جامعة عباس لغرور خنشلة
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Metabolic regulation

HANDOUT intended for 3rd-year biochemistry students

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الجمهورية الجزائرية الديمقراطية الشعبية
وزارة التعليم العالي والبحث العلمي
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Educational handout :

Metabolic regulation

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Preface

Metabolic regulation is a cornerstone of biochemistry, linking the complex network of biochemical pathways that govern the synthesis and breakdown of vital biological molecules. At the molecular level, the delicate balance of these processes ensures cellular and organismal homeostasis. Understanding the intricate regulation of metabolism is not only essential for unraveling the basic principles of life but also for addressing a wide range of pathological conditions that arise when these systems go awry.

This course on Metabolic Regulation is designed to provide students with a comprehensive understanding of how key metabolic pathways are interconnected, both at the molecular and systemic levels. Focusing on both non-endocrine and endocrine regulatory mechanisms, the course will explore how hormones and coenzymes control metabolism in various contexts, including carbohydrate, protein, and lipid metabolism. Students will also delve into how these processes are disrupted in common diseases such as diabetes, hypercholesterolemia, and metabolic syndrome. Furthermore, the course will examine how the regulation of phosphocalcic metabolism and immune-endocrine system interactions contribute to health and disease.

Beyond the theoretical aspect, special attention will be given to understanding the molecular foundations and biochemical mechanisms underlying these regulations. This approach will equip students with the skills needed to analyze and interpret metabolic imbalances observed in various diseases and to better understand the therapeutic strategies suited to these disorders.

By the end of this course, students will have gained a deeper appreciation of the biochemical mechanisms that maintain metabolic balance and how dysregulation of these processes can lead to metabolic disorders. They will also acquire the necessary tools to apply this knowledge in clinical, research, and industrial settings, preparing them for further studies or careers in the ever-evolving field of biochemistry.

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Interrelationships between different metabolisms

1. Introduction:

Metabolism refers to the complex set of biochemical reactions that occur within living organisms to maintain life. These reactions enable organisms to convert energy from food, oxygen, and other resources into usable forms that drive cellular processes. While metabolism is often discussed in terms of specific pathways, such as carbohydrate metabolism or lipid metabolism, it is important to recognize that these various metabolic processes are highly interconnected. In fact, no metabolic pathway operates in isolation; rather, they form a highly integrated network in which the products and byproducts of one pathway can serve as substrates or regulators for another.

The interrelationships between different metabolisms are vital to the organism's ability to adapt to changes in the environment, efficiently use available nutrients, and maintain homeostasis. For example, the breakdown of carbohydrates (glycolysis) produces intermediate molecules that can enter the citric acid cycle, a crucial pathway for energy production. Meanwhile, lipids are stored and mobilized for energy when carbohydrate stores are low, and proteins can be catabolized to supply energy or to provide building blocks for other biochemical processes.

Key metabolic pathways, including those involved in carbohydrate, lipid, protein, and nucleic acid metabolism, do not function in isolation but are connected through a series of molecular interactions. For instance, when glucose is unavailable or in short supply, lipids and proteins can be metabolized to generate ATP, the energy currency of the cell.

Moreover, regulatory networks involving hormones, enzymes, and co-factors tightly coordinate metabolic activities. For example, insulin and glucagon help regulate blood glucose levels, directing the body's response to feeding or fasting states. These hormonal signals impact the metabolism of carbohydrates, lipids, and proteins, showcasing the intricate control mechanisms that integrate different metabolic pathways.

Understanding the interrelationships between different metabolisms is fundamental for various fields of biological research, including physiology, nutrition, medicine, and pharmacology. Disruptions in the coordination of metabolic networks can lead to a variety of disorders, including diabetes, obesity, cardiovascular diseases, and metabolic syndromes.

Thus, studying these interrelationships provides valuable insights into both healthy metabolism and the pathophysiology of diseases.

In this context, the interrelationships between different metabolisms do not merely reflect the integration of biochemical pathways; they are essential for maintaining the energetic and structural needs of the cell and the organism as a whole. The cooperative nature of these pathways allows cells to be flexible and responsive to different physiological conditions, whether they are in a fed or fasting state, resting or active, or adapting to environmental stresses. Understanding this dynamic network is central to advancing biomedical knowledge and developing therapies for metabolic diseases.

2. Metabolism

Metabolism is a catch-all term used to describe all the chemical reactions that take place within cells and organisms. Metabolism can be thought of as the chemical reactions of life. Metabolism performs a variety of essential functions to keep an organism alive and functioning properly:

- metabolism breaks down nutrients to produce energy;
- synthesis of important building blocks of proteins, lipids, nucleic acids and some carbohydrates;
- the elimination of metabolic wastes;
- regulating body temperature;
- managing hormones levels;
- storage of fuels and maintaining and repairing cells.

These functions ensure that an organism can grow, reproduce, respond to the environment, and maintain its structural integrity.

3. Metabolic Processes

The biochemical reactions in the living cell-metabolism-are organized into metabolic pathways. The pathways can be represented as a map follow the fate of metabolites and building blocks, identify enzymes that act on these metabolites, and identify points and agents of regulation. Metabolic reactions can be classified broadly into two categories:

- **Catabolism:** Catabolic reactions involve the breakdown of larger molecules into smaller ones, releasing energy in the process. This energy is often stored in the form of adenosine triphosphate (ATP)**,** which is the primary energy carrier in cells.

Examples include the breakdown of carbohydrates, proteins, and fats to release energy, which is used by the body for various functions, such as muscle contraction, protein synthesis, and cell division.

- **Anabolism**: Anabolic reactions are the processes that build larger, more complex molecules from simpler ones. Anabolic processes are critical for tissue repair, especially after injury, as well as for muscle growth and bone development. These reactions consume energy, usually in the form of ATP.

Examples of anabolic processes include the synthesis of proteins from amino acids, DNA replication, and the creation of glycogen or fat storage from glucose and fatty acids.

This balance between catabolic and anabolic processes is crucial for maintaining energy levels, supporting growth, and repairing the body.

Table 01: Comparison of catabolic and anabolic pathways

Aspect	Catabolic Pathways	Anabolic Pathways
Function	Breakdown of complex molecules into simpler ones.	Building of complex molecules from simpler units.
Energy	Releases energy (usually in the form of ATP).	Requires energy (usually in the form of ATP).
Example	Breakdown of glucose to form ATP (glycolysis), breakdown of fats into fatty acids.	Protein synthesis from amino acids, DNA replication, and muscle growth.
Process Type	Degradative (destructive)	Synthetic (constructive)
Purpose	Provides energy for cellular processes.	Supports growth, repair, and maintenance of tissues.

Key Enzymes	Enzymes like amylase, lipase, and proteases.	Enzymes like polymerases, ribosomes, and synthases.
End Products	Simpler molecules like glucose, fatty acids, amino acids, and ATP.	Larger molecules like proteins, lipids, and nucleic acids.
Example of Pathway	Glycolysis, citric acid cycle (Krebs cycle), beta-oxidation of fats.	Protein synthesis, DNA/RNA synthesis, glycogenesis.
Both are made up of enzyme-catalysed reactions		
Both are coupled to ATP, the principal energy carrier in cells		

4. Interaction of biochemical pathways

A central array of metabolic pathways exists within all living things. These pathways are responsible for the breakdown of essential nutrients into Adenosine Triphosphate (ATP) and other molecules necessary for the release of energy into the body. As shown in figure 1, all metabolic pathways interact in one form or another during the energy production process. The interrelationships of metabolic pathways take various forms and always result in three junction points: glucose-6-phosphate, Pyruvate, and Acetyl CoA.

The interaction of biochemical pathways refers to how different metabolic pathways (both catabolic and anabolic) are interconnected and work together to maintain homeostasis in the body. These pathways don't operate in isolation; they often overlap and influence each other to ensure that energy is produced, stored, and utilized efficiently. Let’s break down a few key interactions:

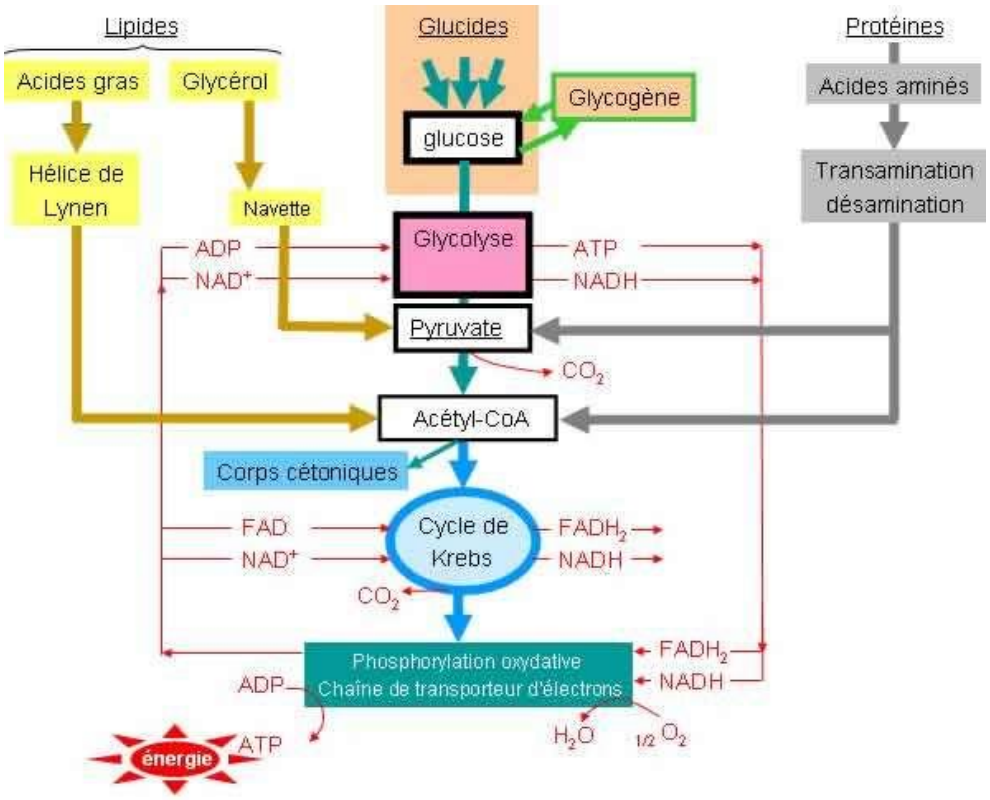


Figure 1: Common gateway for lipid, protein, and carbohydrate metabolism (site 1)

4.1. Connections of Other Sugars to Glucose Metabolism

- The glycogen will be hydrolyzed into glucose monomers (G-1-P) if blood sugar levels drop. When there is adequate ATP present, excess glucose is converted into glycogen for storage.
- Fructose-6-phosphate and glyceraldehyde-3-phosphate are synthesized by the pentose-phosphate pathway. Glucose and glucose-6-phosphate enter the pentose-phosphate pathway.
- Galactose can enter the glucose reserve pathway, UDP-galactose being in equilibrium with UDP-glucose, a reaction catalyzed by UDP-galactose-epimerase and can enter the glycolysis pathway by isomerization between galactose-6-phosphate and glucose-6-phosphate.
- Fructose can also participate in the reserve pathway, with fructose-6-phosphate in equilibrium with glucose-6-phosphate, a reaction catalyzed by phosphohexose isomerase. Most fructose is metabolized in the liver to fructose 1-phosphate, which will be split into glyceraldehyde and dihydroacetone to join the glycolysis pathway.
- It is important to note here that at the Krebs cycle level, citrate is unfavorably transformed into isocitrate, but an excess of ATP will push the citrate to leave the mitochondria allowing the reformation of acetylcoenzyme A which will enter into the formation of fatty acids. Citrate will also have a role in inhibiting 6-phosphofructokinase and therefore glycolysis.

- Glycolysis can also occur anaerobically when the end product is lactate.

4.2. Connections of Proteins to Glucose Metabolism

If there are excess amino acids, however, or if the body is in a state of famine, some amino acids will be shunted into pathways of glucose catabolism. Each amino acid must have its amino group removed prior to entry into these pathways. The amino group is converted into ammonia.

The ketogenic and non-essential amino acids can indirectly from fatty acids. Carbohydrates can also result from the oxidation of the non-essential glucogenic amino acids.

4.3. Connections of Lipids to Glucose Metabolism

Fatty acids may be oxidised to acetyl-CoA by ß-oxidation or esterified with glycerol, forming triacylglycerol (fat) as the body's main fuel reserve. Triglycerides can be both made and broken down through parts of the glucose catabolism pathways. Glycerol can be phosphorylated and proceeds through glycolysis.

These interactions help the body efficiently manage energy, maintain cellular health, and adapt to different physiological states.

Non-endocrine regulations

1. Introduction:

The metabolic pathways are complex and interdependent. With the changing environments the reactions of metabolism must be finely regulated to maintain a constant set of conditions within cells, such as temperature and the intracellular concentration of different chemical species, within a range of normal values, which is called homeostasis. Control of metabolic pathways also allows organisms to respond to signals and interact actively with their environments.

Non-endocrine regulation refers to the control of physiological processes in the body that does not involve the endocrine system (which uses hormones for regulation). Instead, non-endocrine regulation involves other mechanisms such as nervous system control, local signaling, and feedback loops that help maintain homeostasis (the body's internal balance). These regulatory mechanisms are essential for coordinating the body’s responses to both internal and external changes.

2. Levels of metabolic regulation

There are multiple levels of metabolic regulation:

2.1. Intrinsic regulation

For intrinsic regulation of metabolic pathways the reactions self-regulate to respond to changes in the levels of substrates or products. Thus, a decrease in the concentration of the product of a metabolic pathway can increase the flow of metabolites through this pathway to compensate for the scarcity of this compound in the cell. This type of regulation often relies on the allosteric regulation of several enzymes in the metabolic pathway.

2.2. Extrinsic control

Extrinsic control involves a cell in a multicellular organism changing its metabolism in response to signals from other cells. The signals approach the pathways via soluble messengers such as hormones and growth factors. These act by being detected by specific receptors on the cell surface.

These signals are then transmitted inside the cell by second messenger systems that often involved the phosphorylation of proteins. But it is useless to control all enzymatic activities. The most important regulation to control is the slowest reaction; thus we control the metabolic rate.

3. Mechanisms of metabolic control

The magnitude of metabolite flux through any metabolic pathway will depend upon the activities of the individual enzymes involved. It is possible to group mechanisms of metabolic control into two major classes on the basis of the relative lengths of time they take to bring about a change in the velocity of a particular enzyme.

- **Coarse metabolic control** is a long-term (hours to days in eukaryotes; perhaps minutes to hours in rapidly growing prokaryotes), energetically expensive, response that is achieved through changes in the total cellular population of enzyme molecules.

The process is slow as it involves protein synthesis. The total amount of a given enzyme is dependent upon the relative rates of its biosynthesis versus degradation. Thus, any alteration in the rates of gene expression (i.e. transcription, translation, mRNA processing or degradation) or proteolysis can be considered as coarse metabolic control.

- **Fine Control:** control of the activity of the enzyme. This is a fast process (i.e., seconds to minutes) as it involves changing the activity of enzyme already available in the cells. Fine metabolic controls are also regarded as metabolic transducers.

4. Control of metabolism

Sophisticated mechanisms have evolved to control the flow of metabolites through metabolic pathways. These systems ensure that metabolic outputs meet biological demands and prevent the waste of ATP by preventing opposing pathways from running simultaneously in the same cell. Enzymes can be regulated by altering their activity or by changing the amount of enzyme present in the cell.

4.1. Modifying the Activity of Existing Enzymes:

The fastest way to regulate enzyme activity is by modifying the function of enzymes that are already present in the cell. Common methods for regulating enzyme activity include:

4.1.1. Substrate Availability:

Substrates (reactants) bind to enzymes with a characteristic affinity, defined by dissociation constant and a kinetic parameter (Km). If the concentration of a substrate is much lower than Km, enzyme activity is low. If the concentration is much higher than Km, the enzyme becomes saturated with substrate, leading to maximal activity. The change in substrate concentration takes place through increased intake, synthesis or transport of the substrate to the place where we metabolize it.

4.1.2. End product inhibition (Negative Feedback Inhibition):

Often, the product of an enzyme-catalyzed reaction resembles the starting substrate and can bind to the enzyme's active site, though with lower affinity. When the product accumulates, the cell benefits from preventing further product synthesis through product inhibition. This can extend to feedback inhibition, where the final product of a pathway inhibits the first enzyme, thereby shutting down the entire pathway.

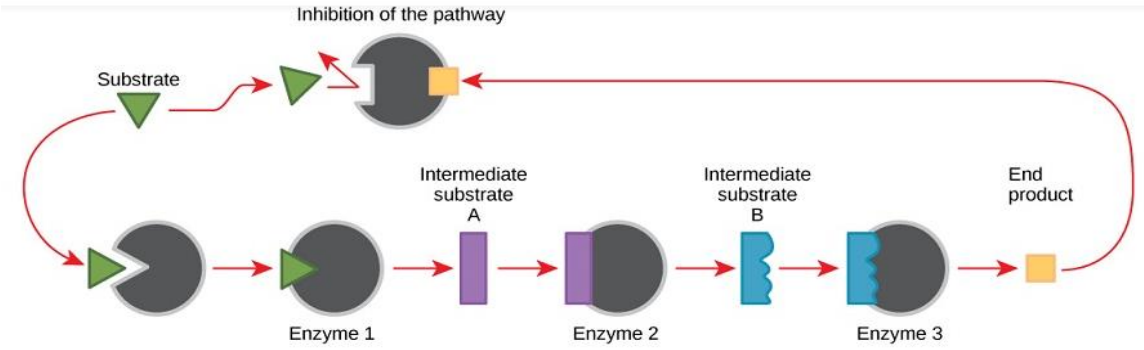


Figure 02: Negative feedback inhibition of enzymes (site 2)

4.1.3. Allosteric Regulation:

Many pathways are interconnected, so molecules from one pathway can regulate enzymes in another pathway, even if the molecules are structurally different from the substrates or products in the second pathway. Molecules that bind to sites other than the enzyme's active

site (allosteric sites) can either activate or inhibit the enzyme by inducing conformational changes.

4.1.4. pH and Enzyme Conformation:

Changes in pH, which can occur during metabolic processes like aerobic glycolysis, can alter an enzyme's conformation and activity. These changes are often due to covalent modifications, such as changes in the protonation state of amino acids, which disrupt protein structure.

4.1.5. Covalent Modification:

Post-translational modifications like phosphorylation, acetylation, methylation, and glycosylation can change enzyme activity by altering the enzyme's shape, its ability to bind to substrates or regulators, or by affecting its location in the cell. Phosphorylation, typically mediated by kinases, is a common regulatory mechanism, as it can activate or inhibit enzymes. These processes are often reversible and regulated through cell signaling pathways. A change in enzyme conformation that is induced by covalent modification normally causes an alteration of enzyme–substrate interactions such that kinetic parameters such as V_{max}, K_m.

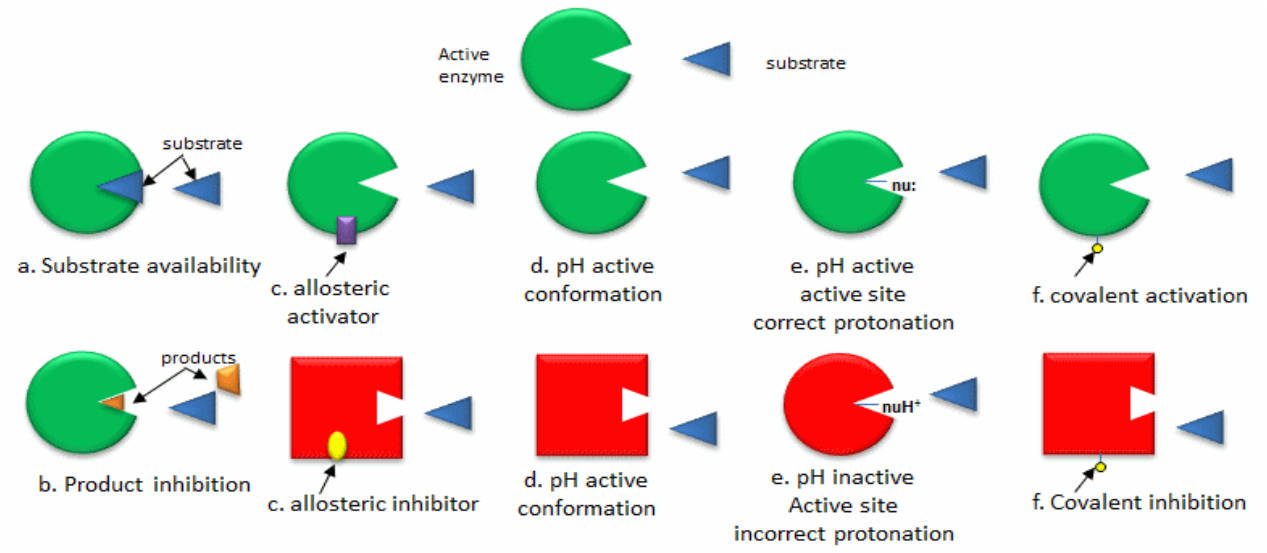


Figure 03: Ways to regulate pre-existing enzymes (site 3)

4.2. Modifying the Amount of Enzyme: A slower but more sustained method of regulating enzyme activity is by adjusting the quantity of enzymes in the cell. This can be achieved through:

4.2.1. Gene Transcription Regulation:

External signals like hormones or neurotransmitters can trigger signal transduction pathways that activate or inhibit the transcription of the gene encoding a specific enzyme. This process involves transcription factors binding to DNA sequences that control gene expression.

4.2.2. Degradation of mRNA:

The amount of enzyme produced is directly related to the amount of its mRNA. Small interfering RNAs (siRNAs) or microRNAs can bind to the mRNA, forming a double-stranded complex that is recognized by enzymes like Dicer, which cleaves the complex and reduces mRNA translation.

4.2.3. Post-translational Modifications:

After translation, enzymes may undergo processing steps like cleavage by proteases to become active. Some enzymes require the assistance of cofactors to adopt their active form, while others may be degraded through proteasomal or lysosomal pathways.

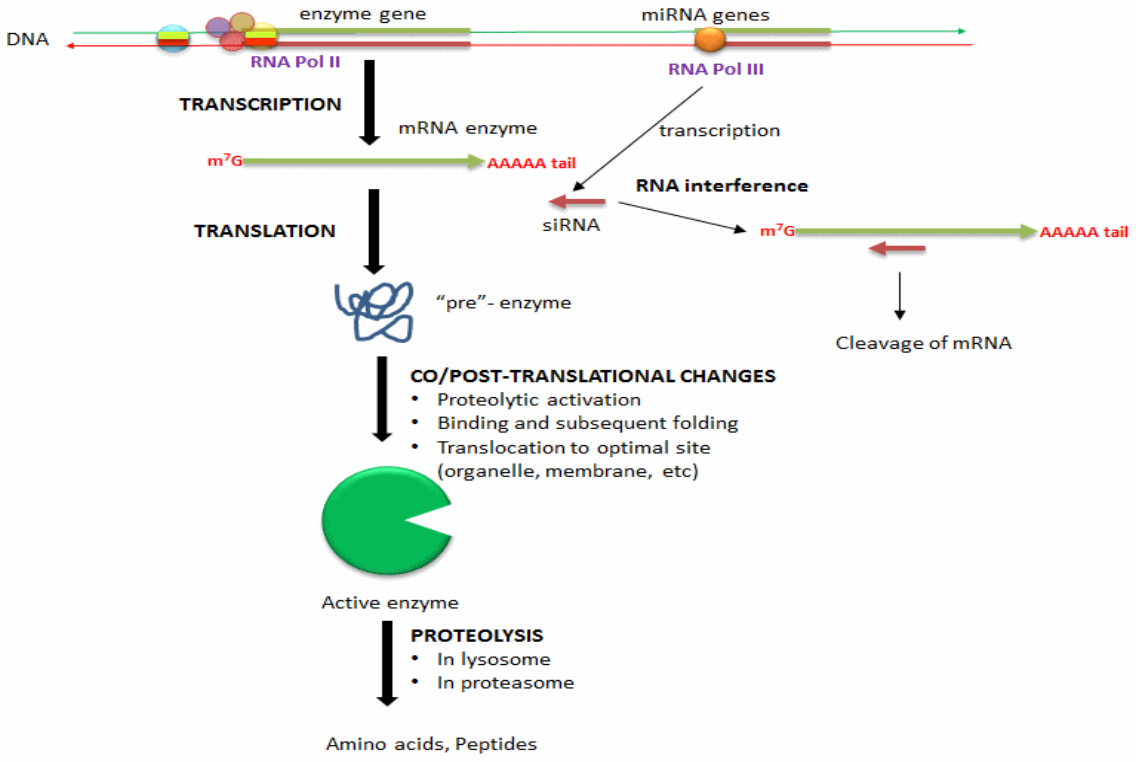


Figure 04 : Ways to regulate the concentration of an enzyme (site 3)

THE ENDOCRINE REGULATION

I. Basic concepts in endocrinology

1. Overview

The two major systems responsible for the regulation of homeostasis are the nervous system and the endocrine system. While the nervous system conducts electrical signals throughout the body with neurons and acts more quickly it has short-term effects. The endocrine system, which is composed of a group of glands placed throughout the body, releases chemical messengers (hormones) that must travel through the circulatory system to reach a target tissue or organ causing that tissue or organ to effect a regulatory change. This is a much slower process but the effect is more long-term. These hormones regulate the body's growth, metabolism, and sexual development and function.

Endocrine tissues and organs secrete hormone into body fluids (mainly blood and lymph) directly using diffusion. Exocrine tissues, such as salivary glands, mammary, lacrimal, prostate and sebaceous glands, secrete chemical substances through ducts into an open space. The locations of the endocrine glands in the body are shown in Figure 5.

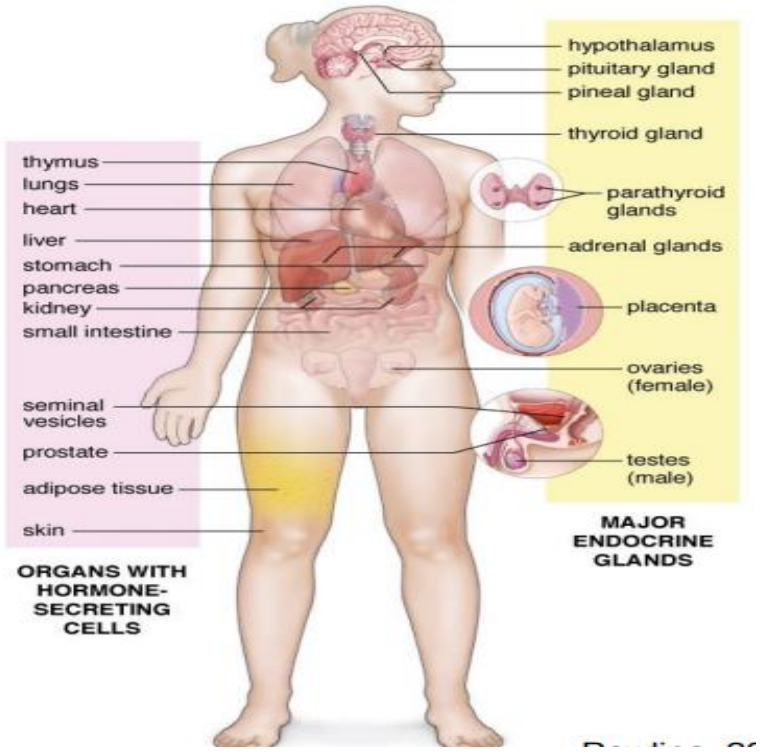


Figure 5: Locations of the major endocrine glands (site 4)

2. The Hormones

2.1. Definition:

Hormones are organic compounds secreted by endocrine glands that have a potent effect in target cells. As such, a hormone can only affect a tissue that has receptors for it. When the hormone binds to the receptors on or within the target cell, it produces a response in the target cell. An overall timeframe for hormone action is very broad, spanning an array of options. Some hormones can act within seconds (epinephrine or adrenaline), others over a few minutes or hours (insulin, glucagon, cortisol), and maybe weeks (estrogen, testosterone), or they can have an effect over many years (human growth hormone).

2.2. Effects in the target cells caused by hormone action

a. A change in cell membrane permeability (e.g. insulin causes muscle cells to have a higher permeability for glucose).

b. A change in chemical reaction rate (e.g. growth hormone stimulates higher chemical reaction rates in muscle and bone cells).

c. Enzyme activation (e.g. epinephrine increases enzyme action in muscle cells).

d. Activation of cell secretion (e.g. melanocytestimulating hormone activates more melanin secretion from the melanocytes).

e. Initiates protein synthesis and changes ate of protein synthesis.

2.3. Types of hormones

Human hormones can be categorized into two main groups based on their chemical structure: those derived from amino acids and those derived from lipids. Amino acid-derived hormones include amines, peptides, and proteins, while lipid-derived hormones consist of steroids. These chemical structures influence various aspects of a hormone's function, such as its distribution, receptor binding, and overall activity.

2.3.1. Amino acid derivatives: Derivatives of the amino acid tyrosine secreted by the thyroid (thyroxine and triiodothyronine) and the adrenal medullae catecholamins (epinephrine

and norepinephrine) which are involved in the fight-or-flight response.Tryptophan derivatives (Melatonin secreted by the pineal gland).

2.3.2. Peptide and Protein Hormones

• Include most hormones of body
• Synthesized as prohormones converted to active form
• Range from short polypeptide chains of amino acids (such as antidiuretic hormone ADH and oxytocin) to small proteins (such as insulin, growth hormone GH, and prolactin)
• Glycoproteins may also function as hormones – Polypeptides with carbohydrate side chains
♣ Examples: TSH, LH, follicle-stimulating hormone FSH.

2.3.3. Lipid derivatives

Consist of carbon rings and side chains built from either fatty acids (eicosanoids) or cholesterol (steroid molecules)

• **Eicosanoids** – Important paracrine factors that coordinate cellular activities and enzymatic processes (such as blood clotting) in extracellular fluids oLeukotrienes (secondary roles as hormones)

o Prostaglandins (involved primarily in coordinating local cellular activities)

• Steroid hormones

-Released by reproductive organs (androgens by testes in males; estrogen and progesterone by ovaries in females), adrenal gland (like aldosterone, corticosteroids) and Kidneys (calcitriol).

-Bound to specific transport proteins in blood to reach their target cells. This binding extends the half-life of steroid hormones, making them more stable than amino acid-derived hormones. The half-life of a hormone is the time it takes for half of its concentration to be eliminated. For instance, cortisol, a lipid-derived hormone, has a half-life of approximately 60 to 90 minutes, while the amino acid-derived hormone epinephrine has a half-life of only about one minute.

2.4. Pathways of Hormone Action

Although a hormone circulates throughout the body via the bloodstream, it only influences the activity of its target cells—those with receptors specific to that hormone. The hormone's message is detected by its receptor, a protein found either inside the cell or on the cell membrane. Upon binding, the receptor processes the signal by activating various signaling pathways or cellular mechanisms that lead to the target cell's response. Hormone receptors are selective, recognizing molecules with specific shapes and side groups, and will only respond to hormones that match these characteristics. The same type of receptor can be found on cells in different tissues, potentially eliciting varying responses. Therefore, the effect of a hormone depends not only on the hormone itself but also on the target cell.

Once the target cell receives the hormone signal, it can respond in several ways. These responses may involve stimulating protein synthesis, activating or inhibiting enzymes, changing the permeability of the cell membrane, altering the rates of mitosis and cell growth, or triggering the secretion of various products. Additionally, a single hormone may provoke different responses within the same cell.

2.4.1. Binds to intracellular receptor (cytoplasm or nucleus):

They are lipophilic in nature, and commonly derived from cholesterol, e.g: estrogens. Diffuse through plasma membrane also diffuses across the nuclear envelope (Figure 6). This binding of the hormone causes allosteric transformation of the receptor, and the resulting complex travels to the nucleus (guided by the nuclear localization signal, NLS), where it binds to DNA and regulates the transcription of specific genes, changing pattern of protein synthesis.

Other steroid hormones (e.g., estrogens, progestogens) bind to their specific receptors directly in the nucleus (blue arrows in figure). In membrane-initiated steroid signaling, the steroid receptors are expressed on the cell membrane, usually in the caveolae, and their pathway is similar to that of the cell surface receptor signaling.

2.4.2. Bind to cell surface (plasma membrane) receptors:

A protein hormone is transported in the blood or lymph without a transporter, binds with a specific receptor site on membrane of its target cell, and stimulates the release (or activation) of special substance (second messengers), because hormone consider first messenger. They can then change the cells activity by opening or closing gated ions channels directly (ionotropic effect), or, more commonly in the endocrine system, by activating G proteins and

then generating cAMP as a 2nd messenger that can change the activity of the cell (metabotropic effect).

The second messenger is cAMP, e.g: FSH. II. The second messenger is cGMP, e.g: ANF. III. The second messenger is phosphatidylinositol/calcium, e.g: TRH. IV. The second messenger is a kinase or phosphatase, e.g: Insulin.

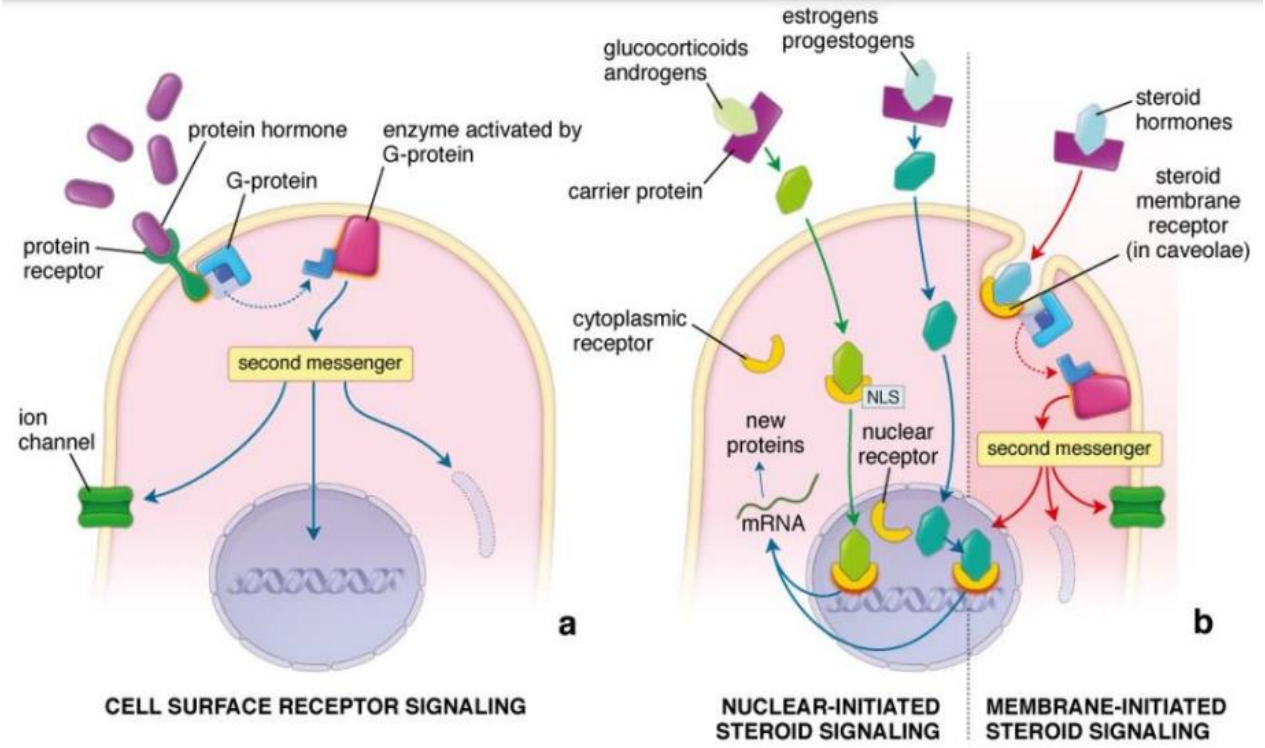


Figure 6: General mechanisms of protein and steroid hormone actions (Site 5)

2.5. Hormone interactions

- The various hormones released by the many endocrine glands interact to produce coordinated physiological responses. Cells have more than one type of hormone receptors, so can respond to multiple hormones simultaneously.
- Receiving instructions from two hormones at the same time has four possible outcomes:

2.5.1. Antagonistic effects (opposing) observed effects are weaker than those produced by either hormone unopposed. One may increase a parameter and the other decreases it. Examples in the Body • PTH vs have opposing effects on blood Ca2+ levels. calcitonin Insulin vs. glucagon have opposing effects on blood glucose levels.

2.5.2. Permissive effects: One hormone is needed for second hormone to produce its effect. The presence of first hormone enables the subsequent hormone to act to its greatest potential. Examples in the Body: Estrogen and progesterone are released at specific times in order to coordinate the uterine cycle. Cortisol significantly enhances the effects of norepinephrine as a vasoconstrictor. Epinephrine changes rate of cellular energy consumption only in presence of thyroid hormones.

2.5.3. Synergistic Effect. This is when two or more hormones with similar effects produce an amplified response. When the hormones act together they have a greater effect than the sum of them separately. Examples in the Body: Testosterone and follicular stimulating hormone both promote sperm production. Prolactin and oxytocin are both required for adequate lactation.

2.6. Types of Chemical Signaling

There are four different types of chemical signaling occurring in multicellular organisms:

- **Endocrine:** hormones secreted into the extracellular fluid spreads into the blood or lymphatic system, and can, therefore, travel great distances throughout the body.
- **Paracrine:** occurs amongst neighbouring cells. Although paracrines may enter the bloodstream, their concentration is generally too low to elicit a response from distant tissues.
- **Autocrine:** occurs within the same cell, hormone released feeds-back on the cell of origin, again without entering blood circulation.
- **Neuroendocrine:** Hormone is produced and released by a neuron, delivered to target cells by blood.

2.7. Control of hormone secretion

The control of hormone secretion is a complex process regulated by several mechanisms to maintain homeostasis in the body.

2.7.1. Negative feedback mechanism:

This is the most common mechanism for regulating hormone levels. When a hormone's effect reaches a certain threshold or when the desired result is achieved, an inhibitory signal (hormone, nerve impulse, or enzyme) will be sent from the target cells to the endocrine gland.

For example, the synthesis and secretion of thyroid hormones are regulated by a negative feedback loop involving the hypothalamus, pituitary gland, and thyroid as shown in Figure 4. When thyroid hormone levels drop, the hypothalamus releases thyrotropin releasing hormone (TRH), stimulating the pituitary to secrete thyroid stimulating hormone (TSH). TSH prompts the thyroid to produce more hormones, and once levels are sufficient, the feedback loop halts the secretion of TRH and TSH, stopping further thyroid hormone production until levels decrease again.

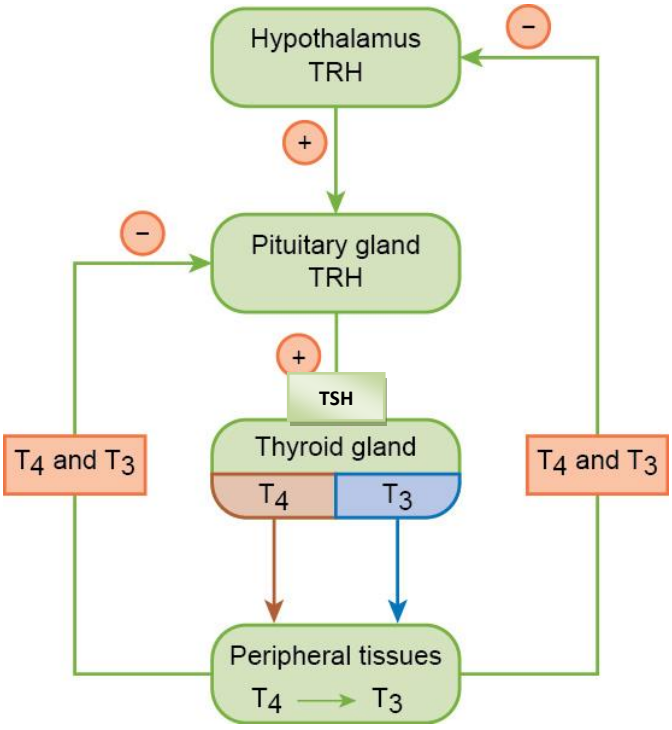


Figure 7: Control of thyroxine secretion: a negative feedback loop by the thyroid hormones

An example of a negative feedback loop is the release of glucocorticoid hormones from the adrenal glands, which is regulated by the hypothalamus and pituitary gland. As the levels of glucocorticoids in the blood increase, the hypothalamus and pituitary gland decrease their signaling to the adrenal glands to stop further secretion of glucocorticoids (see Figure 8).

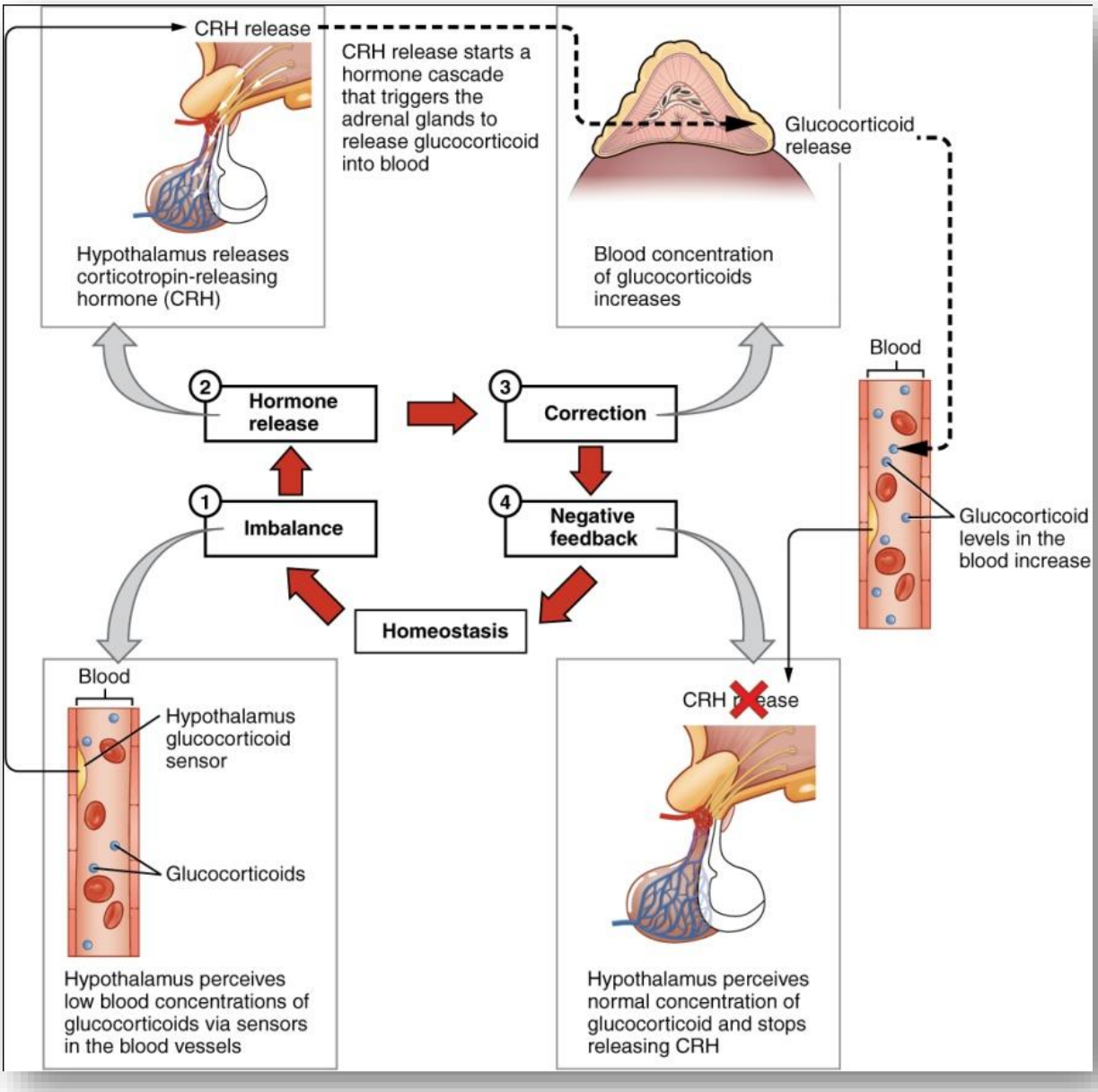


Figure 8: Negative Feedback Loop. *The release of adrenal glucocorticoids is stimulated by the release of hormones from the hypothalamus and pituitary gland. This signaling is inhibited when glucocorticoid levels become elevated by causing negative signals to the pituitary gland and hypothalamus.* (Betts, et al., 2013).

The hypothalamus detects low blood glucocorticoid levels and releases corticotropin-releasing hormone (CRH). This triggers a hormone cascade, causing the adrenal glands to release glucocorticoids, raising their concentration in the blood. Once normal levels are reached, the hypothalamus stops releasing CRH, restoring blood glucocorticoid levels to homeostasis.

2.7.2. **Positive Feedback**:

In contrast to negative feedback, positive feedback amplifies the secretion of a hormone. This is less common but occurs in specific situations, such as during childbirth.

For example, during labor, the release of oxytocin increases uterine contractions, which stimulate the further release of more oxytocin, intensifying the contractions until delivery. This cycle is triggered by the stretching of the cervix as the fetus moves downward, signaling the pituitary gland to release more oxytocin. After childbirth, oxytocin secretion decreases.

The regulation of prolactin, secreted by the pituitary gland that stimulates milk production in nursing mothers, follows a positive feedback loop triggered by the baby's suckling, which stimulates the release of more prolactin. This loop continues until the baby stops suckling.

2.7.3. Neural Control:

Neural control of hormone secretion involves the nervous system influencing the release of hormones through direct signals. In this process, the brain, particularly the hypothalamus, sends signals via neurons to endocrine glands, triggering hormone secretion. These signals can be either excitatory or inhibitory, depending on the body's needs. For example, during stress, the hypothalamus stimulates the adrenal glands to release cortisol, a stress hormone, via neural signals. In other cases, neural inputs can regulate hormone release based on environmental stimuli or internal body states, ensuring that hormone levels are adapted to changing conditions.

2.8. Stimuli for hormonal secretion

Hormonal secretion can be triggered by different stimuli, including humoral stimuli, hormonal stimuli, and neural stimuli.

2.8.1. Humoral stimuli refer to the control of hormonal release in response to changes in blood levels of nutrients or ions. For example, changes in blood osmolarity are detected by osmoreceptors in the hypothalamus, which then regulate the release of antidiuretic hormone (ADH) to maintain normal solute levels. The pancreas also responds to blood glucose levels by secreting insulin or glucagon to regulate glucose. Similarly, the parathyroid gland controls calcium levels by adjusting parathyroid hormone secretion based on calcium levels in the blood.

2.8.2. Hormonal stimuli refer to the release of hormones in response to hormones released by other endocrine glands. The hypothalamus produces releasing and inhibiting hormones that control pituitary hormone secretion, which in turn affects other endocrine glands. For instance, the hypothalamus and pituitary regulate the release of glucocorticoid hormones from the adrenal glands. When glucocorticoid levels rise in the blood, negative feedback signals the hypothalamus and pituitary to reduce their hormone secretion, leading to decreased glucocorticoid release.

2.8.3. A **neural stimulus** refers to the release of hormones in response to neural stimulation. example – nervous stimulation of the adrenal medulla triggers release of epinephrine.

II. Endocrine glands

1. The major glands of the endocrine system

The endocrine system is a network of cells, tissues, and organs that primarily or secondarily produce and secrete hormones. The endocrine glands are central to this system, with their main function being the direct secretion of hormones into the surrounding fluid. The major endocrine glands include the pituitary, thyroid, parathyroid, adrenal, and pineal glands (Figure 2). Other organs, such as the hypothalamus, thymus, heart, kidneys, stomach, small intestine, liver, skin, and the reproductive organs (ovaries in females and testes in males), also contain cells with endocrine roles. Some of these glands also have non-endocrine functions.

For example, the pancreas has both digestive and endocrine functions, with cells that secrete hormones like insulin and glucagon to regulate blood glucose levels, also has an exocrine function where most of its cells secrete pancreatic juice into the small intestine through ducts.

2. Exocrine and Endocrine Glands

All glandular tissues are responsible for producing secretions. Most glands are derived from epithelial tissue and are often structured with folds that organize them into glands with ducts. Glands that possess ducts are called exocrine glands. These ducts serve as channels for secretions to be transported to specific target locations. Exocrine glands include digestive glands in the gastrointestinal tract, sebaceous and sweat sweat glands in the skin, and mucus-producing glands in the mucous membranes of the mouth and reproductive systems.

In contrast, endocrine glands do not have ducts and secrete their hormones, directly into the bloodstream (Fig. 9). This characteristic of endocrine glands is supported by their highly vascularized structure, with many of their cells in direct contact with blood capillaries. This close connection allows hormones to be directly released into the blood and enables the continuous monitoring of physiological changes that trigger hormone secretion. For example, insulin-producing cells in the pancreas release insulin when they detect a rise in blood glucose levels after carbohydrate consumption.

The vascularized nature of endocrine glands also facilitates the transmission of signals from other glands in the form of hormones, which regulate the release of other hormones.

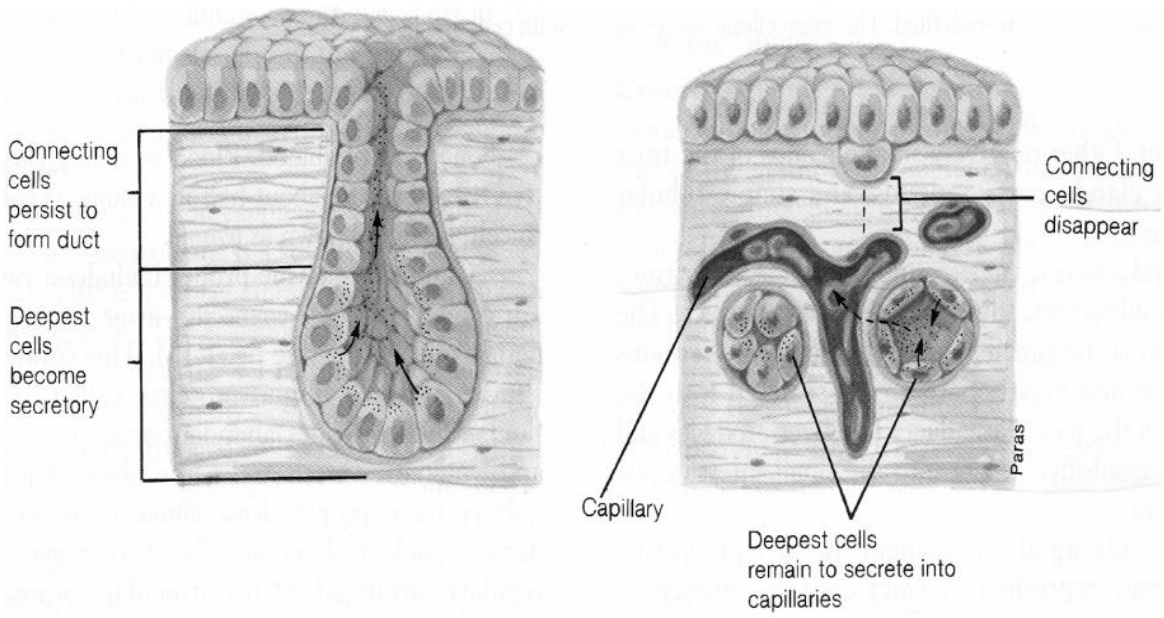


Figure 9: Exocrine and Endocrine Glands (site 7)

3. The Hypothalamus and Pituitary Gland

The hypothalamus-pituitary complex is the "command center" of the endocrine system, controlling hormone secretion and regulating other endocrine glands. It also coordinates messages between the endocrine and nervous systems. The hypothalamus, located in the brain's diencephalon, is functionally connected to the pituitary gland, which has an anterior and posterior lobe. The anterior pituitary secretes hormones in response to signals from the hypothalamus, which sends releasing or inhibiting hormones.

These hormones are transported through a capillary system, the hypophyseal portal system, to regulate the anterior pituitary's secretion of hormones, which then enter the bloodstream.

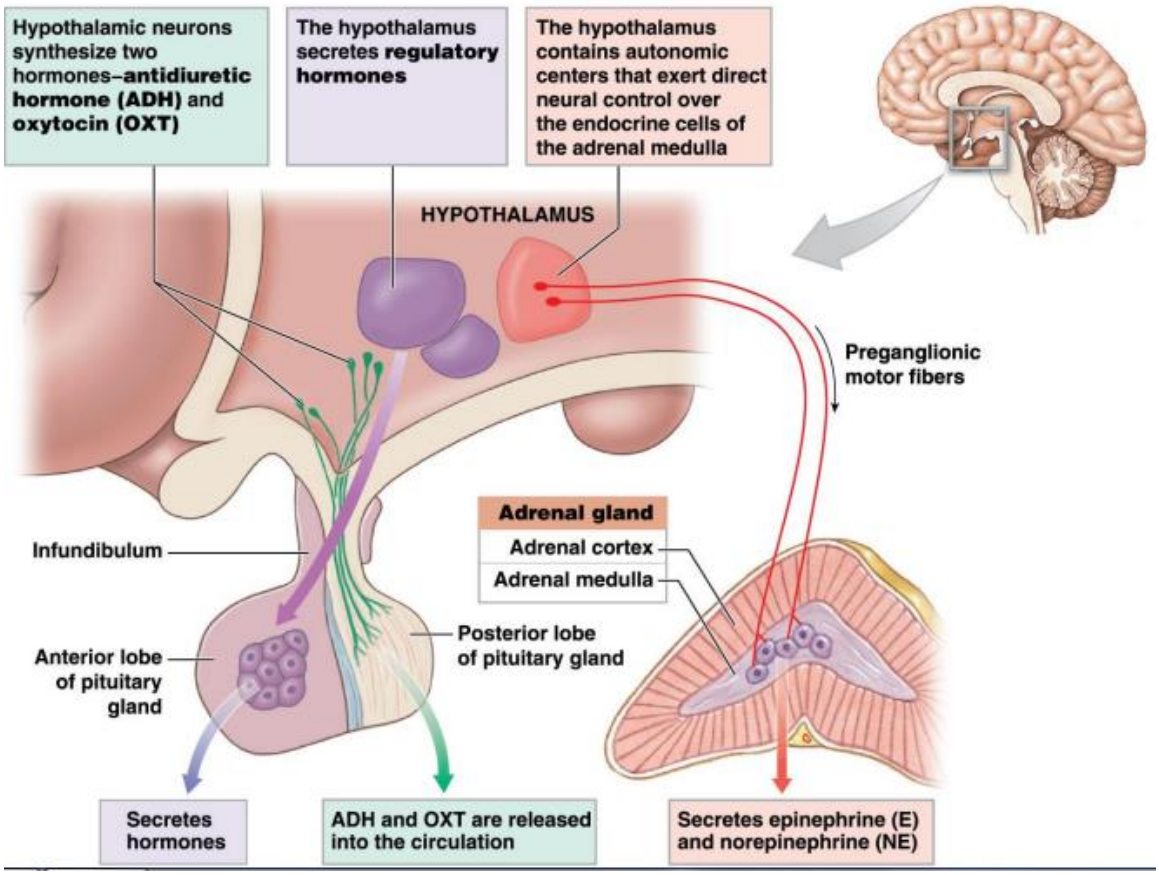


Figure 10: Hypothalamus–Pituitary Complex. *The hypothalamus is located beneath and in front of the thalamus, and it is connected to the pituitary gland by the infundibulum, a stalk-like structure. The pituitary gland is made up of two lobes, anterior and posterior, each of which releases different hormones in response to signals from the hypothalamus.*

The hypothalamus produces four releasing hormones that stimulate the secretion of five hormones from the anterior pituitary (Figure 11). These releasing hormones are named after the pituitary hormones they trigger:

- Adrenocorticotropic hormone-releasing hormone (ACTHRH) or Corticotropin-releasing hormone (CRH) which is part of the hormone system regulating carbohydrate, protein, and fat metabolism as well as sodium and water balance in the body.

-Thyroid-stimulating hormone-releasing hormone (TSHRH) or Thyrotropin-releasing hormone (TRH) which is part of the hormone system controlling the metabolic processes of all cells and which contributes to the hormonal regulation of lactation.

- Growth hormone-releasing hormone (GHRH), which is an essential component of the system promoting the organism's growth

- Gonadotropin-releasing hormone (GnRH), which triggers the release of FSH (follicle-stimulating hormone) and LH (luteinizing hormone).

The hypothalamus also produces inhibiting hormones, such as growth hormone inhibiting hormone (GHIH) and prolactin inhibiting hormone (PIH).

Additionally, the hypothalamus produces oxytocin and antidiuretic hormone (ADH), which are stored and secreted by the posterior pituitary gland, rather than being released directly from the hypothalamus.

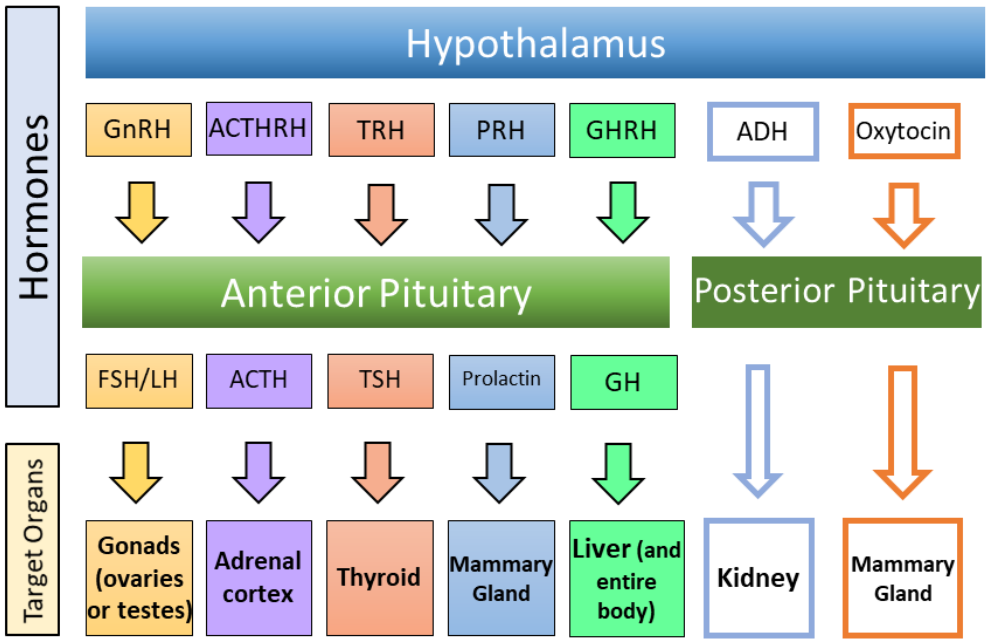


Figure 11: Hypothalamus-pituitary-peripheral endocrine system. *The hypothalamus releases hormones that either control the release of other hormones from the anterior pituitary, or produces hormones (ADH and oxytocin) that are released by the posterior pituitary.* (Site 8)

A. Posterior Pituitary

The posterior pituitary is an extension of neurons from the hypothalamus, specifically the paraventricular and supraoptic nuclei. These neurons send axons through the infundibulum to the posterior pituitary, where hormones are stored and released into the bloodstream. Two primary hormones are released: oxytocin (OT) and antidiuretic hormone (ADH). OT is produced by the paraventricular nucleus and ADH by the supraoptic nucleus. Both are transported along axons to the posterior pituitary and released when needed.

- **Oxytocin** plays a key role in childbirth by stimulating uterine contractions and cervical dilation, especially towards the end of pregnancy. It is released during labor via a positive feedback loop, intensifying contractions until birth. After delivery, oxytocin also aids in breastfeeding by triggering milk ejection and helps with parent-newborn bonding.

- **ADH** regulates blood osmolarity. When osmolarity is high, such as during dehydration, ADH is released to promote water reabsorption by the kidneys, reducing urine production. It also constricts blood vessels, raising blood pressure. ADH release follows a negative feedback loop, decreasing when osmolarity drops. Alcohol can inhibit ADH release, causing dehydration, and diabetes insipidus is a condition marked by low ADH, leading to chronic dehydration.

Table 2. Pituitary Hormones

Pituitary lobe	Associated hormones	Chemical class	Effect
Anterior	Growth hormone (GH)	Protein	Promotes growth of body tissues
Anterior	Prolactin (PRL)	Peptide	Promotes milk production from mammary glands
Anterior	Thyroid-stimulating hormone (TSH)	Glycoprotein	Stimulates thyroid hormone release from thyroid
Anterior	Adrenocorticotropic hormone (ACTH)	Peptide	Stimulates hormone release by adrenal cortex
Anterior	Follicle-stimulating hormone (FSH)	Glycoprotein	Stimulates gamete production in gonads
Anterior	Luteinizing hormone (LH)	Glycoprotein	Stimulates androgen production by gonads
Posterior	Antidiuretic hormone (ADH)	Peptide	Stimulates water reabsorption by kidneys
Posterior	Oxytocin	Peptide	Stimulates uterine contractions during childbirth
Intermediate	Melanocyte-stimulating	Peptide	Stimulates melanin formation in

zone	hormone	melanocytes

B. Anterior Pituitary

The anterior pituitary produces seven hormones: growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), beta endorphin, and prolactin. TSH, ACTH, FSH, and LH are called tropic hormones because they regulate the function of other endocrine glands.

- Growth Hormone (GH) GH, also known as somatotropin, promotes protein synthesis and tissue growth by stimulating protein synthesis in muscle and bone. It also has a glucose-sparing effect, promoting lipolysis (fat breakdown) and increasing blood glucose levels. GH triggers the liver and other tissues to produce insulin-like growth factors (IGFs), which support cellular growth and inhibit cell death. Disorders related to GH include gigantism in children and acromegaly in adults. A deficiency in GH can cause pituitary dwarfism.

Breaking down of fats, and releasing of fatty acids from cells – influences the liver to produce and secrete somatomedins (protein chemical signals, which bind to cells of other tissue (like bone and cartilage) stimulating growth), neurons synapse with capillaries by releasing vesicles filled with releasing factors that disperse into the capillaries by exocytosis and are carried to the anterior pituitary gland – stimulates uptake f amino acids into cells giving them more raw materials to manufacture tissues with (3 main tissues effected; muscle, bone, and adipose)

- Thyroid-Stimulating Hormone (TSH)

TSH regulates the thyroid glands activity by triggering the secretion of thyroid hormones. Its release is controlled by thyrotropin-releasing hormone (TRH) from the hypothalamus. Elevated thyroid hormones in the blood reduce TRH and TSH production through a negative feedback loop.

- Adrenocorticotropic Hormone (ACTH)

ACTH stimulates the adrenal cortex to release corticosteroids like cortisol. It is derived from pro-opiomelanotropin (POMC), a precursor molecule. ACTH release is controlled by

corticotropin-releasing hormone (CRH) from the hypothalamus, influenced by physiological rhythms and stress.

- Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH)

FSH and LH, known as gonadotropins, regulate the reproductive system. FSH stimulates the maturation of sex cells (ova in females, sperm in males) and follicular growth in females. LH triggers ovulation and hormone production (estrogens, progesterone) in females and testosterone production in males. Their release is stimulated by gonadotropin-releasing hormone (GnRH) from the hypothalamus, which is regulated by negative feedback from reproductive hormones.

- Prolactin

Prolactin stimulates milk production in women. It also helps in the development of mammary glands during pregnancy. In non-pregnant women, its secretion is inhibited by prolactin-inhibiting hormone (PIH) (dopamine) from the hypothalamus. During pregnancy, prolactin-releasing hormone (PRH) from the hypothalamus increases prolactin levels to promote lactation after birth.

C. The intermediate pituitary

Secretes melanocyte-stimulating hormone (MSH), which is derived from the cleavage of the pro-opiomelanocortin (POMC) precursor protein. MSH produced locally in the skin stimulates melanin production in response to UV light. However, MSH from the pituitary has a more complex role. People with lighter and darker skin typically have similar MSH levels, but MSH can still darken the skin by inducing melanin production in melanocytes. During pregnancy, women experience increased MSH production, which, in combination with estrogens, can darken areas like the areolas and labia minora.

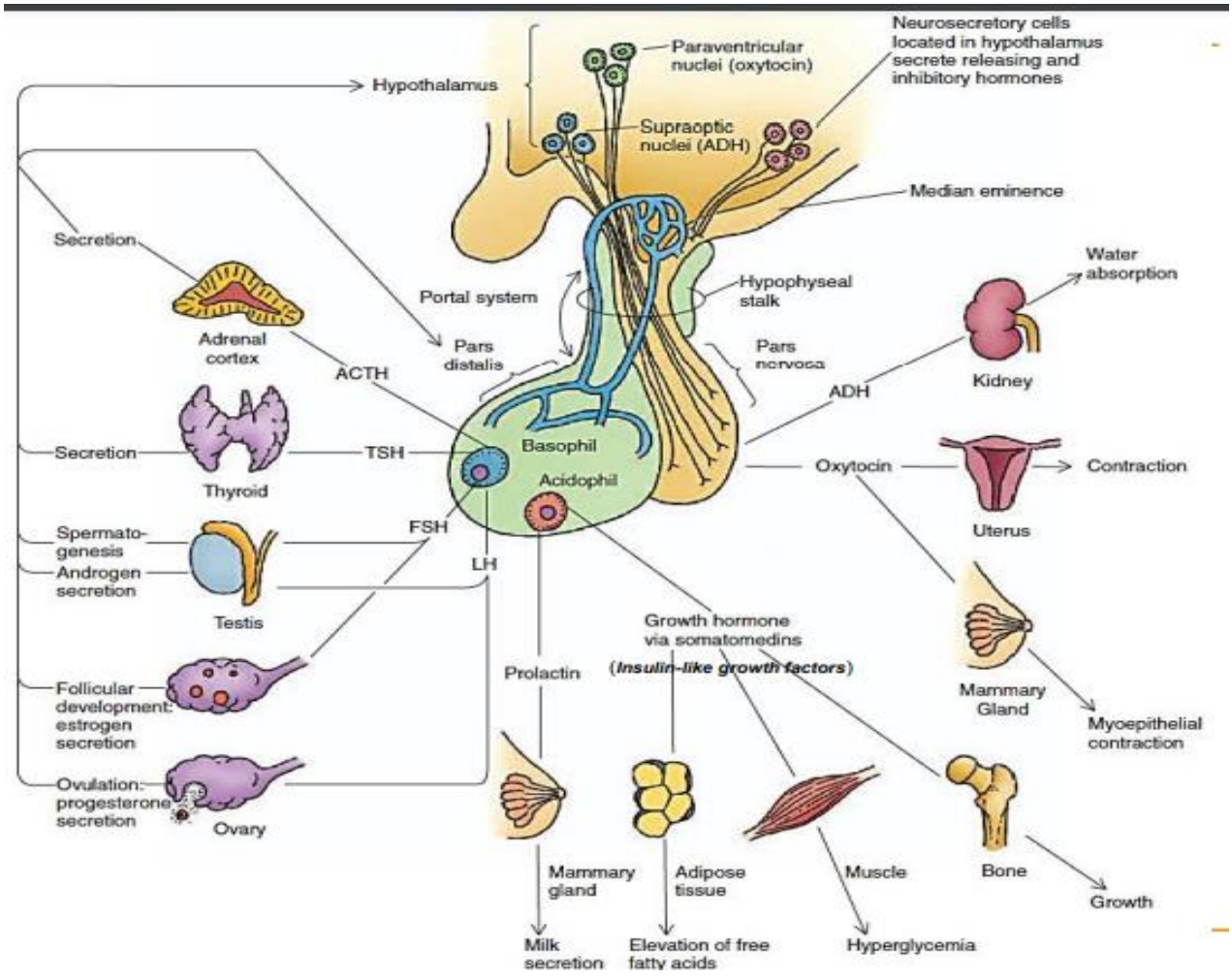


Figure 12: Hormones of the pituitary gland and their targets (site 9)

4. Pineal Gland

The pineal gland, a small endocrine gland, produces and secretes melatonin, a hormone derived from serotonin. Its secretion is influenced by light levels: when light stimulates the retina, it reduces melatonin production, promoting wakefulness, while in darkness, melatonin levels rise, leading to drowsiness. Melatonin plays a key role in regulating circadian rhythms, which affect sleep, appetite, and body temperature. Children have higher melatonin levels than adults, which may delay puberty by inhibiting gonadotropin release.

5. Thyroid Gland

The thyroid gland, located in front of the trachea below the larynx, is shaped like a butterfly with a central isthmus and two lateral lobes. Each lobe contains parathyroid glands on its posterior surface. The thyroid's tissue consists mainly of follicles, which produce thyroid hormones T3 and T4 in response to iodine. Their release is regulated by thyroid-stimulating hormone (TSH), which is controlled by a feedback system involving the hypothalamus and pituitary gland. These hormones regulate the body's basal metabolic rate (energy use at rest). The thyroid also secretes calcitonin, which helps lower blood calcium levels when they rise.

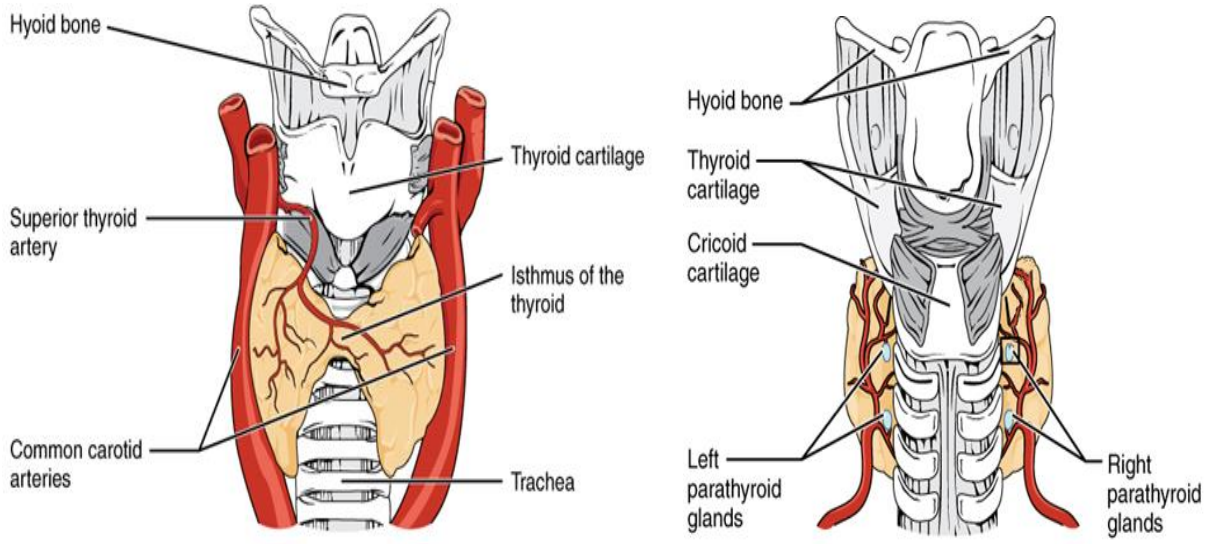


Figure 13. Anterior view of thyroid gland and parathyroid Glands. *The small parathyroid glands are embedded in the posterior surface of the thyroid gland.*

6. Parathyroid Gland

The parathyroid glands are small, round structures typically located on the posterior surface of the thyroid gland, separated by a connective tissue capsule. Most people have four, though some may have more. The function of oxyphil cells in the parathyroid is unclear, while the chief cells are responsible for producing and secreting parathyroid hormone (PTH). PTH plays a crucial role in regulating blood calcium levels.

7. Adrenal Gland

The adrenal glands are wedge-shaped structures located on top of the kidneys, surrounded by a fibrous capsule. These glands have a high blood flow, one of the highest in the body, and are supplied by several arteries branching from the aorta, including the suprarenal and renal arteries. Blood flows through the adrenal cortex before draining into the adrenal medulla, from where adrenal hormones are released into the bloodstream through the left and right suprarenal veins.

The adrenal glands, part of the body's stress response system, consist of the adrenal cortex and adrenal medulla. The adrenal cortex, regulated by the hypothalamic-pituitary-adrenal (HPA) axis, secretes steroid hormones that manage long-term stress, blood pressure, nutrient storage, and inflammation. These hormones include cortisol, which helps the body respond to prolonged stress by breaking down nutrients for energy, and aldosterone, which regulates fluid and electrolyte balance, primarily through the renin-angiotensin-aldosterone system (RAAS).

The adrenal medulla, composed of sympathetic nervous system neurons, secretes epinephrine and norepinephrine in response to acute stress via the sympathomedullary (SAM) pathway. These hormones prepare the body for immediate action by increasing heart rate, blood pressure, and blood glucose while redirecting blood flow to essential organs.

The adrenal cortex is structured into three zones:

- **Zona Glomerulosa**: is responsible of the production of mineralocorticoids, aminly aldosterone, which regulates blood pressure and electrolyte balance of sodium and potassium levels.

- **Zona Fasciculata**: Produces glucocorticoids like cortisol, which manage metabolism and the immune response. This zone secretes cortisol both at basal level and as a reponse to the release of adrenocorticotropic hormone (ACTH) from the pituitary gland.

- **Zona Reticularis:** Produces gonadocorticoids and is responsible for administering these hormones to the reproductive regions of the body. Most of the hormones released by this layer are androgens.

Both the adrenal cortex and medulla are crucial in the body's stress response, with the cortex managing long-term adaptation and the medulla handling immediate reactions.

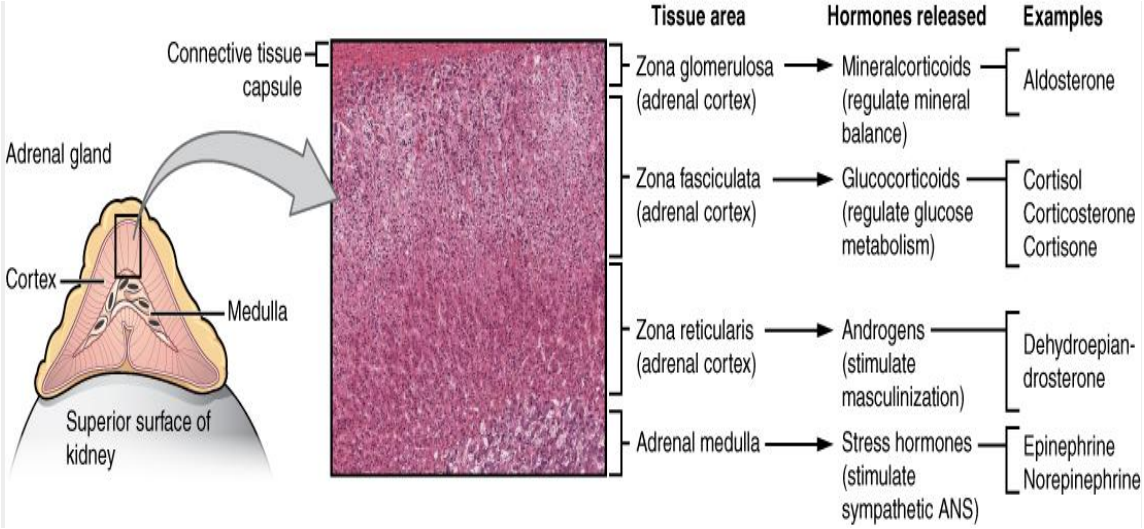


Figure 14. Adrenal Glands**.** *Both adrenal glands sit atop the kidneys and are composed of an outer cortex and an inner medulla, all surrounded by a connective tissue capsule. The cortex can be subdivided into additional zones, all of which produce different types of hormones. LM × 204. (Micrograph provided by the Regents of University of Michigan Medical School © 2012). (Knowledge of the zones' names and responsibility for particular hormone production is not required as examinable material.)* (Site 10)

8. Pancreas

The pancreas is a long, slender organ located behind the lower half of the stomach. While it mainly functions as an exocrine gland that secretes digestive enzymes, it also has an endocrine role through its pancreatic islets, which secrete important hormones: glucagon, insulin, somatostatin, and pancreatic polypeptide (PP).

The pancreatic islets contain four types of cells:

1. Alpha cells (20%) produce glucagon, which increases blood glucose levels when they are low.
2. Beta cells (75%) produce insulin, which lowers blood glucose levels when they are high.
3. Delta cells (4%) secrete somatostatin, which inhibits both glucagon and insulin release.
4. PP cells (1%) secrete pancreatic polypeptide, which is involved in regulating appetite and pancreatic secretions.

Insulin and glucagon help regulate blood glucose levels, ensuring cells have the glucose they need for energy. Excess glucose is stored as glycogen in the liver and muscles or converted to fat in adipose tissue, with hormonal regulation controlling storage and usage based on the body's needs.

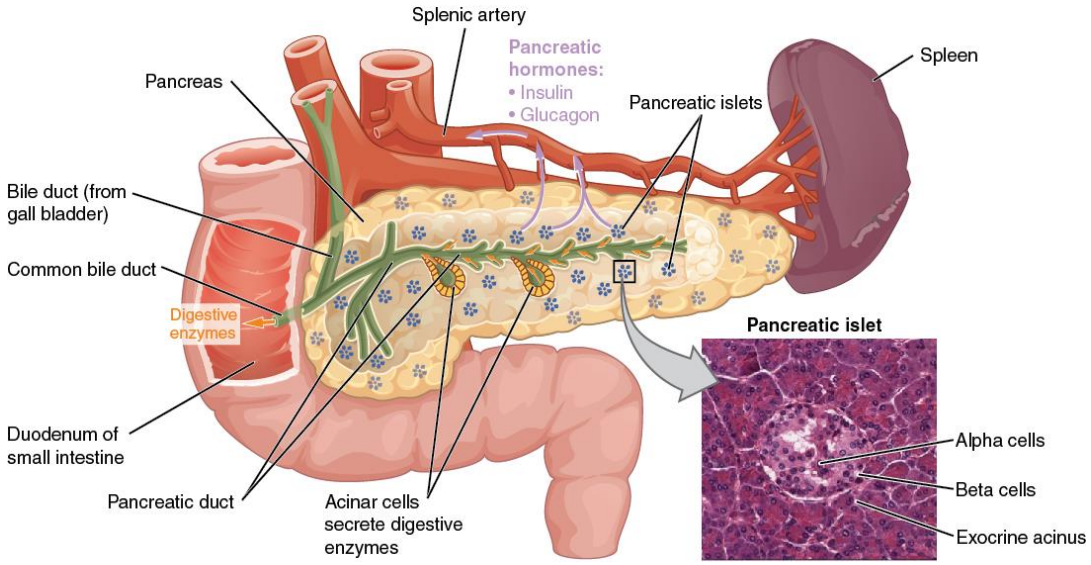


Figure 15: Pancreas. *The pancreatic exocrine function involves the acinar cells secreting digestive enzymes that are transported into the small intestine by the pancreatic duct. Its endocrine function involves the secretion of insulin (produced by beta cells) and glucagon (produced by alpha cells) within the pancreatic islets. These two hormones regulate the rate of glucose metabolism in the body.* (Site 11)

9. The gonadal glands

Testes in males and ovaries in females—produce sex cells (sperm and ova) and secrete gonadal hormones. These hormones are influenced by gonadotropins (FSH and LH) from the anterior pituitary.

In males, the testes primarily produce testosterone, a steroid hormone essential for the development of the male reproductive system, sperm maturation, and male secondary sex characteristics like a deep voice and increased muscle mass. The testes also produce inhibin, which inhibits FSH secretion, thus regulating spermatogenesis.

In females, the ovaries produce estrogens (estradiol, estriol, estrone), which regulate the female reproductive system, menstrual cycle, and secondary sex characteristics such as breast development and increased fat. They also produce progesterone, important for menstrual cycle regulation and pregnancy maintenance. Granulosa cells in the ovaries also produce inhibin, which inhibits FSH secretion.

During pregnancy, the placenta, an organ that forms in the uterus, plays a crucial role by supplying nutrients to the fetus and secreting hormones such as estrogen, progesterone, human chorionic gonadotropin (hCG), human placental lactogen (hPL), and relaxin. hCG promotes progesterone synthesis and protects the fetus from immune rejection, while hPL prepares the breasts for lactation and relaxin helps soften the pubic symphysis for childbirth.
The hypothalamus and pituitary gland are neuroendocrine glands and function to link the nervous and endocrine systems.

10. Thymus Gland

Located in the upper part of the thoracic cavity in the mediastinum just superior to the heart – is a key player in the development of the immune system – is a large gland in children and shrinks with aging 1. Thymosin – hormone secreted by the thymus – responsible for the maturation of T lymphocytes (T-cells) (produced in the red bone-marrow – migrate to the thymus for maturation – function in immunity)

III. Functional relationships between the nervous system, endocrine system and immune system

The nervous, endocrine, and immune systems are interconnected in a complex network that ensures the body maintains homeostasis and responds effectively to both internal and external stimuli. These systems work together to regulate physiological processes, adapt to environmental changes, and protect the body from pathogens and stressors.

The nervous system communicates with the immune system and the endocrine glands through direct axonal connections, particularly via the hypothalamo-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS).

Hormonal signals from the endocrine system, such as cortisol and adrenaline, influence both the nervous and immune systems, modulating stress responses, metabolism, and immune activity. Conversely, immune cells release cytokines and neurotransmitters that can affect the nervous and endocrine systems, influencing inflammation, behavior, and overall health. This crosstalk between the systems ensures a coordinated response to stressors and pathogens, with bidirectional communication enabling adaptive responses that support the body’s defense mechanisms and overall well-being.

1. Nervous System and Endocrine System

- **Hypothalamus as a Control Center**: The hypothalamus plays a central role by receiving input from the nervous system and regulating hormone release from the pituitary gland. This gland, in turn, controls various endocrine functions.

- **Stress Response**: In response to stress, the nervous system triggers the "fight-or-flight" reaction, stimulating the release of hormones such as adrenaline and cortisol. These hormones prepare the body for immediate action, altering metabolic processes and influencing various organ functions.

2. Endocrine System and Immune System

- Hormonal Regulation: Hormones, particularly cortisol and thyroid hormones, are essential for modulating immune responses. These hormones can either enhance or suppress immune activity, depending on the physiological situation.

- Cytokine Release: endocrine system also influences the release of cytokines—small proteins that mediate immune responses, inflammation, and blood cell production. These signaling molecules help coordinate the body's defense mechanisms.

3. Nervous System and Immune System

- Neuroimmune Interaction: Nerve fibers release neurotransmitters and neuropeptides that can directly impact immune cells function. These molecules influence immune responses, particularly in terms of inflammation and the regulation of immune activity.

- Impact of Stress on Immunity: Chronic stress negatively affects the immune system by promoting the release of stress hormones like cortisol. This weakened immune response makes the body more susceptible to infections and diseases.

4. Integrative Function: Bidirectional Communication

- Communication Across Systems: The nervous, endocrine, and immune systems interact in a bidirectional manner. For example, immune cells can release signaling molecules that influence the nervous and endocrine systems, affecting behaviors such as fatigue during illness or modifying stress responses.

- **Coordinated Defense "Holistic Response":** When the body encounters pathogens, all three systems collaborate to mount an effective defense. This integrated response involves regulating inflammation, managing stress, and supporting overall health.

The nervous, endocrine, and immune systems are not isolated but interconnected in a dynamic system that coordinates the body's responses to stressors, pathogens, and environmental changes. The bidirectional communication between these systems is crucial for maintaining homeostasis and supporting overall health. By understanding their interactions, we can better appreciate how the body adapts to its surroundings and defends itself against internal and external challenges.

Hormonal regulation of carbohydrate metabolism

1. Introduction

Carbohydrate metabolism is a crucial biochemical process that allows the body to extract energy from carbohydrates, a primary energy source for cells. The metabolic pathways involved in the breakdown, storage, and synthesis of carbohydrates are essential for maintaining energy balance and supporting normal cellular functions. Carbohydrates, mainly in the form of glucose, are a key energy source for various tissues, including the brain, muscles, and red blood cells, all of which rely heavily on glucose for energy, particularly during periods of high activity.

The regulation of carbohydrate metabolism is tightly controlled by a variety of enzymes, metabolic intermediates, and most notably, hormones. These hormonal regulators coordinate the balance between glucose production, storage, and consumption to ensure that the body maintains an optimal blood glucose concentration, thus providing energy while preventing hyperglycemia or hypoglycemia. The primary hormones involved in carbohydrate metabolism are insulin and glucagon, which function to regulate blood glucose levels in a feedback loop. Insulin promotes the uptake and storage of glucose in tissues like muscles and adipose tissue, while glucagon stimulates the release of glucose from the liver when blood sugar levels are low.

Beyond insulin and glucagon, other hormones also play a significant role in modulating carbohydrate metabolism. Catecholamines (such as adrenaline), thyroid hormones, glucocorticoids, and digestive hormones such as secretin and cholecystokinin can either promote or inhibit glucose metabolism in response to physiological conditions like stress, exercise, and food intake.

This chapter will delve into the processes of carbohydrate metabolism, including the pathways of glycolysis, gluconeogenesis, glycogen synthesis, and glycogenolysis, and explore how these processes are regulated hormonally. Additionally, we will examine disorders related to the deregulation of carbohydrate metabolism, such as diabetes, lactose intolerance, and rare metabolic conditions like Fabry disease, which illustrate how abnormalities in these pathways can lead to significant health complications.

I. Reminders on carbohydrate metabolism

1. Digestion and absorption of carbohydrates

1.1. Digestion and hydrolysis of carbohydrates

Carbohydrate digestion begins in the mouth, where salivary amylase breaks down polysaccharides to smaller polysaccharides (dextrins), disaccharide (maltose), and some glucose.

The majority of carbohydrate digestion takes place in the small intestine where pancreatic amylase hydrolyzes dextrins to maltose and glucose. Finally, on the surface of intestinal mucosal cells, enzymes that are bound to the membrane further break down disaccharides into their monosaccharide components; maltase hydrolyzes maltose into two glucose molecules, sucrase breaks down sucrose into glucose and fructose, and lactase splits lactose into glucose and galactose. These monosaccharides are then absorbed into the bloodstream for use as energy by the body.

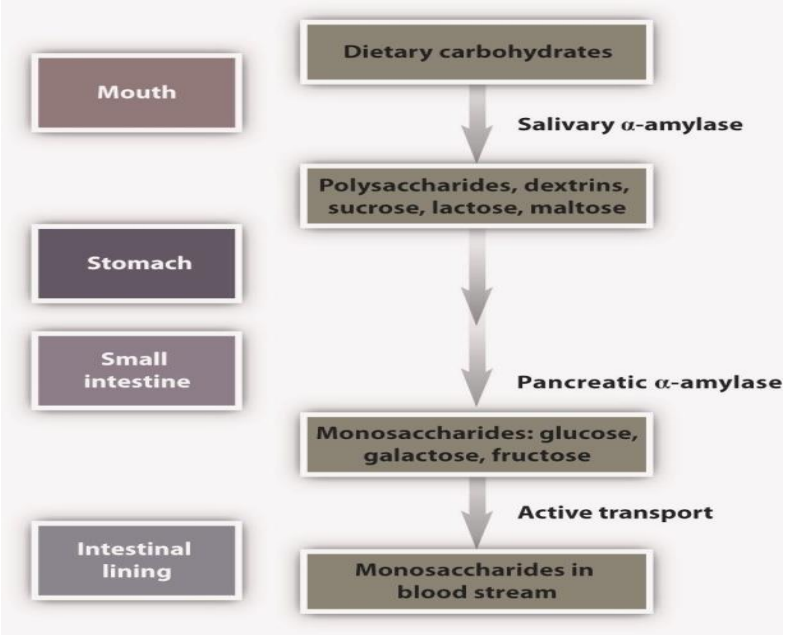


Figure 16: Carbohydrate digestion

1.2. The absorption of carbohydrates

Once carbohydrates are digested, the products must be absorbed and transported to the portal circulation. The absorption of carbohydrates occurs primarily in the small intestine, and the process involves several key steps:

A. Transport into epithelial cells (villi):

- Glucose and galactose are absorbed into the epithelial cells of the small intestine via active transport through a sodium-dependent glucose transporter (SGLT1).

This process is coupled with the movement of sodium ions, which are transported down their concentration gradient.

- Fructose, unlike glucose and galactose, is absorbed through facilitated diffusion via the GLUT5 transporter and cannot be absorbed against a concentration gradient.

B. Transport from epithelial cells into the bloodstream:

- Once inside the epithelial cells, glucose, galactose, and fructose are transported into the bloodstream via facilitated diffusion through the GLUT2 transporter on the basolateral membrane of the epithelial cells. This transporter moves glucose and fructose from the inside of the cell into the blood, where they are carried to various tissues.

C. Entry of glucose into cells The regulation of glucose entry into cells depends on both insulin-dependent and insulin-independent transport systems.resistance, especially in muscle and fat cells.

- Insulin-independent transport: Glucose enters cells in certain tissues (like liver, red blood cells, and the brain) through GLUT1 receptors, which do not require insulin.
- Insulin-dependent transport: In muscle and adipose tissue, glucose entry relies on GLUT4 receptors, which are activated by insulin. In type 2 diabetes, GLUT4 receptors are reduced, leading to insulin resistance and decreased glucose uptake in muscle and fat cells.
- GLUT2 also transports glucose in liver cells independently of insulin.

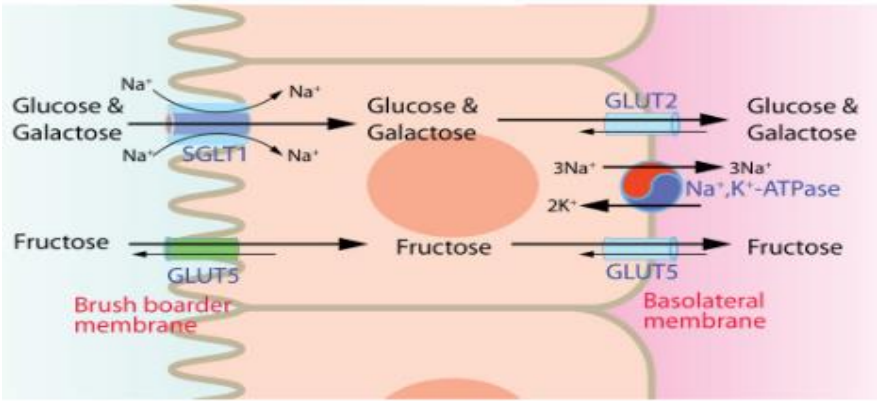


Figure 17: mechanism of carbohydrate-absorption (site 12)

D. Fate of glucose after absorption

In the liver, glucose undergoes variety of chemical changes depending upon the physiological need of the body.

1. Body need for energy: glucose oxidized completely to CO2, H2O and energy by (glycolysis and citric acid cycle).
2. Excess glucose may be converted to glycogen, deposit in liver, muscle tissues By (glycogenesis).
3. To maintain glucose blood level, liver glycogen reconverted to glucose enters blood By (glycogenolysis).
4. excess glucose after conversion to glycogen , convert to fatty acids stored in adipose tissue as triglycerides (lipogenesis).
5. small amounts of glucose may be utilized for the synthesis of ribose and deoxyribosee for synthesis of nucleic acids.
6. in muscle contraction, only partial degradation of glucose may take place, resulting in formation of lactic acid disposed off by the liver.

The metabolism of CHO may be subdivided in the following categories.

2. Glycolysis

2.1. Definition:

Glycolysis (from glycose, an term for glucose + -lysis degradation) is a set of reactions that converts glucose to pyruvate or lactate. This is the first metabolic pathway to be elucidated and hence is considered as a paradigm of metabolic pathways. Glycolysis is also called Embden-Meyerhoff pathway. The complete set of reactions occurs in the cytoplasm of virtually every animal cell. The entire process occurs without molecular oxygen.

2.2. Steps of glycolytic pathway: It is divided into two stages:

A- Five reactions and consume energy: in reactions 1-5 of glycolysis, Energy is required to add phosphate groups to glucose. Glucose is converted through five enzymatically catalyzed reactions to two three-carbon molecules.

B- Five reactions that produce energy: in reactions 6-10 of glycolysis, energy is generated as: Sugar phosphates are cleaved to triose phosphates. Four ATP molecules are produced.

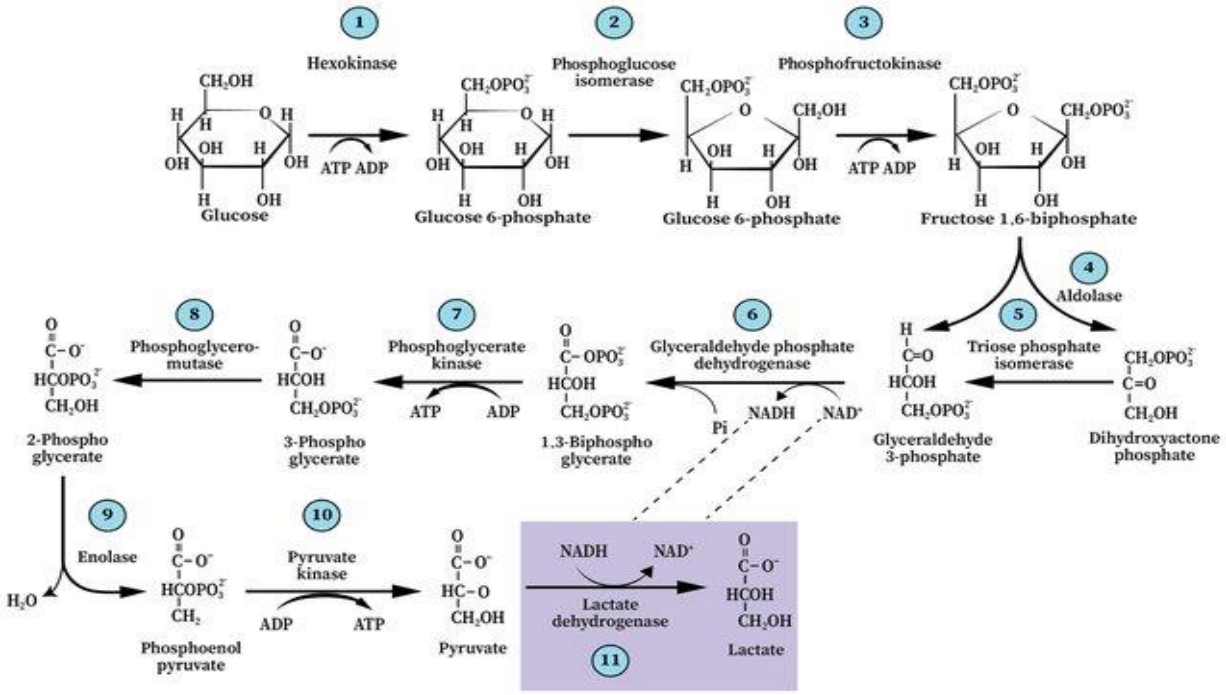
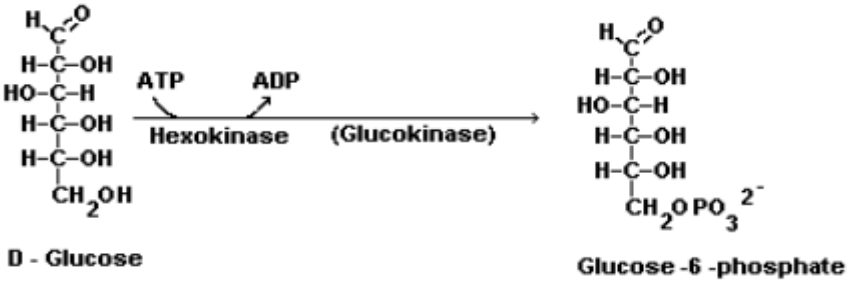


Figure 18: The glycolytic pathway and the 10 enzymatic steps that break down one molecule of glucose into two trios molecules, ending with pyruvate (aerobically) or, with an 11th step, lactate (anaerobically). (Schurr, 2018).

Stage 1: Energy Investment Phase (First 5 Steps)

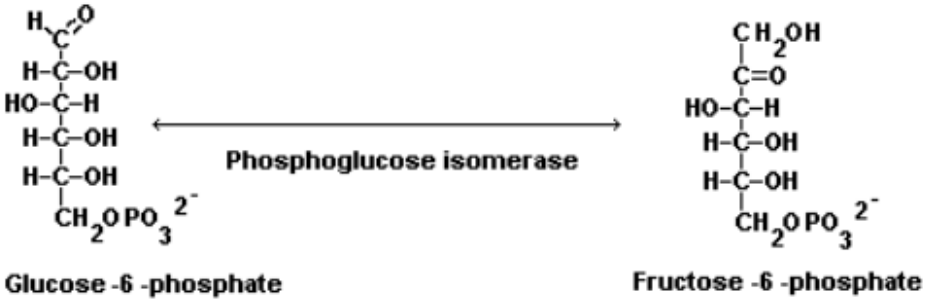
- Reaction 1. Synthesis of glucose -6- phosphate

Glucose is phosphorylated to glucose -6-phosphate. The enzyme is hexokinase, which splits ATP into ADP and the Pi is added on to the glucose. The energy released by hydrolysis of ATP is utilised for the forward reaction. Hexokinase is the key glycolytic enzyme and the reaction is irreversible. This reaction is a kinase reaction , added a phosphate to glucose immediately when glucose enter in the cell, due this phosphorylation glucose transport out of cell prevents and reactivity of oxygen of is also increase.



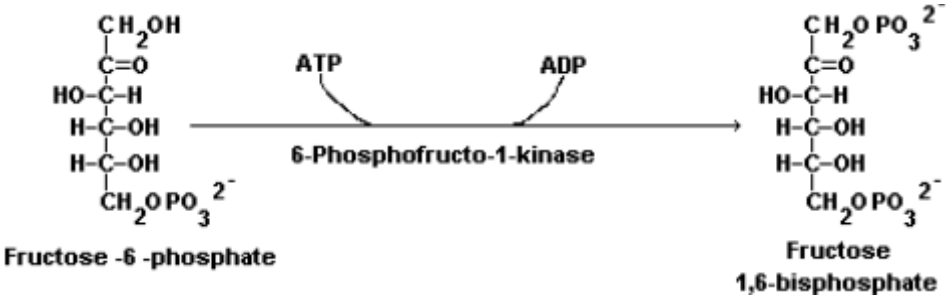
-Reaction 2. Conversion of glucose -6-phosphate to fructose -6-phosphate

The reaction is catalysed by phosphoglucoisomarase. This enzymatic step prepares the first carom (C-1) for phosphorylation. It is freely reversible reaction controlled by substrate-product levels. Small change in standard free energy, the reaction proceeds readily in either direction, and require Mg^{2+}.

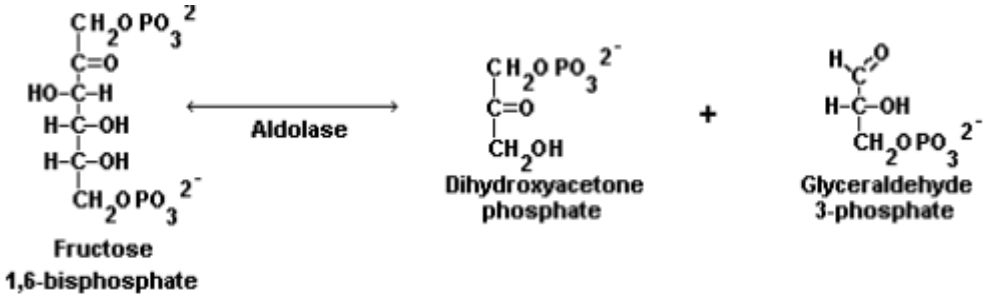


- Reaction 3. Fructose -6-phosphate to 1,6 diphosphate

The reaction is catalyzed by phosphofructokinase, the reaction is irreversible. In this reaction, phopshofructokinase -1 catalyzes the transfer of phosphoryl group from ATP to fructose 6-phosphate to yield fructose 1,6- bis phosphates PFK. It is the major regulatory enzyme of the glycolytic pathway.

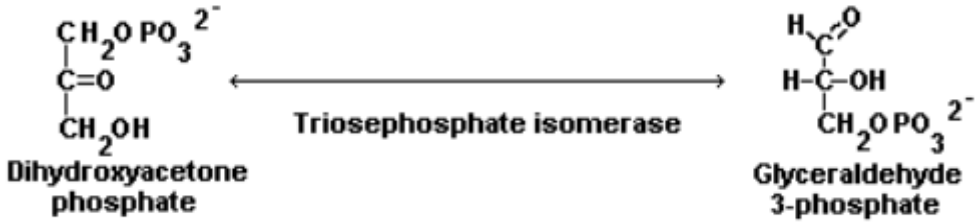


-Reaction 4. Fructose1, 6-bisphosphate to Dihydroxyacetone phosphate and glyceraldehydes -3- phosphate The enzyme fructose 1,6-bisphosphate aldolase, catalyzes a reversible aldol condensation. Fructose -1, 6-bisphosphate is cleaved to yield two different triose phosphates, glyceraldehydes -3- phosphate, an aldose, and Dihydroxyacetone phosphate, a ketose. It is an energetically unfavorable reaction in the direction written, with standard free energy change ΔG 0 of+5.73 kcal, but the rapid conversion of G3P to pyruvates drives the reaction. This reaction completes the first stages of Glycolysis.



-Reaction 5. The inter conversion of triose phosphate

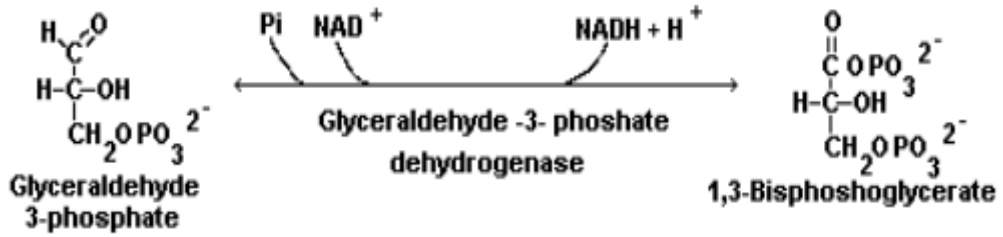
Only one of the two triose phosphates formed by aldolase, glyceraldehydes 3- Phosphate , can be directly degraded in the subsequent step of Glycolysis . The other product DHAP, is rapidly converted to, glyceraldehydes 3- Phosphate by fifth enzyme triose phosphate isomarase.



Stage 2:

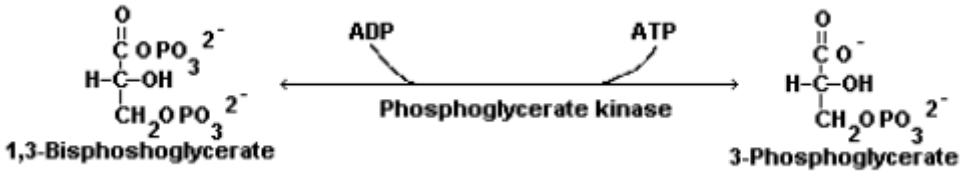
-Reaction 6. Oxidation of glyceradehyde -3 – phosphate

The reaction catalyzed by Glyceradehyde -3-posphate dehyrogenase , requires nicotinamide adenine dinucleotide (NAD+)as an electron carrier. In its oxidized form NAD+ binds tightly to the enzyme. Aldehyde group is dehydrogenated to an acyl phosphate. In this reaction, the phosphorylation occurs at expense of inorganic phosphate. This reaction generates a high energy phosphate bond in 1,3,DPG, which is a mixed anhydride of phosphoric acid and a carboxylic acid. Because of this, 1,3 –DPG has ahigh group transfer potential.



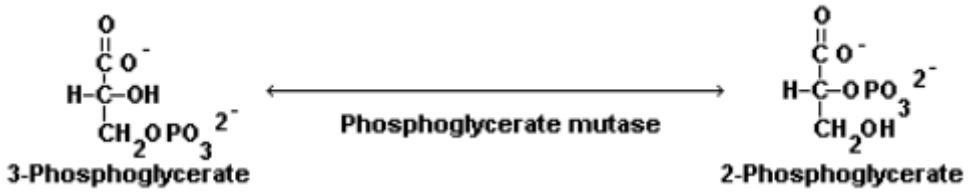
-Reaction 7. Phosphoryl group transfer

Phosphoglycerate kinase transfers a phosphate group from 1,3-bisphosphoglycerate to ADP to form ATP and 3-phosphoglycerate. This is the first step in the Glycolysis that generates ATP. The molecular structure of phosphoglycerate kinase is similar to hexokinase in that it has two lobes (jaws) that each bind one of the substrates (ADP-Mg2+ or 1,3- bisphosphoglycerate) leading to a large conformational change in the enzyme that brings the substrates close together and excludes H2O from the active site.



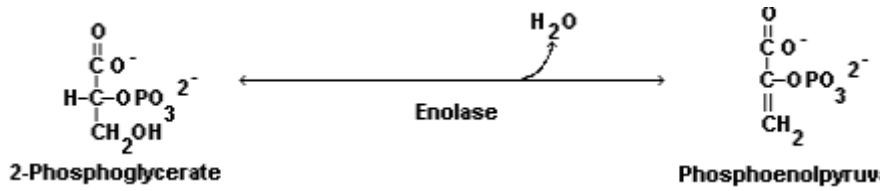
-Reaction 8. Phosphoglycerate Mutase 3-phosphoglycerate is isomerised to 2-phosphoglycerate by shifting the phosphate group from 3rd to 2nd carbon atom. The enzyme is phosphoglucomutase.

The reaction mechanism proceeds by first adding an additional phosphate group to the 2′ position of the 3 phosphoglycerate. The enzyme then removes the phosphate from the 3′ position leaving just the 2′ phosphate, and thus yielding 2 phsophoglycerate. In this way, the enzyme is also restored to its original, phosphorylated state.



-Reaction 9. Dehydration of 2-phosphoglycerate

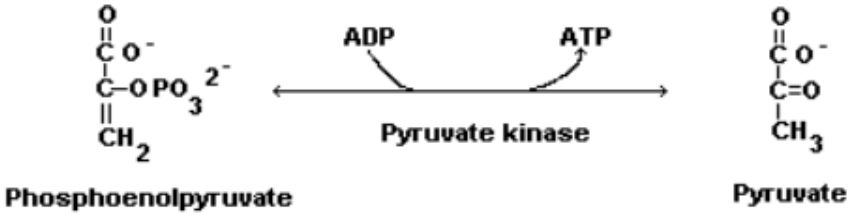
In this step of glycolysis 2-phosphoglycerate is convert in to phosphoenol pyruvate by dehydration reaction, which is catalyzed by enzyme enolase.



It is interesting that the change in standard free energy for this reaction is relatively small ($\Delta G^{o'}$ = +1.7) kJ/mol), meaning that the overall metabolic energy available fromm2-phosphoglycerate and phosphoenol pyruvate is similar. However, when enolase converts 2-phosphoglycerate to phosphoenol pyruvate, it traps the phosphate group in an unstable enol form, resulting in a dramatic increase in the phosphoryl transfer potential of the triose sugar.

-Reaction 10. Synthesis of pyruvate

The final step of glycolysis converts phosphoenolpyruvate into pyruvate with the help of the enzyme pyruvate kinase. As the enzyme's name suggests, this reaction involves the transfer of a phosphate group. This step is also an important site of regulation. In this reaction, the high phosphoryl transfer potential of PEP is used by the enzyme pyruvate kinase to generate pyruvate, the end product of glycolysis, and 2 ATP are formed for every glucose molecule entering the pathway.



This reaction completes that part of glycolysis that is common to both anaerobic and aerobic metabolism.

The overall process of glycolysis is:

Glucose + 2 NAD^+ + 2 ADP + 2 Pi → 2 Pyruvate + 2 NADH + 2 H+ + 2 ATP + 2 H_2O

In glycolysis,

- Two ATP add phosphate to glucose and fructose-6-phosphate.
- Four ATP are formed in energy-generation by direct transfers of phosphate groups to four ADP.
- There is a net gain of 2 ATP and 2 NADH.

2.3. The fate of pyruvate produced from glycolysis

The presence or absence of oxygen determines the fates of the pyruvate produced in glycolysis. When plenty of oxygen is available (aerobic conditions), pyruvate is first converted to acetyl-CoA, the entry-level substrate for the citric acid cycle, an amphibolic

pathway that completely oxidizes the two acetyl carbons to form CO_2 and the reduced molecules NADH and $FADH_2$.

However, in the absence of oxygen (anaerobic conditions), the fate of pyruvate is different in different organisms. In vertebrates, pyruvate is converted to lactate, while other organisms, such as yeast, convert pyruvate to ethanol and carbon dioxide.

Formation of lactate from pyruvate is the major steps in RBCs, lens and cornea, kidney, medulla, and leukocytes. These possible fates of pyruvate are summarized in Figure 19.

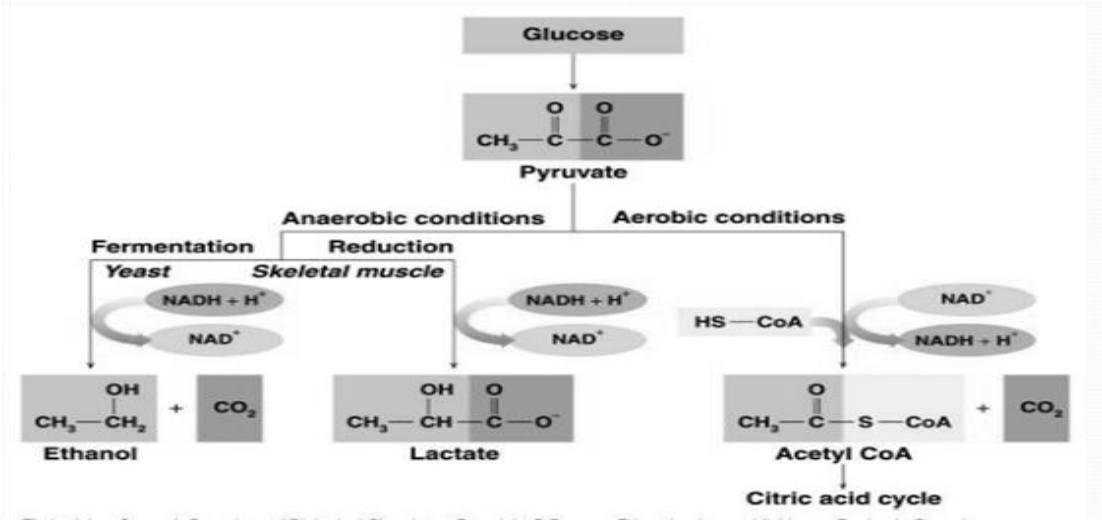


Figure 19: Metabolic Fates of Pyruvate

2.4. Krebs cycle /Tricarboxylic Acid cycle (TCA).

Krebs cycle or Citric acid cycle is the final pathway of oxidation of glucose, fats and amino acids. The citric acid cycle begins by acetyl-CoA (2 carbons) combining with oxaloacetate to form citrate. A series of transformations occur before a carbon is given off as carbon dioxide and NADH is produced. This leaves alpha-ketoglutarate (5 carbons). Another carbon is given off as CO_2 to form succinyl CoA (4 carbons) and produce another NADH. In the next step, one guanosine triphosphate (GTP) is produced as succinyl-CoA is converted to succinate. GTP is readily converted to ATP, thus this step is essentially the generation of 1 ATP. In the next step, an $FADH_2$ is produced along with fumarate. Then, after more steps, another NADH is produced as oxaloacetate is regenerated.

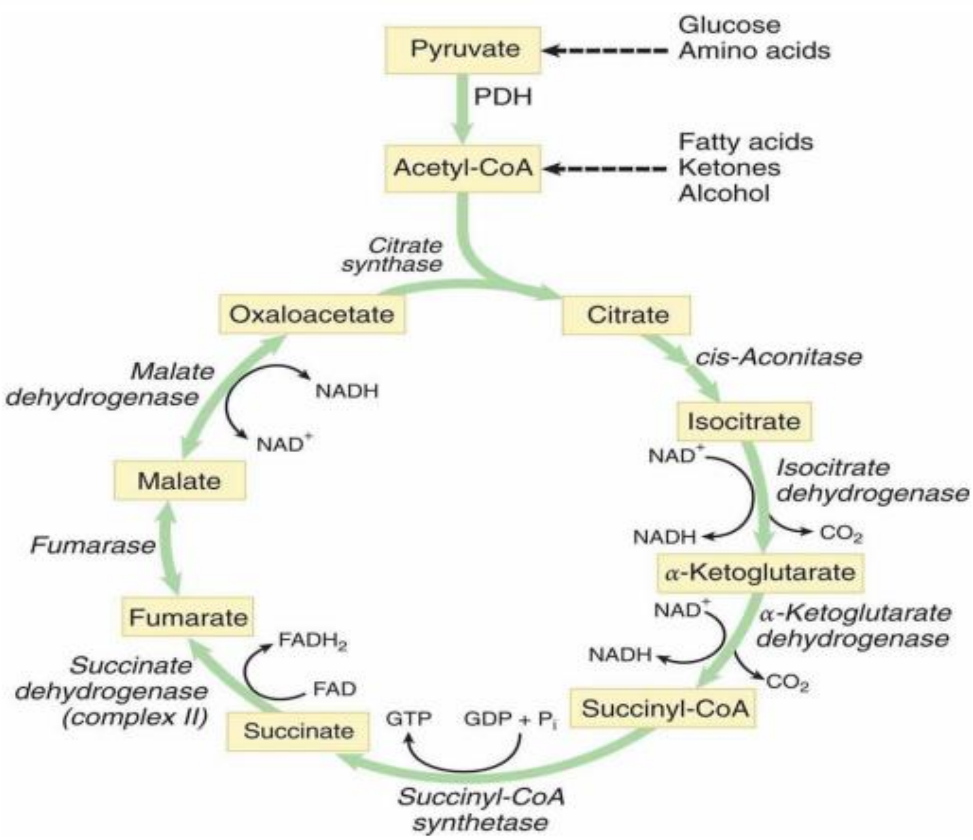


Figure 20: Tricarboxylic Acid cycle (TCA). (Site 13)

Krebs cycle equation To Sum up

2 Acetyl CoA+ 6 NAD^+ +2 FAD^+ + 2 ADP + 2 Pi+ 2 H_2O → 4 CO_2 + 6 NADH +2 $FADH_2$ + 2 ATP + 2 CoA

ATP generated in TCA cycle Convertion of:

-pyruvic acid to acetyl COA 1 NADH= 3ATP
-Isocitric acid to α-ketoglutarate 1NADH =3ATP
-α –ketoglutarare to succinyl COA 1NADH =3ATP
-Succinyl COA to succinic acid 1GTP =1ATP

-Succinic acid to fumeric acid 1FAD =2 ATP -
Malic acid to oxaloacitic acid 1NADH =3ATP

total 15 ATP

Net ATP produced per glucose molecule = 15 × 2= 30 ATP

Total ATP per glucose (aerobic oxidation + anaerobic) 30 + 8= 38 ATP

Regulation

- If energy levels (in this case NADH or $FADH_2$, which are converted to ATP via the later oxidative phosphorylation pathway) are high, the citric acid cycle is slowed or intermediates are diverted to other purposes.
- NADH accumulates if more is made than can be oxidized by the electron transport system.
- NADH inhibits isocitrate dehydrogenase, which causes citrate to accumulate.
- Citrate is transported out of the mitochondria by a specific transporter.

3. Gluconeogenesis

• Gluconeogenesis is the generation of glucose from non-sugar carbon substrates like glycerol, lactate, pyruvate, and glucogenic amino acids.

• The vast majority of gluconeogenesis takes place in the liver (90%) and in smaller extent, in the kidney (10%) cortex.

• Gluconeogenesis occurs during periods of fasting, starvation, or intense exercise and it is highly endergonic process(energy intensive), gluconeogenesis is often associated with ketosis.

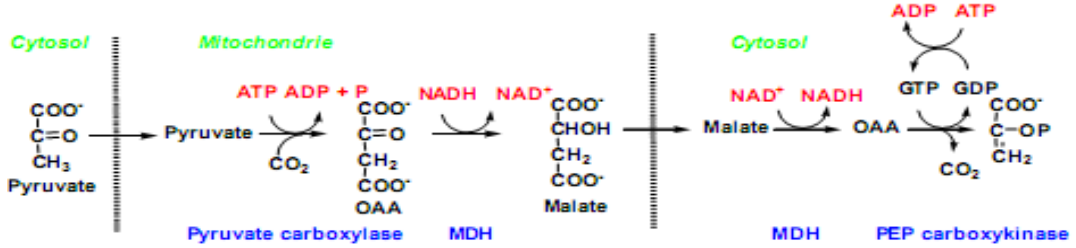
• Most reactions of the gluconeogenesis take place in the cytoplasm while two reactions occur in the mitochondria. 6 ATP molecules are consumed per molecule of glucose produced.

• Gluconeogenesis is not a simple reversal of glycolysis. In fact, gluconeogenesis requires 4 unique reactions to circumvent the 3 irreversible reactions of glycolysis.

• In Gluconeogenesis PK by passed by two reactions:

1. pyruvate is carboxylated to oxaloacetate by **pyruvate Carboxylase** in mitochondria, Oxaloacetate comes out of mitochondria with the help of the malate shuttle

2. oxaloacetate is decarboxylated and phosphorylated to yield PEP, this reaction is catalyzed by **PEP Carboxykinase** in cytosol. Cost 2 ATP per pyruvate (x2).



• In Gluconeogenesis PFK bypassed by Fructose 1,6 - bisphosphatase reaction (Removes phosphate group). fructose-1,6-bisP + H_2O ⟶ fructose-6-P + Pi

•In Gluconeogenesis Glucose-6-phosphatase converts Glucose-6-phosphate into Glucose this: Free glucose is formed by the action of glucose-6-phosphatase in liver and kidney while it is absent in muscles and adipose tissues glucose cannot be formed by these organs.

4. Regulation of Glycolysis and gluconeogenesis

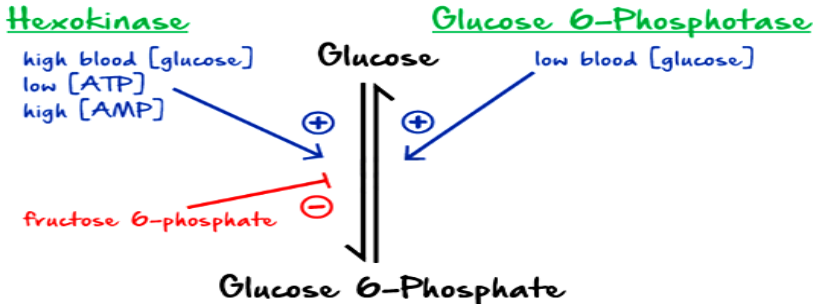
Metabolic regulation occurs at several key steps of glycolysis and gluconeogenesis. In each of these steps, external factors, such as the concentration of a downstream molecule, can activate or inhibit the enzymes that catalyze the step.

4.1. Regulation of Hexokinase and Glucose-6-Phosphotase

Hexokinase is regulated only by excess glucose-6-phosphate. High AMP/ADP levels are activators of this enzyme, while high ATP levels are inhibitory (energy charge).

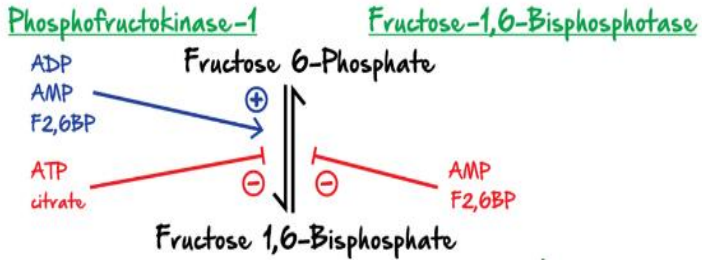
In gluconeogenesis, the reverse reaction, glucose 6-phosphate to glucose, is catalyzed by glucose 6-phosphatase.

Glucose 6-phosphatase is activated by low blood glucose concentrations.



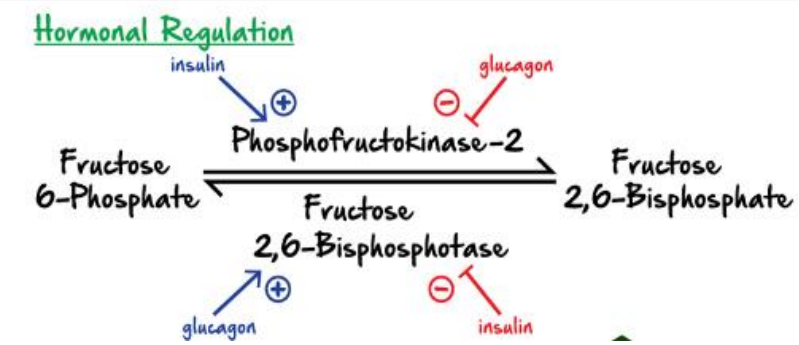
4.2. Regulation of PFK-1 and Fructose-1,6-Bisphosphotase

Phosphofructokinase-1 (PFK-1): activated by AMP and fructose 2,6 bisphosphate inhibited by high levels of ATP, citrate, fatty acids. In gluconeogenesis, by contrast, where fructose 1,6-bisphosphate is converted to fructose 6-phosphate, AMP, an indicator of a low-energy state, inhibits the reaction enzyme.



Fructose 2,6-bisphosphate is an important factor because it mediates the effects of insulin and glucagon on glycolysis and gluconeogenesis. fructose 2,6-bisphosphate interacts with PFK-1, activating it in order to upregulate glycolysis. F2,6 BP inhibits fructose-1,6-bisphosphatase (FBPase-1), a key enzyme in gluconeogenesis. This prevents the conversion of fructose-1,6-bisphosphate back to fructose-6-phosphate, effectively slowing down gluconeogenesis when glycolysis is favored. PFK-2 itself is regulated by insulin and glucagon;

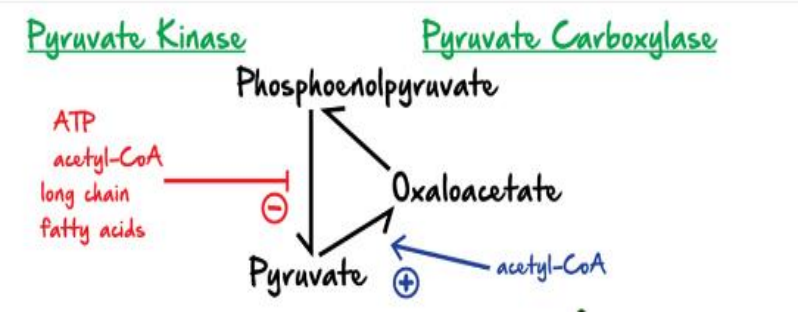
- **Insulin**, increases the levels of F2,6BP by activating PFK-2 in response to elevated blood glucose levels. This enhances glycolysis and inhibits gluconeogenesis.
- **Glucagon**: Decreases the levels of F2,6BP by promoting the activity of fructose-2,6-bisphosphatase (the enzyme that degrades F2,6BP). This reduction leads to increased gluconeogenesis and decreased glycolysis during fasting or low glucose availability.



4.3. Regulation of Pyruvate Kinase and Pyruvate Carboxylase

Pyruvate kinase PK is an allosteric enzyme activated by fructose 1,6 bisphosphate inhibited by ATP (negative feedback), alanine.

Pyruvate carboxylase is an imp regulatory step in gluconeogenesis. Acetyl CoA and ATP are positive effectors while AMP/ADP are inhibitors



• Glycolysis and gluconeogenesis are regulated by hormones. Insulin stimulates synthesis and activity of glycolytic enzymes by increasing the expression of key enzymes and enhancing the uptake of glucose in muscle and adipose tissue while glucagon turns on gluconeogenic enzymes, decreasing glycolysis and promoting gluconeogenesis in the liver by activating cAMP-dependent pathways that lead to the phosphorylation of pyruvate kinase.

5. Hormones effect on blood glucose level

5.1. Hormones decrease blood glucose level

- **Insulin** secreate from β-cells of pancreas in response to high blood glucose levels after meals. It promotes glucose uptake by cells, facilitating the storage of glucose as glycogen in the liver and muscles, and also stimulates fat storage.

- about 2/3 of body cells (primarily muscle and fat tissue cells) take up glucose from the blood, thus decreasing blood sugar.

5.2. Hormones increase blood glucose level

- **Catecholamines (Epinephrine, Norepinephrine),** also known as adrenalin or nor adrenaline, is a hormone, neurotransmitter and medication. Increase blood glucose by promoting glycogen breakdown and gluconeogenesis and enhances release of fatty acids from adipose tissue (lipolysis). They also inhibit insulin release, preventing glucose from being stored and ensuring more glucose is available for energy during stress or fight-or-flight situations.
- **Glucocorticoids (Cortisol),** is a steroid hormone produced by the adrenal cortex during stress. Cortisol raises blood glucose by promoting gluconeogenesis in the liver and inhibiting glucose uptake by peripheral tissues. It also antagonizes Insulin and stimulates the breakdown of proteins and lipids to provide substrates for glucose production. Chronic high levels of cortisol, such as in Cushing's syndrome, can lead to prolonged elevated blood glucose levels, contributing to insulin resistance and even diabetes.
- **Thyroid hormones (Triiodothyronine, T3, and Thyroxine, T4)** regulate metabolism by increasing the basal metabolic rate (BMR) and influencing glucose uptake. These hormones promote the catabolism of fats and proteins, thereby increasing the availability of glucose and free fatty acids. They also enhance absorption of sugars from intestine and insulin sensitivity, indirectly influencing blood glucose levels by improving glucose utilization by cells.

In cases of hyperthyroidism (excess thyroid hormone), blood glucose levels may rise due to the increased metabolic rate and increased glucose production. In hypothyroidism (insufficient thyroid hormone), glucose uptake can be impaired, and there may be a relative increase in blood glucose.

- **ACTH**, Enhances release of fatty acids from adipose tissue (Lipolysis).
- **Digestive Hormones (Glucagon, Gastrin, etc.):**

- **Glucagon**, released when blood glucose is low (e.g., during fasting). It stimulates glycogen breakdown (glycogenolysis) and gluconeogenesis in the liver, raising blood glucose levels.

- **Gastrin:** Although primarily involved in the digestive process, gastrin can have an indirect effect on blood glucose by stimulating the secretion of insulin.

- **Amino acid-derived hormones (Serotonin, Dopamine):** Impact glucose regulation, with serotonin improving insulin sensitivity with glucose uptake in cells and dopamine influencing insulin release. Dopamine's role in glucose regulation is less direct but still significant in overall metabolic processes.

These hormones work in a highly coordinated manner to maintain blood glucose homeostasis, ensuring that the body has enough glucose for energy, especially during periods of stress or fasting.

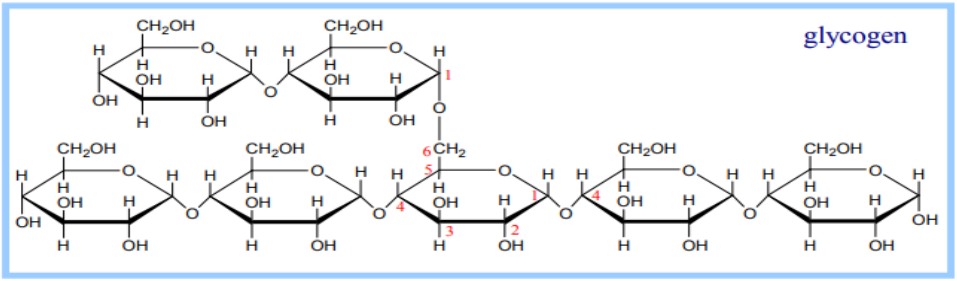
6. Glycogen metabolism

Glycogen is the storage form of carbohydrates in the human body. The major sites of storage are liver and muscle. Glycogen metabolism involves two primary processes: **glycogenesis** (the formation of glycogen) and **glycogenolysis** (the breakdown of glycogen). These processes regulate the storage and mobilization of glucose to maintain blood glucose homeostasis, especially during periods of fasting, exercise, or stress.

6.1. Glycogen: Structure, Localization, and Function

Glycogen is a large, branched polymer composed of glucose units linked by α (1-4) glycosidic bonds, with branches formed through α (1-6) glycosidic bonds every 10 glucose residues.

This highly branched structure allows for the rapid mobilization of glucose when needed.



Glycogen is primarily stored in the liver and skeletal muscles. While the liver has a higher concentration of glycogen (about 10% by weight), skeletal muscles store more glycogen overall due to their larger mass (approximately 300 grams in muscle tissue versus 75 grams in the liver). Within cells, glycogen is found in the cytosol as granules that range from 10–40 nm in size, containing up to 120,000 glucose units. These granules also house enzymes involved in both the synthesis and degradation of glycogen, as well as regulatory enzymes. In the liver, glycogen metabolism is regulated to maintain blood glucose levels, with the liver releasing glucose into the bloodstream when levels drop and storing excess glucose when levels rise.

In skeletal muscles, glycogen is used locally to fuel muscle activity during exercise.

The glycogen stored in muscles primarily supports the energy needs of the muscle itself, particularly during physical exertion, without directly affecting blood glucose levels. Therefore, while both the liver and muscles store glycogen, their roles differ: the liver regulates blood glucose for the entire body, while muscles use glycogen to meet their own energy demands.

6.2. Glycogenesis

In glycogenesis pathway, glucose molecules are the first activated to uridine diphosphate glucose (UDP-G). Then these UDP-G molecules are added to a glycogen primer to form glycogen.

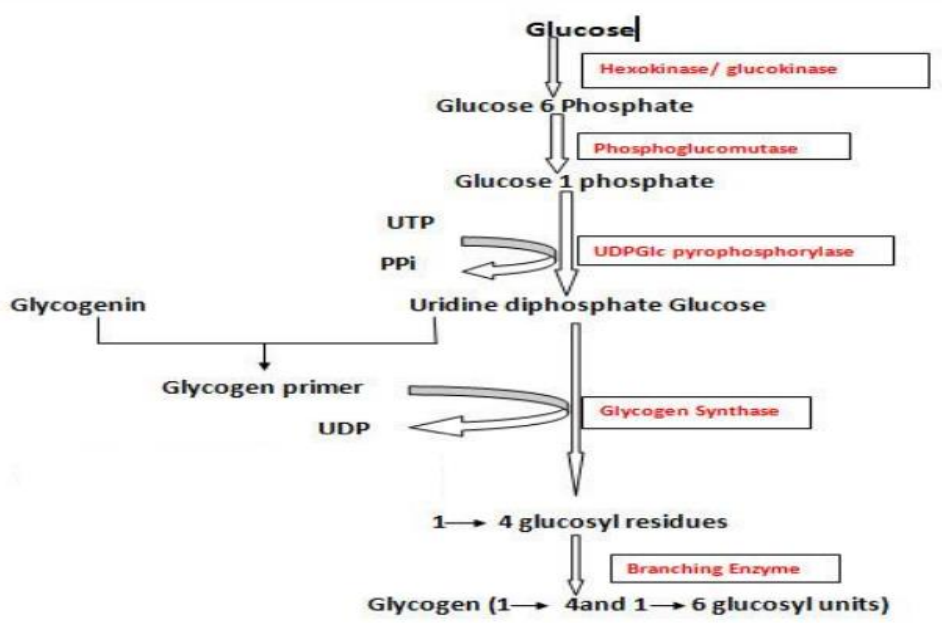


Figure 21: Steps of glycogensis

6.2.1. Formation of UDP-Glucose (UDP-G)

• The starting point for synthesis of glycogen is glucose 6-phosphate, derived from free glucose in a reaction catalyzed by hexokinase in muscle and glucokinase in liver.

D-Glucose + ATP ----------> D-glucose-6-phosphate + ADP

• Glucose 6-phosphate, is converted into glucose 1-phosphate by phosphoglucomutase reaction.

Glucose-6-phosphate <----------> glucose-1-phosphate

• The product of this reaction is converted to UDP-glucose by the action of UDP-glucose pyrophosphorylase.

Glucose-1-phosphate + UTP <----------> UDP-glucose + PPi

6.2.2 Formation of glycogen:

a) UDP-Glucose reacts with glycogen primer, which may be:

1) Few molecules of glucose linked together by α.1-4 linkage.

2) A protein called glycogenin. UDP-G molecules react with -OH of tyrosine of that protein to initiate glycogen synthesis.

b) Glycogen synthase enzyme:

By the action of glycogen synthase (key enzyme of glycogenesis), UDP-G molecules are added to glycogen primer causing elongation of the α1-4 branches up to 12-14 glucose units.

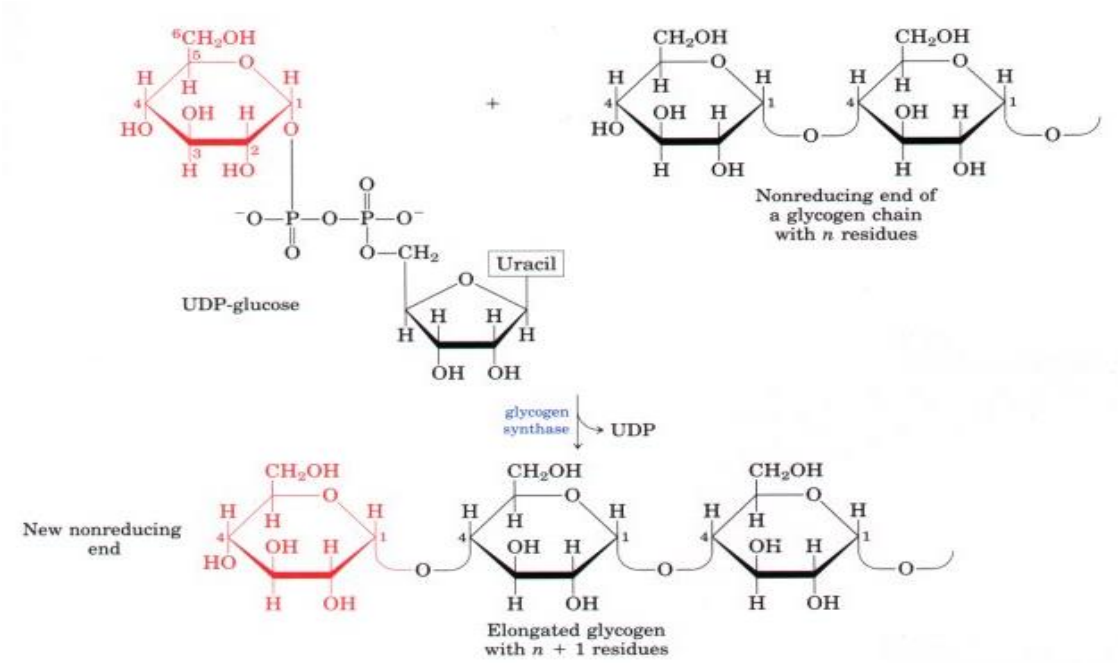


Figure 22: Creation of α-1,4 Linkages by Glycogen Synthase (site 14)

c) Branching enzyme:

It transfers parts of the elongated chains (5-8 glucose residues) to the next chain forming a new α I-6 glycosidic bond. The new branches are elongated by the glycogen synthase and the process is repeated.

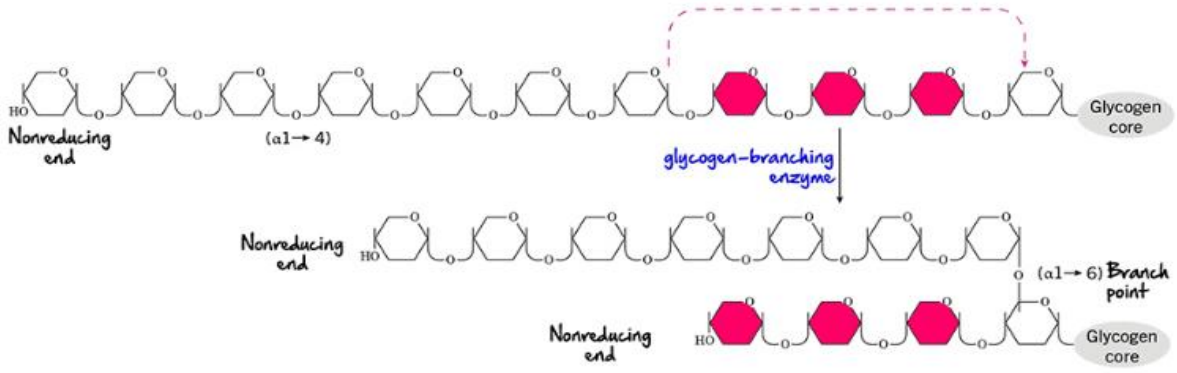


Figure 23: Formation of α-1,6 Linkages by Glycogen Branching Enzyme (site 15)

Energy Balance:

The storage of one glucose molecule requires the consumption of two ATP molecules.

6.3. Glycogenolysis

It is the breakdown of glycogen into glucose (in liver) and lactic acid (in muscles).

- **Phosphorylase** acts on α.1-4 bonds, breaking it down by phosphorolysis, it removes glucose units in the form of glucose-1-phosphate. Phosphorylase enzyme acts on the branches containing more than 4 glucosyl units.
- When the branch contains 4 glucose units, 3 of them are transferred to a next branch by transferase enzyme, leaving the last one.
- The last glucose unit that is attached to the original branch by α 1-6 bond is removed by debranching enzyme by hydrolysis (i.e. breaking the bond down by addition of H_20).
- Glucose-1-phosphate molecules are converted to glucose-6- phosphate, by mutase enzyme.

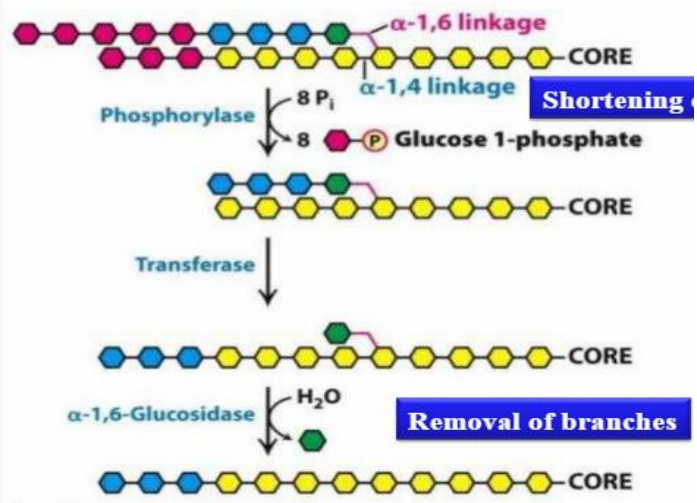


Figure 24: Degradation of glycogen (site 16)

6.4. Regulation of glycogenesis & Glycogenolysis

The regulation of glycogen metabolism involves intricate control mechanisms that ensure the body maintains stable blood glucose levels and provides energy to tissues, particularly the liver and muscles. The hormonal regulation of glycogen metabolism helps coordinate glycogenesis and glycogenolysis to meet the body's energy demands, especially in response to fasting, feeding, and physical activity.

6.4.1. Allosteric regulation of glycogen metabolism

- When substrate availability & energy level is high, Glycogen synthesis is increased.
- When glucose concentration is low & energy level low, Glycogen breakdown is enhanced.
- In well-fed state, Glucose-6-P allosterically activates Glycogen Synthase. At the same time, allosterically inhibits Glycogen Phosphorylase.
- Free Glucose in the liver is also a allosteric inhibitor of Glycogen Phosphorylase.

6.4.2. Hormonal regulation of glycogen metabolism

The key hormones that regulate glycogen metabolism are insulin**,** glucagon**,** epinephrine (adrenaline), and cortisol. These hormones work in different ways depending on the tissue (liver vs. muscle), ensuring the appropriate balance of glycogen storage and mobilization. Hormones control glycogen synthesis & degradation by covalent modification ie., phosphorylation & dephosphorylation of key enzymes. cAMP acts as second messenger. cAMP activates Protein Kinase. Protein Kinase causes phosphorylation of enzymes, either activating or deactivating them.

- **Glycogen Synthase (Glycogenesis)**:
  - When glycogen synthase is dephosphorylated, it becomes active and promotes glycogen synthesis.
  - Insulin activates phosphatases that dephosphorylate and activate glycogen synthase**.**
- **Glycogen Phosphorylase (Glycogenolysis)**:
  - When **glycogen** phosphorylase is phosphorylated, it becomes active and promotes glycogen breakdown.
  - Glucagon**,** epinephrine, and cortisol activate protein kinases that phosphorylate and activate glycogen phosphorylase**.**

A. Insulin (Promotes Glycogenesis)

- **Liver**: Insulin stimulates glycogenesis by activating glycogen synthase, the enzyme that adds glucose to the glycogen chain. It also inhibits glycogenolysis by inactivating glycogen phosphorylase**.**
- **Muscle**: Insulin promotes glycogen storage by activating glycogen synthase and increasing glucose uptake into muscle cells via GLUT4 transporters.

- **Overall Effect**: Insulin promotes the storage of glucose as glycogen, reducing blood glucose levels.

B. Glucagon (Stimulates Glycogenolysis)

- **Liver**: Glucagon activates glycogen phosphorylase, which breaks down glycogen into glucose-1-phosphate and glucose, which is then released into the bloodstream to raise blood glucose levels. It also inhibits glycogenesis by deactivating glycogen synthase**.**
- **Muscle**: Glucagon does not significantly affect muscle glycogen metabolism, as muscle cells do not have glucagon receptors.
- **Overall Effect**: Glucagon stimulates glycogenolysis in the liver to increase blood glucose levels.

C. Epinephrine (Adrenaline) (Stimulates Glycogenolysis)

- **Liver**: Epinephrine stimulates **glycogenolysis** by activating **glycogen phosphorylase** in the liver, resulting in the release of glucose into the blood. It also inhibits **glycogenesis** by deactivating **glycogen synthase**.
- **Muscle**: Epinephrine also stimulates **glycogenolysis** in muscle by activating **glycogen phosphorylase**, providing glucose for local energy needs during exercise.
- **Overall Effect**: **Epinephrine** prepares the body for "fight or flight" by increasing glucose availability, both in the liver for systemic energy and in muscles for immediate energy.

D. Cortisol (Stimulates Glycogenolysis and Gluconeogenesis)

- **Liver**: Cortisol stimulates glycogenolysis by promoting the action of glycogen phosphorylase and also stimulates gluconeogenesis (the production of new glucose from non-carbohydrate sources), further increasing blood glucose.
- **Muscle**: Cortisol does not directly affect glycogenolysis in muscles but promotes protein catabolism to provide amino acids for gluconeogenesis in the liver.
- **Overall Effect**: Cortisol supports glucose production during prolonged stress or fasting by promoting glycogenolysis and gluconeogenesis.

6.5. Liver vs. Muscle Differences in Glycogen Metabolism

- **Liver**:
  - **Primary Role**: To maintain blood glucose levels. It releases glucose into the bloodstream after glycogen breakdown (glycogenolysis).
  - **Regulation**: Glucagon, epinephrine, and cortisol play significant roles in activating glycogen breakdown to release glucose. Insulin inhibits glycogen breakdown.
  - **Key Enzymes**: Glycogen synthase (for glycogenesis), glycogen phosphorylase (for glycogenolysis), glucose-6-phosphatase (for glucose release).
- **Muscle**:
  - **Primary Role**: To use glycogen for local energy production during exercise. Muscle glycogen cannot be released into the bloodstream.
  - **Regulation**: Epinephrine and insulin play a significant role in regulating muscle glycogen. While glucagon doesn't directly affect muscles, epinephrine's action on muscle glycogen is crucial for exercise.
  - **Key Enzymes**: Glycogen synthase (for glycogenesis), glycogen phosphorylase (for glycogenolysis), but muscle cells lack glucose-6-phosphatase (so glucose cannot be released into the bloodstream).

Table 3 : Summary of Hormonal Regulation

Hormone	Effect on Liver	Effect on Muscle	Primary Action
Insulin	Stimulates **glycogenesis**, inhibits **glycogenolysis**	Stimulates **glycogenesis**, glucose uptake	Lowers blood glucose
Glucagon	Stimulates **glycogenolysis**, inhibits **glycogenesis**	No direct effect	Raises blood glucose
Epinephrine	Stimulates **glycogenolysis**, inhibits **glycogenesis**	Stimulates **glycogenolysis**	Prepares for "fight or flight"
Cortisol	Stimulates **glycogenolysis** and **gluconeogenesis**	Promotes protein breakdown (for gluconeogenesis)	Supports long-term stress adaptation

III. Disorders and pathologies in CHOs metabolism

1. Abnormalities in blood glucose level

Abnormalities in blood glucose levels can occur due to several factors and result in various health conditions. The body typically maintains blood glucose levels within a narrow range (70–100 mg/dL when fasting), but when this regulation is disrupted, it can lead to either hypoglycemia (low blood glucose) or hyperglycemia (high blood glucose), both of which have serious health consequences.

1.1. Hyperglycemia: Hyperglycemia is an abnormally high blood glucose (blood sugar) level. Hyperglycemia is a hallmark sign of diabetes (both type 1 diabetes and type 2 diabetes) and prediabetes. Diabetes is the most common cause of hyperglycemia.

- Causes of hyperglycemia: pancreatitis, Cushing's syndrome, pancreatic cancer, certain medications, and severe illnesses.

- Common symptoms of diabetes: 1.Urinating often. 2. Feeling very thirsty. 3. Feeling very hungry - even though you Eating. 4. Extreme fatigue. 5. Blurry vision. 6. Weight loss - even though you are eating more (type 1) 7. Tingling, pain, or numbness in the hands/feet (type 2) 8. Cardiac arrhythmia.

- Treatment: This is done by a combination of proper diet, regular exercise, and insulin or other medication such as metformin.

1.2. Hypoglycemia: abnormally low level of sugar (glucose) in the blood. Hypoglycemia is not a disease in itself. The brain needs a continuous supply of glucose to function because it can neither store nor manufacture glucose. Hypoglycemia is not a disease, it is commonly linked with diabetes or caused by other conditions.

- Common symptomes of low sugar levels: include hunger, trembling, heart racing, nausea, and sweating.

- Causes of hypoglycemia:

1. medication: Quinine, a drug used for malaria, can also cause hypoglycemia. Salicylates, which are used for treating rheumatic disease, and propanolol for (high blood pressure)

2. Alcohol abuse if somebody has been drinking heavily.
3. Some liver diseases -hepatites can cause hypoglycemia.
4. Kidney disorders
5. Some disorders of the adrenal and pituitary glands can lead to hypoglycemia.
6. Not eating enough - people with eating disorders, such as anorexia nervosa, may find that their blood sugar levels drop dramatically.
7. Insulinoma - this is a tumor in the pancreas which can make the pancreas produce too much insulin.

Test used in determining blood sugar:

1. Fasting blood sugar (F.B.S). 2. Random blood sugar (R.B.S). 3. 2hrs postprandial test 4. Oral glucose tolerance test (OGTT).

2. Pathologies due to a deregulation of carbohydrate metabolism

Deregulation of carbohydrate metabolism can lead to a variety of pathologies that impact the body's ability to process sugars, leading to either excess or deficiency of glucose or other carbohydrates. Here are several examples of such pathologies:

2.1. Lactose Intolerance

Lactose intolerance is a condition where the body is unable to properly digest lactose, a sugar found in milk and dairy products, due to a deficiency of the enzyme lactase.

- Cause:

- Lactase deficiency: Lactase is the enzyme responsible for breaking down lactose into its component sugars, glucose, and galactose, which can then be absorbed into the bloodstream. Without enough lactase, lactose remains undigested in the intestine.

- Genetic predisposition: Lactose intolerance is common in adults, especially in populations with a history of low dairy consumption. In some individuals, lactase production decreases with age.

- Symptoms: Bloating, diarrhea, abdominal pain, and flatulence after consuming dairy products.

- Treatment:

- Lactase supplements or lactose-free dairy products to aid digestion.
- Dietary changes to limit lactose-containing foods.

2.2. Type 1 Diabetes

Type 1 diabetes is an autoimmune disorder where the immune system attacks and destroys the beta cells of the pancreas, which are responsible for producing insulin.

- Cause:

- Insulin deficiency: Since insulin is essential for promoting the uptake of glucose by cells, a lack of insulin means that glucose cannot be efficiently utilized by tissues, leading to hyperglycemia (high blood glucose levels).

- Genetic and environmental factors: The exact cause is unknown, but a combination of genetic predisposition and environmental triggers (such as viral infections) may initiate the autoimmune response.

- Symptoms:

- Increased thirst (polydipsia), frequent urination (polyuria), extreme hunger (polyphagia), weight loss, and fatigue.

- Treatment:

- Insulin therapy to replace the missing insulin.

- Monitoring blood glucose levels regularly.

2.3. Type 2 Diabetes

Type 2 diabetes is characterized by insulin resistance, where the body's cells become less responsive to insulin, and beta cell dysfunction, where the pancreas produces insufficient insulin over time.

- Cause:

- Insulin resistance: The body's cells, especially muscle, liver, and fat cells, are less responsive to insulin, so glucose is not taken up effectively, leading to high blood glucose levels.

- Beta-cell dysfunction: Over time, the pancreas may fail to produce enough insulin to overcome resistance.

- Risk Factors: Obesity, sedentary lifestyle, poor diet, and genetic predisposition.

- Symptoms:

- Increased thirst, frequent urination, blurred vision, slow wound healing, and fatigue.

- Treatment:

- Lifestyle changes (diet, exercise), oral medications (e.g., metformin), and sometimes insulin therapy.

2.4. Galactosemia

Galactosemia is a rare inherited metabolic disorder that prevents the normal conversion of galactose (a sugar found in milk) into glucose.

- Cause:

- Deficiency of galactose-1-phosphate uridylyltransferase (GALT), the enzyme that converts galactose into glucose-1-phosphate. This leads to the accumulation of galactose and its toxic byproducts in the body.

- Symptoms:

- Jaundice, liver enlargement, cataracts, developmental delays, and in severe cases, intellectual disability if not treated early.

- Treatment:

- Strict galactose-free diet, especially avoiding milk and dairy products, to prevent the accumulation of galactose in the body.

2.5. Glycogen Storage Diseases (GSDs)

Glycogen storage diseases are a group of inherited metabolic disorders that result from deficiencies in the enzymes involved in glycogen synthesis or glycogen breakdown, impairing the body’s ability to store or release glucose from glycogen.

- Examples:

- GSD type I (von Gierke disease): Deficiency of glucose-6-phosphatase, which impairs the liver's ability to release glucose into the bloodstream. Leads to hypoglycemia (low blood sugar) and an accumulation of glycogen in the liver and kidneys.

- GSD type II (Pompe disease): Deficiency of lysosomal acid alpha-glucosidase, resulting in the accumulation of glycogen in muscles and other tissues, leading to muscle weakness and heart failure.

- Symptoms:

- Hypoglycemia, enlarged liver (hepatomegaly), muscle weakness, fatigue, and in severe cases, organ failure.

- Treatment:

-Dietary management to maintain blood glucose levels (e.g., frequent feeding, glucose supplements).

- Enzyme replacement therapy for certain GSDs (e.g., Pompe disease).

2.6. Fabry Disease

Fabry disease is a lysosomal storage disorder caused by a deficiency of the enzyme alpha-galactosidase A, leading to the accumulation of globotriaosylceramide (Gb3) in cells, including those involved in carbohydrate metabolism.

- Cause:

- X-linked recessive genetic mutation leading to the deficiency of alpha-galactosidase A, an enzyme that breaks down certain lipids. The buildup of Gb3 affects various organs, including the kidneys, heart, and skin.

- Symptoms:

- Pain (especially in hands and feet), skin rashes (angiokeratomas), kidney dysfunction, heart issues (enlarged heart, arrhythmias), and stroke.

- Treatment:

- Enzyme replacement therapy (ERT) to replace the missing enzyme.

- Symptomatic treatments to manage pain and organ dysfunction.

2.7. Hyperinsulinemia/Insulin Resistance (Metabolic Syndrome)

Metabolic syndrome is characterized by a group of risk factors that increase the likelihood of developing type 2 diabetes, heart disease, and stroke. One of the key features is insulin resistance.

- Cause:

- Insulin resistance occurs when the body's cells do not respond properly to insulin, leading to higher levels of insulin in the blood. Over time, the pancreas cannot produce enough insulin to maintain normal glucose levels, leading to hyperglycemia.

- Risk Factors:

Obesity, especially abdominal obesity, physical inactivity, high blood pressure, and high cholesterol levels.

- Symptoms:

High blood sugar, high blood pressure, abdominal obesity, and dyslipidemia (abnormal levels of fats in the blood).

- Treatment:

Lifestyle changes (e.g., weight loss, exercise), medications (e.g., metformin), and blood pressure and cholesterol management.

Hormonal regulation of protein metabolism

Introduction

Protein metabolism is a vital biological process responsible for the synthesis, breakdown, and turnover of proteins in the body. Hormones play a crucial role in regulating these processes, ensuring the maintenance of homeostasis and the efficient use of proteins for various physiological functions. The hormonal regulation of protein metabolism involves a complex interplay of anabolic and catabolic signals that control protein synthesis and degradation, ultimately influencing muscle mass, enzyme activity, and tissue repair. Key hormones involved in this regulation include insulin, glucagon, cortisol, growth hormone, and anabolic steroids, each having a distinct effect on protein balance. Understanding how these hormones modulate protein metabolism is essential for comprehending various metabolic disorders and can offer insights into optimizing health, fitness, and recovery.

I. Protein biosynthesis

Proteins are macromolecules made up of many amino acids that linked together by peptide bond to make a protein molecule. The sequence and the number of amino acids determine each protein unique structure and specific function. Proteins play a vital role in living systems and play important biological functions.

Biosynthesis of protein is the process by which cells construct proteins, following the instructions encoded in DNA. It involves two main stages: transcription and translation. The process occurs in all living cells, allowing them to build proteins needed for cellular functions, structure, and regulation. Here's an overview of the steps involved in protein biosynthesis:

1. Transcription: Synthesis of mRNA

Transcription is the first step in the process of protein synthesis, where the genetic information in DNA is copied into messenger RNA (mRNA). This process occurs in the nucleus of eukaryotic cells (or in the cytoplasm for prokaryotic cells). Here's an overview of the key steps involved in transcription:

1.1. Initiation:

- The process begins when the RNA polymerase enzyme binds to a specific region on the DNA called the promoter. The promoter marks the start site for transcription.

- Transcription factors (proteins that help RNA polymerase bind to DNA) assist in the formation of the transcription initiation complex.

- Once the RNA polymerase is properly positioned, it separates the two strands of the DNA helix, creating a "bubble" and exposing the template strand.

1.2. Elongation:

- The RNA polymerase moves along the template strand of DNA in the 3' to 5' direction. As it moves, it synthesizes the mRNA strand in the 5' to 3' direction by adding complementary RNA nucleotides (adenine [A], uracil [U], cytosine [C], and guanine [G]).

- Base pairing rules are followed:

- Adenine (A) pairs with uracil (U) in RNA (instead of thymine [T], which is found in DNA).

- Cytosine (C) pairs with guanine (G), and guanine (G) pairs with cytosine (C).

- The mRNA strand grows as RNA polymerase continues to move along the DNA template.

1.3. Termination:

- Transcription ends when RNA polymerase reaches a specific sequence in the DNA called the terminator sequence. This signals the end of the gene.

- The mRNA is then released, and RNA polymerase detaches from the DNA. The DNA strands rejoin, and the mRNA is ready for processing (in eukaryotes).

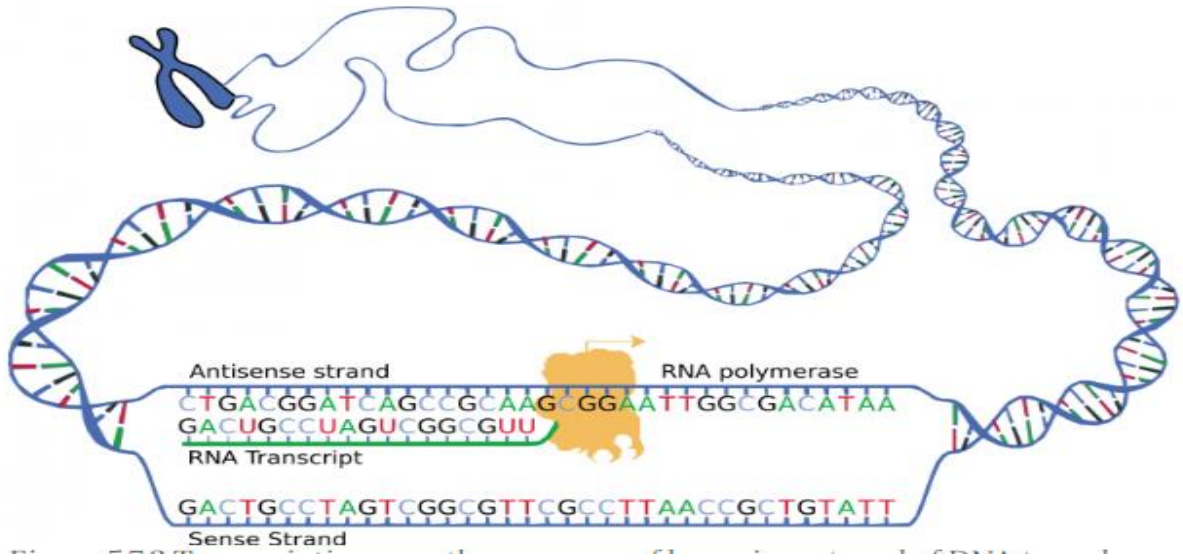


Figure 25: Transcription uses the sequence of bases in a strand of DNA to make a complementary strand of mRNA (Miller, 2020).

After transcription, the pre-mRNA undergoes further processing, such as the addition of a 5' cap and a poly-A tail, and splicing of introns (non-coding regions) to form the final mRNA.

- **5' capping**: A methylated cap is added to the 5' end of the mRNA, which protects the mRNA from breaking down and helps in ribosome binding.
- **Splicing:** Non-coding regions called introns are removed, and the coding regions, exons, are joined together.
- **Polyadenylation**: A poly-A tail is added to the 3' end.The tail consists of a string of As (adenine bases). It signals the end of mRNA. It is also involved in exporting mRNA from the nucleus, and it protects mRNA from enzymes that might break it down.

This mRNA then exits the nucleus (in eukaryotes) and enters the **cytoplasm**, where it is translated by ribosomes to synthesize proteins.

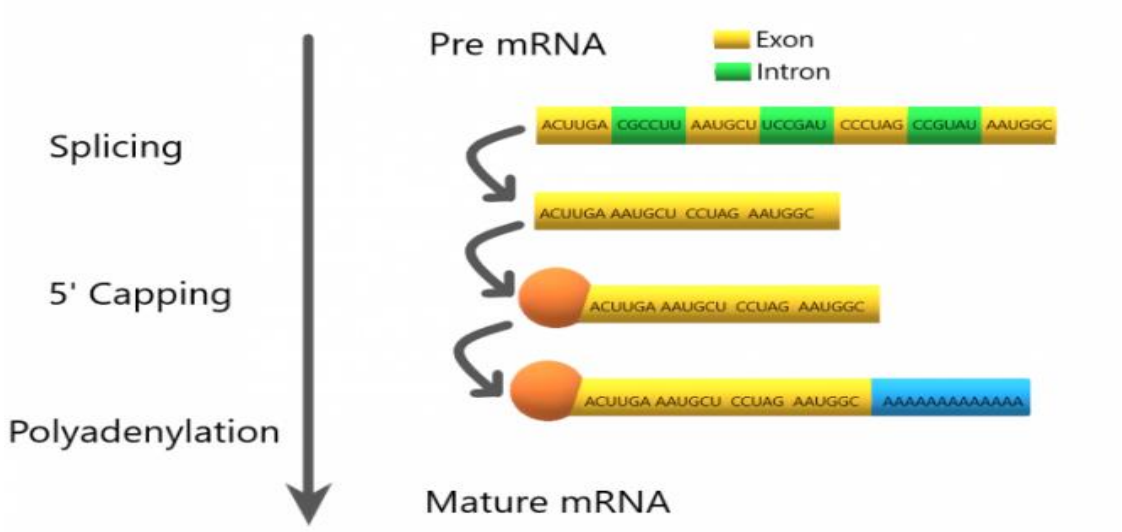


Figure 26: Pre mRNA processing. mRNA requires processing before it leaves the nucleus. (Site 17)

2. Translation:

2.1. Protein Synthesis in the Ribosome

Translation is the second step in protein synthesis, where the information encoded in mRNA is used to build a polypeptide chain (a protein). This process occurs in the **cytoplasm**, specifically in the **ribosomes**, which are complex molecular machines responsible for synthesizing proteins. After mRNA leaves the nucleus , it moves to a ribosome, which

consists of rRNA and proteins. The ribosome reads the sequence of codons in mRNA, and molecules of tRNA bring amino acids to the ribosome in the correct sequence.

2.2. Steps of Translation: Translation occurs in three stages: Initiation, Elongation and Termination.

2.2.1. Initiation:

The translation process begins with the binding of mRNA to the small subunit of the ribosome in the cytoplasm. In eukaryotes, the ribosome attaches to the 5' end of the mRNA. The small ribosomal subunit scans along the mRNA to find the start codon (AUG), which signals the beginning of translation. Once the start codon is recognized, the large ribosomal subunit binds to the small subunit, forming a functional ribosome. At the same time, a transfer RNA (tRNA) molecule carrying the amino acid methionine binds to the start codon on the mRNA through complementary base pairing between the mRNA codon and the tRNA anticodon. This marks the initiation of protein synthesis.

2.2.2. Elongation:

During elongation, the ribosome moves along the mRNA, reading each codon (a sequence of three nucleotides) in the 5' to 3' direction. For each codon, a corresponding tRNA with the complementary anticodon and a specific amino acid binds to the ribosome. The ribosome then catalyzes the formation of a peptide bond between the incoming amino acid and the growing polypeptide chain, which is attached to the tRNA in the P site. Following this, the ribosome shifts one codon forward along the mRNA (a process called translocation), moving the tRNA from the A site (where the new tRNA enters) to the P site, and the empty tRNA exits through the E site. This process is repeated, with each new tRNA bringing the appropriate amino acid, extending the polypeptide chain.

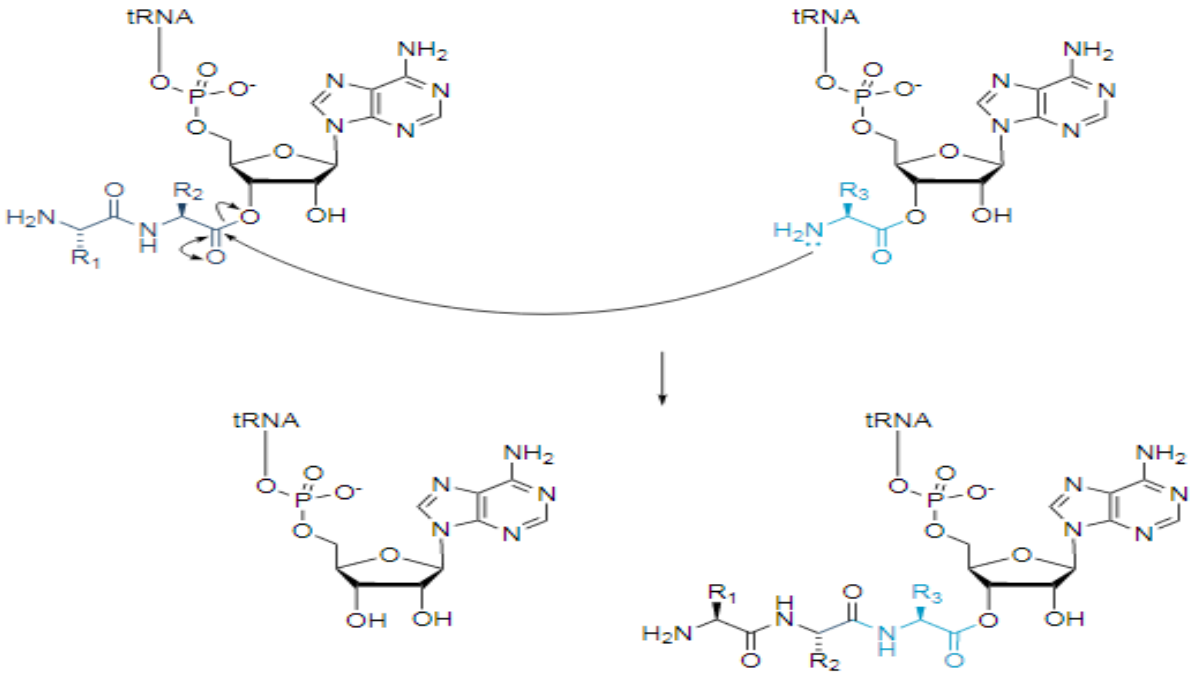


Figure 27: Protein synthesis Reaction of the growing polypeptide chain with the 3'-end of the charged tRNA. The amino acid is transferred from the tRNA molecule to the protein. (site18)

2.2.3. Termination:

Translation terminates when the ribosome encounters a stop codon (UAA, UAG, or UGA) on the mRNA. Since stop codons do not correspond to any amino acid, no tRNA enters the A site. Instead, a release factor binds to the stop codon, prompting the ribosome to release the newly synthesized polypeptide chain. The ribosome then dissociates into its large and small subunits, and the mRNA is also released. The polypeptide undergoes folding into its functional three-dimensional structure, and may undergo additional modifications, such as phosphorylation or glycosylation, to become a fully functional protein. The translation process is now complete, resulting in a newly synthesized protein ready to perform its cellular function.

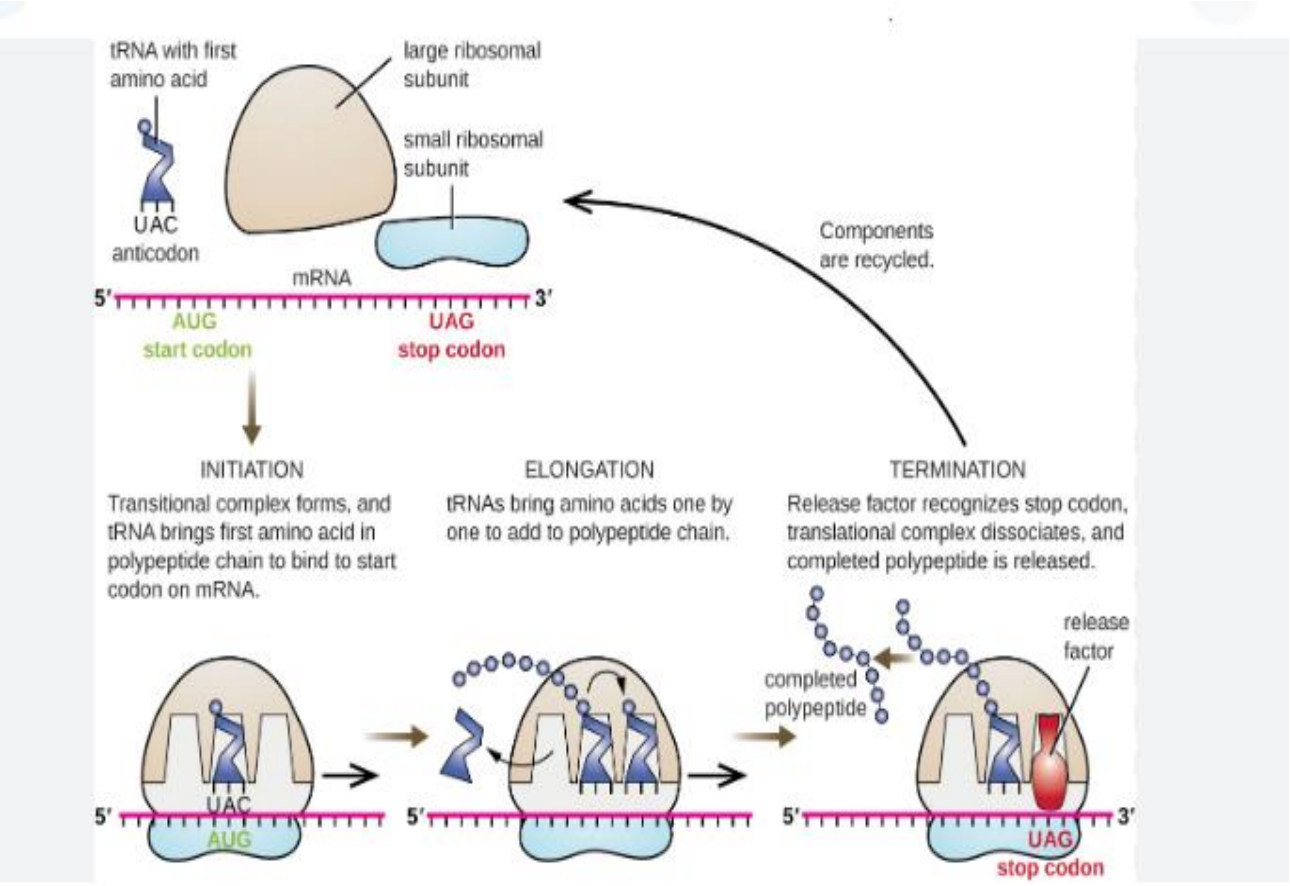


Figure 28: stages of translation.(site 19)

3. Post-Translational Modifications

Post-translational modifications (PTMs) refer to the chemical changes that a protein undergoes after its synthesis during translation. These modifications are crucial for regulating the protein's activity, stability, location, and interaction with other molecules. PTMs allow a single protein to acquire multiple functional forms, enabling greater cellular complexity and regulation. Some common types of post-translational modifications include:

- **Phosphorylation**: The addition of a phosphate group (PO_4) to specific amino acids, typically serine, threonine, or tyrosine, by enzymes called kinases. Phosphorylation can activate or deactivate proteins, playing a key role in signal transduction, metabolism, and cell division.
- **Glycosylation**: The attachment of carbohydrate groups to proteins, usually on asparagine, serine, or threonine residues. Glycosylation affects protein folding, stability, and interactions with other molecules. It is important for protein function in cell recognition, immune response, and cellular adhesion.

- **Acetylation**: The addition of an acetyl group ($COCH_3$) to lysine residues, commonly occurring in histones and other regulatory proteins. Acetylation is involved in regulating gene expression, protein stability, and protein interactions.
- **Ubiquitination**: The attachment of ubiquitin molecules to lysine residues of a protein, often marking it for degradation by the proteasome. Ubiquitination regulates protein turnover and controls many cellular processes, including the cell cycle and DNA repair.
- **Methylation**: The addition of a methyl group (CH_3) to the nitrogen atom of lysine or arginine residues, often affecting protein interactions and gene expression. Methylation is common in histones and plays a role in chromatin structure and gene regulation.
- **Proteolytic Cleavage**: The enzymatic cutting of a protein chain to activate or deactivate its function. For example, some enzymes are synthesized as inactive precursors (zymogens) and must be cleaved to become active. This modification is essential for processes like blood clotting and digestion (e.g., insulin).
- **Sumoylation**: The attachment of small ubiquitin-like modifier (SUMO) proteins to target proteins. Sumoylation regulates protein stability, localization, and interactions, playing a role in cellular stress responses, nuclear transport, and gene expression.

These modifications are highly dynamic and can be reversible, allowing cells to respond to changing conditions. They play a central role in regulating virtually every aspect of cellular function and are crucial for maintaining cellular homeostasis.

II. Gluconeogenesis

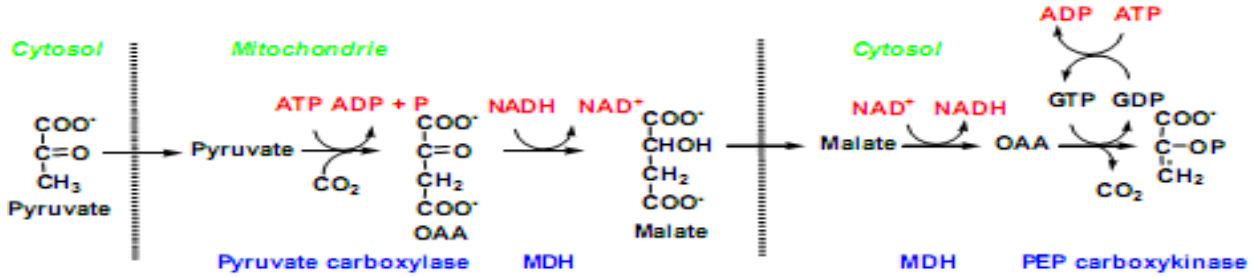
Gluconeogenesis is the metabolic pathway through which the body synthesizes glucose from non-carbohydrate precursors like glycerol, lactate, pyruvate, and glucogenic amino acids. The vast majority of gluconeogenesis takes place in the liver (90%) and in smaller extent, in the kidney (10%) cortex. It is essential for maintaining blood glucose levels, particularly during periods of fasting, prolonged exercise, or starvation when carbohydrate stores are depleted and it is highly endergonic process(energy intensive), gluconeogenesis is often associated with ketosis. Gluconeogenesis is essentially the reverse of glycolysis, although it involves several unique enzymes to bypass the irreversible steps of glycolysis.

1. Key Steps in Gluconeogenesis:

Most reactions of the gluconeogenesis take place in the cytoplasm while two reactions occur in the mitochondria. 6 ATP molecules are consumed per molecule of glucose produced.

Gluconeogenesis is not a simple reversal of glycolysis. In fact, gluconeogenesis requires 4 unique reactions to circumvent the 3 irreversible reactions of glycolysis.

1. **Conversion of Pyruvate to Phosphoenolpyruvate (PEP)**:
    - The process begins with pyruvate, which is generated from lactate, amino acids (especially alanine), or glycerol.
    - Pyruvate is first carboxylated to oxaloacetate by the enzyme pyruvate carboxylase in the mitochondria. This step requires ATP and biotin, Oxaloacetate comes out of mitochondria with the help of the malate shuttle
    - Oxaloacetate is then decarboxylated and phosphorylated to phosphoenolpyruvate (PEP) by the enzyme phosphoenolpyruvate carboxykinase (PEPCK) in cytosol, which requires GTP.
    - These two steps bypass the irreversible enzyme pyruvate kinase in glycolysis.



2. **Conversion of PEP to Fructose-1,6-bisphosphate**:
    - Phosphoenolpyruvate undergoes a series of reactions similar to those in glycolysis, eventually forming fructose-1,6-bisphosphate. These reactions are catalyzed by enzymes like aldolase and triose phosphate isomerase.
3. **Bypassing the Irreversible Step of Phosphofructokinase**:
    - The enzyme fructose-1,6-bisphosphatase converts fructose-1,6-bisphosphate to fructose-6-phosphate, bypassing the irreversible step catalyzed by phosphofructokinase-1 (PFK-1) in glycolysis. This is a key regulatory step in gluconeogenesis.
4. **Conversion of Fructose-6-phosphate to Glucose-6-phosphate**:
    - Fructose-6-phosphate is then converted to glucose-6-phosphate by the enzyme phosphoglucoisomerase.
5. **Dephosphorylation to Glucose**:

- Finally, glucose-6-phosphate is dephosphorylated to form glucose by the enzyme glucose-6-phosphatase. This step is crucial for the release of free glucose into the bloodstream.

Free glucose is formed by the action of glucose-6-phosphatase in liver and kidney while it is absent in muscles and adipose tissues glucose cannot be formed by these organs.

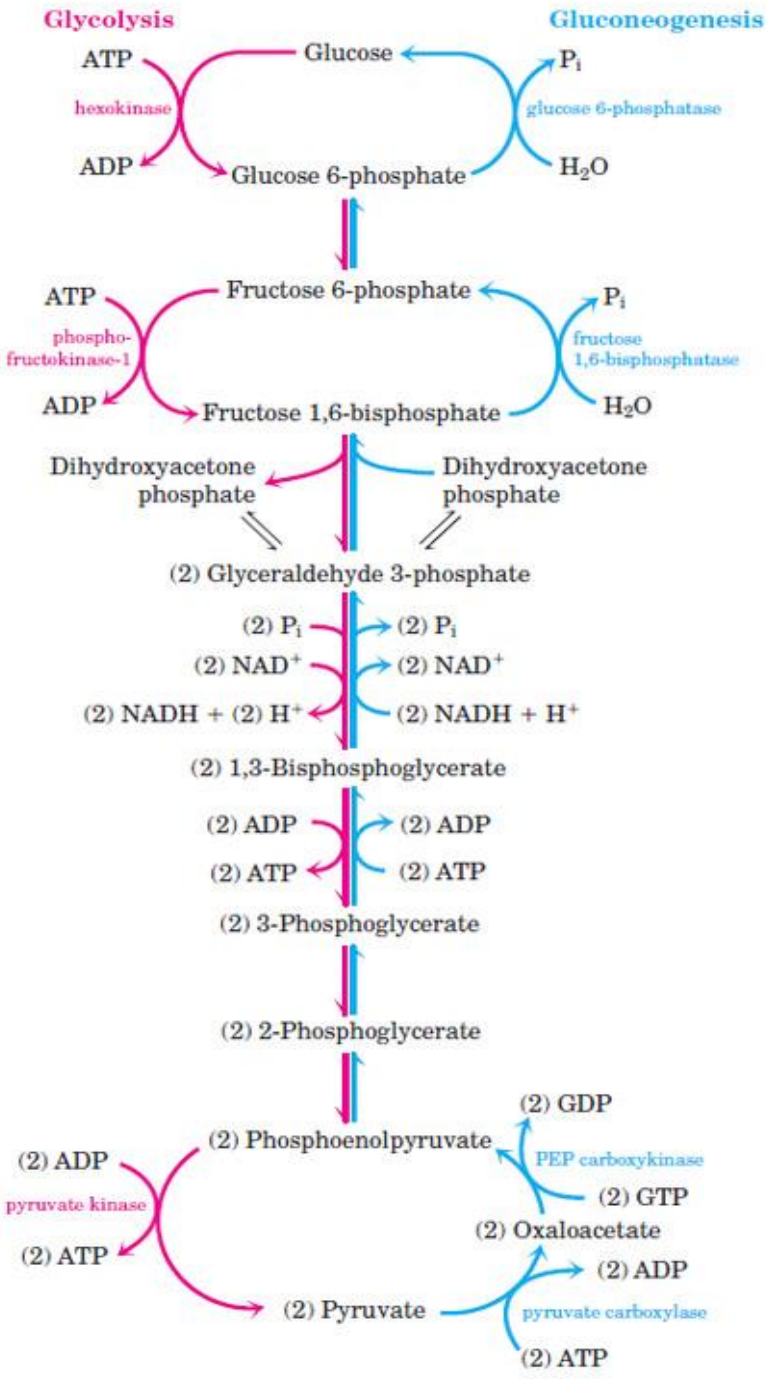


Figure 29: Opposing pathways of glycolysis and gluconeogenesis. (Site 20)

2. **Regulation of Gluconeogenesis:**

Gluconeogenesis is tightly regulated to ensure that glucose is synthesized only when necessary. This regulation occurs at several key steps:

- **Allosteric regulation**: High levels of ATP and acetyl-CoA (from fatty acid oxidation) activate gluconeogenesis, while high levels of AMP (indicating low energy) inhibit the process.
- **Hormonal regulation**: Hormones like glucagon and cortisol promote gluconeogenesis, especially during fasting or stress. On the other hand, insulin inhibits gluconeogenesis to prevent excessive glucose production when glucose is abundant.

3. **The connection between gluconeogenesis and protein metabolism:**

The connection between gluconeogenesis and protein metabolism is crucial for maintaining energy balance and blood glucose stability, particularly during periods of fasting or stress. When proteins are broken down, the released amino acids are used as precursors for gluconeogenesis, a process through which the body synthesizes glucose from non-carbohydrate sources. Some amino acids, known as glucogenic like alanine, glutamine, and others, can be converted into intermediates such as pyruvate or alpha-ketoglutarate, which then enter the gluconeogenesis pathway to produce glucose. Thus, during times of low carbohydrate intake, such as prolonged fasting or intense exercise, the breakdown of proteins provides the necessary amino acids to sustain glucose production and ensure a stable energy supply for the body.

III. Hormonal regulation of protein metabolism

Hormonal regulation is a complex process involving various hormones that control the synthesis, breakdown, and overall balance of proteins in the body. These hormones influence processes such as protein anabolism (synthesis) and catabolism (breakdown). The primary hormones involved in the regulation of protein metabolism include:

1. Insulin: Secreted by the pancreas, Insulin plays a key role in anabolic processes. It is released after meals, when blood glucose levels are elevated, and supports protein storage and muscle growth by stimulating muscle protein synthesis. It does this by stimulating the uptake

of amino acids into cells, enhancing the activity of ribosomes, and promoting the synthesis of proteins from amino acids.

2. Glucagon: Also secreted by the pancreas. It works in a catabolic manner to raise blood glucose levels during periods of fasting, thereby ensuring energy supply, especially in tissues such as the brain and muscle. It does this by stimulating the breakdown of muscle proteins into amino acids, which can then be used by the liver to produce glucose through gluconeogenesis, particularly during fasting or periods of low blood sugar.

3. Cortisol: Produced by the adrenal glands in response to stress (via the hypothalamic-pituitary-adrenal axis). During chronic stress or prolonged fasting, cortisol can lead to muscle wasting and increased protein breakdown, to release amino acids. These amino acids are then used by the liver to produce glucose via gluconeogenesis.

4. Growth Hormone (GH): Secreted by the pituitary gland. GH stimulates protein synthesis and muscle growth. It enhances the uptake of amino acids by cells, encourages the production of insulin-like growth factor 1 (IGF-1) in the liver, and promotes anabolism (building of muscle tissue). GH also helps in the breakdown of fats for energy, sparing proteins for muscle building.

5. Thyroid Hormones (T3 and T4): Produced by the thyroid gland. Thyroid hormones increase the rate of protein turnover, meaning they increase both protein synthesis and catabolism, but overall they tend to increase metabolic rate and are critical in maintaining normal growth and energy balance. Abnormal thyroid function (hypothyroidism or hyperthyroidism) can disrupt protein metabolism.

6. Testosterone: Produced primarily by the testes (in males) and ovaries (in females), with small amounts produced by the adrenal glands. Testosterone is a potent anabolic hormone that promotes muscle mass development, strength, and the maintenance of muscle tissue, particularly in males, by increasing protein synthesis.

It enhances nitrogen retention, which is a marker of positive protein balance. It also helps increase red blood cell production, improving oxygen delivery to muscles during exercise.

7. Estrogen: Produced by the ovaries (primarily in females). Estrogen has both anabolic and anti-catabolic effects on protein metabolism. It can help preserve muscle mass by reducing protein breakdown, especially in women. During periods like pregnancy or post-menopause,

estrogen plays a key role in maintaining lean muscle mass. Estrogen can also contribute to bone health and fat distribution, with its effects on protein metabolism supporting muscle preservation during various life stages.

8. Catecholamines (Adrenaline, Noradrenaline) : Anabolic (promote protein synthesis and reduce breakdown). Activate beta-adrenergic receptors leading to increased protein synthesis and reduced proteolysis. Increase energy substrates for muscle growth.

9. Glucocorticoids (Cortisol) **Catabolic** (increase protein breakdown and inhibit synthesis) - Stimulate proteolysis by upregulating protein degradation pathways (e.g., proteasomes). - Inhibit protein synthesis by downregulating translation machinery and anabolic signaling.

10. **Leptin**: Leptin is a hormone produced by adipose (fat) tissue that helps regulate energy balance, appetite, and fat storage. Leptin has an indirect effect on protein metabolism. It promotes energy expenditure and fat utilization, which can alter the body's nutrient partitioning and protein balance. Leptin can reduce protein degradation by promoting a positive energy balance, which helps preserve muscle mass. In states of energy deficiency or fasting, leptin levels drop, contributing to increased protein catabolism.

11. Insulin-like Growth Factor 1 (IGF-1):

IGF-1 is a hormone primarily produced in the liver in response to growth hormone stimulation. It plays a key role in mediating the anabolic effects of growth hormone. IGF-1 stimulates protein synthesis in muscle tissue by promoting amino acid uptake and activating anabolic pathways, such as mTOR.

IGF-1 helps inhibit protein breakdown by reducing the activity of proteolytic enzymes. It also helps maintain muscle mass and repair by promoting muscle cell growth and differentiation.

In protein metabolism, anabolic hormones like insulin, growth hormone and testosteronepromote protein synthesis and muscle growth, while catabolic hormones like cortisol, glucagon, and thyroid hormones (in excess) promote protein breakdown. The balance between these hormones ensures proper regulation of muscle mass, energy storage, and overall metabolic homeostasis, adjusting in response to factors like nutrition, exercise, and stress.

Table 4: Summary of hormonal effects on protein metabolism

Hormone	Effect on Protein Synthesis	Effect on Protein Breakdown	Additional Notes
Insulin	Promotes protein synthesis by enhancing amino acid uptake and activating anabolic pathways (e.g., mTOR).	Inhibits protein breakdown by suppressing proteolytic pathways (e.g., proteasomes).	Anabolic hormone, mainly active after meals when blood glucose is high.
Glucagon	Inhibits protein synthesis, reducing the anabolic environment.	Promotes protein breakdown, releasing amino acids for gluconeogenesis.	Released during fasting or low blood glucose states.
Cortisol (Corticosteroid)	Inhibits protein synthesis, reducing mTOR activity and decreasing muscle cell anabolism.	Promotes protein breakdown via the ubiquitin-proteasome system and other pathways, especially in muscle tissue.	A catabolic hormone released during stress, injury, or fasting, leading to muscle wasting in prolonged exposure.
Growth Hormone (GH)	Stimulates protein synthesis by promoting amino acid uptake and IGF-1 production.	Slight inhibitory effect on protein breakdown.	Strongly anabolic, important for muscle growth and repair, especially during growth or recovery.
Testosterone	Stimulates protein synthesis, increasing mTOR activity.	Inhibits protein breakdown by reducing proteolytic pathways.	Anabolic steroid hormone, key for muscle growth and maintenance, more prominent in males.
Thyroid	Enhances protein	Can increase protein	Regulates overall

Hormones (T3 and T4)	synthesis by increasing metabolic rate.	breakdown at high levels (hyperthyroidism).	metabolism; imbalance can lead to muscle wasting (hyperthyroidism) or muscle retention (hypothyroidism).
Leptin	Indirectly supports protein synthesis by promoting energy balance.	Can reduce protein breakdown by supporting a positive energy balance.	Produced by fat cells, influences appetite and energy expenditure, indirectly affecting protein metabolism.
Insulin-like Growth Factor 1 (IGF-1)	Stimulates protein synthesis by promoting amino acid uptake and activating anabolic pathways like mTOR.	Inhibits protein breakdown by reducing proteolytic activity.	Mediates growth hormone's effects, important for muscle growth and repair.
Catecholamines (Adrenaline, Noradrenaline)	Inhibits protein synthesis by reducing anabolic pathways and promoting a catabolic environment.	Stimulates protein breakdown, especially in muscle tissue, for energy during stress or exercise.	Released during stress, exercise, and fight-or-flight response; increases muscle catabolism to provide energy.

Hormonal regulation of lipid metabolism

I. Introduction

Lipid metabolism refers to the complex set of biochemical processes through which the body processes fats and lipids to generate energy, build cellular structures, and produce essential molecules. Lipids, including triglycerides, phospholipids, and cholesterol, play crucial roles in the body, not only serving as major energy reserves but also as vital components of cell membranes and precursors for hormone production.

The body constantly balances lipid synthesis and breakdown to meet its energy needs, particularly during fasting, exercise, or periods of excess nutrient intake. Lipid metabolism involves key processes like lipogenesis (the formation of fats from carbohydrates), lipolysis (the breakdown of stored fats into fatty acids and glycerol), and fatty acid oxidation (the conversion of fatty acids into energy). Additionally, the liver plays a central role in generating ketone bodies when carbohydrate availability is low, providing an alternative fuel source for the brain and muscles.

The regulation of lipid metabolism is highly intricate and involves a variety of hormones, each contributing to the balance between fat storage and fat breakdown. Understanding these processes is essential for comprehending how the body responds to nutritional changes and for addressing metabolic diseases such as obesity, diabetes, and cardiovascular conditions.

II. Key Processes in Lipid Metabolism

lipid metabolism refers to the processes by which the body converts and utilizes lipids (fats and oils) for energy, structural components, and signaling molecules. These metabolic processes are crucial for maintaining cellular functions and overall energy homeostasis. Lipid metabolism involves several key processes: lipogenesis, lipolysis, cholesterol metabolism, and ketogenesis.

1. Digestion and Absorption of Lipids:

- **Dietary fats** are primarily triglycerides, which are broken down into fatty acids and glycerol during digestion in the small intestine.
- The enzyme lipase (produced in the pancreas) acts on triglycerides in the small intestine to break them down into monoglycerides and free fatty acids.

- These fatty acids and monoglycerides are absorbed by the intestinal cells (enterocytes), reassembled into triglycerides, and then incorporated into chylomicrons, which are lipoproteins that transport lipids through the lymphatic system into the bloodstream.

❖ **Transport of Lipids:**

- **Chylomicrons** and other lipoproteins (e.g., **VLDL**, **LDL**, and **HDL**) are responsible for transporting lipids to various tissues for storage or energy production.
- **VLDL** (very-low-density lipoprotein) carries triglycerides from the liver to peripheral tissues.
- **LDL** (low-density lipoprotein) primarily carries cholesterol to tissues, which is important for membrane structure and hormone synthesis.
- **HDL** (high-density lipoprotein) helps transport excess cholesterol from tissues back to the liver for excretion or recycling.

2. Lipogenesis (Fatty Acid and Triglyceride Synthesis)

Lipogenesis is the biochemical process through which the body synthesizes fatty acids and triglycerides (the storage form of fat) from non-fat sources, primarily carbohydrates. This process occurs primarily in the liver and adipose tissue, especially when there is an excess of dietary carbohydrates. Lipogenesis is critical for energy storage and maintaining cellular function, as fatty acids and triglycerides serve as long-term energy reserves.

2.1. Pathway of lipogenesis

Glucose is broken down into pyruvate, which is then converted into acetyl-CoA. Acetyl-CoA is the building block for fatty acids, which are synthesized and stored as triglycerides.

2.1.1. Glucose Conversion to Acetyl-CoA

- The process begins with glucose, which is converted to pyruvate through glycolysis.
- Pyruvate then enters the mitochondria, where it is converted to acetyl-CoA by the enzyme pyruvate dehydrogenase.
- Acetyl-CoA is a central molecule in metabolism and is the building block for fatty acid synthesis.

2.1.2. Citrate Shuttle

- In the mitochondria, acetyl-CoA combines with oxaloacetate to form citrate in the citric acid cycle (Krebs cycle).
- Due to the membrane's impermeability to acetyl-CoA, citrate is transported out of the mitochondria into the cytoplasm, where it is broken back down into acetyl-CoA by the enzyme ATP-citrate lyase.

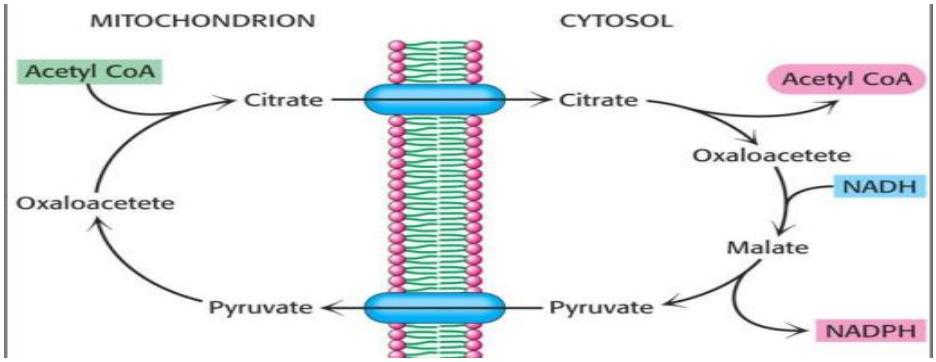


Figure 30: Citrate Shuttle

2.1.3. Fatty Acid Synthesis

- In the cytoplasm, acetyl-CoA is converted into malonyl-CoA by acetyl-CoA carboxylase (ACC), a key regulatory enzyme in lipogenesis.

$$\text{acetyl-CoA} + HCO_3^- + \text{ATP} \text{ ---> } \text{malonyl-CoA} + \text{ADP} + \text{Pi} + H^+$$

- Malonyl-CoA is then used to build long-chain fatty acids through a repetitive series of reactions catalyzed by the fatty acid synthase (FAS) complex, comprised of seven enzymes linked together with an acyl carrier protein (ACP).
- The acetyl-CoA and malonyl-CoA are linked to the synthase and ACP, then there is a sequence of acetyl group transfers (figure) that runs a total of seven times to form palmitoyl-ACP, from which the palmitic acid is finally released. Palmitic acid, a 16-carbon saturated fatty acid, is the precursor for variety of long-chain fatty acids such as stearic acid, palmitoleic acid, and oleic acid. Generally, there is either an elongation or sometimes a desaturation step.

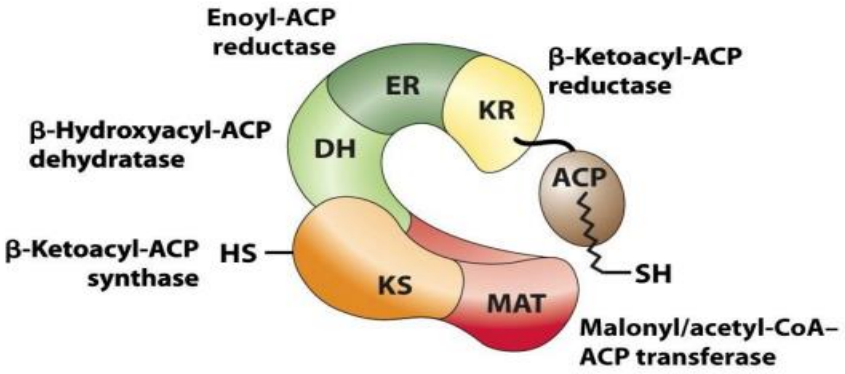


Figure 31: Fatty acid synthase. *Mammalian fatty acid synthase (FAS) is a large homodimeric multifunctional enzyme that regulates the de novo biosynthesis of long-chain fatty acids. The FAS monomer contains 7 catalytic activities and from the N-terminus the order is beta-ketoacyl synthase (KS), acetyl/malonyl transacylase (MAT), beta-hydroxyacyl dehydratase (DH), enoyl reductase (ER), beta-ketoacyl reductase (KR), acyl carrier protein (ACP), and thioesterase (TE).* (site 21)

The overall reaction for the synthesis of palmitic acid from acetyl CoA is as follows: 8 Acetyl CoA (2C)+ 14 NADPH + 13H^+ + 7 ATP→ Palmitate (16C) + 8 CoA-SH + 6 H_2O + 14 $NADP^+$ + 7 ADP + 7 Pi.

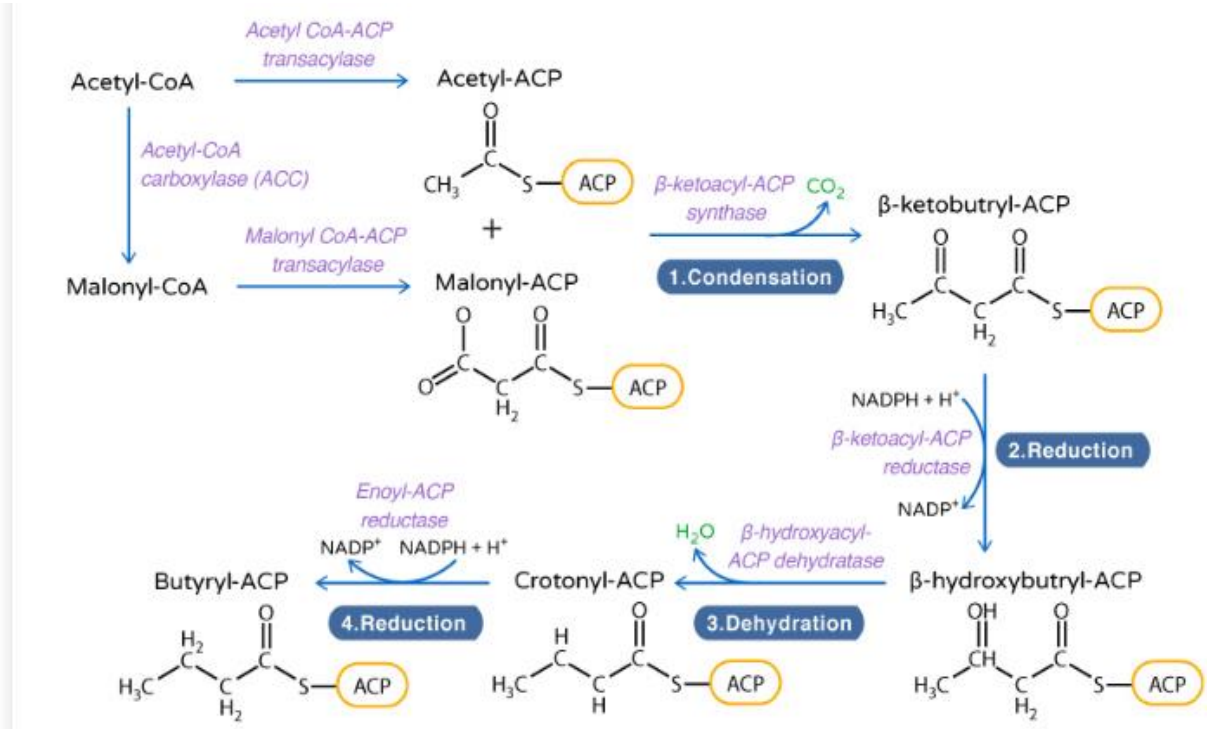


Figure 32: Fatty Acid Synthesis Pathway (site 22)

2.2. Triglyceride Formation

- Fatty acids synthesized in this process can then combine with glycerol (derived from glucose metabolism) to form triglycerides (triacylglycerols), the storage form of fat.
- The enzyme glycerol-3-phosphate acyltransferase catalyzes the esterification of fatty acids to glycerol, forming triglycerides, which are then stored in adipocytes (fat cells).

2.3. Physiological Importance of Lipogenesis

Lipogenesis plays an essential role in the storage of excess energy. When there is an abundance of nutrients (especially carbohydrates), lipogenesis helps convert these nutrients into stored fat for future use, especially during times of fasting or caloric deficit. Additionally, the fats stored in adipose tissue serve as a reserve energy source and contribute to insulation and protection of internal organs.

Fatty acids and triglycerides produced during lipogenesis are also important for various cellular functions, such as membrane structure, signaling pathways, and hormone production. For example, omega-3 and omega-6 fatty acids are essential components of cell membranes and are involved in inflammatory responses and cell signaling.

3. Lipolysis (Fat Breakdown)

Lipolysis is the breakdown of stored triglycerides into free fatty acids (FFAs) and glycerol, which can be used as energy, especially during periods of fasting, exercise, or energy deficits. In adipose tissue, triglycerides are hydrolyzed by lipases into free fatty acids and glycerol. These fatty acids are released into the bloodstream and transported to tissues like muscles and the liver for energy production.

3.1. Steps of Lipolysis:

3.1.1. Breakdown:

- **Triglycerides** are composed of one glycerol molecule bound to three fatty acids. In lipolysis, these triglycerides are broken down by the enzyme hormone-sensitive lipase (HSL) and other enzymes, including adipose triglyceride lipase (ATGL) and monoglyceride lipase (MGL).

- The process begins with the activation of hormone-sensitive lipase by various signaling molecules, such as catecholamines (e.g., adrenaline) and glucagon, in response to low energy states or fasting.

3.1.2. Hydrolysis of Triglycerides:

- ATGL initiates lipolysis by hydrolyzing the first ester bond of triglycerides, forming diacylglycerol (DAG) and a free fatty acid.
- Hormone-sensitive lipase (HSL) then hydrolyzes DAG into monoglyceride (MAG) and another free fatty acid.
- Finally, monoglyceride lipase (MGL) breaks down MAG into glycerol and a free fatty acid.

3.1.3. Release of Fatty Acids and Glycerol:

- The free fatty acids are released into the bloodstream, where they are bound to albumin for transport to various tissues (e.g., muscle or liver) for energy production.
- Glycerol, on the other hand, is taken up by the liver and can be converted into glucose via gluconeogenesis.

3.2. Regulation of Lipolysis:

- **Stimulated by:**
  - **Catecholamines** (e.g., adrenaline) via **beta-adrenergic receptors**.
  - **Glucagon**, which activates HSL.
  - **Growth hormone** and **cortisol** also promote lipolysis.
- **Inhibited by:**
  - **Insulin**: Insulin inhibits lipolysis by promoting the dephosphorylation of HSL, rendering it inactive. It acts to promote fat storage and prevent fat breakdown.

3.3. Fatty Acid Oxidation

Fatty acid oxidation refers to the process by which fatty acids are broken down to generate energy, primarily in the form of ATP. There are several types of fatty acid oxidation processes that occur under different physiological conditions. The two main types are beta-oxidation and alpha-oxidation, but there are also specialized forms such as omega-oxidation.

- **Beta-Oxidation**: Primary pathway for fatty acid breakdown, producing acetyl-CoA, NADH, and $FADH_2$. Occurs in the mitochondria.
- **Alpha-Oxidation**: Used for branched-chain fatty acids (e.g., phytanic acid), primarily in peroxisomes.
- **Omega-Oxidation**: Minor pathway for medium-chain fatty acids, occurring in the endoplasmic reticulum.
- **Peroxisomal Oxidation**: Specialized pathway for the breakdown of very-long-chain fatty acids, also occurring in the peroxisomes.

3.3.1. Beta-Oxidation (Primary Fatty Acid Oxidation)

Beta-oxidation is the most common and significant pathway for fatty acid degradation. It takes place primarily in the mitochondria (and also in peroxisomes to a lesser extent). In this process, fatty acids are broken down into acetyl-CoA units, which are then used in the citric acid cycle (TCA cycle) for further ATP production.

3.3.2. Steps of Beta-Oxidation:

A. Activation of Fatty Acids

Before fatty acids can enter the mitochondria for beta-oxidation, they must first be activated to form fatty acyl-CoA. This occurs in the cytoplasm and involves the enzyme acyl-CoA synthetase (also known as fatty acyl-CoA synthetase).

- The fatty acid (in its free form) reacts with Coenzyme A (CoA) and ATP to form fatty acyl-CoA.
- The reaction is:

  $$\text{Fatty acid} + \text{ATP} + \text{CoA} \rightarrow \text{Fatty acyl-CoA} + \text{AMP} + \text{PPi}$$

- This fatty acyl-CoA then enters the mitochondria via a transport system (the carnitine shuttle), as the inner mitochondrial membrane is impermeable to fatty acyl-CoA.

B. Transport into the Mitochondrion

- **Carnitine acyltransferase I** (CAT-I) on the outer mitochondrial membrane replaces the CoA group of fatty acyl-CoA with carnitine, forming fatty acyl-carnitine.

- The fatty acyl-carnitine is then transported across the inner mitochondrial membrane by the **carnitine-acylcarnitine translocase** (CACT).
- Once inside the matrix, **carnitine acyltransferase II** (CAT-II) on the inner mitochondrial membrane converts fatty acyl-carnitine back to fatty acyl-CoA, and carnitine is returned to the cytoplasm.

C. Beta-Oxidation Cycle

The actual beta-oxidation occurs in four main steps, each reducing the length of the fatty acyl-CoA by two carbon atoms and producing acetyl-CoA. Here's a breakdown of each step:

- **Step 1: Dehydrogenation (Formation of Trans-Δ^2-Enoyl-CoA)**
  - The first reaction involves the enzyme acyl-CoA dehydrogenase. This enzyme catalyzes the formation of a double bond between the alpha (C2) and beta (C3) carbons of the fatty acyl-CoA molecule, resulting in a trans-Δ^2-enoyl-CoA intermediate.
  - This step also produces $FADH_2$, which enters the electron transport chain for ATP production.
- **Step 2: Hydration (Formation of L-3-Hydroxyacyl-CoA)**
  - The next step is the hydration of the double bond in trans-Δ^2-enoyl-CoA. This reaction is catalyzed by the enzyme enoyl-CoA hydratase.
  - A water molecule is added across the double bond, yielding L-3-hydroxyacyl-CoA.
- **Step 3: Dehydrogenation (Formation of 3-Ketoacyl-CoA)**
  - The third step is another dehydrogenation reaction, catalyzed by hydroxyacyl-CoA dehydrogenase. This enzyme oxidizes the hydroxyl group (-OH) at the beta carbon of L-3-hydroxyacyl-CoA, converting it into a keto group, forming 3-ketoacyl-CoA.
  - This step produces NADH, which can also enter the electron transport chain to generate ATP.
- **Step 4: Thiolysis (Cleavage to Form Acetyl-CoA and Shortened Fatty Acyl-CoA)**
  - The final step is thiolysis, which is the cleavage of the bond between the alpha and beta carbons. This is catalyzed by β-ketothiolase.

- A molecule of CoA (Coenzyme A) is added, resulting in the formation of acetyl-CoA and a shortened fatty acyl-CoA (two carbon atoms shorter than the original fatty acid).
- The acetyl-CoA enters the citric acid cycle for further energy production (ATP, NADH, and $FADH_2$).

D. Repeat of Beta-Oxidation Cycle

- The shortened fatty acyl-CoA now goes through another round of beta-oxidation. The cycle repeats itself until the fatty acid is completely broken down into acetyl-CoA units.
- Each round of beta-oxidation removes two carbon atoms from the fatty acid, so for a fatty acid of n carbon atoms, the number of cycles will be $n/2-1$.

E. End of Beta-Oxidation

- When the fatty acid is reduced to two carbon atoms in the form of acetyl-CoA, the process ends, and the acetyl-CoA enters the citric acid cycle (TCA cycle) for further ATP generation.

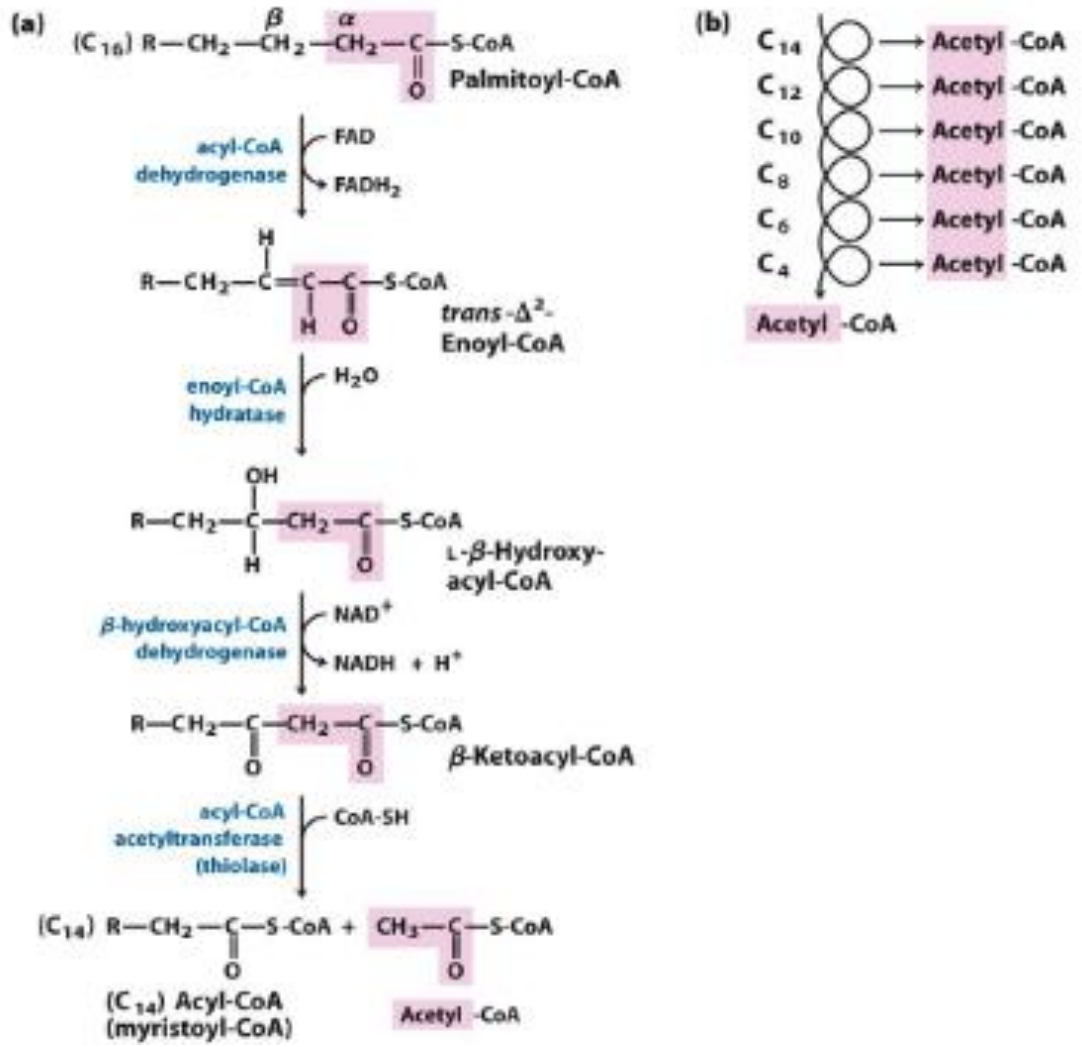


Figure 33: Complete beta oxidation of Palmitoyl-CoA results in 8 molecules of Acetyl-CoA. (Davis et al., 2008)

- **ATP Yield from Beta-Oxidation**
- The overall reaction can be represented as;

C_n-Acyl CoA+FAD+NAD+H_2O+CoA ⟶ C_{n-2}-acyl CoA+ $FADH_2$+ NADH+ acetyl CoA+ H^+

Thus, the ATP yield depends on the length of the fatty acid chain. For example, a 16-carbon fatty acid (palmitic acid) will undergo 7 rounds of beta-oxidation, resulting in the production of 8 acetyl-CoA molecules, 7 NADH, and 7 $FADH_2$,

Every acetyl CoA yields 3 NADH + 1 FADH2 + 1 GTP (=ATP) during Krebs cycle. Considering an average production of 3 ATP per NADH and 2 ATP per $FADH_2$ using the respiratory chain, we have 131 ATP molecules.

However, 2 ATP molecules are used for the initial activation of every fatty acid that is going to be oxidized in the mitochondria. Hence, net 129 ATP molecules are produced.

4. Ketogenesis

4.1 Ketogenesis is the metabolic process by which ketone bodies are produced from fatty acids (specifically from acetyl-CoA) in the liver, primarily during periods of fasting, prolonged exercise, or when carbohydrate intake is low (such as in a low-carbohydrate diet or starvation). Ketone bodies serve as an alternative fuel source when glucose is in limited supply. The three primary ketone bodies are:

- **Acetoacetate**
- **Beta-hydroxybutyrate**
- **Acetone** (which is produced in small amounts and is mostly exhaled)

4.2. Why Does Ketogenesis Occur?

During periods of fasting or carbohydrate restriction, the body relies on stored fats for energy. As the body metabolizes fatty acids through beta-oxidation, acetyl-CoA is generated. However, the liver's citric acid cycle (TCA cycle) becomes saturated with acetyl-CoA when glucose is not available to combine with oxaloacetate (a TCA cycle intermediate), and the excess acetyl-CoA cannot enter the cycle. This is where ketogenesis comes in: it converts excess acetyl-CoA into ketone bodies, which can be used as an alternative energy source, particularly by tissues like the brain, heart, and muscles.

4.3. Overview of Ketogenesis Pathway

The process of ketogenesis occurs in the mitochondria of liver cells (hepatocytes). Here are the key steps involved in the formation of ketone bodies:

4.3.1. Fatty Acid Mobilization (Lipolysis)

- First, during fasting or low-carb states, triglycerides stored in adipose tissue are broken down into fatty acids and glycerol by the enzyme hormone-sensitive lipase (HSL) during lipolysis.
- These fatty acids are transported via the bloodstream to the liver, where they undergo beta-oxidation to form acetyl-CoA.

4.3.2. Conversion of Acetyl-CoA to Acetoacetyl-CoA

- Once in the liver mitochondria, acetyl-CoA undergoes condensation to form acetoacetyl-CoA through the enzyme thiolase (also known as acetyl-CoA acetyltransferase).

4.3.3. Formation of HMG-CoA

- Acetoacetyl-CoA then reacts with another molecule of acetyl-CoA, catalyzed by the enzyme HMG-CoA synthase, to form 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA).

4.3.4. Cleavage of HMG-CoA to Form Acetoacetate

- HMG-CoA is then cleaved by the enzyme HMG-CoA lyase to form acetoacetate and acetyl-CoA (one molecule of acetyl-CoA is released per HMG-CoA molecule).

4.3.5. Conversion of Acetoacetate to Beta-Hydroxybutyrate

- Some acetoacetate is converted into beta-hydroxybutyrate through the enzyme beta-hydroxybutyrate dehydrogenase. This step involves the reduction of acetoacetate using NADH as the reducing agent.

Acetoacetate+NADH→Beta-hydroxybutyrate dehydrogenase hydroxybutyrate+NAD+

Beta-hydroxybutyrate is the major ketone body in the blood during ketosis because it is more stable and can be easily transported to other tissues.

4.3.6. Acetone Production

- Acetone is a small, volatile ketone body that is produced as a byproduct of acetoacetate's spontaneous decarboxylation (loss of a CO_2 molecule). It is released in small amounts and is mainly exhaled through the lungs.

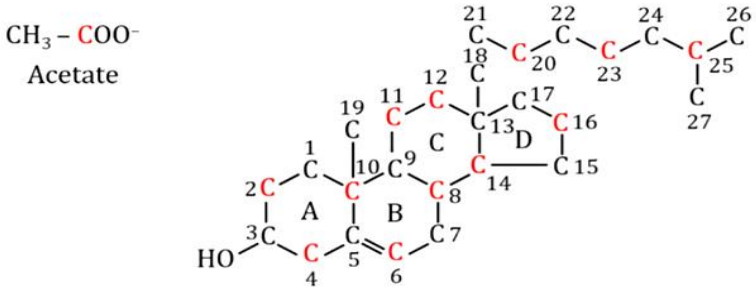
4.4. Ketone Bodies in the Bloodstream

Once ketone bodies are synthesized in the liver, they are released into the bloodstream, where they are transported to various tissues, including the brain, heart, and muscles. These tissues can use beta-hydroxybutyrate and acetoacetate as an energy source by converting them back to acetyl-CoA and entering the citric acid cycle for ATP production.

- Beta-hydroxybutyrate and acetoacetate are transported across the mitochondrial membranes of target cells.
- Inside these cells, beta-hydroxybutyrate is oxidized back to acetoacetate (by beta-hydroxybutyrate dehydrogenase), and acetoacetate is converted to acetyl-CoA by a thiolase enzyme, which can then enter the citric acid cycle.

5. Cholesterol Metabolism

5.1. Cholesterol is a crucial lipid molecule that plays vital roles in the body, including as a structural component of cell membranes, a precursor for bile acids, steroid hormones (such as cortisol, estrogen, and testosterone), and vitamin D. However, cholesterol levels need to be tightly regulated, as imbalances can lead to cardiovascular diseases. Cholesterol metabolism involves both the synthesis and the breakdown of cholesterol, with complex regulation mechanisms to maintain homeostasis.



Cholesterol

5.2. Sources of Cholesterol in the Body

Cholesterol in the body comes from two primary sources:

1. **Dietary Cholesterol**: Cholesterol obtained from animal products (meat, dairy, eggs).

2. **Endogenous Cholesterol**: Cholesterol synthesized by the body, predominantly in the **liver** and **intestinal cells**. In fact, most of the cholesterol in the body is made endogenously rather than from the diet.

5.3. Cholesterol Synthesis

The biosynthesis of cholesterol primarily occurs in the liver, but also in other tissues like the intestines, adrenal glands, and gonads. The process is complex, and several key enzymes play critical roles in its synthesis. Here's a breakdown of the steps:

5.3.1. Acetyl-CoA to Mevalonate

- Cholesterol synthesis starts with acetyl-CoA, a molecule derived from carbohydrates and fatty acids, which enters the cytoplasm.
- Acetyl-CoA condenses to form HMG-CoA (3-hydroxy-3-methylglutaryl-CoA), a reaction catalyzed by HMG-CoA synthase.
- HMG-CoA is then reduced to mevalonate by HMG-CoA reductase, an enzyme that is considered the rate-limiting step of cholesterol synthesis.
    - This reaction is crucial because HMG-CoA reductase is the target of statin drugs, which are commonly prescribed to lower cholesterol levels in patients at risk of cardiovascular diseases.

$$\text{HMG-CoA} + 2\text{NADPH} \xrightarrow{\text{HMG-CoA reductase}} \text{Mevalonate} + 2\text{NADP}^+$$

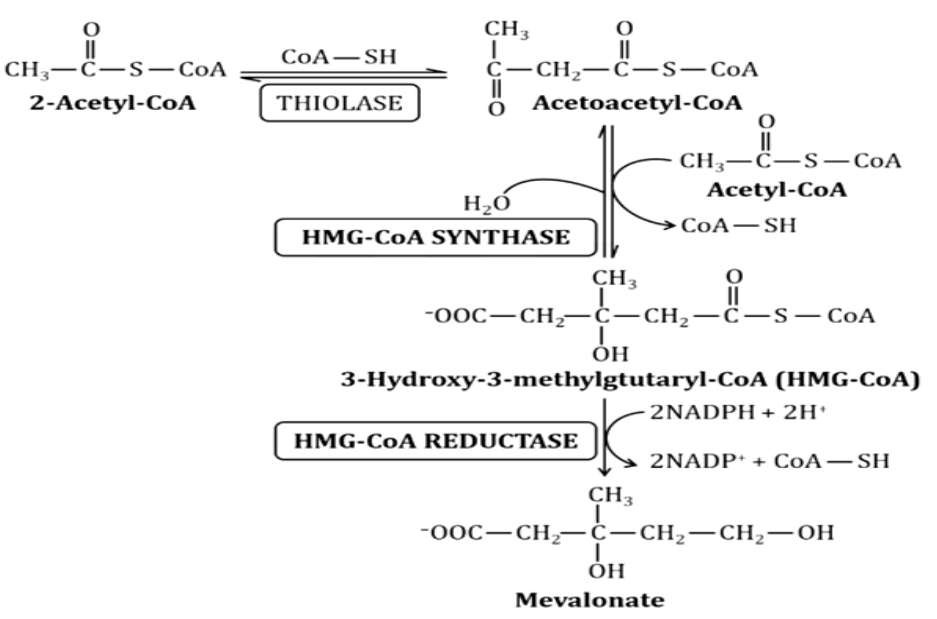


Figure 34: Synthesis of Mevalonate from Acetate (site 23)

5.3.2. Mevalonate to Isoprenoid Intermediates

- Mevalonate is phosphorylated and decarboxylated to produce isoprenoid intermediates (e.g., isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP)), which are essential building blocks for the synthesis of cholesterol.
- Mevalonate kinase, phosphomevalonate kinase, and mevalonate pyrophosphate decarboxylase catalyze these steps.

5.3.3. Formation of Squalene

- The isoprenoid intermediates are then used to form squalene, a precursor to sterols.
- Squalene synthetase catalyzes the condensation of two farnesyl pyrophosphate molecules to form squalene.

5.3.4. Squalene to Cholesterol

- Squalene undergoes cyclization to form lanosterol, which is further modified through a series of steps (demethylation, reduction, and isomerization) to produce cholesterol.

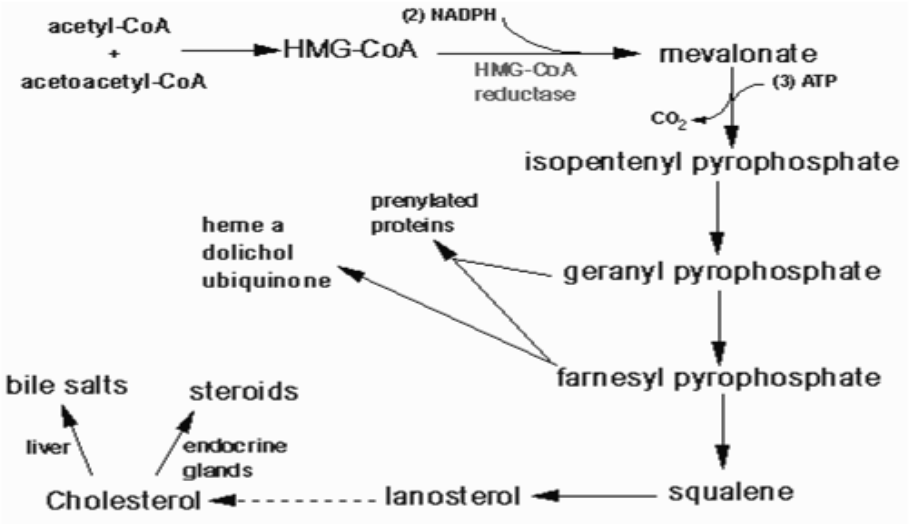


Figure 35: pathway of cholesterol biosynthesis (site 24)

5.4. Cholesterol Transport and Esterification

Once synthesized, cholesterol is transported in the bloodstream and is esterified for storage or transport in lipoproteins. The two main forms of cholesterol in circulation are free cholesterol and cholesterol esters.

5.4.1. Lipoprotein Transport

- Cholesterol is carried by **lipoproteins**, which are complexes of lipids and proteins. The main types of lipoproteins that transport cholesterol are:
  - **Low-Density Lipoprotein (LDL)**: Often referred to as "bad cholesterol," LDL is the primary carrier of cholesterol in the bloodstream. It delivers cholesterol to peripheral tissues and the liver.
  - **High-Density Lipoprotein (HDL)**: Often referred to as "good cholesterol," HDL helps transport cholesterol from peripheral tissues back to the liver for recycling or excretion.
  - **Very Low-Density Lipoprotein (VLDL)** and **Chylomicrons** also carry triglycerides and cholesterol, but their primary role is triglyceride transport.

5.4.2. Cholesterol Esterification

- Cholesterol can be esterified (bound to fatty acids) for storage or transport. The enzyme lecithin-cholesterol acyltransferase (LCAT) catalyzes this reaction, converting free

cholesterol to cholesteryl esters, which are more hydrophobic and can be stored in lipoproteins like HDL.

5.5. Regulation of Cholesterol Metabolism

The body tightly regulates cholesterol synthesis to maintain a balance. Several mechanisms are involved in regulating the synthesis and uptake of cholesterol:

5.5.1. Regulation of HMG-CoA Reductase

- **Feedback inhibition**: High levels of cholesterol in the liver inhibit the activity of HMG-CoA reductase, the enzyme responsible for the rate-limiting step in cholesterol synthesis.
- **Transcriptional regulation**: The liver senses cholesterol levels and adjusts the transcription of genes involved in cholesterol synthesis. The sterol regulatory element-binding proteins (SREBPs) are key transcription factors that increase the expression of HMG-CoA reductase when cholesterol levels are low. When intracellular cholesterol levels decrease, it is released and migrates to the nucleus where it binds to the SRE (sterol regulatory element). of the HMG-CoA reductase gene; it then activates transcription. On the other hand, when intracellular cholesterol levels increase, the release of SREBP is inhibited and nuclear SREBP is proteolyzed.
- **Proteolytic degradation**: When cellular cholesterol levels are high, HMG-CoA reductase undergoes proteolytic degradation, reducing its activity.
- **Hormonal regulation**: The HMG CoA reductase exists in two interconvertible forms. Insulin and thyroid hormones Increase HMG CoA reductase activity The dephosphorylated form of the enzyme is more active. Hormones exert their influence through Camp. Glucagon and glucocorticoids decrease HMG-CoA reductase activity
- **Inhibition by drugs:** The drugs Compactin andλ lovastatin, mevastatin, simvastin are competitive inhibitors used to decrease the cholesterol.

5.5.2. LDL Receptor-Mediated Uptake

- The **LDL receptor** on hepatocytes (liver cells) and other cells mediates the uptake of LDL particles, which contain cholesterol. When cellular cholesterol levels are low, the number of LDL receptors on cell membranes increases to enhance cholesterol uptake.

- **Familial hypercholesterolemia** is a genetic disorder where LDL receptor activity is impaired, leading to high blood cholesterol levels.

5.5.3. Bile Acid Synthesis and Excretion

- Cholesterol is converted into bile acids in the liver, which are then excreted into the intestines to aid in digestion and absorption of dietary fats.
- A portion of bile acids is reabsorbed and returned to the liver through the enterohepatic circulation. However, a portion is excreted, removing cholesterol from the body.

II. Hormonal Regulation of Lipid Metabolism

Lipid metabolism is finely regulated by a range of hormones that control key processes such as **lipogenesis**, **lipolysis**, **cholesterol metabolism**, and **ketogenesis**. These hormones play crucial roles in maintaining energy balance, managing fat storage and breakdown, and regulating cholesterol and ketone body production. Here's a detailed breakdown of how hormones regulate these processes:

1. Hormonal Regulation of Lipogenesis (Fat Synthesis)

Lipogenesis is the process of synthesizing fatty acids and triglycerides (fat) from acetyl-CoA and malonyl-CoA. This occurs primarily in the liver and adipose tissue. Key hormones that regulate lipogenesis include insulin, glucagon, and cortisol.

1.1. Insulin (Primary Regulator)

- Insulin is the most important hormone in the regulation of lipogenesis. It promotes the synthesis of fatty acids and triglycerides when there is a surplus of glucose or nutrients (post-meal state).
- **Mechanisms**:
    - **Activation of acetyl-CoA carboxylase (ACC)**: Insulin activates ACC, which is the rate-limiting enzyme in fatty acid synthesis. ACC converts acetyl-CoA into malonyl-CoA, the building block for fatty acid elongation.
    - **Activation of fatty acid synthase (FAS)**: Insulin promotes the activity of fatty acid synthase, the enzyme that catalyzes the elongation of fatty acids.

- **Inhibition of lipolysis**: Insulin inhibits hormone-sensitive lipase (HSL), reducing the breakdown of stored fat.
- **Gene expression**: Insulin increases the expression of genes involved in lipogenesis (e.g., SREBP-1c).

1.2.Glucagon (Opposes Lipogenesis)

- **Glucagon** is released during fasting or low blood sugar states and has an antagonistic effect to insulin, inhibiting lipogenesis.
- **Mechanisms**:
  - Inhibition of ACC: Glucagon inhibits acetyl-CoA carboxylase (ACC), reducing malonyl-CoA levels and, consequently, inhibiting fatty acid synthesis.
  - Activation of lipolysis: Glucagon activates HSL in adipose tissue, increasing the breakdown of triglycerides into free fatty acids.

1.3.Cortisol (Stress Hormone)

- **Cortisol**, a glucocorticoid released during stress or fasting, has a minor role in stimulating lipogenesis, especially in adipose tissue. Cortisol enhances the transcription of lipogenic genes.
- **Mechanisms**:
  - Cortisol stimulates SREBP-1 (sterol regulatory element-binding protein-1), which activates genes involved in fatty acid synthesis.

2. Hormonal Regulation of Lipolysis (Fat Breakdown)

Lipolysis is the process by which stored triglycerides are broken down into free fatty acids and glycerol, which are released into the bloodstream and used as energy.

2.1. Insulin (Inhibits Lipolysis)

- **Insulin** is the main inhibitor of lipolysis. It suppresses fat breakdown by reducing the activity of hormone-sensitive lipase (HSL).
- **Mechanisms**:

- Insulin activates phosphodiesterase, which reduces the levels of cyclic AMP (cAMP). Lower cAMP levels lead to reduced activation of protein kinase A (PKA), which would otherwise activate HSL.
- Insulin also promotes lipogenesis while suppressing lipolysis, thus ensuring energy is stored when food is abundant.

2.2. Epinephrine and Norepinephrine (Stimulate Lipolysis)

- **Epinephrine** (adrenaline) and **norepinephrine** (noradrenaline) are released during the "fight or flight" response to increase energy availability by promoting lipolysis.
- **Mechanisms**:
  - **Activation of cAMP**: Epinephrine binds to β-adrenergic receptors on adipocytes, leading to the activation of adenylate cyclase and increased cAMP levels.
  - **Activation of PKA**: High cAMP activates PKA, which phosphorylates and activates hormone-sensitive lipase (HSL), leading to triglyceride breakdown into free fatty acids and glycerol.

2.3. Glucagon (Stimulates Lipolysis)

- **Glucagon** promotes lipolysis during fasting or low blood sugar levels.
- **Mechanisms**:
  - Activation of cAMP/PKA pathway: Like epinephrine, glucagon stimulates the β-adrenergic pathway, leading to increased cAMP levels and activation of PKA, which in turn activates HSL and promotes lipolysis.

2.4. Cortisol (Stimulates Lipolysis)

- Cortisol also stimulates lipolysis, particularly in the visceral fat (fat around internal organs).
- **Mechanisms**:
  - Cortisol induces the expression of genes involved in lipolysis, particularly in adipose tissue, which results in the breakdown of triglycerides.

3. Hormonal Regulation of Cholesterol Metabolism (Synthesis and Catabolism)

Cholesterol metabolism is tightly regulated because cholesterol is essential for membrane structure, steroid hormone synthesis, and bile acid production. The regulation of cholesterol synthesis and catabolism is controlled by several key hormones, including insulin, glucagon, thyroid hormones, and statins (medications).

3.1. Cholesterol Synthesis

- **Insulin**: Promotes cholesterol synthesis by stimulating the enzyme HMG-CoA reductase, the rate-limiting enzyme in the mevalonate pathway (the pathway for cholesterol synthesis).
- **Glucagon**: Inhibits cholesterol synthesis by decreasing HMG-CoA reductase activity.
- **Thyroid Hormones (T3 and T4)**: Thyroid hormones upregulate HMG-CoA reductase and enhance cholesterol synthesis, increasing the overall cholesterol pool.
- **Statins**: Statins are drugs that inhibit HMG-CoA reductase, decreasing cholesterol synthesis. Statins are commonly used to reduce blood cholesterol levels, particularly LDL cholesterol.

3.3. Cholesterol Catabolism (Excretion and Conversion to Bile Acids)

- **Bile Acid Synthesis**: Cholesterol is converted to bile acids in the liver. This process is regulated by feedback inhibition. High levels of cholesterol reduce the activity of cholesterol 7α-hydroxylase, the rate-limiting enzyme in bile acid synthesis.
- **Feedback Inhibition**: Elevated levels of LDL cholesterol in the blood reduce the expression of LDL receptors on liver cells, decreasing the uptake of cholesterol and thereby reducing cholesterol synthesis.

4. Hormonal Regulation of Ketogenesis

Ketogenesis is the process of producing ketone bodies (acetoacetate, beta-hydroxybutyrate, and acetone) from acetyl-CoA during periods of low carbohydrate availability (fasting, prolonged exercise, or a ketogenic diet). The liver is the primary organ responsible for ketogenesis.

4.1. Glucagon (Promotes Ketogenesis)

- Glucagon is released during fasting or low blood glucose conditions. It stimulates ketogenesis by promoting the breakdown of fatty acids into acetyl-CoA in the liver, which is the precursor for ketone bodies.
- **Mechanism**:
  - Activation of HSL: Glucagon promotes lipolysis by activating HSL, which releases fatty acids from adipocytes.
  - Acetyl-CoA Production: The fatty acids released are oxidized in the liver to generate acetyl-CoA, which enters the ketogenesis pathway to form ketone bodies.

4.2. Insulin (Inhibits Ketogenesis)

- **Insulin** inhibits ketogenesis. When insulin levels are high (such as after eating), fatty acid oxidation is suppressed, leading to lower acetyl-CoA production and decreased ketone body formation.
- **Mechanism**:
  - High insulin levels suppress lipolysis, decreasing fatty acid availability for acetyl-CoA production.
  - Insulin also inhibits the activity of HMG-CoA synthase, the enzyme involved in the production of acetoacetate from acetyl-CoA.

4.3. Cortisol (Enhances Ketogenesis)

- Cortisol, a stress hormone, promotes ketogenesis by increasing the breakdown of fat (lipolysis) and the release of fatty acids for acetyl-CoA production.
- **Mechanism**:
  - Cortisol stimulates the release of fatty acids from adipose tissue, which increases the availability of acetyl-CoA in the liver, thus enhancing ketogenesis.

4.4. Thyroid Hormones (Regulate Ketogenesis)

- Thyroid hormones (especially T3) also regulate ketogenesis, with hypothyroidism leading to decreased ketone production and hyperthyroidism leading to increased ketogenesis.

- **Mechanism**: Thyroid hormones influence the enzymes involved in fatty acid oxidation and ketogenesis, including HMG-CoA synthase, the rate-limiting enzyme in ketone production.

5. Regulation of metabolism by steroid hormones (cortisol)

Cortisol, a steroid hormone produced by the adrenal glands, plays a significant role in regulating lipid metabolism, particularly in response to stress, fasting, and other metabolic demands. It influences multiple aspects of lipid metabolism, including lipolysis, fat storage, and the mobilization of fatty acids for energy production. However, prolonged or excessive cortisol levels, as seen in chronic stress or certain medical conditions, can lead to abnormal fat accumulation (particularly in the abdominal area), insulin resistance, and metabolic disturbances. Here's a detailed overview of how cortisol regulates lipid metabolism:

5.1. Lipolysis (Fat Breakdown):

- **Cortisol promotes lipolysis**, the breakdown of triglycerides stored in adipose tissue into free fatty acids (FFAs) and glycerol. This process is crucial for providing an energy source, especially during periods of stress or fasting, when glucose reserves are low.
- Cortisol increases the activity of enzymes involved in lipolysis, such as hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL). These enzymes facilitate the breakdown of stored triglycerides into FFAs and glycerol, which can then be used by the liver and muscles for energy production.
- This action helps increase the availability of free fatty acids, which can be used as an alternative energy source when glucose levels are low, thus ensuring a constant supply of energy to vital organs like the heart and muscles during stress.

5.2. Fat Distribution:

- Although cortisol promotes lipolysis, it also influences where fat is stored. Chronic elevated cortisol levels (such as in prolonged stress or conditions like Cushing's syndrome) tend to cause redistribution of fat.
- **Visceral fat** (fat around internal organs) tends to accumulate more readily under high cortisol levels, while subcutaneous fat (fat beneath the skin) may decrease. This

visceral fat accumulation is linked to various metabolic disorders, including insulin resistance, obesity, and cardiovascular disease.

5.3. Increased Fatty Acid Mobilization:

- Cortisol encourages the mobilization of fatty acids from adipose tissue, which can then enter circulation to be used for energy by other tissues. This is particularly important during fasting or physical exertion, when the body needs an alternative fuel source to glucose.
- The mobilized fatty acids are taken up by the liver, where they can be converted into acetyl-CoA for use in beta-oxidation, generating ATP. They can also be used in the production of ketone bodies during prolonged fasting or carbohydrate restriction.

5.4. Inhibition of Insulin Sensitivity:

- Cortisol increases insulin resistance, which can exacerbate the body's reliance on fatty acids for energy. As insulin resistance increases, the ability of adipose tissue to store fat is impaired, while fat breakdown (lipolysis) is enhanced. This results in higher circulating free fatty acids.
- Elevated free fatty acids can contribute to further insulin resistance, especially in muscle and liver tissues, creating a feedback loop that promotes fat mobilization and accumulation.

5.5. Regulation of Fat Synthesis (Lipogenesis):

- While cortisol promotes lipolysis (fat breakdown), it can also have a dual effect on lipogenesis (fat synthesis). In the short term, cortisol may slightly increase the synthesis of fatty acids and triglycerides to maintain energy balance and ensure proper fat storage. However, chronic exposure to high cortisol levels typically leads to the promotion of fat breakdown over fat storage.
- Cortisol's role in fat synthesis is less pronounced compared to its role in promoting lipolysis, but prolonged elevated cortisol may lead to an increase in lipogenesis in specific tissues (such as the liver) to cope with excessive fatty acid mobilization.

5.6. Impact on Fatty Acid Oxidation:

- Cortisol also influences fatty acid oxidation (the process by which fatty acids are broken down to produce ATP) by increasing the availability of fatty acids for oxidation. During periods of stress or fasting, cortisol increases the supply of fatty acids and stimulates their oxidation in tissues like muscles and the liver, providing energy when glucose is limited.

5.7. Interaction with Other Hormones:

- Cortisol interacts with other hormones involved in lipid metabolism, such as insulin, growth hormone, and epinephrine.
    - Insulin counteracts the effects of cortisol by promoting fat storage and inhibiting lipolysis. Elevated cortisol levels can make tissues less responsive to insulin, further increasing fat mobilization.
    - Epinephrine and norepinephrine work synergistically with cortisol during stress, amplifying the effects of lipolysis to ensure that sufficient energy is available.
    - Growth hormone also interacts with cortisol, with cortisol stimulating some of the growth hormone effects, including lipolysis, though excessive cortisol may reduce the effectiveness of growth hormone in muscle tissues.

III. Pathologies due to a deregulation of lipid metabolism

Deregulation of lipid metabolism can lead to a variety of pathologies, particularly those associated with abnormal levels of lipids in the bloodstream. The most common lipid-related disorders include **hypercholesterolemia**, **atherosclerosis**, **hypertriglyceridemia**, and others. These conditions can contribute to a range of cardiovascular and metabolic diseases.

1. Hypercholesterolemia

Hypercholesterolemia refers to elevated levels of cholesterol in the blood, particularly low-density lipoprotein (LDL) cholesterol. Cholesterol is an essential component of cell membranes and a precursor for steroid hormones, bile acids, and vitamin D. However, when cholesterol levels are abnormally high, especially LDL cholesterol, it can lead to the accumulation of cholesterol in blood vessels, promoting atherosclerosis and increasing the risk of cardiovascular diseases (CVD).

Causes:

- **Primary Hypercholesterolemia**: Genetic conditions like familial hypercholesterolemia (FH) lead to defective or absent LDL receptors, which impairs the liver's ability to clear LDL cholesterol from the bloodstream, causing elevated cholesterol levels. This is often inherited in an autosomal dominant pattern.
- **Secondary Hypercholesterolemia**: Caused by lifestyle factors such as a high-fat diet, physical inactivity, smoking, and excessive alcohol consumption, or secondary to other conditions like diabetes, hypothyroidism, or kidney disease.

Consequences:

- **Atherosclerosis**: High LDL cholesterol levels contribute to the formation of **plaques** in arterial walls. Over time, these plaques can narrow and harden the arteries, leading to reduced blood flow, increasing the risk of coronary artery disease (CAD), stroke, and peripheral artery disease (PAD).
- **Cardiovascular Disease (CVD)**: Chronic hypercholesterolemia significantly increases the risk of heart attacks and other cardiovascular events due to the development of atherosclerotic plaques.
- **Xanthomas**: Fatty deposits that form under the skin, especially around the eyes, elbows, and knees, can occur in patients with extremely high cholesterol levels.

Treatment:

- **Statins**: Medications that **inhibit HMG-CoA reductase**, the rate-limiting enzyme in cholesterol synthesis, thereby lowering cholesterol levels.
- **PCSK9 inhibitors**: Newer drugs that increase LDL receptor activity, enhancing the clearance of LDL from the bloodstream.
- **Lifestyle changes**: A low-fat, high-fiber diet, regular physical activity, and weight management.

2. Atherosclerosis

Atherosclerosis is the thickening and hardening of the arterial walls due to the accumulation of lipids, cholesterol, and other substances (such as calcium) in the intima of the arteries. The process begins with the accumulation of LDL cholesterol in the arterial wall, which is

oxidized and taken up by macrophages, forming foam cells and eventually leading to the formation of atherosclerotic plaques.

Pathophysiology:

- The process of atherosclerosis begins when LDL cholesterol accumulates in the walls of arteries, particularly in areas with high shear stress (like bifurcations of large arteries). These cholesterol deposits trigger an inflammatory response, recruiting immune cells such as monocytes, which differentiate into macrophages. The macrophages consume the oxidized LDL, transforming into foam cells that aggregate and contribute to the plaque.
- As the plaques grow, they can obstruct blood flow, increasing the risk of ischemia (lack of oxygen to tissues) and causing complications such as heart attacks or strokes. Over time, plaques may rupture, leading to the formation of a blood clot (thrombus), which can completely block an artery, causing acute cardiovascular events.

Risk Factors:

- High LDL cholesterol and low HDL cholesterol levels.
- Hypertension (high blood pressure), smoking, diabetes, and a sedentary lifestyle.
- Genetic predisposition, family history of CVD, and increasing age.

Treatment:

- **Statins** and other lipid-lowering agents to reduce LDL cholesterol.
- **Aspirin** and **anticoagulants** may be used to reduce the risk of clot formation.
- **Lifestyle changes**, including diet modification and exercise.

3. Hypertriglyceridemia

Hypertriglyceridemia refers to elevated levels of triglycerides (the most common form of fat found in the blood). Triglycerides are essential for energy storage, but when their levels exceed normal ranges, they can contribute to cardiovascular risk and other metabolic disorders.

Causes:

- **Primary Hypertriglyceridemia**: Can be due to genetic conditions such as familial hypertriglyceridemia or familial combined hyperlipidemia, which impair the metabolism of triglycerides.
- **Secondary Hypertriglyceridemia**: Common causes include obesity, type 2 diabetes, alcohol consumption, hypothyroidism, and certain medications such as beta-blockers, thiazide diuretics, and steroids.

Consequences:

- **Pancreatitis**: Extremely high triglyceride levels (usually above 1000 mg/dL) can lead to acute pancreatitis, a severe inflammation of the pancreas.
- **Cardiovascular Disease**: Hypertriglyceridemia is associated with an increased risk of atherosclerosis and CVD, particularly when accompanied by low HDL cholesterol levels and high LDL cholesterol levels.
- **Metabolic Syndrome**: High triglyceride levels are a component of metabolic syndrome, which also includes insulin resistance, hypertension, and central obesity. This cluster of conditions increases the risk of type 2 diabetes and CVD.

Treatment:

- **Fibrates**: Medications that lower triglycerides by increasing the activity of **lipoprotein lipase**, which breaks down triglycerides in the blood.
- **Omega-3 fatty acids**: Supplements can lower triglyceride levels.
- **Lifestyle changes**: Weight loss, reducing alcohol intake, and improving insulin sensitivity through diet and exercise.

4. Dyslipidemia

Dyslipidemia refers to abnormal levels of lipids in the blood, including high LDL cholesterol, low HDL cholesterol, and high triglycerides. Dyslipidemia is a major risk factor for cardiovascular diseases, particularly atherosclerosis, and is often associated with other conditions like diabetes, obesity, and metabolic syndrome.

Causes:

- **Genetic Factors**: Familial hypercholesterolemia, familial combined hyperlipidemia, and familial dysbetalipoproteinemia.
- **Secondary Causes**: Obesity, insulin resistance, uncontrolled diabetes, poor diet (especially high in trans fats and saturated fats), and lack of physical activity.

Consequences:

- **Atherosclerosis**: An imbalance in lipid levels, such as elevated LDL and triglycerides with low HDL, contributes to plaque formation in arteries, increasing the risk of atherosclerosis and subsequent cardiovascular events.
- **Metabolic Syndrome**: Dyslipidemia is a core component of metabolic syndrome, which includes abdominal obesity, insulin resistance, hypertension, and dyslipidemia. These factors collectively increase the risk of type 2 diabetes and CVD.

Treatment:

- **Statins**, **fibrates**, **niacin**, and **omega-3 fatty acids** are used to manage dyslipidemia by targeting elevated LDL, triglycerides, or low HDL levels.
- **Lifestyle modifications** such as weight management, increased physical activity, and a diet low in saturated and trans fats, as well as smoking cessation.

5. Other Lipid Metabolism Disorders

Familial Hypertriglyceridemia

A genetic condition characterized by extremely high triglyceride levels, often due to a defect in lipoprotein lipase activity, leading to impaired triglyceride clearance. It increases the risk of pancreatitis and cardiovascular disease.

Abetalipoproteinemia

A rare genetic disorder that impairs the production of lipoproteins, particularly chylomicrons and VLDL, resulting in deficiencies in essential fatty acids and fat-soluble vitamins. It leads to malabsorption, growth failure, and neurological symptoms.

Tangier Disease

A rare lipid storage disorder where there is an accumulation of phospholipids in tissues due to a defect in the ABCA1 transporter, which impairs HDL cholesterol formation. This leads to high cholesterol levels in the blood and accumulation of lipids in various tissues.

These disorders can have serious cardiovascular consequences, including heart attacks, strokes, and peripheral artery disease, and are often associated with other risk factors such as insulin resistance and obesity. Early detection, lifestyle modifications (such as diet and exercise), and pharmacological interventions (such as statins, fibrates, and PCSK9 inhibitors) play a key role in managing lipid imbalances and reducing the risk of associated cardiovascular diseases.

Regulation of phosphocalcic metabolism and pathologies

I. Phosphocalcic metabolism

Phosphocalcic metabolism, also known as calcium-phosphate metabolism, involves the regulation of calcium (Ca^{2+}) and phosphate (PO_4^{3-}) levels in the body. Proper regulation of these minerals is essential for many physiological functions, including bone formation, neuromuscular function, and cell signaling. Imbalances in calcium and phosphate levels can lead to various pathologies such as osteoporosis, rickets, hypercalcemia, hypocalcemia, and chronic kidney disease. The regulation of phosphocalcic metabolism is a tightly controlled process involving several organs, hormones, and biochemical pathways.

1. Key Players in Phosphocalcic Metabolism

1.1.Calcium (Ca^{2+})

Calcium is a vital element for a range of physiological functions, and its concentration in the blood must be carefully regulated. The body contains about 99% of its calcium in the bones and teeth, and the remaining 1% is found in the blood and soft tissues.

Calcium is involved in processes such as:

- **Bone and teeth mineralization**: Hydroxyapatite crystals formed from calcium and phosphate are the structural components of bone and teeth.
- **Muscle contraction**: Calcium ions interact with proteins in muscle cells to initiate contraction.
- **Nerve signaling**: Calcium plays a key role in neurotransmitter release and nerve impulse transmission.
- **Blood clotting**: Calcium is a cofactor in several steps of the blood clotting cascade.
- **Cell signaling**: Calcium ions serve as secondary messengers in various signaling pathways.

It is present in the body in three forms:

- **Ionized calcium** (the biologically active form)
- **Calcium bound to proteins** (mainly albumin)
- **Calcium as part of salts** (mainly in bones and teeth)

The regulation of calcium involves maintaining the balance between these various forms to ensure proper cellular function and homeostasis.

1.2. Phosphate (PO_4^{3-})

Phosphate is primarily stored in the bones and teeth in the form of hydroxyapatite but is also crucial in:

- **Bone and teeth mineralization**.
- **ATP production**: Phosphate groups are integral to the structure of ATP, the energy currency of the cell.
- **DNA and RNA**: Phosphate groups form the backbone of the DNA and RNA molecules.
- **Cell signaling**: Phosphate groups play key roles in phosphorylation and dephosphorylation events in cellular pathways.

The regulation of calcium and phosphate levels is important to prevent disturbances like calcification in soft tissues or improper bone mineralization.

2. Organs Involved in Phosphocalcic Metabolism

2.1. Bone

Bone serves as the primary reservoir of calcium and phosphate, holding about 99% of the body's calcium and 85% of phosphate. Bone remodeling, which involves the resorption of old bone and the formation of new bone, is crucial in regulating the levels of these minerals. Bone is dynamic and continually exchanges calcium and phosphate with the bloodstream, especially in response to hormonal signals.

- **Osteoclasts**(bone-resorbing cells): Cells responsible for resorbing bone, releasing calcium and phosphate into the bloodstream.
- **Osteoblasts**(bone-forming cells): Cells that are involved in bone formation, using calcium and phosphate to create new bone matrix.

2.2. Kidneys

The kidneys play a central role in regulating calcium and phosphate by filtering them from the bloodstream and determining the amount to excrete in the urine.

- **Calcium regulation**: The kidneys reabsorb most of the filtered calcium (approximately **99%**) to maintain calcium homeostasis.
- **Phosphate regulation**: Phosphate is also filtered by the kidneys, but only about 70-80% is reabsorbed. The rest is excreted in the urine, and its reabsorption can be influenced by various hormones, notably PTH and FGF23.

The kidneys also convert vitamin D into its active form (calcitriol), which is essential for calcium and phosphate absorption from the intestines.

2.3. Intestines

The small intestine is the primary site for the absorption of calcium and phosphate. The absorption is regulated by calcitriol (1,25-dihydroxyvitamin D), which enhances the intestinal uptake of these minerals.

2.4. Parathyroid Glands

The parathyroid glands, located behind the thyroid, play a pivotal role in regulating calcium and phosphate levels through the secretion of parathyroid hormone (PTH).

3. Hormonal Regulation of Phosphocalcic Metabolism

3.1. Parathyroid Hormone (PTH)

- **Source**: Produced by the parathyroid glands in response to low blood calcium levels.
- **Function**: PTH increases blood calcium levels and decreases phosphate levels through several mechanisms:
    - **Bone resorption**: PTH activates osteoclasts in bone, causing the release of calcium and phosphate into the blood.
    - **Kidney effects**: PTH increases calcium reabsorption from the kidneys, which reduces calcium excretion. Simultaneously, it inhibits phosphate reabsorption, increasing phosphate excretion.

- **Vitamin D activation**: PTH stimulates the conversion of vitamin D into its active form, calcitriol, in the kidneys, which enhances intestinal absorption of calcium and phosphate.

3.2. Vitamin D (Calcitriol)

- **Source**: Calcitriol is the active form of vitamin D, which is synthesized in the skin upon exposure to sunlight and converted to its active form in the kidneys.
- **Function**:
  - **Intestinal absorption**: Calcitriol increases the absorption of calcium and phosphate from the intestine.
  - **Bone mineralization**: It promotes bone mineralization by aiding in calcium and phosphate availability for bone matrix formation.
  - **Kidney effects**: Calcitriol enhances phosphate reabsorption in the kidneys and increases calcium reabsorption in the renal tubules.

3.3. Calcitonin

- **Source**: Secreted by the thyroid gland.
- **Function**: Calcitonin is released in response to high blood calcium levels. It works to reduce calcium levels by:
  - **Inhibiting osteoclast activity**: Reduces bone resorption, thereby decreasing the release of calcium and phosphate into the bloodstream.
  - **Increasing renal excretion of calcium**: Promotes calcium excretion in the urine.

3.4. Fibroblast Growth Factor 23 (FGF23)

- **Source**: Produced by **osteocytes** and **osteoblasts** in bone.
- **Function**: FGF23 is a key regulator of phosphate homeostasis and works to lower phosphate levels in the blood. It does so by:
  - **Inhibiting phosphate reabsorption in the kidneys**, leading to increased phosphate excretion in the urine.
  - **Inhibiting the production of calcitriol**, which in turn reduces calcium and phosphate absorption in the intestines.

3.5. Klotho

- **Source**: Klotho is a protein expressed mainly in the kidneys and parathyroid glands.
- **Function**: Klotho enhances the activity of FGF23, helping to regulate phosphate balance and calcium homeostasis. It plays a key role in the activation of vitamin D and phosphate excretion in the kidneys.

4. Regulation of Calcium and Phosphate Balance

The regulation of calcium and phosphate levels is tightly coordinated to ensure proper bone health and function. These two minerals must exist in a balanced ratio to avoid pathological conditions such as soft tissue calcification or improper bone mineralization.

- **PTH and Calcitriol** promote calcium release from bone, increase calcium reabsorption from the kidneys, and stimulate calcium absorption in the intestines.
- **PTH** also increases phosphate excretion to maintain a healthy calcium-phosphate ratio, while calcitriol promotes phosphate absorption in the intestines and phosphate reabsorption in the kidneys.
- **FGF23** counterbalances the effects of PTH by reducing phosphate reabsorption and calcitriol production to prevent excessive phosphate buildup.
- **Calcitonin** acts as an antagonist to PTH, inhibiting osteoclast activity to decrease bone resorption and lower blood calcium levels.

II. Pathologies Related to Phosphocalcic Metabolism

Several diseases and conditions arise from the dysregulation of calcium and phosphate homeostasis:

1. Hypocalcemia (Low Calcium Levels)

Hypocalcemia is a condition characterized by low levels of calcium in the blood. It can be caused by various factors, including:

- **Hypoparathyroidism:** The parathyroid glands produce parathyroid hormone (PTH), which regulates calcium levels. In hypoparathyroidism, there is insufficient PTH production, leading to low calcium levels.
- **Vitamin D Deficiency:** Vitamin D enhances calcium absorption in the intestines. A deficiency in vitamin D (due to lack of sunlight, poor diet, or malabsorption disorders) can result in hypocalcemia.
- **Chronic Kidney Disease (CKD):** Kidneys are crucial for converting vitamin D into its active form, and in CKD, this function is impaired, leading to hypocalcemia.
- **Calcium Deposits in Soft Tissues:** Conditions like pseudohypoparathyroidism or magnesium deficiency may lead to improper calcium distribution in tissues.

Symptoms:

- Tetany (muscle cramps and spasms)
- Numbness or tingling in the fingers, toes, and lips
- Seizures
- Cardiac arrhythmias

2. Hypercalcemia (High Calcium Levels)

Hypercalcemia is characterized by elevated levels of calcium in the blood. Causes include:

- **Primary Hyperparathyroidism:** Overproduction of parathyroid hormone (PTH) by the parathyroid glands causes increased calcium release from bones into the bloodstream.
- **Malignancy (Cancer):** Certain cancers, such as lung, breast, or multiple myeloma, can lead to increased calcium levels due to tumor secretion of parathyroid hormone-related peptide (PTHrP), which mimics PTH.
- **Vitamin D Toxicity:** Excessive intake of vitamin D can lead to excessive calcium absorption, resulting in hypercalcemia.
- **Immobilization:** Long-term immobilization (e.g., in patients who are bedridden) can lead to bone resorption and elevated calcium levels.

Symptoms:

- Fatigue

- Nausea and vomiting
- Constipation
- Polyuria (excessive urination)
- Renal stones (calcium deposits in kidneys)
- Confusion or altered mental status

3. Osteoporosis

Osteoporosis is a condition where the bones become weak and brittle due to a decrease in bone mineral density (BMD). It is often associated with disturbed phosphocalcic metabolism. The key contributors to osteoporosis include:

- **Calcium Deficiency:** Insufficient dietary calcium, often seen in postmenopausal women due to a decrease in estrogen, can lead to osteoporosis.
- **Vitamin D Deficiency:** Vitamin D is crucial for calcium absorption. A deficiency in vitamin D can impair calcium absorption, leading to reduced calcium availability for bone mineralization.
- **Hyperparathyroidism:** Elevated PTH levels increase bone resorption, leading to the loss of bone mass over time.
- **Chronic Kidney Disease:** Impaired kidney function leads to decreased activation of vitamin D, which in turn reduces calcium absorption and bone mineralization.

Symptoms:

- Increased risk of fractures, particularly in the hip, spine, and wrist
- Back pain
- Loss of height
- Stooped posture

4. Rickets and Osteomalacia

Both rickets (in children) and osteomalacia (in adults) are conditions caused by impaired mineralization of bone, primarily due to vitamin D deficiency or disturbances in phosphate metabolism.

- **Rickets (in children):** The failure to mineralize the growing bones results in deformities such as bowed legs, a protruding breastbone, and delayed growth. The deficiency of vitamin D, calcium, or phosphate is the most common cause.
- **Osteomalacia (in adults):** Similar to rickets but occurs in adults. It is usually caused by vitamin D deficiency or phosphate wasting, leading to soft, weakened bones. It is commonly seen in people with poor sun exposure, poor diet, or malabsorption disorders.

Symptoms:

- Bone pain
- Muscle weakness
- Deformities in growing bones (rickets)
- Increased risk of fractures (osteomalacia)

5. Renal Osteodystrophy

Renal osteodystrophy refers to the bone changes associated with chronic kidney disease (CKD) and its effects on phosphocalcic metabolism. In CKD, the kidneys are unable to properly excrete phosphate or activate vitamin D, leading to a combination of:

- **Hyperphosphatemia:** Elevated phosphate levels due to impaired kidney function.
- **Hypocalcemia:** Reduced calcium levels due to impaired vitamin D activation and phosphate retention.
- **Secondary Hyperparathyroidism:** The low calcium levels trigger increased PTH secretion, leading to bone resorption and osteitis fibrosa cystica (a bone condition characterized by the formation of cysts and fibrosis).

Symptoms:

- Bone pain
- Pruritus (itching)
- Bone deformities
- Increased risk of fractures

6. Hyperphosphatemia (High Phosphate Levels)

Hyperphosphatemia is an abnormal increase in phosphate levels in the blood. Causes include:

- **Chronic Kidney Disease (CKD):** The kidneys' inability to excrete phosphate properly leads to hyperphosphatemia.
- **Excessive Phosphate Intake:** This can occur in individuals who consume phosphate-based supplements or have excessive intake of phosphate-rich foods.
- **Tumor Lysis Syndrome:** In this condition, large numbers of cancer cells break down rapidly, releasing large amounts of phosphate into the bloodstream.

Symptoms:

- Itching
- Calcification of soft tissues, especially in the skin, eyes, and lungs
- Increased risk of cardiovascular events

7. Hypophosphatemia (Low Phosphate Levels)

Hypophosphatemia is a condition in which phosphate levels are abnormally low. Causes include:

- **Vitamin D Deficiency:** Vitamin D is essential for phosphate absorption in the gut. Deficiency can lead to hypophosphatemia.
- **Alcoholism:** Chronic alcohol consumption can impair phosphate absorption and increase renal phosphate excretion.
- **Hyperparathyroidism:** Elevated PTH levels increase renal phosphate excretion, leading to hypophosphatemia.
- **Refeeding Syndrome:** In malnourished individuals receiving nutrition after a period of starvation, rapid shifts in phosphate into cells can lead to hypophosphatemia.

Symptoms:

- Muscle weakness
- Bone pain
- Hemolysis (destruction of red blood cells)
- Respiratory failure (due to muscle weakness)

8. Paget's Disease of Bone

Paget's disease is a chronic disorder that causes abnormal bone remodeling, leading to enlarged and deformed bones. It often involves the abnormal regulation of calcium and phosphate metabolism:

- **Excessive Bone Resorption:** The condition typically involves increased activity of osteoclasts, leading to excessive bone resorption followed by disorganized bone formation.
- **Hypercalcemia:** In severe cases, increased bone turnover can lead to the release of large amounts of calcium into the bloodstream.

Symptoms:

- Bone pain
- Deformities in affected bones (e.g., enlarged skull, bowed legs)
- Increased risk of fractures
- Hearing loss (if the skull is involved)

9. Tumor-Induced Osteomalacia

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome in which tumors, often benign, secrete substances (such as fibroblast growth factor 23 or FGF-23) that impair phosphate reabsorption in the kidneys, leading to hypophosphatemia and bone mineralization defects.

Symptoms:

- Bone pain
- Muscle weakness
- Fractures
- Skeletal deformities

10. Idiopathic Hypercalciuria

Idiopathic hypercalciuria is characterized by the excessive excretion of calcium in urine without an apparent underlying cause. It can predispose individuals to the formation of kidney stones and may also be associated with bone mineral loss.

Symptoms:

- Recurrent kidney stones
- Bone loss or osteoporosis

The proper regulation of calcium and phosphate is essential for the maintenance of healthy bones, muscles, and overall physiological function. Disruptions in phosphocalcic metabolism can result in a wide variety of clinical conditions, ranging from bone diseases like osteoporosis and rickets to severe disturbances like hypercalcemia and hypophosphatemia. Early diagnosis and treatment are key to managing these disorders and preventing long-term complications. Treatment often involves managing underlying conditions, supplementing deficiencies, and correcting metabolic abnormalities

Functional relationships between the nervous system, endocrine system, and immune system

The nervous, endocrine, and immune systems are three major regulatory systems in the body that maintain homeostasis and protect the organism from harmful stimuli. These systems are interconnected in a complex, bidirectional way, allowing them to communicate with and influence each other. Their interactions are essential for normal physiological functioning and the body's ability to respond to stress, infection, injury, and disease. Below is a detailed examination of how these three systems are functionally related.

1. Major regulatory systems in the body

1.1 The Nervous System

The nervous system is responsible for rapid communication throughout the body using electrical signals (action potentials) and chemical messengers (neurotransmitters). The central nervous system (CNS) communicates with the immune system through the hypothalamo-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). The nervous system is essential for rapid response to external and internal stimuli, including threats, pain, and stress.

1.2 The Endocrine System

The endocrine system consists of glands that secrete hormones into the bloodstream. These hormones travel throughout the body to target organs, affecting functions such as metabolism, growth, reproduction, and stress responses. The endocrine system works closely with the nervous system, particularly during the fight-or-flight response, where the nervous system triggers the release of hormones such as adrenaline and cortisol.

1.3 The Immune System

The immune system protects the body from infections and diseases by detecting and responding to harmful pathogens. It also plays a role in inflammation, healing, and tissue repair. Immune cells communicate with the nervous and endocrine systems through the release of cytokines and neurotransmitters, signaling various physiological responses to infection and stress.

Table 05: the major characteristics of the endocrine, immune, and nervous systems:

System	Major Characteristics
Endocrine System	- **Function**: Regulates body functions through hormones, which are secreted by endocrine glands into the bloodstream.

	- **Communication**: Hormonal signaling (chemical messages).
	- **Speed**: Slower than the nervous system. Effects are longer-lasting.
	- **Control**: Regulates growth, metabolism, reproduction, and homeostasis.
	- **Major Glands**: Pituitary, thyroid, adrenal, pancreas, gonads (testes and ovaries).
	- **Key Hormones**: Insulin, cortisol, adrenaline, thyroid hormones, estrogen, testosterone.
Immune System	- **Function**: Defends the body against infections, pathogens, and abnormal cells (e.g., cancer).
	- **Communication**: Involves signaling molecules like cytokines and antibodies.
	- **Speed**: Can be immediate (innate immunity) or take time to develop (adaptive immunity).
	- **Control**: Identifies and attacks foreign invaders (pathogens) and dysfunctional cells, and maintains self-tolerance to avoid autoimmune reactions.
	- **Major Components**: White blood cells (leukocytes), lymphatic system, spleen, thymus, bone marrow.
	- **Key Cells**: T-cells, B-cells, macrophages, neutrophils, dendritic cells.
Nervous System	- **Function**: Transmits electrical impulses for communication and control of body functions.
	- **Communication**: Nerve impulses (electrical signals) and neurotransmitters (chemical signals).
	- **Speed**: Very rapid response, with immediate effects.
	- **Control**: Regulates sensory input, motor output, and processes such as cognition, memory, and reflexes.
	- **Major Components**: Brain, spinal cord, peripheral nerves.
	- **Key Cells**: Neurons, glial cells.

2. Mechanisms of crosstalk between the systems

2.1. Nervous system and endocrine system

The nervous and endocrine systems work together to coordinate the body's responses to both internal and external stimuli. Although they use different mechanisms (electrical signals in the nervous system and chemical signals in the endocrine system), these systems are closely integrated through the hypothalamus and pituitary gland.

- **Hypothalamic-Pituitary Axis:** The hypothalamus, part of the brain, acts as a bridge between the nervous and endocrine systems. It receives sensory input from the body and the brain, particularly in response to stress, environmental changes, and internal stimuli. The hypothalamus releases hormones that regulate the anterior pituitary gland, which in turn secretes hormones that control various other endocrine glands (e.g., thyroid, adrenal glands, gonads).
- **Autonomic Nervous System (ANS):** The autonomic nervous system (ANS), a division of the nervous system that controls involuntary functions, interacts with the endocrine system to regulate physiological processes like heart rate, digestion, and metabolism. For example, during stress, the sympathetic branch of the ANS stimulates the adrenal glands to release cortisol and adrenaline (epinephrine), hormones that prepare the body for the "fight or flight" response.
- **Neuroendocrine Feedback Loops:** Hormones like cortisol (released from the adrenal glands) influence the nervous system by modulating the brain's activity, including mood, memory, and cognition. Conversely, neurotransmitters like serotonin or dopamine can affect the release of hormones like growth hormone or thyroid hormone. This feedback loop helps fine-tune responses to stress, emotions, and environmental factors.

2.2. Nervous system and immune system

The nervous system also plays a critical role in regulating immune function. This interaction is known as **neuroimmunology**, which studies how the brain and nervous system communicate with immune cells to influence immune responses.

- **Innate Immunity Activation:** The central nervous system (CNS) and immune system communicate through cytokines, which are signaling molecules produced by immune cells. When the body is under attack (e.g., by pathogens), immune cells release pro-inflammatory cytokines, which can signal the brain to induce fever, fatigue, and changes in behavior, collectively known as "sickness behavior."

- **Neural Regulation of Immune Responses:** The brain communicates with the immune system through both the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis. The vagus nerve, a key part of the parasympathetic nervous system, can directly inhibit pro-inflammatory cytokine release by immune cells, essentially "calming down" an overactive immune response. This is known as the **cholinergic anti-inflammatory pathway**.
- **Stress and Immune Function:** Psychological stress activates the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, leading to the release of stress hormones like cortisol. While cortisol is initially anti-inflammatory, prolonged or chronic stress can suppress the immune response, making the body more susceptible to infections or autoimmune conditions.

2.3. Endocrine system and immune system

The endocrine system and the immune system are also intricately connected. Hormones influence immune responses, and immune cells produce signaling molecules that affect hormone levels. This dynamic interaction is essential for maintaining immune homeostasis and coordinating the body's defense mechanisms.

- **Corticosteroids (e.g., Cortisol):** One of the key hormones involved in regulating both immune and endocrine responses is cortisol, a steroid hormone produced by the adrenal glands. Cortisol is released in response to stress and has both immunosuppressive and anti-inflammatory effects. In acute stress, cortisol helps prevent excessive immune activation and tissue damage. However, chronic stress or prolonged high cortisol levels can impair immune function, leading to a higher susceptibility to infections and autoimmune diseases.
- **Thyroid Hormones and Immunity:** Thyroid hormones, produced by the thyroid gland, also affect immune function. Thyroid hormone receptors are present on a variety of immune cells, and thyroid hormones regulate the expression of cytokines and other immune molecules. Imbalances in thyroid hormones, such as in hypothyroidism or hyperthyroidism, can lead to immune system dysregulation, affecting susceptibility to infections or autoimmune diseases.
- **Sex Hormones and Immune Function:** Estrogen, progesterone, and testosterone also play a role in modulating immune responses. Estrogen generally enhances immune

function, which can make women more responsive to vaccines but also more susceptible to autoimmune diseases. On the other hand, testosterone tends to have immunosuppressive effects, which might explain why men generally have a lower incidence of autoimmune diseases compared to women.

- **Immunological Endocrine Feedback:** The immune system also produces certain cytokines that can influence endocrine functions. For example, pro-inflammatory cytokines like IL-1 and TNF-α can trigger the release of cortisol from the adrenal glands, thus creating a feedback loop between immune and endocrine systems.

3. Integration and coordination of systems

These three systems—nervous, endocrine, and immune—work together to maintain a finely tuned balance in the body, adapting to changes in the environment, managing stress, and defending against pathogens.

- **Homeostasis:** All three systems contribute to maintaining homeostasis, the body's ability to regulate internal conditions within a narrow range. For example, the nervous system detects environmental changes and sends signals to the brain, which in turn communicates with the endocrine and immune systems to adjust body temperature, metabolic rate, or immune responses.
- **Adaptation to Stress:** When the body encounters stress, the nervous system triggers the "fight or flight" response, activating the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, leading to the release of cortisol and catecholamines (adrenaline and norepinephrine). These hormones influence immune function, both activating and regulating the immune system to manage stress while preparing the body for an appropriate response.
- **Inflammation and Chronic Disease:** Dysregulation of any one of these systems can lead to chronic inflammation, autoimmune diseases, or metabolic disorders. For instance, chronic stress can overwhelm the nervous and endocrine systems, leading to sustained high cortisol levels, which in turn suppress immune function and make the body more vulnerable to illness.

In summary, the nervous, endocrine, and immune systems are intricately connected through a network of signaling pathways and feedback mechanisms. These systems collaborate to ensure that the body responds appropriately to changes in the internal and external

environment, manages stress, and defends against disease. Understanding the functional relationships between these systems is crucial for comprehending the body's overall health and developing strategies to manage stress, inflammation, and immune-related conditions.

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