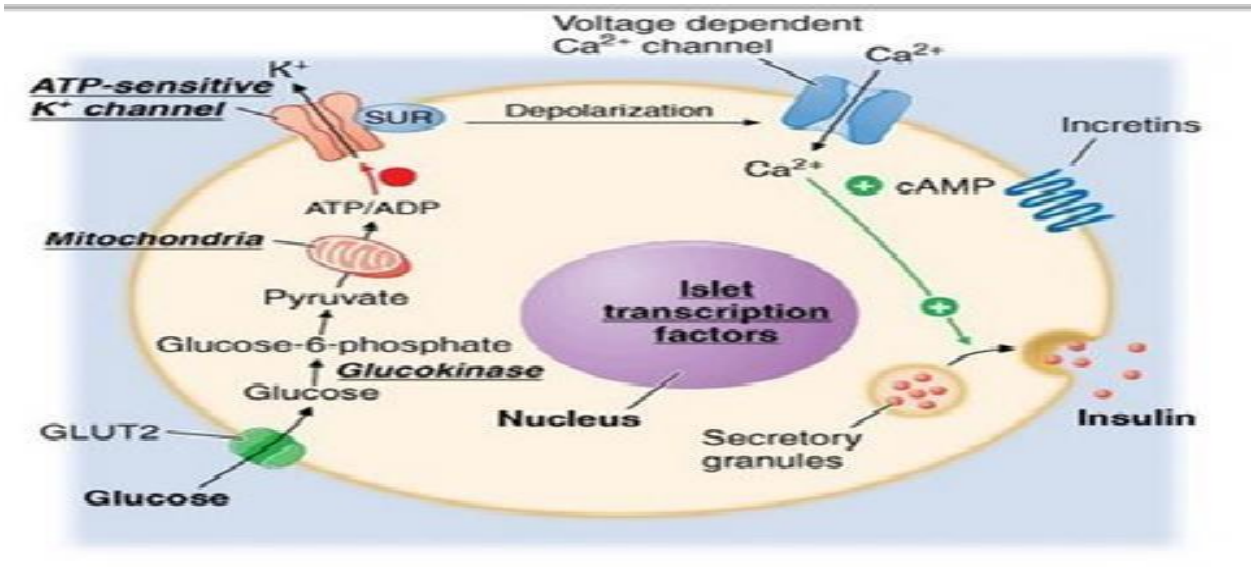
② The β-cell imports glucose via a non-saturable GLUT2 transporter (unlike other body cells, which have easily saturated receptors), meaning intracellular glucose concentration mirrors that of the blood.

③ Upon entry, glucose is immediately phosphorylated by glucokinase.

④ Glycolysis increases the ATP/ADP ratio within the β-cell, and this rise in ATP leads to the closure of potassium channels (see Figure V.23).

⑤ As potassium (K^+) ions stop exiting the cell, the β-cell—being excitable—undergoes depolarization (triggered at blood glucose ≥ 5 mmol/L).

⑥ This depolarization opens voltage-dependent calcium channels, allowing calcium to enter the cell and trigger the exocytosis of insulin-containing vesicles.



FigureV.23. Secretion of Insulin.

2.3. Reminder on Signaling Pathways

Binding of insulin to its receptor Tyrosine kinase. Phosphorylation of substrate proteins, which serve as the starting point for two major signaling pathways:

- The **PDK/PKB pathway**
- The **MAPK pathway = Erk**

V.6.3. Metabolic Effects

Insulin has a threefold action:

3.1 Carbohydrate Metabolism

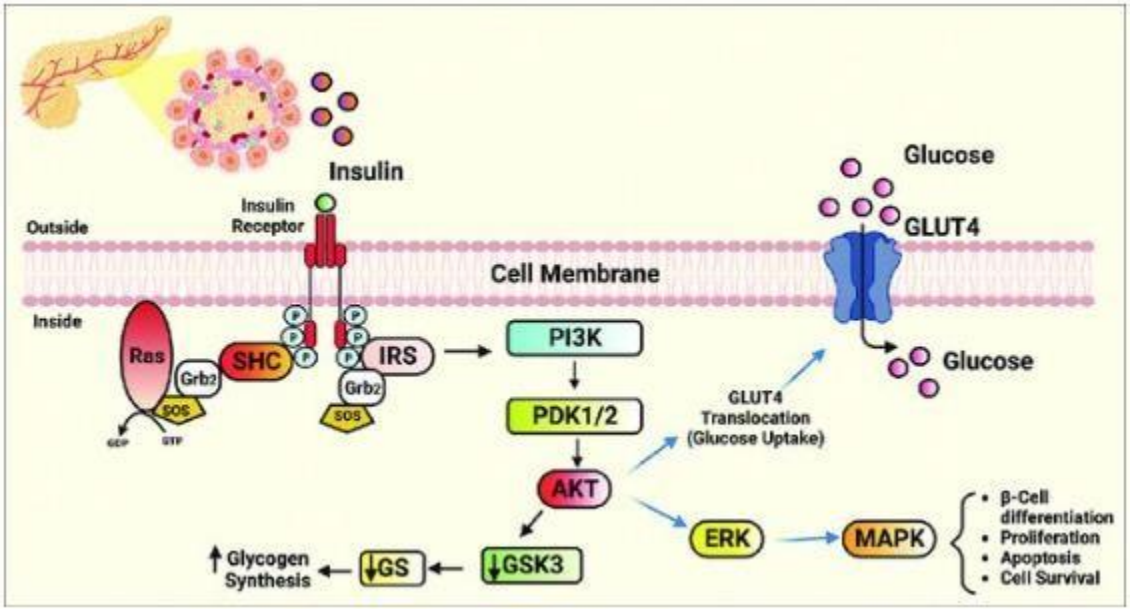
By Stimulation of glucose uptake, Stimulation of glycogen synthesis, and Inhibition of hepatic gluconeogenesis (see Figure V.24)

1. Stimulation of Glucose Uptake (via the PDK/PKB Pathway);

2. Stimulation of Glycogen Synthesis (via the PDK/PKB Pathway);

3. Inhibition of Hepatic Gluconeogenesis (via the PDK/PKB Pathway);

PEPCK and G6Pase are **critical regulatory enzymes** in the gluconeogenesis pathway. This pathway is typically **activated during fasting** to allow the **liver to produce glucose**.



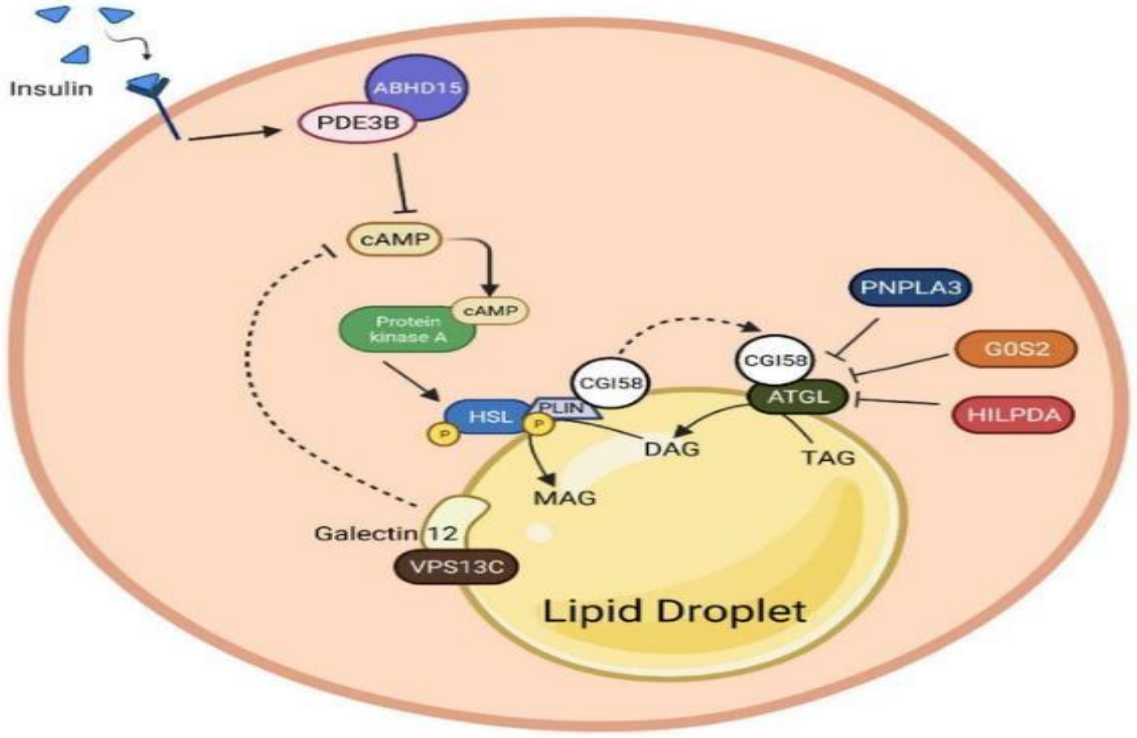
FigureV.24. Insulin signaling pathway. **IRS:** The substrate of the insulin receptor, Phosphoinositide 3 kinase, or PI3K **AKT:** Protein kinase B, **PDK1:** Phosphoinositide-dependent kinase-1, **GS:** Glycogen synthase, **GSK3:** Glycogen synthase kinase 3, **ERK:** Signal-regulated kinase outside of cells, Mitogen-activated protein kinase, or MAPK, Growth factor receptor-bound protein 2 is known as Grb2. **SHC:** A chemical that signals GLUT4: Type 4 glucose transporter

3.2 Protein Metabolism

- Stimulation of protein synthesis

3.3 Lipid Metabolism

Stimulation of lipogenesis and Inhibition of lipolysis. When insulin binds to its receptor, it stabilizes a complex between **PDE3B** and **ABHD15**. This complex helps degrade **cAMP**, leading to the **inactivation of PKA**, which in turn **prevents phosphorylation of HSL (hormone-sensitive lipase)**. PKA also directly affects **PLIN1 (perilipin 1)**. When PLIN1 is activated, it causes **CGI-58** to dissociate from the PLIN1–HSL complex and bind to **ATGL (adipose triglyceride lipase)**, thereby stimulating ATGL's enzyme activity (see Figure V.25). However, the CGI-58/HSL interaction can be **inhibited** by certain proteins such as **G0S2**, **HILPDA**, and **PNPLA3**. In addition, **Galectin-12**, a lipid droplet-associated protein, along with its coactivator **VPS13C**, may reduce cAMP levels by **blocking PDE recruitment**, ultimately **suppressing lipolysis**.



FigureV.25. Roles of Protein–Protein Interactions in Adipocyte Lipolysis:

3. Nuclear Effects

Starting from **IRS/Grb2**, the sequence of events involves a series of **protein–protein interactions**, followed by a **phosphorylation cascade** that activates **transcription factors**—notably **c-Fos**, which triggers a **proliferative response**.

Signaling Pathways and Cellular Responses

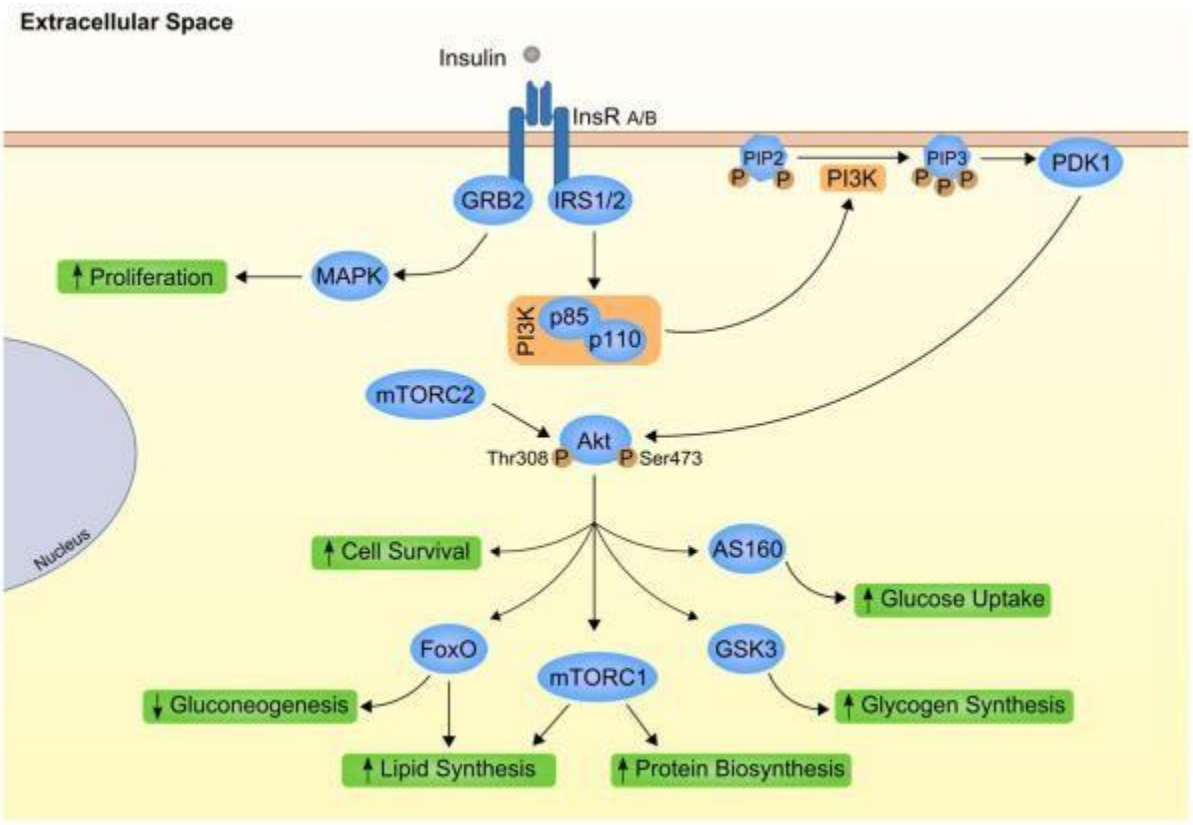
When **insulin** (represented as a gray circle) binds to its **transmembrane receptor** on the cell surface, it initiates the **insulin signaling cascade**. The insulin receptor exists in two isoforms—**INSR-A and INSR-B**—which differ in their affinity for insulin and the rate at which they are internalized. Upon insulin binding, the receptor **autophosphorylates** on **tyrosine residue 960**, enabling the recruitment and phosphorylation of **IRS-1 and IRS-2**.

This leads to the activation of **PI3K (phosphoinositide 3-kinase)**, which converts **PIP2** into **PIP3**, allowing activation of **PDK1 (phosphoinositide-dependent kinase 1)**. PDK1 then phosphorylates and

activates **Akt**, a central signaling molecule. Akt requires phosphorylation at **two key sites** to be fully active: **Thr308** (by PDK1) and **Ser473** (by **mTORC2**).

Once activated, **Akt** influences several downstream targets—such as **AS160**, promoting **glucose uptake**, and **GSK3**, enhancing **glycogen synthesis (**see Figure V.26).

In parallel, insulin receptor activation also recruits **GRB2**, which interacts with **Shc proteins** to trigger the **MAPK pathway**, contributing to insulin's **mitogenic (cell proliferation) effects**.



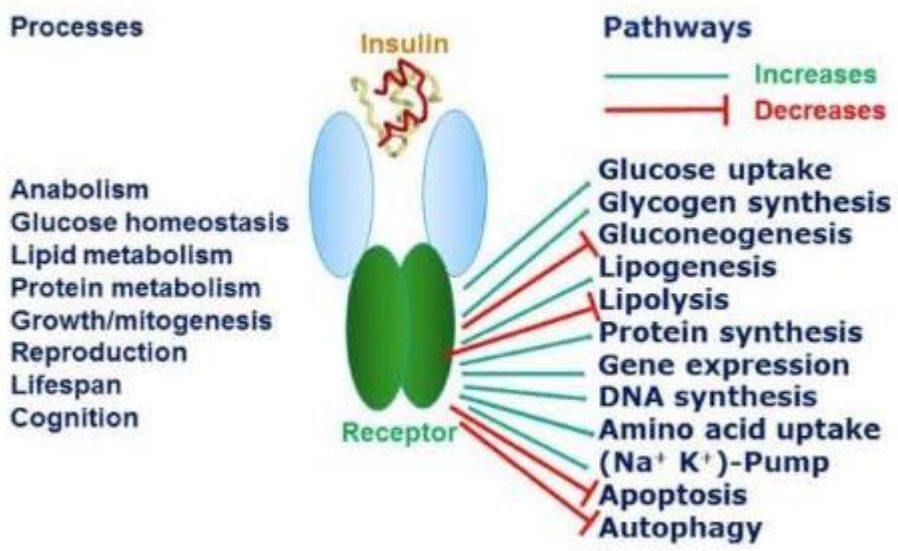
FigurV.26. Overview of the Canonical Insulin Signaling Cascade

4. The Pleiotropic Effects of Insulin

Across all its target tissues, insulin exerts an **anabolic effect** by stimulating the **synthesis of carbohydrates, lipids, and proteins**.

At the same time, it has an **anti-catabolic effect**, as it inhibits **glycogenolysis**, **lipolysis**, and **proteolysis** in those same tissues (see Figure V.27).

Insulin is the **only hormone** with this dual action—**both anabolic and anti-catabolic**. This is why, in people with diabetes, the **absence of endogenous insulin** or a **defect in insulin signaling** leads to **major disruptions in overall metabolism**.



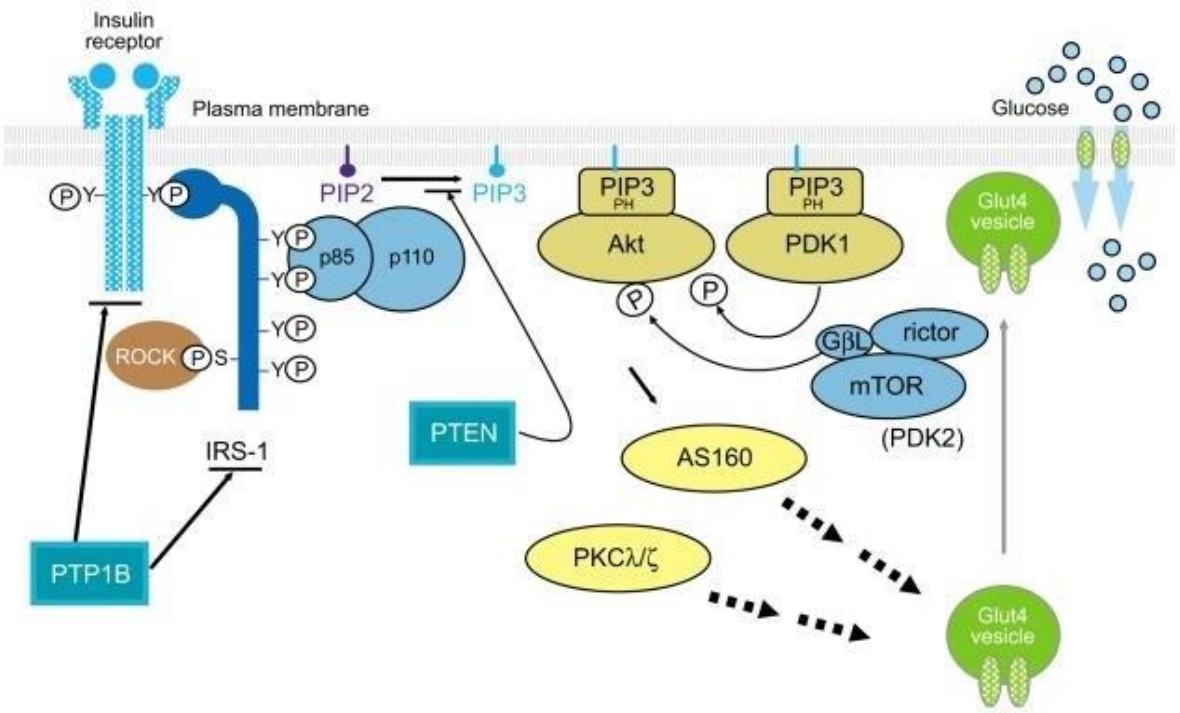
FigureV.27. Insulin's Pleiotropic Effects via Its Receptor: Through binding to its receptor, insulin influences a wide range of **physiological functions** throughout the body (left side), by either **activating** (indicated by green arrows) or **inhibiting** (red arrows) several **intracellular metabolic pathways** (right side).

V.6.4. Signal Attenuation

Both at the receptor and post-receptor phases, there are numerous ways to lessen or stop the insulin-induced signal. Tyrosine protein phosphatases, serine phosphorylation, and ligand-induced downregulation all adversely affect the insulin receptor and IRS proteins. Phosphates also regulate subsequent stages of protein kinase cascades. A crucial function of negative feedback loops is to fine-tune the signaling network.

Two mechanisms must be distinguished:

- **Endocytosis:**
  Common to all membrane receptors, this involves the **internalization and degradation** of the receptor (see Figure V.28).
- **Inactivation of the signaling pathway:** This relies on the action of specific **phosphatases and kinases** such as **PTEN** and **PTP1B**.



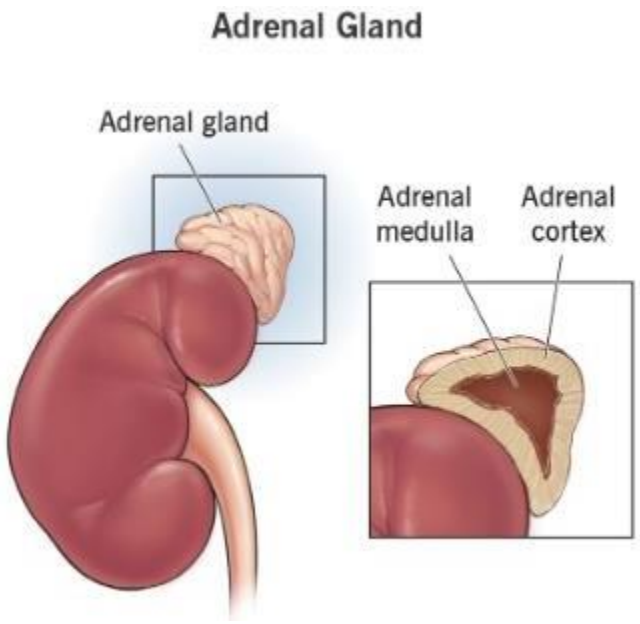
FigureV.28. Signal attenuation.

V.7. The steroids of the adrenal cortex

V.7.1. General Introduction

The adrenal glands (see Figure V.29), of which there are two, are small pyramid-shaped structures located at the top of the kidneys (one on the right and the other on the left). These glands have two distinct functional parts (in a cross-sectional view):

- **The Cortex (Cortico-Adrenal):** An essential endocrine gland for life, it produces three classes of steroid hormones: **GC** (Glucocorticoids), **MC** (Mineralocorticoids), and **AND** (Androgens).
- **The Medulla (Medullo-Adrenal):** Part of the sympathetic **autonomic nervous system (SNA)**. Its significance lies in the synthesis of **catecholamines**.



FigureV.29. Adrenal gland

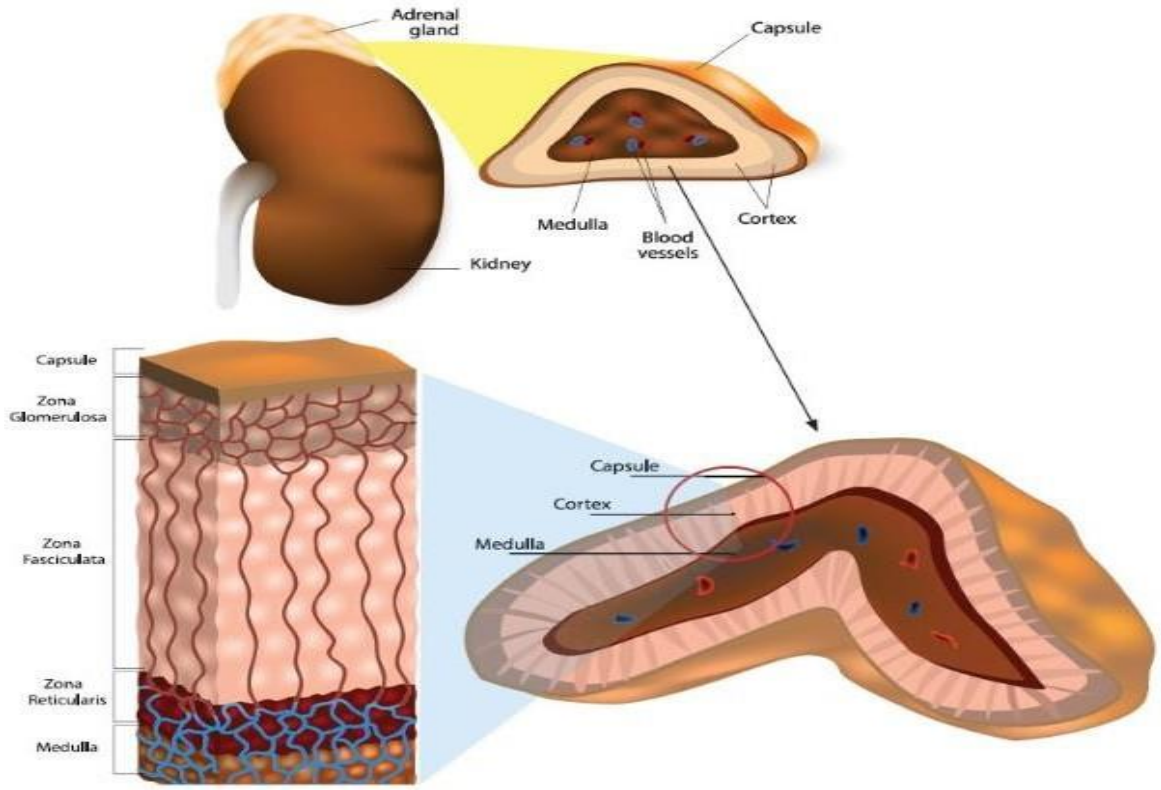
V.7.2. Anatomical and Physiological Overview

The adrenal glands are also known as suprarenal glands since they are a pair of organs situated on the front side of the kidneys. The outer adrenal cortex and the inner adrenal medulla are the two primary structural components of each gland.

From a histological perspective, the **adrenal cortex** is divided into three distinct zones:

- **Zona glomerulosa**: This outermost and thinnest layer makes up about **15%** of the cortex and is responsible for producing **mineralocorticoids**.
- **Zona fasciculata**: The largest and central layer, it comprises about **75%** of the cortex and primarily secretes **glucocorticoids** like **cortisol** and **corticosterone**, along with small amounts of **androgens** and **estrogens**.
- **Zona reticularis**: This innermost layer forms around **10%** of the cortex and secretes **adrenal androgens**, minor amounts of **estrogens**, and some **glucocorticoids** (see Figure V.30).

The **adrenal medulla**, found at the center of the gland, is made up of **ovoid and columnar cells** arranged around a rich capillary network. It produces two main **catecholamines**: **adrenaline (epinephrine)** and **noradrenaline (norepinephrine)**.

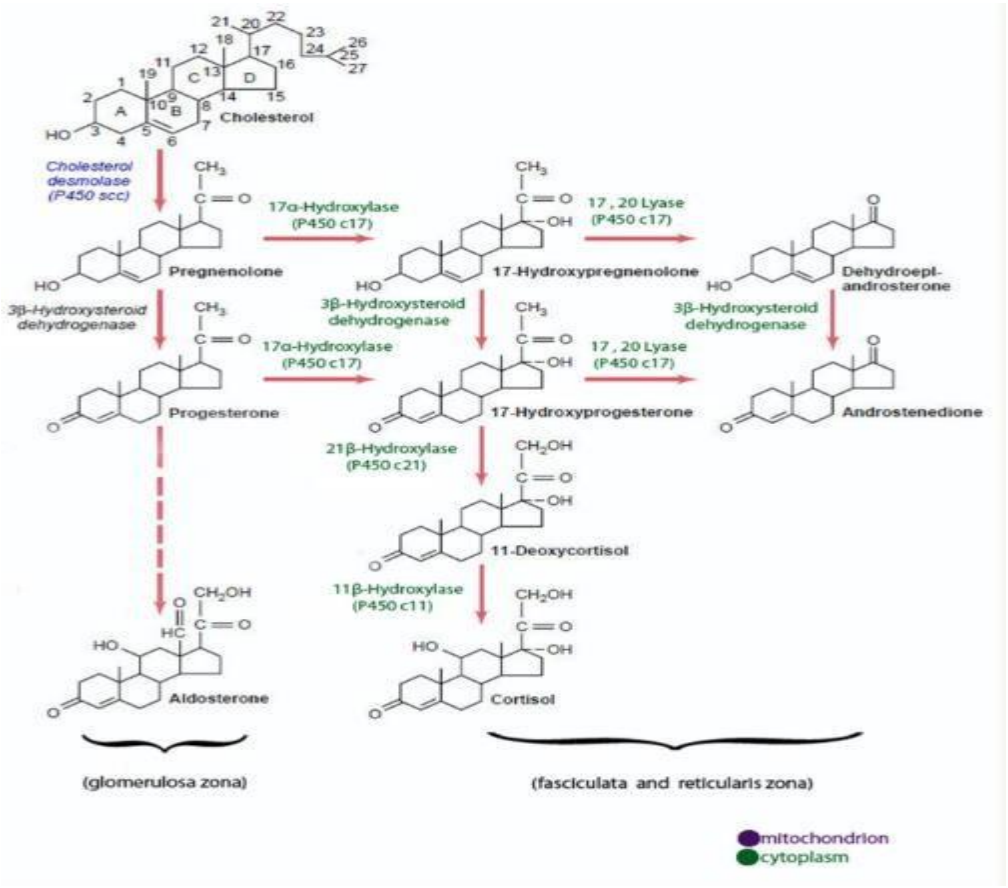


FigureV.30. Structure of Adrenal gland.

V.7.3. Biosynthesis in Distinct Zones

The synthesis of steroid hormones from cholesterol is carried out by four types of enzymes:

- **Desmolases:** responsible for cleavage reactions
- **Hydroxylases:** introduce hydroxyl groups
- **Dehydrogenases:** involved in oxidation-reduction reactions (see Figure V.31)
- **Isomerases:** rearrange double bonds



FigureV.31. Adrenal androgen biosynthetic pathway.

V.7.4. Regulation of the Adrenal Cortex

The hypothalamic-pituitary-adrenal (HPA) axis strongly controls the activity of the adrenal cortex:

4.1. Hypothalamus

- **Produces CRH (*Corticotropin-Releasing Hormone*)**
- Stimulates the anterior pituitary gland

4.2. Anterior Pituitary (Adenohypophysis)

- **Releases ACTH (*Adrenocorticotropic Hormone*)** in response to CRH
- **ACTH** acts on the adrenal cortex, especially the zona fasciculata and zona reticularis

4.3. Adrenal Cortex

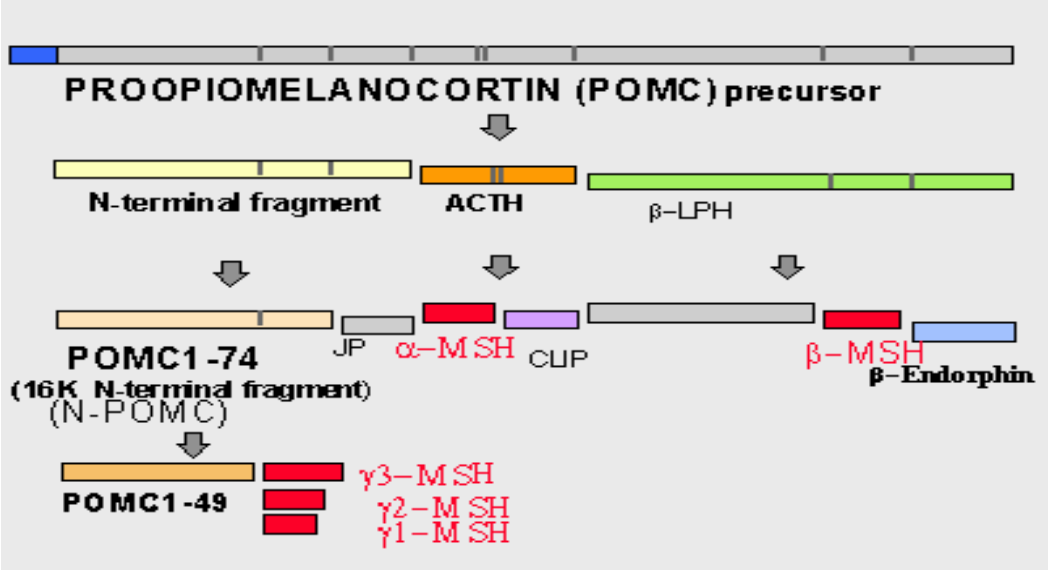
- **ACTH** stimulates the secretion of:
    - **Glucocorticoids (e.g., cortisol)**
    - **Androgens (e.g., DHEA)**
- **Aldosterone (from the zona glomerulosa)** is mostly controlled by potassium levels and the renin-angiotensin-aldosterone system (RAAS), not ACTH directly.

4.4. Negative Feedback

The circadian rhythm is governed by the central nervous system through the regulation of CRH and ACTH secretion over a 24-hour cycle. The primary hormone surges occur between the sixth and eighth hour of sleep, then taper off as the person awakens. Cortisol levels continue to decrease throughout the day, with fewer secretion pulses. This rhythmic pattern of adrenal androgen release remains consistent across various physiological and pathological states. For instance, individuals with nonclassical 21-hydroxylase deficiency exhibit a distinct adrenal steroid secretion pattern, marked by frequent 17-hydroxyprogesterone release and comparatively low nighttime cortisol levels. ACTH and cortisol levels can rise within minutes after physical stress begins, disrupting the normal circadian rhythm if the stress is sustained. These stress responses are initiated in the central nervous system and lead to increased CRH and ACTH production. Cortisol, once stimulated by ACTH, provides negative feedback to both the hypothalamus and anterior pituitary by inhibiting further CRH and ACTH production. So, Cortisol inhibits both CRH and ACTH secretion to maintain hormonal balance.

V.7.5. ACTH as a Pituitary Marker: Adrenocorticotropic Hormone or Corticotropin

ACTH (adrenocorticotropic hormone or corticotropin) is a pituitary hormone derived from the cleavage of pro-opiomelanocortin (POMC) and plays a key role in regulating cortisol secretion. It is a 39-amino-acid peptide secreted by corticotropic cells in the anterior pituitary (see Figure V.32). ACTH is released in a pulsatile manner, which drives the circadian rhythm of cortisol, with peak levels occurring between 6 and 9 AM and the lowest levels between 11 PM and midnight. It controls the function of the adrenal cortex, except for the zona glomerulosa.



FigureV.32. Pro-opio-mélano-corticotrophine (POMC) structure

V.7.5.1. Regulation of ACTH

ACTH secretion is influenced by various factors. It is triggered by arginine vasopressin (AVP) and hypothalamic corticotropin-releasing hormone (CRH), while excessive cortisol levels inhibit its release through negative feedback. CRH secretion itself is promoted by serotonin and inhibited by GABA and opioids.

There is a negative feedback mechanism at both the pituitary and hypothalamic levels mediated by circulating cortisol, integrated into the hypothalamic-pituitary-adrenal (HPA) axis. ACTH regulates cortisol secretion, and in turn, cortisol exerts negative feedback to inhibit further release of both ACTH from the pituitary and CRH from the hypothalamus

.

V.7.5.2. Role of ACTH

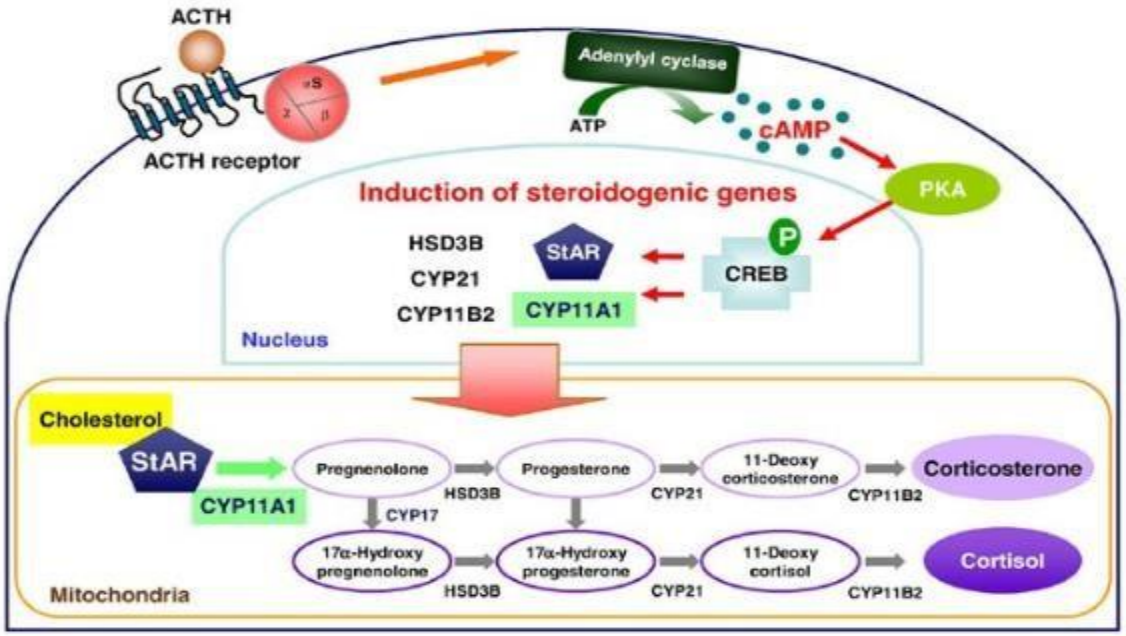
ACTH facilitates the transport of cholesterol from the cytoplasm into the mitochondria, where it promotes the conversion of cholesterol into pregnenolone within the mitochondria—an essential first step in steroid hormone synthesis.

Once released into the bloodstream, it binds to G protein-coupled receptors, initiating the conversion of cholesterol into Δ5-pregnenolone within the mitochondria (see Figure V.33).

-It has a trophic (growth-promoting) effect on the adrenal cortex.

-In acute administration, it plays a role in the positive regulation of aldosterone.

-It has a short half-life (less than 20 minutes) *in vivo*; *in vitro*, it is sensitive to proteases (unstable).



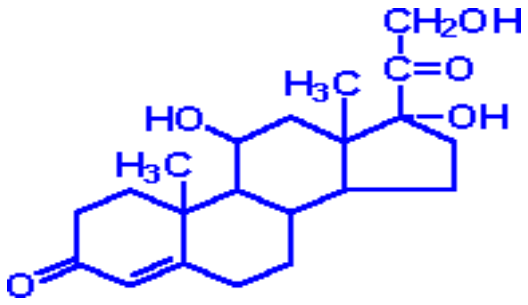
FigureV.33. Adrenal steroid hormone production, particularly glucocorticoids (GC), occurs primarily in specialized steroid-producing cells of the adrenal cortex through a series of enzymatic steps that modify cholesterol within the mitochondria. The movement of cholesterol from the cytosol into the mitochondria—facilitated by the StAR protein—is the rate-limiting step of this process. In response to stress, ACTH stimulates glucocorticoid synthesis by enhancing the expression of steroidogenic genes via activation of the ACTH receptor and the cAMP/PKA/CREB signaling pathway.

V.7.5.3. Glucocorticoids

Cortisol is the primary glucocorticoid (along with cortisone) produced in the zona fasciculata of the adrenal cortex under the control of ACTH. It is synthesized from pregnenolone through the action of three key hydroxylase enzymes: 17α-hydroxylase, 21-hydroxylase, and 11β-hydroxylase.

A. Synthesis of Cortisol from Cholesterol

The synthesis of cortisol in the adrenal cortex involves several enzymatic steps starting from cholesterol. Here's a simplified outline of the process (see Figure V.34):



FigureV.34. Cortisol structure**.**

1. **Cholesterol Uptake**: Cholesterol is transported into the adrenal cortex cells, primarily into the mitochondria, facilitated by the StAR (Steroidogenic Acute Regulatory) protein.
2. **Conversion to Pregnenolone**: Cholesterol undergoes cleavage by the enzyme **P450scc** (also known as cholesterol desmolase or CYP11A1), converting it into **pregnenolone** in the mitochondria.
3. **Conversion to 17-Hydroxypregnenolone**: Pregnenolone is then converted into **17-hydroxypregnenolone** by the enzyme **17α-hydroxylase** (CYP17A1).
4. **Formation of 11-Deoxycortisol**: 17-hydroxypregnenolone is further processed by **21-hydroxylase** (CYP21A2), producing **11-deoxycortisol**.
5. **Cortisol Synthesis**: Finally, **11-deoxycortisol** is converted into **cortisol** by the enzyme **11β-hydroxylase** (CYP11B1).

This series of enzymatic changes, which mostly take place in the zona fasciculata of the adrenal cortex, r esults in the synthesis of cortisol, which is essential for controlling metabolism and the body's stress resp onse.

B. Plasma Transport of Cortisol

Cortisol is transported in the bloodstream primarily in two forms:

1. **Bound to Plasma Proteins**:
    - **Corticosteroid-binding globulin (CBG)**, also known as transcortin, binds the majority of cortisol in the plasma (around 90-95%). This binding is essential for regulating cortisol's availability and stability.
    - **Albumin** also binds a smaller portion of cortisol (about 5-10%), but with lower affinity compared to CBG.
2. **Free (Unbound) Cortisol**:
    - A small fraction of cortisol (about 1-3%) circulates in its free, unbound form. This free cortisol is biologically active and capable of entering cells to exert its effects.

CBG (corticosteroid-binding globulin) binds 75% of cortisol with high affinity and also binds progesterone.

- Albumin binds 15% of cortisol.
- Free cortisol: 10%, the only active form (measured in saliva or urine).
- Total cortisol = free cortisol + bound cortisol.

CBG levels increase during pregnancy or when using estrogen-progestin contraceptive pills.

D. Elimination

Cortisol is primarily eliminated through the **urine**, with a half-life of about **1 hour**. In the urine, the following are typically found:

- **17α-hydroxysteroids (17 OH)**, which are metabolites derived from cortisol.
- **17-ketosteroids (17 keto)**, which are metabolites originating from both **androgens** and **cortisol**.

- **Free cortisol (1%)**, which is the biologically active form.

E. Regulation of Cortisol Secretion

Cortisol secretion is primarily regulated through the **hypothalamic-pituitary-adrenal (HPA) axis**, involving a feedback loop between the brain, pituitary gland, and adrenal cortex.

1. **Hypothalamus**: The hypothalamus releases **corticotropin-releasing hormone (CRH)** in response to stress or other stimuli. CRH stimulates the pituitary gland to secrete **adrenocorticotropic hormone (ACTH)**.
2. **Pituitary Gland**: ACTH is secreted by the anterior pituitary and travels through the bloodstream to the adrenal cortex. ACTH stimulates the adrenal cortex, particularly the **zona fasciculata**, to produce and release **cortisol**.
3. **Adrenal Cortex**: The secretion of cortisol is mainly regulated by the enzyme **11β-hydroxylase** and is triggered by ACTH. Cortisol then enters the bloodstream, where it exerts its effects on various tissues involved in stress responses, metabolism, and immune regulation.
4. **Negative Feedback**:
    - Cortisol exerts negative feedback at both the **hypothalamus** and the **pituitary**. It inhibits further release of CRH and ACTH, thereby regulating its own production and preventing overproduction.
    - This feedback loop ensures cortisol levels stay within a physiological range and prevents excessive secretion.

Regulation Under Stress: Under stressful conditions, the hypothalamus increases CRH secretion, stimulating the release of ACTH and cortisol. This system helps the body respond to acute stress.

Daily Rhythm: Cortisol secretion follows a **diurnal rhythm**, with levels peaking early in the morning (usually between 6-8 AM) and gradually decreasing throughout the day, reaching their lowest point late at night.

F. Physiological Actions of Cortisol

Cortisol's actions are vital for maintaining energy homeostasis, responding to stress, and regulating immune function, but when its secretion is dysregulated (either too high or too low), It may result in a number of health issues, including metabolic disorders, immune suppression, and cardiovascular issues.

G. Physiological Effects of Glucocorticoids

Cortisol has several significant physiological effects: it induces a hyperglycemic effect by activating gluconeogenesis and promotes lipolysis, increasing free fatty acids and lipoproteins while redistributing fat to visceral areas and stimulating abdominal lipogenesis. In protein metabolism, cortisol triggers proteolysis in muscles, skin, and connective tissues to release amino acids for gluconeogenesis. It also exerts a minor mineralocorticoid effect, encouraging sodium retention and potassium excretion, which can influence fluid balance and blood pressure. Additionally, cortisol has anti-inflammatory, immunosuppressive, and antiallergic properties, making it useful in treating inflammatory and allergic conditions. Finally, in bone metabolism, cortisol enhances bone resorption and reduces cartilage growth, potentially leading to bone loss and impaired bone formation over time.

V.7.5.4. Mineralocorticoids: Aldosterone

4.1. Structure

Aldosterone is a steroid hormone with a structure derived from cholesterol, consisting of a four-ring steroid backbone common to all steroid hormones. Its structure includes an aldehyde group at the 18th carbon position, distinguishing it from other steroids, as well as hydroxyl (-OH) groups at the 11th and 21st carbon positions (see Figure V.35). These functional groups enable aldosterone to bind to mineralocorticoid receptors. It is lipophilic (fat-soluble), allowing it to pass through cell membranes easily and regulate sodium and potassium balance in tissues like the kidneys. Its chemical formula is $C_{21}H_{28}O_5$, and it has a molecular weight of 358.46 g/mol. Aldosterone's function in preserving fluid and electrolyte balance and controlling blood pressure depends on this structure.

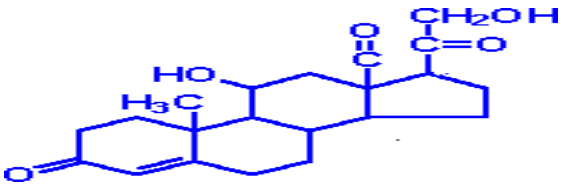


Figure.35. Aldosterone structure

4.2. Biosynthesis

The adrenal cortex's zona glomerulosa converts cholesterol into aldosterone. The process starts with the side-chain cleavage enzyme P450scc converting cholesterol to pregnenolone. Due to the absence of **17-hydroxylase** in the zona glomerulosa, pregnenolone is not converted into 17-hydroxypregnenolone, a precursor for cortisol and sex hormones. Instead, it is further processed into **deoxycorticosterone (DOC)** by **P450c21 (21-hydroxylase)**. Finally, **P450c11 (11β-hydroxylase)** and **P450c18 (aldosterone synthase)** complete the conversion of DOC into aldosterone. The production of aldosterone is mainly regulated by the **renin-angiotensin-aldosterone system (RAAS)**, with **ACTH** also playing a minor role in its stimulation.

4.3. Metabolism

Plasma Transport

Aldosterone is weakly bound to two plasma transport proteins: **albumin** and **CBG (corticosteroid-binding globulin)**. Despite this binding, aldosterone is considered to be largely **free** in its active form in circulation.

Catabolism

The metabolism of aldosterone occurs mainly in the **liver**, where it undergoes **reduction** at positions **C5**, **C3**, and **C20**, resulting in **hydrogenated derivatives**. Following their conjugation with glucuronic acid or sulfate, these metabolites become more soluble and easier to eliminate in the urine. This conjugation helps to increase the water solubility of aldosterone metabolites, allowing for more efficient elimination from the body.

Elimination

Aldosterone and its metabolites are primarily eliminated through the **urine**. In the urine, **free aldosterone** is found in small amounts, along with several major metabolites, such as **TetraHydroAldosterone (THA)**,

which accounts for **30%** of urinary metabolites, and **Hexahydroaldosterone**. Another significant metabolite is **Aldosterone-18-glucuronide**, which makes up about **10%** of urinary metabolites. This form is created by the attachment of **glucuronic acid** at the **C18** position and is hydrolyzed in acidic conditions (pH 1). These conjugated metabolites enhance aldosterone's solubility, facilitating its efficient excretion.

Physiological Actions

Aldosterone acts on the **kidney** (specifically on the terminal parts of the nephron), the **intestine**, and the **colon**. It helps regulate the excretion of **sodium** and **potassium** by promoting **Na+ reabsorption** and **K+ elimination**. It also plays a role in **blood volume regulation** and helps maintain **blood pressure** by promoting the reabsorption of **water and Na+** in the kidneys. Additionally, aldosterone contributes to the **acid-base balance**.

4.4. Regulation of Aldosterone Secretion

4.4.1. Stimulating Factors

1. **The Renin-Angiotensin System (+++)**: The most significant regulator of aldosterone secretion, activated when blood pressure or blood volume is low.
2. **Potassium Levels (Kaliemia)**: High potassium levels in the blood stimulate aldosterone secretion to promote potassium excretion by the kidneys.
3. **ACTH (Adrenocorticotropic Hormone)**: While ACTH plays a minor role, it can also stimulate aldosterone release, particularly during stress.

4.4.2. Inhibitory Factors

- **ANP (Atrial Natriuretic Peptide):**

This hormone, produced by the **right atrium** of the heart, inhibits the release of both **aldosterone** and **renin**. It promotes the elimination of **sodium (Na+)** from the body, counteracting the effects of aldosterone.

- **Progesterone and 17-alpha (OH) P4:**

These substances act as competitive inhibitors of aldosterone. They can bind to aldosterone receptors and block aldosterone's actions, thereby reducing its physiological effects.

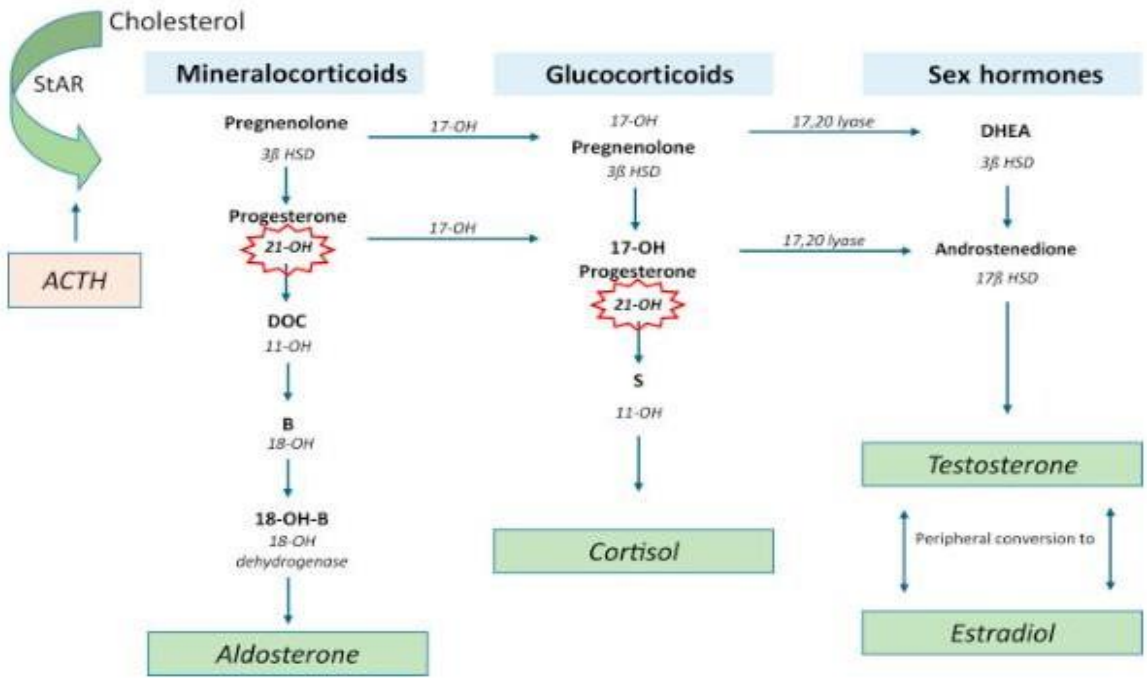
V.7.5.5. Adrenal Androgens (Minor Androgens)

Adrenal androgens are synthesized in the **zona reticularis** of the adrenal glands. Key adrenal androgens include **Dehydroepiandrosterone (DHEA)**, **DHEA sulfate**, and **Delta-4 androstenedione**. These androgens have a **low androgenic activity** compared to gonadal androgens (testicular and ovarian). Some adrenal androgens are converted into **testosterone**, but the amount of testosterone derived from the adrenal glands remains **very low** in comparison to the testosterone produced by the testes.

DHEA Sulfate (SDHEA) is a **storage form** of DHEA and is produced **exclusively by the adrenal glands**, except during pregnancy. In terms of androgen origin, **two-thirds** come from the **adrenal glands** and **one-third** from the **gonads**, with the **gonadal portion being more biologically active**. Additionally, about **80% (4/5)** of DHEA is secreted in its **sulfated form (SDHEA)**, which serves as a circulating reservoir that can be converted back into active androgens when needed.

5.1. Biosynthesis

Adrenal androgens are synthesized in the **zona reticularis** of the adrenal cortex from **cholesterol**, through a series of enzymatic steps (see Figure V.36). The key adrenal androgens include **DHEA (dehydroepiandrosterone)**, **DHEA sulfate (DHEA-S or SDHEA)**, and **androstenedione**. These are considered **weak androgens** compared to testosterone.



FigureV.36. Adrenal steroidogenic pathways.

5.2. Metabolism of Adrenal Androgens

Transport

Adrenal androgens such as **DHEA** are primarily linked to albumin and carried in the blood **(90%)**, and to a lesser extent to **TeBG (3%)**, while binding to **CBG** is negligible. The **plasma concentration of DHEA** follows a **circadian rhythm**, similar to cortisol. In contrast, **DHEA sulfate (SDHEA)** has a **longer half-life (8–10 hours)** and **does not follow a circadian pattern**, providing a more stable circulating form.

Catabolism

In **men**, adrenal androgens are metabolized mainly in the **liver and target tissues**, while in **women**, metabolism occurs mostly in the **liver**. The **Δ⁴-androstenedione** is catabolized into **tetrahydrogenated derivatives**, which are then conjugated (e.g., with glucuronic acid or sulfate) to increase solubility and facilitate excretion. Both **DHEA** and **SDHEA** can be converted into **Δ⁴-androstenedione**, serving as precursors to more potent androgens like testosterone in peripheral tissues.

5.3. Actions of Adrenal Androgens

Androgens exert a **dual effect**:

1. **Androgenic or Virilizing Actions**:
    - Deepening of the voice
    - Growth of body hair (e.g., facial and pubic hair)
2. **Metabolic Actions**:
    - **Protein anabolism**, promoting muscle growth and bone development, contributing to increased strength and skeletal mass.

V.8. Phosphocalcic metabolism

V.8.1. Introduction

Calcium and phosphorus are essential ions for the body, and their metabolism is closely linked. Both play an essential part in the mineralization of the skeleton and various biological processes. The balance of the calcium-phosphate equilibrium requires the involvement of the intestine, kidneys, and bone tissue. Phosphocalcic homeostasis is primarily regulated by two hormones: vitamin D and parathyroid hormone (PTH).

V.8.2. Calium metabolism

2.1. Roles of calcium

- **Structural role (bones, teeth)**: Calcium is a key component of hydroxyapatite crystals in bones and teeth.
- **Neuromuscular role**: Controls excitability, Facilitates the release of neurotransmitters, and Initiates muscle contraction.
- **Intracellular second messenger**: Transcription regulation, Cell proliferation, Meiosis, and Apoptosis.
- **Enzymatic cofactor**: Essential in coagulation processes.

2.2. Distribution of Calcium

a. Bone calcium

The adult body contains about 1000g of calcium, of which 99% is found in the skeleton, primarily in the form of hydroxyapatite (85%) and calcium carbonate (15%). It contributes to bone strength through the mineralization process and serves as a reservoir that can be mobilized when needed.

b. Blood calcium

Approximately 1% of the body's calcium pool is in the blood, where it is involved in numerous biological processes. Total blood calcium is divided into two main fractions:

- **Non-diffusible fraction (40%)**: Primarily bound to albumin and secondarily to globulins.

- **Diffusible or ultrafiltrable fraction (60%)**, which includes:

  -Ionized calcium (50%): This is the physiologically active form, measurable in laboratory tests but not frequently requested.

  -Complexed Calcium (10%): This calcium is bound to anions, primarily in the form of phosphate, oxalate, citrate, and bicarbonate salts. The equilibrium between these two states depends on pH and protein concentration.

- **Effect of pH**:

  -Acidosis: H+ ions shift the equilibrium as follows:

  Pr-+Ca^{2+} +H^{+} give (Pr-H)+Ca^{2+}

  -Alkalosis:

  Pr-+ H^{+}+Ca^{2+} give (Pr-Ca) + H^{+}

- **Effect of Proteins**:

Hypoproteinemia, especially hypoalbuminemia, can lead to false hypocalcemia.

c. Intracellular Calcium

Most intracellular calcium is bound, primarily in the form of phosphate salts within the mitochondria and endoplasmic reticulum (ER).

2.3. Daily requirements

The daily calcium requirements vary with age. The recommended daily intake is as follows:

- Adults: 800 - 1000 mg/day
- Pregnant and lactating women: 1200 mg/day
- Adolescents: 1500 mg/day

2.4. Intestinal absorption

Only ionized calcium is absorbable by the duodenal mucosa (20% - 30%), through two mechanisms:

- **Passive**: Follows a concentration gradient, non-regulated, and non-saturable.

- **Active**: The calcium channel facilitates the passage across the mucosa, while a calcium-ATPase pumps calcium into the bloodstream. This process is regulated by vitamin D3.

Absorption is reduced if calcium precipitates in the digestive tract due to:

- Excess phosphates (forming insoluble calcium phosphate salts)
- Presence of phytates (in grains like wheat, rice, maize, oats)
- Presence of oxalates (in tea, green beans, dried figs, etc.)

2.5. Elimination

- **Digestive**: 400 - 600 mg/24h

This consists of unabsorbed dietary calcium and calcium secreted into the intestinal lumen.

- **Renal**: 150 - 300 mg/l

99% of filtered calcium is reabsorbed, primarily at the proximal convoluted tubule (PCT).

V.8.3. Phosphorus metabolism

3.1. Roles

Phosphorus is essential for building strong bones and teeth as a key component of hydroxyapatite crystals. It plays a critical role in energy metabolism, enzyme regulation, and the structure of vital molecules like ATP, phospholipids, and nucleic acids. Additionally, phosphorus helps maintain the body's acid-base balance through its function in the phosphate buffer system.

3.2. Distribution in the body

The body contains approximately 550g of phosphorus, which exists in two forms:

- **Non-active organic phosphorus** (phospholipids, phosphoproteins, ATP, nucleic acids).
- **Inorganic phosphorus (Pi)** in the form of phosphate, which is biologically active. The distribution of phosphorus is similar to calcium:
- 85% in bone (as hydroxyapatite).
- 14% in soft tissues (muscle, skin, viscera, tendons).

- 1% in extracellular fluid.

In plasma, phosphate is present as inorganic phosphate. At physiological pH, 80% of phosphate is in the divalent form (HPO_4^{2-}) and 20% in the monovalent form ($H_2PO_4^-$).

3.3. Daily requirements

- **Adults**: 800 - 1000 mg/day
- **Pregnant and lactating women**: 1000 - 1200 mg/day
- **Children**: 400 - 900 mg/day

3.4. Intestinal absorption

Occurs primarily in the **duodeno-jejunum**, **Vitamin D3-dependent**, **Passive transport**: Accounts for 85% of absorption, **Active transport**: Accounts for 15%, through a Na^+/Pi cotransport mechanism.

3.5. Elimination

- **Digestive**: Composed of unabsorbed dietary Pi and Pi secreted into the intestinal lumen.
- **Renal**: 500 - 1500 mg/24h
    - 90% of filtered Pi is reabsorbed at the proximal convoluted tubule (PCT) via the NPT2a cotransporter. However, there is a maximum reabsorption rate (TmPi), beyond which urinary excretion of phosphate is proportional to blood phosphate levels.

V.8.4. Regulation of phosphocalcic metabolism

The balance of the phosphocalcic equilibrium is primarily regulated by two hormones: Vitamin D and parathyroid hormone (PTH). Calcitonin also plays a role, but to a lesser extent. Recently, **phosphatonins**, such as FGF23, have been discovered, and they primarily affect phosphate metabolism.

4.1. PARATHYROID HORMONE (PTH)

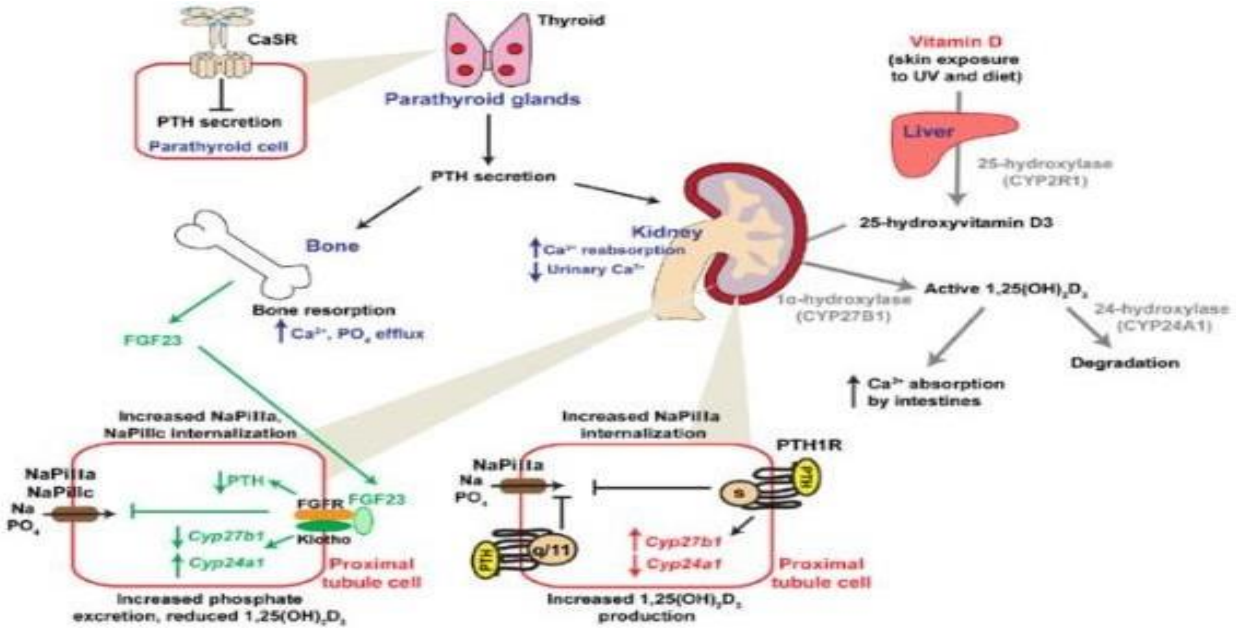
- **Metabolism**

The primary cells of the parathyroid glands produce PTH as a precursor called pre-pro-PTH (115 amino acids), which is cleaved to form pro-PTH (90 amino acids), the storage form. After proteolysis, the active

hormone PTH (84 amino acids) is secreted into the bloodstream. Parathyroid cells have a calcium-sensing receptor (Ca^{2+} SR) that detects local changes in blood calcium levels.

- **Biological Actions**

Parathyroid hormone (PTH) exerts a strong hypercalcemic effect by promoting bone resorption, which releases calcium into the bloodstream (see Figure V.37). It enhances calcium reabsorption in the kidneys while indirectly increasing intestinal calcium absorption by stimulating the production of active vitamin D (calcitriol). Additionally, PTH regulates phosphate balance by decreasing its reabsorption in the kidneys, leading to increased phosphate excretion.



FigureV.37. Calcium regulation involves coordinated actions across the parathyroid glands, bones, kidneys, and intestines.

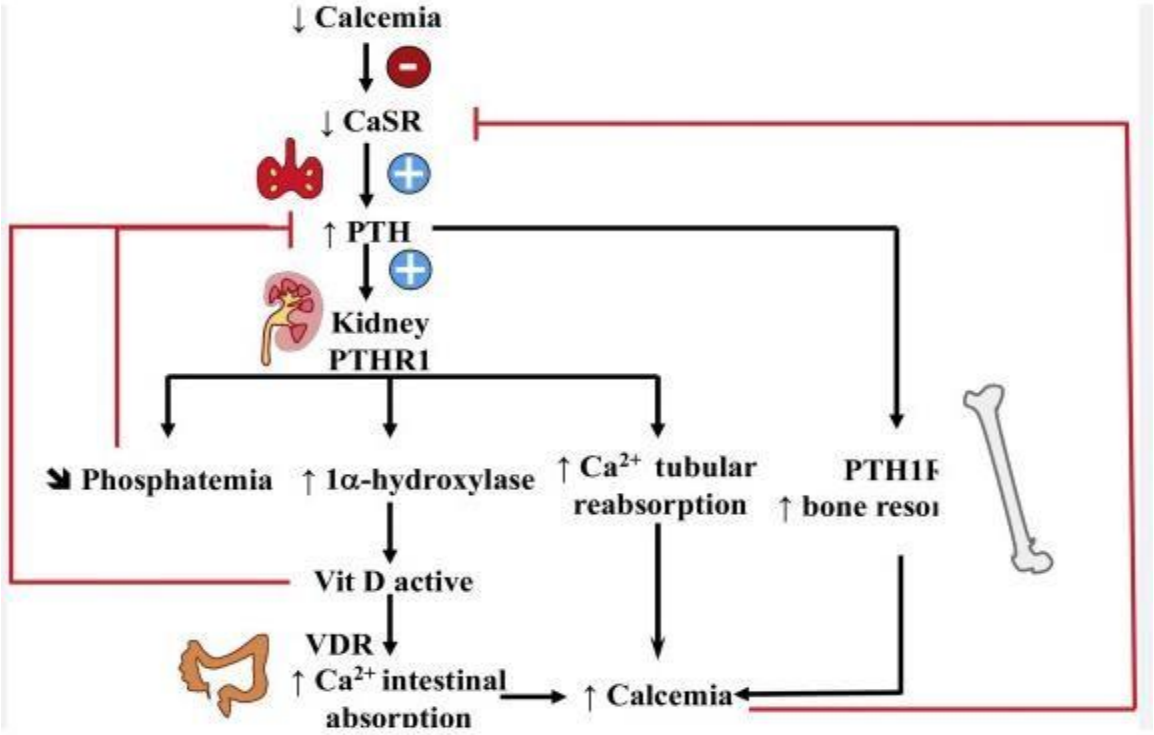
- **Regulation**
    - **Positive Effectors**: Hypocalcemia.
    - **Negative Effectors**: Hypercalcemia, hypomagnesemia, and calcitriol.

4.2. Vitamin D3

- **Origin**: Circulating vitamin D has two main sources:
    - **Exogenous (dietary)**: D3 or cholecalciferol (found in fatty fish) and D2 or ergocalciferol (from plants).
    - **Endogenous**: Synthesized in the skin from 7-dehydrocholesterol under the action of UVB rays. This is converted into vitamin D3 in the skin. Vitamin D3 is hydroxylated at position 25 by the hepatic 25.OHase enzyme, forming 25OH vitamin D3 or calcidiol (the storage form). Calcidiol is then further hydroxylated at position 1 by the renal 1α-OHase enzyme to produce 1,25 diOH vitamin D3 or calcitriol, which is the biologically active form.
- **Biological Actions:** Vitamin D is a hypercalcemic and hyperphosphatemic hormone.
- **Intestine**: It stimulates the absorption of calcium (Ca^{2+}) and phosphate (P), as well as the expression and synthesis of proteins that facilitate the transport of calcium and phosphate within enterocytes.
- **Bone**: It increases the resorption of old bone and stimulates the synthesis of bone matrix proteins by osteoblasts.
- **Parathyroid**: It acts directly by inhibiting the synthesis of pre-pro-PTH mRNA.

Regulation

This regulation is primarily managed by hormones such as **parathyroid hormone (PTH)**, **vitamin D (calcitriol)**, and **calcitonin** (see Figure V.38). These hormones work together to maintain a delicate balance by controlling calcium and phosphate absorption in the intestines, reabsorption in the kidneys, and storage or release from bones.



FigureV.38. Phophocalcic Regulation

4.3. Calcitonin

- **Metabolism**: Calcitonin is secreted by the parafollicular (C) cells of the thyroid in the form of procalcitonin, which is converted into the active hormone through proteolysis.
- **Biological Actions**
  - ↓ Decreases bone resorption by osteoclasts.
  - ↓ Reduces renal reabsorption of calcium (Ca^{2+}) and phosphate (Pi).

- **Regulation**
    - **Positive effectors**: Hypercalcemia, gastrin, 1,25-dihydroxyvitamin D_3
    - **Negative effector**: Hypocalcemia

4. 5. Other hormones

- **Estrogens:** Increase intestinal calcium absorption, enhance protein synthesis and bone mineralization
- **Cortisol:** Reduces bone mineralization, Decreases bone protein synthesis
- **Thyroid Hormones:** In excess, they promote bone resorption

V.8.5. Bone remodeling

5.1. Bone structure

Bone tissue is a highly specialized connective tissue composed of a mineralized organic matrix made up of:

- **Mineral component**: calcium hydroxyapatite
- **Protein matrix**: osteoid tissue
    - **Type I collagen**: a fibrillar protein made of three helical strands linked by bridges, most commonly pyridinoline and deoxypyridinoline, twisted together like a cable
    - **Non-collagenous proteins**, with osteocalcin being the most abundant

Bone tissue undergoes continuous remodeling by three main cell types:

- **Osteoclasts**: resorptive cells of hematopoietic origin
- **Osteoblasts**: bone-forming cells of mesenchymal origin
- **Osteocytes**: embedded within the matrix, derived from osteoblasts, responsible for transmitting chemical and mechanical signals

5.2. Bone remodeling

The process of bone remodeling is dynamic and ongoing of tissue renewal within the skeleton. The life cycle of bone includes three main phases:

- **Bone mass acquisition phase**: marked by a rapid increase in bone mass, occurring from birth to around age 30 (the peak bone mass period).
- **Bone mass stabilization phase**: corresponds to adult maturity, lasting until menopause in women.
- **Bone loss phase**: begins post-menopause in women and around age 70 in men, characterized by a significant reduction in bone mass.

5.3. Bone formation markers

Osteoblast activity produces biochemical indicators of bone formation, such as osteocalcin, bone-specific alkaline phosphatase, and the N- and C-terminal propeptides of type I collagen (see Table V.1). This article explores the biochemical and physiological aspects of these markers, reviews the different available measurement techniques, and discusses their clinical relevance in managing osteoporosis.

Table V.1: Bone Formation Markers

Markers	Origin	Specificity
Total Alkaline Phosphatase (PALt)	Bone, liver, intestine	Low specificity
Bone-specific Alkaline Phosphatase (PALo)	Bone, cartilage	Specific to osteoblasts
Osteocalcin	Bone	Specific to osteoblasts
N- and C-terminal propeptides (PINP, PICP)	Bone, soft tissues, skin	Low specificity

5.4. Bone resorption markers

Bone resorption markers reflect osteoclast activity and the breakdown of the bone matrix (see Table V.2). They are useful for assessing bone turnover, especially in conditions such as osteoporosis or Paget's disease.

Table V.2. Main resorption markers

Marker	**Origin**	**Specificity**
Calciuria	Bone, soft tissues, blood	Non-specific
Tartrate-Resistant Acid Phosphatase (TRAP5b)	Bone, prostate, RBCs, platelets	Low specificity
Urinary Hydroxyproline	Collagen	Low specificity
Pyridinoline	Bone, cartilage	Low specificity
Deoxypyridinoline	Bone, dentine	Specific
Terminal Telopeptides (CTX, NTX)	**Terminal Telopeptides (CTX, NTX)**	**Terminal Telopeptides (CTX, NTX)**

V.9. The gonads

V.9.1. Introduction

A gonad, from the Greek word "gone," is a feminine noun referring to the sexual gland that produces gametes and secretes sex hormones. In females, the gonads are the ovaries, located at the ends of each fallopian tube; they secrete female sex hormones—estrogens and progesterone—and contain a large number of oocytes. In males, the gonads are the testes, which are glands that produce male sex hormones—mainly testosterone—and generate sperm cells.

V.9.2. Anatomical and Histological Overview

2.1. The Ovaries

The ovaries are located in the abdominal cavity. Each ovary is positioned near a fallopian tube and is held in place by ligaments that connect it to the uterus or the peritoneum.

The ovaries are almond-shaped with a pinkish-white color (see Figure V.9.1). Their size varies with age: in children, an ovary weighs between 2 and 3 grams, while in adult women it weighs between 6 and 8 grams and measures approximately 1 cm in thickness, 2 cm in width, and 4 cm in length.

The protrusions on the ovary correspond to the underlying Graafian follicles, while the depressions are post-ovulatory scars.

After menopause, the ovary weighs between 1 and 2 grams as it tends to atrophy, becoming smooth and firm.

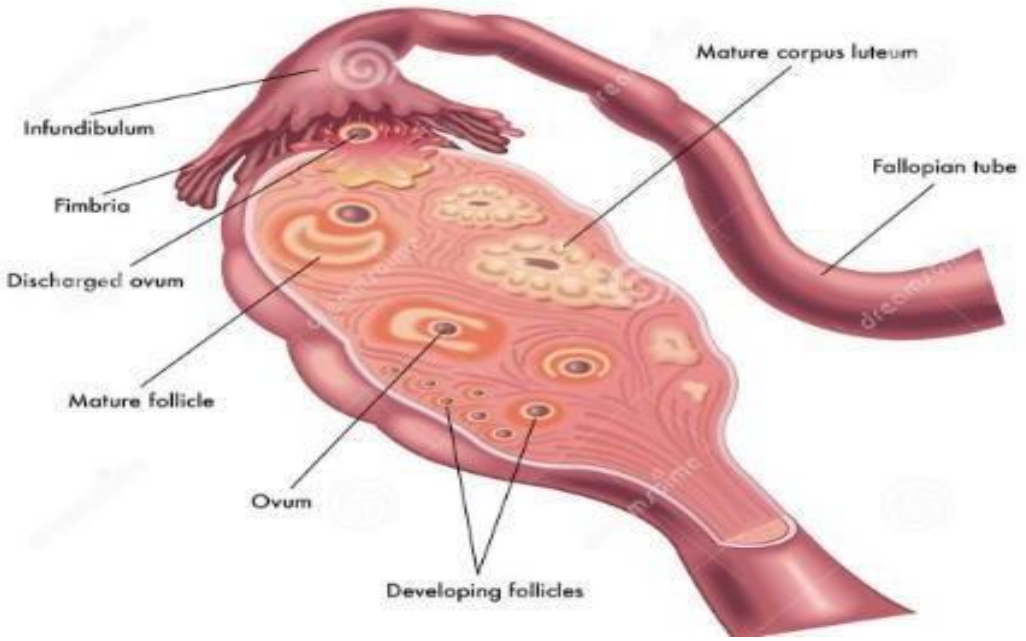


Figure V.9.1. Transverse section of an ovary.

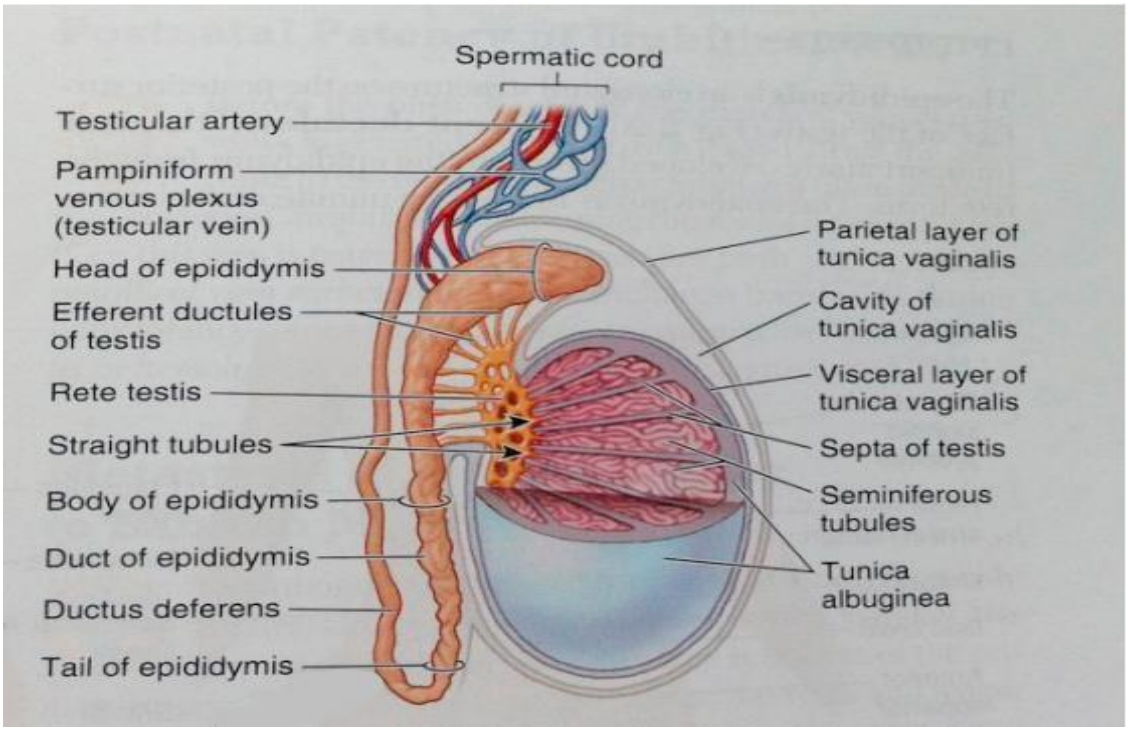
2.2. The Testes

There are two testes in men. They are housed in an external skin sac called the scrotum, which hangs between the legs from the base of the penis (see Figure V.9.2).

The testes are ovoid in shape, measuring approximately 4 cm in length and 2.5 cm in diameter, with an average weight of about 20 grams.

The seminiferous tubules contain Sertoli cells and germline cells, which give rise to spermatozoa; each lobule contains between one and four of these tubules.

The spermatozoa then enter a duct called the epididymis. From there, they move into the vas deferens. The epididymis is a comma-shaped structure that sits atop the testis and then descends along its edge. The interstitial tissue contains Leydig cells, which are responsible for synthesizing testosterone.



FigureV.9.2. Testicular and epididymal structures.

V.9.3. Ovarian hormones

3.1. The Ovary

The ovary has two main functions: an **exocrine function**, which involves the production of oocytes (egg cells), and an **endocrine function**, which involves the production of hormones. The ovarian cycle, also known as the menstrual cycle, lasts approximately 28 days and is divided into two phases by **ovulation**, which occurs around day 14. The **pre-ovulatory phase** is called the **follicular phase**, during which follicles in the ovary mature. The **post-ovulatory phase** is known as the **luteal phase**, during which the corpus luteum forms and secretes hormones to prepare the uterus for possible implantation.

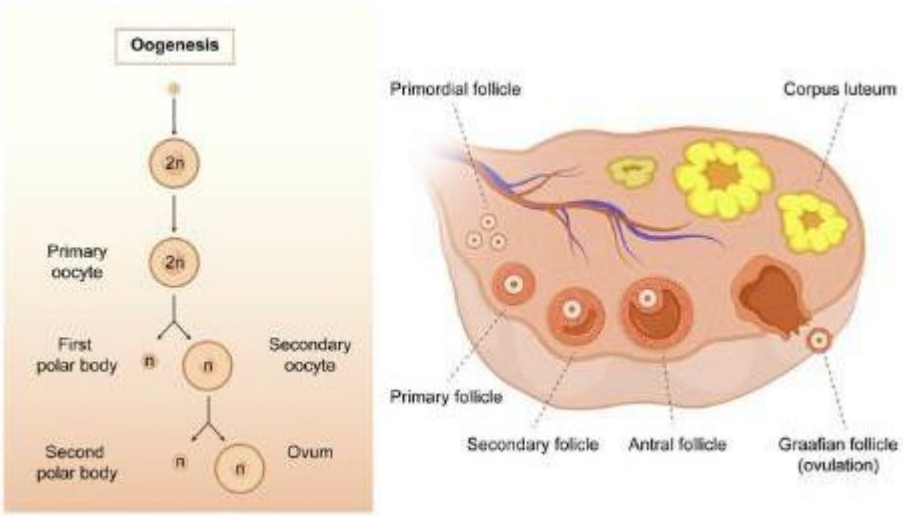
The menstrual cycle typically lasts between **24 to 35 days**, with **menstruation** lasting about **2 to 7 days**. This cycle occurs from **puberty to menopause**. The **first menstrual period** is called the **menarche.**

The **ovary secretes** several substances, including **estrogens**, **progesterone**, and **ovarian peptides**. These peptides include **cytokines** such as **interleukin-1β** and **TNFα**; **growth factors** such as **IGF-1**, **IGF-2**, **IGFBPs**, **EGF**, **TGF-β**, and **FGF-2**; as well as peptides synthesized by the **granulosa cells**, including **anti-Müllerian hormone (AMH)**, **activins**, and **inhibins**.

3.2. Oogenesis and the ovarian (menstrual) cycle

The ovarian reserve is established from the fourth month of fetal life and consists of three types of follicles: primordial follicles, intermediate follicles, and small primary follicles. At birth, a female has about 1 million primary oocytes, many of which degenerate over time. By puberty, the ovaries contain approximately 400,000 oocytes, but only about 400 to 500 will reach maturity and be capable of fertilization between puberty and menopause. Oogenesis begins at puberty under hormonal stimulation, and hormonal activity becomes cyclical, with each cycle lasting around 28 days and divided into three phases (see Figure V.9.3):

- The **follicular phase**, during which about ten follicles begin to grow, but usually only one reaches full maturity—known as the **Graafian follicle**;
- The **menstrual phase**, lasting around 4 days, marks the beginning of the cycle;
- The **ovulatory phase** occurs around **day 14**, when ovulation takes place;
- Finally, the **luteal phase** completes the cycle, during which the **corpus luteum** develops and remains active for about **10 to 14 days** if pregnancy does not occur, after which it degenerates.



FigureV.9.3. The oogenesis process. The oogonia's transition into the main oocytes marks the beginning of oogenesis. Only one mature oocyte will be created throughout the meiotic process, which also produces polar bodies. The primary follicles progressively transform into secondary, antral, and Graafian follicles as follicular development advances.

3.3. Hormonal Regulation of the Ovarian Cycle

The regulation of the ovarian cycle involves the **hypothalamic-pituitary-ovarian axis**. This complex hormonal network includes:

- The **hypothalamus**, which secretes **GnRH (Gonadotropin-Releasing Hormone)**;
- The **pituitary gland (hypophysis)**, which releases **FSH (Follicle-Stimulating Hormone)** and **LH (Luteinizing Hormone)**;
- The **ovaries**, which produce **estrogens**, **progesterone**, **inhibins**, and **Anti-Müllerian Hormone (AMH)**.

  These hormones act in coordination to regulate the development of ovarian follicles, ovulation, and the menstrual cycle.

3.3.1. GnRH (Gonadotropin-Releasing Hormone / LH-RH)

GnRH is a **decapeptide neurohormone** secreted by the **hypothalamus**. It is initially produced as a **92-amino-acid precursor (pre-prohormone)**, which is then cleaved into **active GnRH** and **GAP (GnRH-Associated Peptide)**. GnRH acts on the **gonadotrope cells** of the anterior pituitary by binding to **specific G-protein-coupled receptors**. This binding stimulates the synthesis and secretion of both **FSH** and **LH**.

GnRH is secreted in a **pulsatile manner**, which is essential for the correct regulation of gonadotropin release. The **frequency of pulses varies by phase of the cycle**:

- Every **90 minutes** during the **follicular phase**;
- Every **3 to 4 hours** during the **luteal phase**.

The secretion of GnRH is influenced by various factors, including **sex steroids (estrogens and progesterone)** and neurotransmitters such as **glutamate, GABA, noradrenaline**, as well as **leptin** and **kisspeptins**.

3.3.2. Follicle-Stimulating Hormone (FSH)

FSH is a **heterodimeric glycoprotein hormone** with a molecular weight of about **35 kDa**, secreted by the **anterior pituitary**. It consists of two subunits:

- An **α subunit (89 amino acids)**, which is common to **FSH, LH, hCG, and TSH**;
- A **β subunit (118 amino acids)**, which is specific to FSH and gives it its biological function.

FSH secretion is controlled by **GnRH**, as well as **ovarian hormones** like **estrogens**, **progesterone**, and **inhibin B**. It is secreted in a **continuous fashion** and has a **half-life of 2 to 30 hours**.

FSH binds to **G-protein-coupled receptors** located on **granulosa cells** in the ovary, where it stimulates the production of **aromatase**, an enzyme that converts **androgens into estrogens**. FSH promotes the **growth of ovarian follicles** and the **selection of a dominant follicle** for ovulation. It also enhances the synthesis of its own receptors in **granulosa cells** and **Sertoli cells** in the testes (in males).

3.3.3. Luteinizing Hormone (LH)

LH is another **heterodimeric glycoprotein hormone** produced by the **anterior pituitary**, also weighing about **35 kDa**. Like FSH, it has:

- An **α subunit (89 amino acids)**, shared with FSH, hCG, and TSH;
- A **β subunit (115 amino acids)**, which is unique to LH and gives it its specific function.

The secretion of LH is also regulated by **GnRH** and **ovarian estrogens**, but it follows a **more intense pulsatile pattern** than FSH. This pulsatility is crucial for triggering the **LH surge** that leads to **ovulation** around the middle of the menstrual cycle.

V.9.4. Testicular Hormones

1. The Testes

The testes have two main functions:

- Endocrine function: carried out by Leydig cells and Sertoli cells, this involves the production and transport of testosterone, the primary male sex hormone.
- Exocrine function: carried out by germ cells, this involves spermatogenesis, which is the process of sperm production. The exocrine function is responsible for the initiation and maintenance of spermatogenesis.

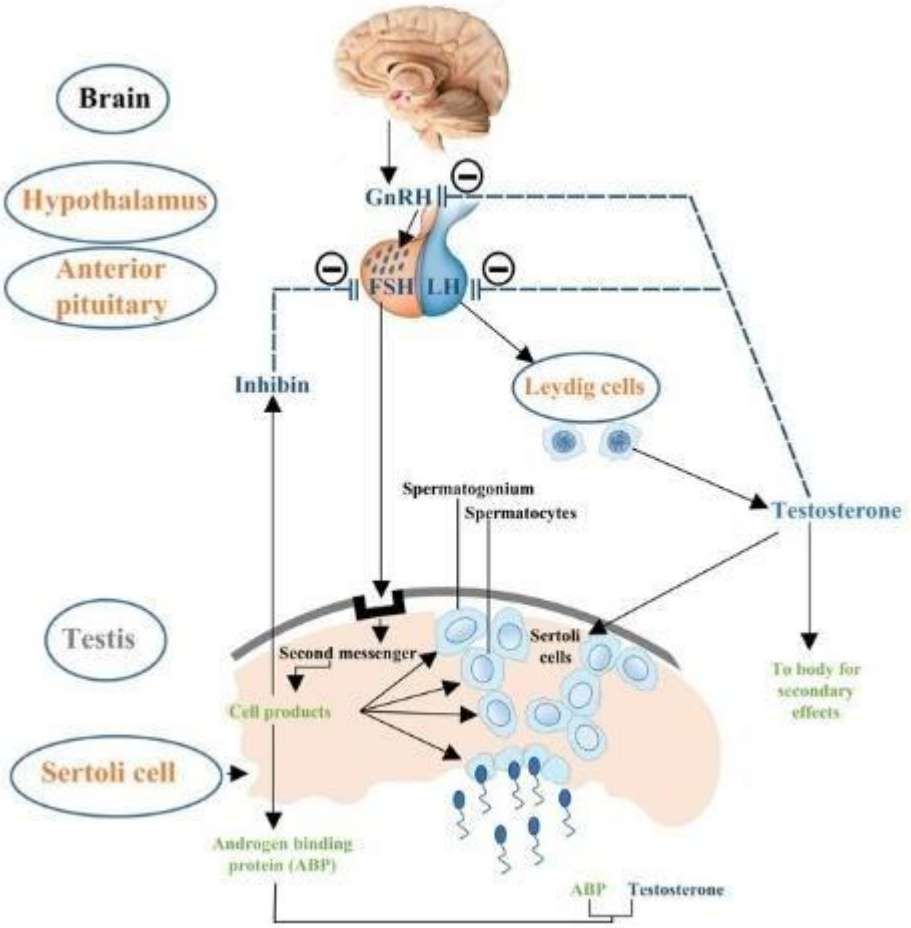
2. Regulation of Testicular Function

The regulation of testicular function is controlled by the **hypothalamic-pituitary-gonadal axis**. The **hypothalamus** secretes **GnRH (Gonadotropin-Releasing Hormone)** in a **pulsatile manner**, approximately **every 90 minutes**, especially during the night. GnRH stimulates the anterior pituitary to release **FSH** and **LH**.

- **FSH (Follicle-Stimulating Hormone)** stimulates the development of the **seminiferous tubules** and promotes **spermatogenesis** by acting on **Sertoli cells**.
- **LH (Luteinizing Hormone)** acts on **Leydig cells**, stimulating them to produce **testosterone**, which is essential for maintaining spermatogenesis and male secondary sexual characteristics.

Inhibin B, secreted by **Sertoli cells** in response to active spermatogenesis, exerts **negative feedback** on the pituitary to **suppress FSH secretion**. The level of inhibin B in the blood is a reliable **marker of spermatogenic activity**. Low levels of inhibin B are typically seen in men with **azoospermia of testicular (gonadal) origin** (see Figure V.9.4).

In addition, **Anti-Müllerian Hormone (AMH)**, also produced by Sertoli cells, plays a role in regulating **androgen production** by **Leydig cells**, particularly during early development.



FigureV.9.4. Hypothalamic–Pituitary Regulation of Testicular Testosterone Synthesis and Spermatogenesis

3. Puberty

Puberty is a physiological process marked by accelerated growth and the emergence of secondary sexual characteristics, culminating in the maturation of gonadal secretory function and the ability to reproduce. In the fetus, GnRH is detectable in the hypothalamus by the 8th week of gestation, and pituitary gonadotrope cells appear by the 10th week. LH and FSH levels peak around the 20th week, then decline due to steroid hormone secretion from fetal gonads, maternal estrogen rise, and negative feedback on the hypothalamic-pituitary axis. After birth, this axis is active for 4–6 months before entering a dormant phase until puberty, with suppressed LH and FSH levels due to the absence of pulsatile GnRH secretion. Puberty begins when GnRH pulses increase in frequency and amplitude, stimulating LH and FSH secretion; FSH promotes gonadal development—follicular maturation in girls and spermatogenesis in boys—while LH stimulates sex steroid secretion (testosterone from Leydig cells and estrogen from granulosa cells). Puberty usually starts between 8–13 years in girls and 9–14 years in boys, preceded by adrenarche (adrenal androgen secretion) about two years earlier.

- **In boys**, puberty begins with testicular enlargement, followed by pubic hair growth, penile enlargement, first ejaculations around age 14 (with sperm production occurring 1–2 years later), muscle development, voice deepening (due to dihydrotestosterone), and skeletal changes, completing around age 18.

-In girls, puberty includes breast development (thelarche), growth, fat and hair distribution (pubarche), and the onset of menstruation (menarche), which is initially anovulatory. Pelvic widening also occurs. Puberty is considered precocious if breast development occurs before age 7.5, pubic hair before 8.5, or menstruation before age 9.

V.9.5. Menopause

Menopause occurs when most ovarian follicles are depleted, leading to a decline in estrogen production and the loss of negative feedback on the hypothalamus, resulting in increased secretion of GnRH, FSH, and LH. Biologically, this is reflected by decreased levels of estradiol and progesterone, alongside elevated FSH and LH, characterizing menopause as a state of hypergonadotropic hypogonadism. Low levels of androgens and estradiol are largely due to the peripheral conversion of adrenal hormones. The typical age for menopause is between 49 and 51 years; it is considered early when it occurs between 35 and 45 years, often due to genetic, autoimmune, or psychogenic causes. Clinically, estrogen deficiency leads to symptoms such as hot flashes, for which hormone replacement therapy may be indicated. In men,

physiological andropause is marked by a gradual decline in androgenic hormonal activity due to aging, without cessation of spermatogenesis. Testosterone levels—both total and free—decline with age, and mild increases in FSH and LH may be seen after the age of 60.

V.9.6. Biological Investigations

6.1. Static Hormone Measurements

6.1.a. FSH, LH, estradiol, progesterone, testosterone

- These hormone levels are typically measured between the **2nd and 5th day** of the menstrual cycle in women, which corresponds to the early follicular phase when baseline hormone levels can be assessed (see Table V.9.1).
- **Progesterone** is specifically measured on the **21st or 22nd day** of the cycle, corresponding to the mid-luteal phase, to evaluate the quality of ovulation and corpus luteum function.

Table V.9.1. Normal values of FSH, LH, estradiol, progesterone, testosterone

Parameters	**Unity**	**Follicular phase**	**Ovulatory peak**	**luteal Phase**	**Menopause**	**Men**	**Child**
FSH	mUI/ml	3.5-12.5	1.70-7	4.7-21.5	25.6-134.8	1.5-12.4	0.2-3.80
LH	mUI/ml	2.4-12.60	14-95.60	1-11.40	7.7-58.5	1.7-8.60	0.2-1.40
Pg	ng/ml	<0.15-1.1	-	1.5-22.6	-	0.15-0.52	-
E2	pg/ml	24.5-195	66.1-411	40-261	24.5	11.-42.9	<10-36

Testosterone

- Male: 4-10µg/l

- Women: 0.1-0.7µg/l

6.1.b- LH-RH (GnRH) Test

This test is used to assess **pituitary gonadotropic function (**see Table V.9.2**)**.

Table V.9.2. Base values of hormones

Base values	**Response**	**Clinic case**
FSH, LH normal	FSH:*1.5-3 LH:*3-5	Normal
FSH, LH normal or low	FSH and LH:low response or absent	Fonctional or organic hypotpituitarisme
FSH, LH normal or low	FSH: normel response LH: low response or absent	Response of prepubertal type Some cases of mental anorexia or amenorrhea (psychogenic)
FSH, LH high	FSH and LH: +/- explosive response	Ovarian hypogonadism Menopause
FSH normal LH normal or high	FSH: response normal LH: explosive response	Polycystic ovary syndrome

6.2. Dynamic tests

6.2.a. Clomid test

The **Clomid test** is a dynamic assessment of the hypothalamic-pituitary-ovarian axis using **Clomiphene citrate (Clomid®)**, which blocks estrogen receptors at the hypothalamic level, thereby antagonizing the negative feedback of estradiol. This mimics an estrogen-deficient state, leading to increased GnRH secretion and subsequent stimulation of **FSH and LH** release from the pituitary. The test involves administering **100 mg/day of Clomid for 5 days**, typically from **day 3 to day 7** of the menstrual cycle (follicular phase). In a normal response, there is a **rise in FSH and LH**, followed by an **increase in estradiol levels** and an **ovulatory LH surge around day 14**. This test is commonly used to evaluate ovulatory function and investigate causes of infertility.

6.2.b- Tamoxifen Test

Tamoxifen is an **anti-estrogen** that blocks estrogen receptors, leading to a **rebound increase in gonadotropin secretion**, which in turn stimulates testosterone production. An **increase in testosterone levels about one month after treatment** indicates a **functioning hypothalamic-pituitary axis** and is used to assess male reproductive endocrine function.

6.2.c- hCG Stimulation Test

This test evaluates **Leydig cell function** by using **hCG**, which has an **LH-like action**. A **single injection of hCG** should trigger an **increase in testosterone** production if Leydig cells are functional (see Table V.9.3). It is particularly useful in the evaluation of **cryptorchidism**, **sexual development disorders**, and **delayed puberty**.

TableV.9.3. LH/RH, clomiphene, and hCG values in Tamoxifen test

Test	**Pratic**	**Normal response**	**Pathologic Response**
LH/RH	Inj IVof 100-150µg of GnRH	Raise of LH in 30mn and FSH in45mn	Hypogonadic Hypogonadotropic = absence of response
clomiphene	100mg/day	Hypothalamic feedback regulation =double of LH 7days later	Hypogonadic Hypogonadotropic = with GnRH test = hypothalamic cause
hCG	2inj IM (50UI/kg) of 3days on interval	Evaluation of function of Leydig cells increase of NI testo	Ryptorchidism = if no response = testicle has no function

V.9.7. Pathologies of the Female Gonad

7.1. Delayed Puberty

Delayed puberty is defined by primary amenorrhea, meaning the absence of menstruation by age 16, or no signs of puberty by age 13. The causes can include a simple constitutional delay of growth, pituitary insufficiency (hypogonadotropic hypogonadism) caused by trauma or tumors, or hypothalamic insufficiency such as psychogenic amenorrhea or tumors. A rare condition called olfacto-genital dysplasia (Kallmann-De Morsier syndrome) presents with hypogonadism, anosmia (loss of smell), and tall stature due to lack of fusion of growth plates. Another cause is hypergonadotropic hypogonadism, as seen in Turner syndrome (karyotype 45, X0), characterized by rudimentary ovaries, absent secondary sexual characteristics, and a female phenotype at birth.

7.2. Precocious Puberty

Precocious puberty involves the early appearance of secondary sexual characteristics. Its causes can be idiopathic or due to premature activation of the hypothalamic-pituitary axis, often related to hypothalamic tumors, meningitis, or hydrocephalus. Peripheral causes include adrenal or ovarian tumors and tumors that secrete hCG.

7.3. Secondary Amenorrhea

Secondary amenorrhea refers to the cessation of menstruation for more than 3 to 6 months in women who previously had normal cycles, often leading to infertility. Hypergonadotropic hypogonadism causes include a history of radiotherapy or chemotherapy, premature ovarian failure from depletion of ovarian follicles, autoimmune oophoritis with anti-ovarian antibodies, and ovarian resistance syndrome. Hypogonadotropic hypogonadism can result from pituitary causes such as surgery (adenomectomy), Sheehan syndrome, trauma, or infiltrative diseases like sarcoidosis. Hypothalamic causes include psychogenic origins. Other causes are hyperprolactinemia, which inhibits GnRH secretion, and post-oral contraceptive amenorrhea.

7.4. Hyperandrogenism

Hyperandrogenism in women is characterized by increased androgen secretion, clinically manifesting as acne, seborrhea, hypertrichosis, and hirsutism. In the fetus, it can cause ambiguous genitalia; in children,

pseudo-precocious puberty; and in adults, symptoms include hirsutism, clitoral hypertrophy, and amenorrhea. The main causes include polycystic ovary syndrome (PCOS) with elevated testosterone (see Table V.9.4), virilizing ovarian tumors, idiopathic hirsutism, congenital adrenal hyperplasia (CAH) marked by elevated DHEA-S, testosterone, and 17-hydroxyprogesterone, and adrenal tumors secreting androgens.

TableV.9.4. Different pathologies related to variation of hormones

Pathologies	**FSH**	**LH**	**LH/FSH**
Stein-Leventhal syndrome Ovarian dystrophy type 1	N or	↗	>2
Sclerocystic oophoritis, Ovarian dystrophy type 2	↘	little ↗	N

7.5. Hyperprolactinemia

Hyperprolactinemia involves an elevated level of prolactin, which disrupts the normal hypothalamic-pituitary-gonadal axis. This condition can lead to menstrual irregularities, galactorrhea, and infertility in women, and may also cause hypogonadism in both sexes by inhibiting GnRH secretion. (For detailed mechanisms, see the prolactin axis course).

V.9.8. Pathologies of the Male Gonad

8.1. Delayed Puberty

Delayed puberty in males is defined as the absence of secondary sexual characteristics by the age of 14 or a stagnation in pubertal development. Causes include constitutional delay, hypogonadotropic hypogonadism due to hypothalamic or pituitary dysfunction, and primary testicular failure (see Table V.9.5). The evaluation focuses on distinguishing between central (hypothalamic-pituitary) and peripheral (testicular) causes.

TableV.9.5. Causes of Hypogonadism

Hypogonadism: Causes	FSH	LH	TESTO
Primary Hypergonadotropic Hypogonadism • Klinefelter syndrome • Testicular agenesis • Testicular tumors • Testicular ectopia • Radiation and chemotherapy	↗	↗	↘
Secondary Hypogonadotropic Hypogonadism • GnRH deficiency • Kallmann syndrome • Hypopituitarism • Hypothalamic-pituitary lesions	↘	↘	↘

8.2. Precocious Puberty

- **True Precocious Puberty**

This involves the early activation of the hypothalamic-pituitary-gonadal axis and can be caused by hypothalamic tumors, idiopathic reasons, or tumors that secrete hCG.

- **Pseudo-Precocious Puberty**

This form results from hormone secretion independent of the central axis, such as in congenital adrenal hyperplasia, which causes excess androgen production.

- **Testotoxicosis**

A rare cause of precocious puberty in younger boys, due to a mutation affecting G-proteins on Leydig cell membranes, leading to autonomous testosterone secretion and early development of secondary sexual characteristics.

8.3. Male Infertility

Male infertility is defined as the inability to achieve pregnancy after 24 months of regular unprotected

intercourse. Causes include chromosomal abnormalities, obstruction of the spermatic ducts, and endocrine disorders affecting spermatogenesis. Endocrinological causes can be classified as:

- **Primary germinal failure**, where LH and testosterone levels are normal but FSH is elevated.
- **Hypergonadotropic hypogonadism**, characterized by high FSH and LH levels but low testosterone.
- **Hypogonadotropic hypogonadism**, with low levels of FSH, LH, and testosterone.
- **Hyperprolactinemia** can also contribute. Other factors include infections, medications, systemic diseases, dysfunction of accessory glands like the prostate, and the presence of anti-sperm antibodies.

8.4. Pseudo-Hermaphroditism

Pseudo-hermaphroditism refers to individuals who are genetically male but have varying degrees of feminization. Causes include:

- **Reduced testosterone synthesis** due to enzyme deficiencies such as 3β-hydroxysteroid dehydrogenase, 17α-20 desmolase, 17α hydroxylase, 17β-hydroxysteroid dehydrogenase, or 20-22 desmolase (see TableV.9.6).
- **Leydig cell hypoplasia**, which shows low testosterone levels with elevated FSH and LH, and negative hCG stimulation test.
- **Defects in peripheral testosterone action** known as "feminizing testicular syndrome," which include 5α-reductase deficiency and partial androgen insensitivity syndrome.

TableV.9.6. Cases of Pseudo-Hermaphroditism

	Pseudo-PP	**True PP**	**Testotoxicose**
LH	↘	↗	↘
FSH	↘	↗	↘
TESTO	↘	↗	↗

VI. Acid-base balance

VI.1. Introduction

Enzyme activity is very sensitive to pH variations. A healthy human body maintains the pH of its blood between 7.35 and 7.45. This maintenance of hydrogen ion concentration within such narrow limits, despite dietary challenges and catabolism, is a very important aspect of homeostasis—perhaps one of the most tightly regulated in the body. This is what is meant by acid-base balance.

VI.2. Balance of Inputs and Outputs

VI.2.1. Inputs

Many end products of metabolism are acidic.

1. **CO_2**

   It is a gas eliminated by the lungs, hence the term "volatile."

$$\mathbf{CO_2 + H_2O \Leftrightarrow H_2CO_3 \Leftrightarrow H^+ + HCO_3^-}$$

The three forms are in equilibrium.

2. **Fixed acids**

- **Strong non-volatile acids**:
  - Sulfuric acid (H_2SO_4) (80%)
  - Phosphoric acid (H_3PO_4)
- **Organic acids** (intermediate products of metabolism):
  - Lactic acid
  - Acetic acid
  - Ketone bodies…

VI.2.2. Outputs

Elimination occurs through **two pathways**:

- **CO_2** is eliminated by the **lungs**
- **Fixed acids** are eliminated by the **kidneys**

VI.3. Stability of Plasma pH

The stability of plasma pH involves the existence of several regulatory mechanisms:

- **An immediate mechanism**: blood **buffer systems**
- **A rapid mechanism**: **pulmonary regulation** of arterial CO_2 pressure (**$PaCO_2$**)
- **A slow mechanism**: **renal regulation** of plasma **bicarbonate concentration** (**$[HCO_3^-]$**)

VI.3.1. Buffer

Systems Concept of a

Buffer

A **buffer substance** tends to minimize changes in the **hydrogen ion (H^+) concentration** of a solution. By definition, a buffer is a **weak acid or base**, not fully dissociated, and in **equilibrium with its dissociated form**:

$$\textbf{Buffer-H} \leftrightarrow \textbf{Buffer}^- + \textbf{H}^+$$

The body protects itself against **excess H^+ ions** by relying on **four major buffer systems**.

A buffer is all the more effective when:

- It is **highly concentrated** (just like a larger sponge absorbs more...)
- The **pH of the solution** is **close to the pKa** of the acid-base pair (e.g., R-COOH / $R\text{-}COO^-$)

This is expressed by the **Henderson-Hasselbalch equation**:

$$\textbf{pH} = \textbf{pKa} + \log\left([A^-]/[AH]\right)$$

According to this formula:

- When $[A^-]=[AH]$, then **pH = pKa**

VI.3.1.1. Bicarbonate–Carbonic Acid Buffer

Composed of a **weak acid** (carbonic acid) and its **salt** (sodium bicarbonate). This buffer system is of great physiological importance due to the high plasma concentration of bicarbonate (24 ± 2 mmol/L), making it a key buffer in both blood and intracellular fluid. It functions as an open system, meaning it is closely linked to the body's acid-base regulation mechanisms. The lungs contribute by eliminating acid in the form

of carbon dioxide (CO_2), while the kidneys help maintain balance by reabsorbing and regenerating bicarbonate ions (HCO_3^-). The system operates through the reversible chemical reaction:

$$CO_2 + H_2O \Leftrightarrow H_2CO_3 \Leftrightarrow H^+ + HCO_3^-$$

VI.3.1.2. The hemoglobin-hemoglobinate buffer

is the most important blood buffer after bicarbonate, with a buffering capacity six times greater than that of plasma proteins. This is due to hemoglobin being four times more concentrated and particularly rich in histidine—an amino acid with a pKa of 7.3, which is very close to the physiological plasma pH. The buffering power of the imidazole group in histidine is influenced by the oxygenation state of hemoglobin; oxyhemoglobin acts as a stronger acid than deoxyhemoglobin.

Bohr Effect: Reduced hemoglobin can accept protons (H^+), while oxygenated hemoglobin releases them. A decrease in blood pH (acidosis) lowers hemoglobin's affinity for oxygen, facilitating the release of O_2. This allows deoxyhemoglobin to effectively bind and buffer the excess H^+ ions.

VI.3.1.3 Proteinate-Protein Buffer

At physiological pH, proteins behave as anions and can bind hydrogen ions (H^+) according to the reaction:

$$PH \leftrightarrow P^- + H^+.$$

This is the most important buffering system in the intracellular environment. Each time intracellular proteins bind an H^+ ion from the extracellular space, a potassium ion (K^+) moves in the opposite direction. As a result, a decrease in extracellular pH leads to an increase in blood potassium levels (hyperkalemia). Although this buffer system also functions in plasma, its effect there is minimal.

VI.3.1.4 Phosphate Buffer

Phosphoric acid (H_3PO_4) has three acidic dissociation steps:

(1) $H_3PO_4 \leftrightarrow H_2PO_4^- + H^+$ ($pKa_1 = 2$),

(2) $H_2PO_4^- \leftrightarrow HPO_4^{2-} + H^+$ ($pKa_2 = 6.8$), and

(3) $HPO_4^{2-} \leftrightarrow PO_4^{3-} + H^+$ ($pKa_3 = 11.5$).

The second dissociation step has a pKa close to physiological pH, making $H_2PO_4^-$ and HPO_4^{2-} the predominant forms in plasma (see Table VI.1). Although phosphate is present at low concentrations in plasma (2–3 mEq/L), and thus has a limited buffering role there, it plays an important role in intracellular pH regulation, where it is a principal anion.

TableVI.1. System buffer

Compartment	**Main Buffer Systems**	**Relative Buffering Power ($mmolH^+.L^{-1}$ / pH unit)**
Extracellular Fluid (e.g., plasma, interstitial fluid)	- **Bicarbonate (HCO_3^-/CO_2)** *(Primary)* - Proteinate/protein buffer *(minor)* - Phosphate buffer *(minimal)*	55 7 0.5
Intracellular Fluid	**Proteinate/protein buffer** *(Primary)* - **Phosphate buffer** *(Significant)* - Bicarbonate *(minor)*	 60 18
Red Blood Cells (RBCs)	- **Hemoglobin buffer** *(Primary)*	30

VI.3.2. Limitations of Buffer Systems

Buffer systems minimize pH changes by temporarily neutralizing hydrogen ions (H^+), but these ions remain present, and over time, the buffer salts become depleted. Therefore, the effectiveness of buffers is limited in duration. Regulatory systems—such as the lungs and kidneys—are essential for eliminating excess acids and regenerating buffer salts to maintain long-term acid-base balance.

VI.3.3. Role of the Lungs

The lungs play a crucial role in eliminating hydrogen ions (H^+) associated with the volatile anion bicarbonate (HCO_3^-). Excess CO_2 produced by the body's cells is buffered primarily by the bicarbonate

system and transported to the lungs in the form of carbonic acid (H_2CO_3), which dissociates into CO_2 and H_2O. The CO_2 is then expelled through respiration.

Reaction: $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$.

Thus, the lungs are essential in adjusting the partial pressure of CO_2 ($PaCO_2$) in response to changes in bicarbonate concentration, helping maintain acid-base balance. This relationship is described by the Henderson-Hasselbalch equation:

$$pH = pKa + \log_{10} ([HCO_3^-] / [H_2CO_3]).$$

To maintain pH stability, any change in bicarbonate concentration ($[HCO_3^-]$) must be matched by a change in carbonic acid ($[H_2CO_3]$) in the same direction, in order to keep their ratio constant. If $[HCO_3^-]$ decreases (as in metabolic acidosis), ventilation is stimulated (hyperventilation) to increase CO_2 elimination, thereby reducing $[H_2CO_3]$ and stabilizing the ratio.

If $[HCO_3^-]$ increases (as in metabolic alkalosis), ventilation decreases (hypoventilation) to retain CO_2 and raise $[H_2CO_3]$.

However, in this case, compensation for metabolic alkalosis through hypoventilation is limited due to the risk of developing hypoxia.

Pulmonary regulation is temporary; ultimately, the kidneys are responsible for eliminating excess bicarbonate ions.

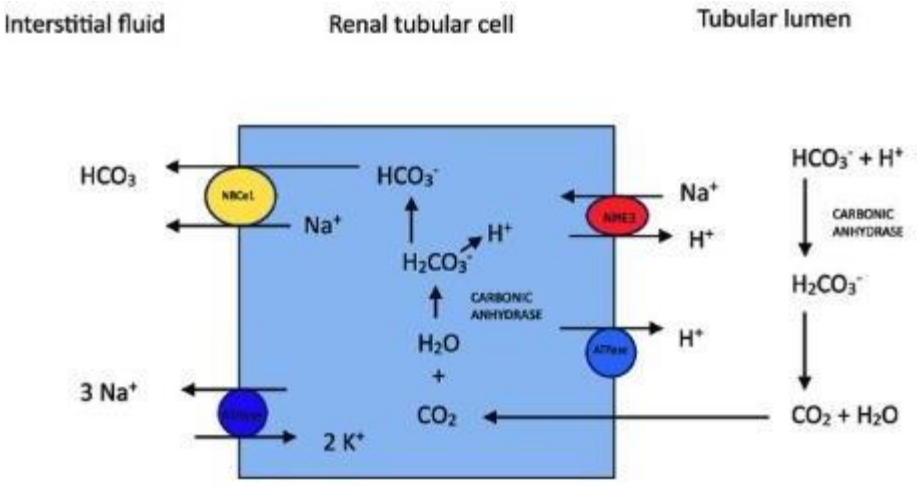
VI.4. Role of the Kidneys in Maintaining Acid-Base Homeostasis

The kidneys provide the ultimate regulation of acid-base balance. In addition to reabsorbing filtered bicarbonate at the glomeruli, they can adjust the excretion of hydrogen ions (H^+) and regenerate lost bicarbonate. This renal regulation directly influences urine pH, which can vary between 4.5 and 8.2 depending on the body's acid-base status.

VI.4.1. Bicarbonate Reabsorption

Under normal conditions, urine is almost free of bicarbonate, as it is reabsorbed primarily in the proximal tubule. Inside the epithelial cells, carbon dioxide and water are converted into bicarbonate (HCO_3^-) and hydrogen ions (H^+) through the catalytic action of **carbonic anhydrase**. The newly formed bicarbonate ions are transported back into the plasma, while the hydrogen ions are secreted into the tubular lumen.

Once in the tubular fluid, the secreted H^+ reacts with the filtered bicarbonate to form carbon dioxide and water (see Figure VI.1). The water is excreted, and the CO_2 diffuses back into the epithelial cell to regenerate bicarbonate, thus conserving plasma bicarbonate levels.



FigureVI.1. Illustration showing how bicarbonate is reabsorbed in the kidneys, mainly within the proximal tubules. Key components involved include carbon dioxide (CO_2), hydrogen ions (H^+), water (H_2O), and carbonic acid (H_2CO_3).

VI.4.2. Titratable Acidity

Titratable acidity refers to the amount of hydrogen ions (H^+) excreted in the urine that are bound to the disodium phosphate buffer (see Figure VI.2). Between 10 and 40 mmol of H^+ are eliminated in this form each day. It is called "titratable" acidity because it is measured by the amount of 0.1 molar sodium hydroxide (NaOH) required to raise the urine pH to 7.40, which matches the pH of plasma.

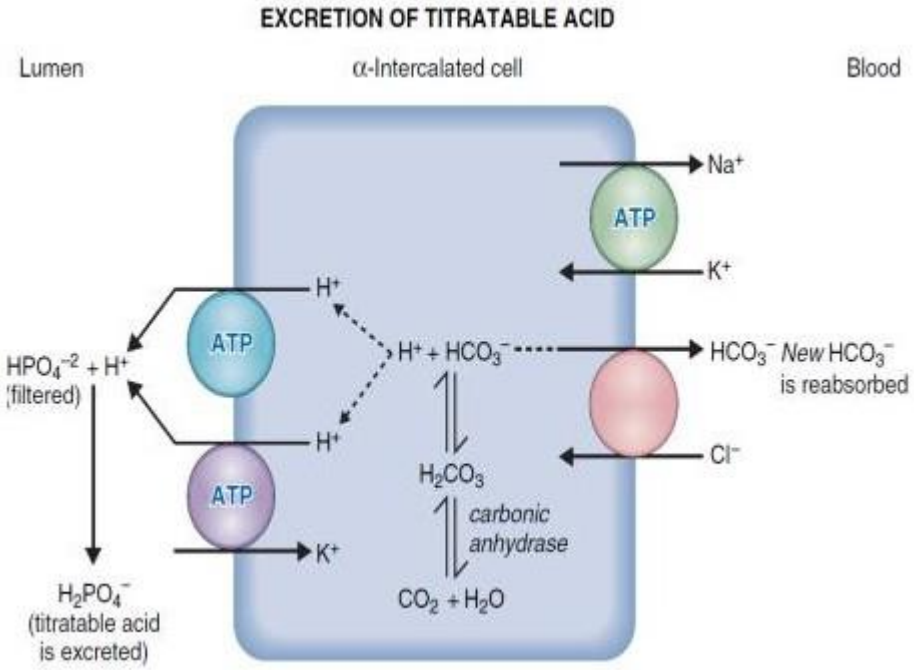


Figure VI.2. Excretion of H+ as Titratable Acid

VI.4.3. Formation of Ammonium Chloride

Ammonium hydroxide (NH_4OH) is a strong base produced in the renal tubular cells. It passively diffuses into the urine, where it combines with hydrogen ions (H^+) to form ammonium (NH_4^+)—a polar, water-soluble compound that cannot cross cell membranes (see Figure VI.3). As a result, it becomes trapped in the tubular lumen. The excretion of H^+ in this form typically ranges from 30 to 50 mmol per day.

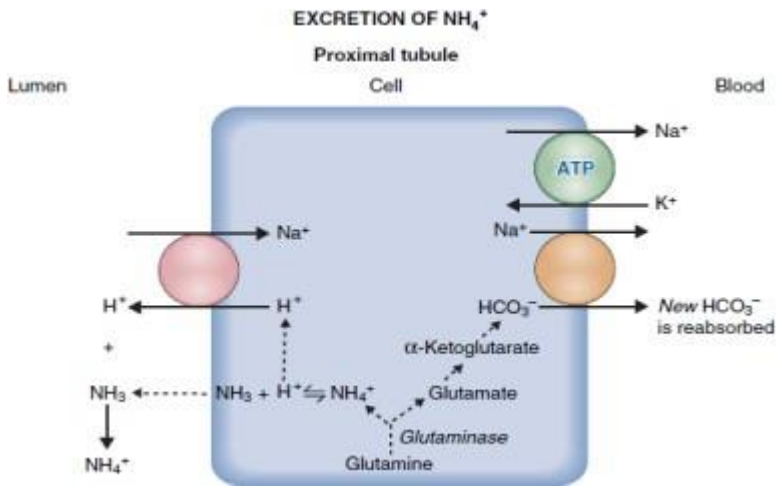


Figure VI.3. Excretion of H + as NH4+.

VI.5. Henderson-Hasselbalch Equation

The Henderson-Hasselbalch equation is a mathematical expression that relates the pH of a solution to the concentration of a weak acid and its conjugate base. It is fundamental for understanding acid-base balance in biological systems, particularly in the blood.

Equation:

$$\mathbf{pH=pKa+log([Base][Acid])}$$

In the context of blood buffering using the bicarbonate system, the equation is:

$$\mathbf{pH=6.1+log([HCO3-]0.03\times PaCO2)}$$

Where:

pH: Acidity of the blood

6.1: pKa of carbonic acid (H_2CO_3)

[HCO_3^-]: Bicarbonate concentration (in mmol/L)

$PaCO_2$: Partial pressure of CO_2 (in mmHg)

0.03: Solubility coefficient of CO_2 in plasma (mmol/L/mmHg)

VI.5.1. Arterial Blood Gas (ABG) Analysis

Arterial blood sampling is most commonly performed from the radial artery, though other arteries such as the femoral or brachial (humeral) arteries may also be used. The blood sample is collected in a syringe containing lithium or sodium heparin as an anticoagulant; other anticoagulants like oxalates, citrates, and EDTA are not recommended due to their potential to interfere with results. Syringes may be made of glass or plastic.

The presence of air bubbles in the syringe can distort the measurement, particularly $PaCO_2$, so it is crucial to remove all air bubbles and perform the analysis within 10 minutes of collection (see Table VI.2)

If the patient is receiving oxygen therapy, it should be paused before the sample is taken. If stopping oxygen is not possible, it is essential to accurately record the amount of oxygen being administered to properly interpret the blood gas results.

TableVI.2. Arterial blood sampling values

Parameters	**Usuelles Values**
pH	**7.38-7.42**
PCO_2	**35-45**
HCO_3^-	**22-28**
PO_2	**80-100**

VI.6. Acid-Base Balance Disorders

The extreme pH values compatible with life range from 6.9 to 7.7. A patient is considered to be in acidosis when blood pH falls below 7.35, and in alkalosis when the pH rises above 7.45.

To analyze these disorders, the Henderson-Hasselbalch equation, applied to the bicarbonate/carbonic acid (HCO_3^-/H_2CO_3) buffer system, is used.

- When the primary disturbance is due to a change in bicarbonate concentration, the disorder is

classified as metabolic.

- When the primary disturbance results from a change in $PaCO_2$ (partial pressure of CO_2), the disorder is considered respiratory.

This distinction is essential for accurate diagnosis and appropriate clinical management of acid-base imbalances.

VI.6.1. Metabolic Disorders

6.1.1. Metabolic Acidosis

Metabolic acidosis results from a **decrease in plasma bicarbonate concentration**.

Mechanisms include:

- **Excessive loss of bicarbonates** (e.g., through diarrhea or renal tubular acidosis)
- **Excess acid load** (e.g., in diabetic ketoacidosis or lactic acidosis)
- **Reduced renal excretion of hydrogen ions (H^+)** (e.g., in chronic kidney disease)

These factors disrupt the acid-base balance, leading to a fall in blood pH.

Physiological Response to Metabolic Acidosis:

- **Buffering:** The initial response involves **intracellular buffers**, primarily **hemoglobin**, which help neutralize excess hydrogen ions (H^+).
- **Respiratory Compensation:** The **second line of defense** is **increased alveolar ventilation (hyperventilation)**, which reduces **$PaCO_2$**, thereby helping to raise blood pH.
- **Renal Correction:** The **third line of defense** is the **renal response**. If kidney function is intact, the kidneys increase the excretion of hydrogen ions via **titratable acids** and **ammonium**, resulting in **very acidic urine**.

Potassium and Metabolic Acidosis:

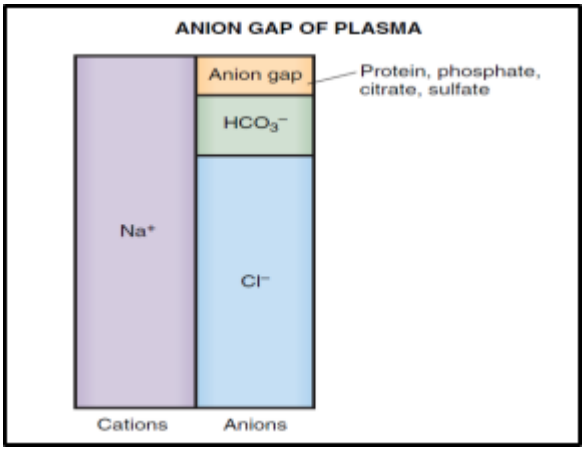
Metabolic acidosis is often associated with **hyperkalemia**. This occurs because **H^+ ions enter cells**, and in exchange, **intracellular potassium (K^+) moves out into the plasma**, raising serum potassium levels.

Based on the Anion Gap

$$\textbf{Anion Gap} = [Na^+ + K^+] - [Cl^- + HCO_3^-] = 12 \pm 2 \text{ mmol/L}$$

This calculation allows for the identification of **two types of metabolic acidosis**. In cases of **hypoalbuminemia**, the anion gap must be **corrected (**see Figure VI.4), as albumin is a major unmeasured anion and low levels can lead to an underestimation of the gap.

$$\text{Corrected Anion Gap} = \text{Measured AG} + 2.5 \times (4.0 - \text{Albumin in g/dL})$$



FigureVI.4. Anion Gap of Plasma.

A. High Anion Gap Metabolic Acidosis (AG > 16 mmol/L) with Normal Chloride Levels:

1. Ketoacidosis

- Diabetic ketoacidosis (DKA): by far the most common.
- Other less common forms of ketoacidosis: prolonged fasting, acute alcoholism, Type I glycogen storage disease.

2. Lactic Acidosis

- Caused by acute tissue hypoxia.
- Or due to disorders of pyruvate metabolism.

3. Acute or Chronic Renal Failure

- Regardless of the underlying cause, reduced renal acid excretion leads to H^+ accumulation.

4. Toxic Ingestions (non-chloride anions)

- Methanol poisoning

- Salicylate (aspirin) overdose
- Ethylene glycol ingestion (e.g., antifreeze)

These conditions all result in the accumulation of organic or non-chloride anions, increasing the anion gap.

B. Normal Anion Gap (Hyperchloremic) Metabolic Acidosis (Normal AG, Elevated Chloride)

This form of acidosis occurs without an increase in the anion gap, but with a rise in plasma chloride to compensate for bicarbonate loss.

Causes include:

1. Intestinal Loss of Bicarbonate

- Severe acute diarrhea (e.g., cholera)
- Hypersecretory villous tumors

2. Renal Tubular Acidosis (RTA)

- Type I (Distal RTA)
- Type II (Proximal RTA)
- Type IV RTA (associated with hyperkalemia)

3. Carbonic Anhydrase Inhibitors

- e.g., Acetazolamide, which reduces bicarbonate reabsorption in the renal tubules

These conditions lead to a direct loss of bicarbonate or impaired renal acid excretion, without accumulating unmeasured anions—hence the normal anion gap.

6.1.2. Metabolic Alkalosis

Metabolic alkalosis is defined as an **increase in plasma bicarbonate concentration**.

Mechanisms of Metabolic Alkalosis

It can occur as a result of:

- A **net loss of hydrogen ions (H^+)** from the extracellular fluid (e.g., through vomiting or nasogastric suction)
- **Addition of alkali** substances (e.g., ingestion of bicarbonate or other bases)
- **Disproportionate loss of chloride ions**, which impairs bicarbonate excretion

In all three scenarios, the principle of **electroneutrality** leads to a **decrease in plasma chloride levels (hypochloremia)**.

Physiological Response to Metabolic Alkalosis

- **Buffering:**
  - The addition of hydrogen ions (H^+) to the extracellular fluid **neutralizes the excess bicarbonate**, reducing its concentration in the blood.
  - This buffering involves the **release of H^+ from intracellular sources**, particularly **phosphates and proteins**.
- **Respiratory Compensation:**
  - In accordance with the **Henderson-Hasselbalch equation**, the body responds with **alveolar hypoventilation**, leading to an **increase in $PaCO_2$**, which helps lower the pH back toward normal.
- **Renal Correction:**
  - The **kidneys are the only organs capable of fully correcting** the disorder by **excreting excess bicarbonate** from the body.

Normally, metabolic alkalosis is quickly corrected by the kidneys, but if the imbalance persists, it is important to investigate **underlying factors that sustain the alkalosis**. There are three main such factors:

1. **Extracellular volume depletion**: This leads to increased reabsorption of sodium in the proximal tubule, often accompanied by bicarbonate (HCO_3^-), which contributes to maintaining alkalosis.
2. **Chloride deficiency**: A lack of chloride impairs the kidney's ability to excrete bicarbonate, thus sustaining the alkalosis.
3. **Potassium depletion**: Low potassium levels (hypokalemia) promote intracellular shifts that favor hydrogen ion loss and bicarbonate retention.
4.

6.1.3. Classification and Etiologies of Metabolic Alkalosis

1. Chloride-Responsive Alkalosis (Urinary Cl^- < 10 mmol/L)

These forms of alkalosis typically respond to **chloride supplementation** and are associated with **low urinary chloride excretion**.

Main Causes:

- **Digestive losses:**
  - **Persistent vomiting**
  - **Gastric suction (nasogastric aspiration)**: Loss of gastric HCl leads to a rise in plasma bicarbonate.
- **Urinary losses:**
  - Often due to **prolonged use of loop diuretics** (e.g., furosemide): Causes greater excretion of Na^+ and K^+ compared to HCO_3^-, indirectly promoting bicarbonate retention.
- **Low dietary chloride intake**: Limits the kidney's ability to excrete bicarbonate.
- **Post-hypercapnic alkalosis:**
  - After correction of chronic hypercapnia (e.g., in COPD), bicarbonate remains elevated temporarily.
- **Cystic fibrosis:**
  - Can lead to chloride loss through sweat, contributing to alkalosis.

2. Chloride-Resistant Alkalosis *(Urinary Cl^- > 25 mmol/L)*

These forms of alkalosis do not correct with chloride supplementation and are associated with high urinary chloride levels. They often involve hormonal or renal tubular dysfunction.

Main Causes:

- **Primary hyperaldosteronism**

Excess aldosterone increases Na^+ reabsorption and promotes K^+ and H^+ loss, leading to metabolic alkalosis.

- **Cushing's syndrome**

Elevated cortisol can mimic aldosterone effects, causing similar electrolyte imbalances.

- **Bartter syndrome**

A rare inherited disorder causing excessive renal loss of Na^+, Cl^-, K^+, and H^+, leading to persistent **alkalosis.**

- **Severe hypokalemia (< 2 mmol/L)**

  Enhances renal bicarbonate reabsorption and H^+ excretion.

- **Hypomagnesemia**

  Contributes to renal potassium wasting and impairs the correction of alkalosis.

VI.6.2. Respiratory Disorders

2.1. Respiratory Acidosis

Respiratory acidosis is an acid-base disturbance caused by an elevation in $PaCO_2$ above 45 mmHg, known as hypercapnia.

Mechanism

It results from reduced alveolar ventilation, which leads to CO_2 retention and a subsequent drop in blood pH.

Physiological Response

- **If acute (< 24 hours):**
  - Compensation is limited to intracellular and extracellular buffer systems (e.g., hemoglobin, proteins, phosphates).
  - Renal compensation has not yet begun.
- **If chronic (> 24 hours):**
  - The kidneys begin to compensate by:
    - Increasing distal tubular secretion of H^+ ions
    - Enhancing proximal reabsorption of bicarbonate (HCO_3^-)
    - Reducing chloride reabsorption to maintain electroneutrality

The acidosis can only be fully corrected if the underlying cause of hypoventilation is resolved.

Etiologies of Respiratory Acidosis

Acute respiratory acidosis can result from airway obstructions such as a foreign body, aspiration of vomit (wrong-way entry), or laryngospasm; major circulatory disturbances like acute pulmonary edema or pulmonary embolism; and central respiratory depression affecting the brain's respiratory centers. Chronic respiratory acidosis, on the other hand, is most commonly caused by chronic obstructive pulmonary diseases (COPD) and neuromuscular disorders that impair respiratory function over time.

2.2 Respiratory Alkalosis

Respiratory alkalosis is an acid-base disorder caused by a **decrease in $PaCO_2$**, known as **hypocapnia**. It is **always the result of increased alveolar ventilation**, meaning that **CO_2 is eliminated faster than it is**

produced—a condition known as **alveolar hyperventilation**. Respiratory alkalosis is the **most common acid-base disturbance**, observed in nearly **50% of patients in intensive care units**.

Etiologies include:

- **Hypoxemia**, such as from living at **high altitudes** or in cases of **severe anemia**
- **Stimulation of the respiratory centers**, either by anxiety, fever, or certain drugs
- **Pulmonary diseases**, such as **pneumonia**, which can trigger hyperventilation due to impaired gas exchange.

Physiological Response of the Body to Respiratory Alkalosis

During the **acute phase**, the body responds by **releasing hydrogen ions (H^+)** from **intracellular and extracellular buffer systems** in an attempt to **lower plasma bicarbonate levels** and restore acid-base balance.

If the alkalosis **persists for more than 6 hours**, the **kidneys begin to compensate** by:

- **Increasing the excretion of bicarbonate (HCO_3^-)**
- **Reducing the excretion of ammonium ions (NH_4^+)** and **titratable acids**, thereby helping to retain more H^+ and gradually correct the alkalosis.

Conclusion

A comprehensive and prioritized assessment of renal function, trace elements, vitamins, and hormones are essential for maintaining physiological balance and preventing disease. Each of these areas contributes uniquely and critically to human health.

Renal function assessment—using markers such as serum creatinine and estimated glomerular filtration rate (eGFR)—is fundamental for detecting early kidney dysfunction, such as in chronic kidney disease (CKD). More specialized tests like renal imaging or biopsy may be needed to identify structural abnormalities or glomerular damage.

Trace elements, though required in minute amounts, play pivotal roles in enzymatic activity and cellular function. For instance, zinc deficiency can impair immune function and wound healing, while excess iron can lead to conditions like hemochromatosis, affecting the liver, heart, and pancreas.

Vitamins are essential for countless biological processes. A deficiency in vitamin D can result in osteomalacia or rickets, compromising bone health, while vitamin B12 deficiency can cause megaloblastic anemia and neurological disturbances. These examples highlight how vital adequate vitamin levels are to tissue repair, immunity, and metabolic health.

Hormones regulate nearly every body system, and even slight imbalances can have widespread consequences. For example, reduced thyroid hormone levels (hypothyroidism) can cause fatigue, weight gain, and depression, while excessive cortisol production (as in Cushing's syndrome) may lead to hypertension, diabetes, and immune suppression.

In conclusion, the interconnected nature of these systems underscores the importance of a multidisciplinary approach to clinical evaluation. Timely and targeted assessments of renal markers, trace elements, vitamins, and hormones not only aid in early diagnosis but also enhance treatment outcomes and long-term patient care.

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