BHARATHIDASAN UNIVERSITY

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Tamil Nadu, India.

Programme: Biochemistry

Course Title: Intermediary Metabolism

COURSE CODE: BC201CR

Unit: 2

CARBOHYDRATE METABOLISM

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Glycolysis:

- Glycolysis is a metabolic pathway that converts glucose into pyruvate, releasing energy used to form molecules of ATP and NADH, primarily occurring in the cytosol of cells.

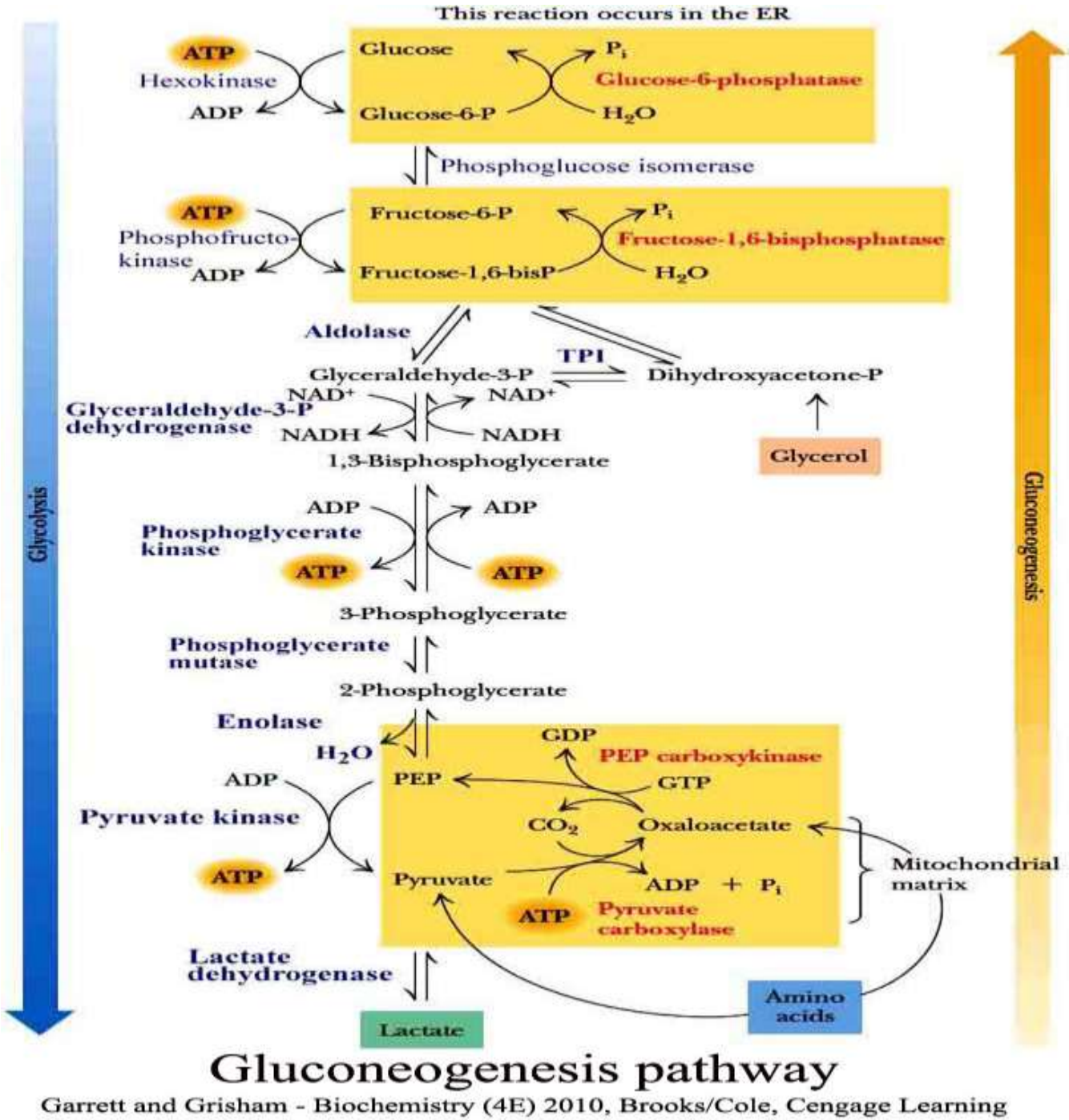
Types of Glycolysis:

- Aerobic Glycolysis: This form of glycolysis transpires in the presence of ample oxygen. The end product of this pathway is pyruvate. Concurrently, there is the synthesis of adenosine triphosphate (ATP) molecules, which serve as the primary energy currency of the cell.
- Anaerobic Glycolysis: In conditions where oxygen is limited or absent, glycolysis proceeds anaerobically. Under such circumstances, lactate is produced as the terminal product. Similar to its aerobic counterpart, ATP molecules are generated during this process.

The glycolytic pathway can be succinctly represented by the following chemical equation:

- $C6H12O6+2ADP+2Pi+2NAD+\rightarrow 2C3H4O3+2H2O+2ATP+2NADH+2H+$

Glycolysis and Glyconeogenesis:



Gluconeogenesis pathway

Garrett and Grisham - Biochemistry (4E) 2010, Brooks/Cole, Cengage Learning

Source:https://biotechnologymcq.com/gluconeogenesis-reactions-and-the-key-enzymes-of-gluconeogenesis-regulation-of-gluconeogenesis-and-cori-cycle/

Regulation of Glycolysis:

1. Allosteric Modification:

- Enzymes involved in glycolysis can be modulated by the binding of specific molecules at regulatory sites.
- Allosteric regulation generally follows the principle that substrates stimulate enzyme activity, whereas products inhibit it. When substrate concentrations are high, enzyme activity is stimulated, favoring product formation.

2. Gene Expression:

- The expression of genes coding for glycolytic enzymes can be regulated to control the overall rate of glycolysis. Changes in gene expression can lead to alterations in enzyme levels within the cell, impacting glycolytic flux.

3. Protein-Protein Interaction:

- Protein-protein interactions can influence the activity of glycolytic enzymes. Complexes formed between different enzymes or regulatory proteins can either enhance or inhibit glycolytic reactions.

4. Post-Translational Modification:

- Enzyme activity can be altered through post-translational modifications, such as phosphorylation and dephosphorylation.
- Phosphorylation, in particular, is a common regulatory mechanism. Phosphorylated enzymes are often inactive, while dephosphorylation activates them.

5. Cellular Localization: The subcellular localization of glycolytic enzymes can impact their activity. Enzymes may be sequestered in specific cellular compartments or brought into proximity with their substrates.

6. Hormonal Regulation (Insulin and Glucagon in Animals): Low blood glucose levels stimulate the release of glucagon and epinephrine. These hormones activate protein kinase A, which phosphorylates glycolytic enzymes, rendering them inactive. This occurs during fasting states, where glycolysis is inhibited.

- High blood glucose levels trigger the release of insulin, which activates phosphatases. These enzymes dephosphorylate glycolytic enzymes, restoring their activity. Under the influence of insulin, glycolysis is promoted.

Regulation of Rate-Limiting Enzymes:

- Four key enzymes in glycolysis are particularly critical for regulation:
- Glucokinase and Hexokinase: These enzymes catalyze the first step of glycolysis. Glucokinase is inducible and found in specific cells like liver and pancreas, while hexokinase is ubiquitous. Their properties and regulation differ, with glucokinase being induced by insulin and having low affinity for glucose.
- Phosphofructokinase-1 (PFK-1): PFK-1 catalyzes an irreversible step in glycolysis. It is regulated by allosteric effectors, including AMP and fructose-2,6-bisphosphate (F2,6BP). A low insulin/glucagon ratio leads to phosphorylation/inactivation of PFK-1, while high insulin/glucagon ratio results in its activation.
- Pyruvate Kinase: Pyruvate kinase in the liver is phosphorylated and deactivated by epinephrine/glucagon-induced protein kinase A during fasting. In contrast, muscle pyruvate kinase remains unaffected, allowing glycolysis to continue in muscle tissues.

Gluconeogenesis:

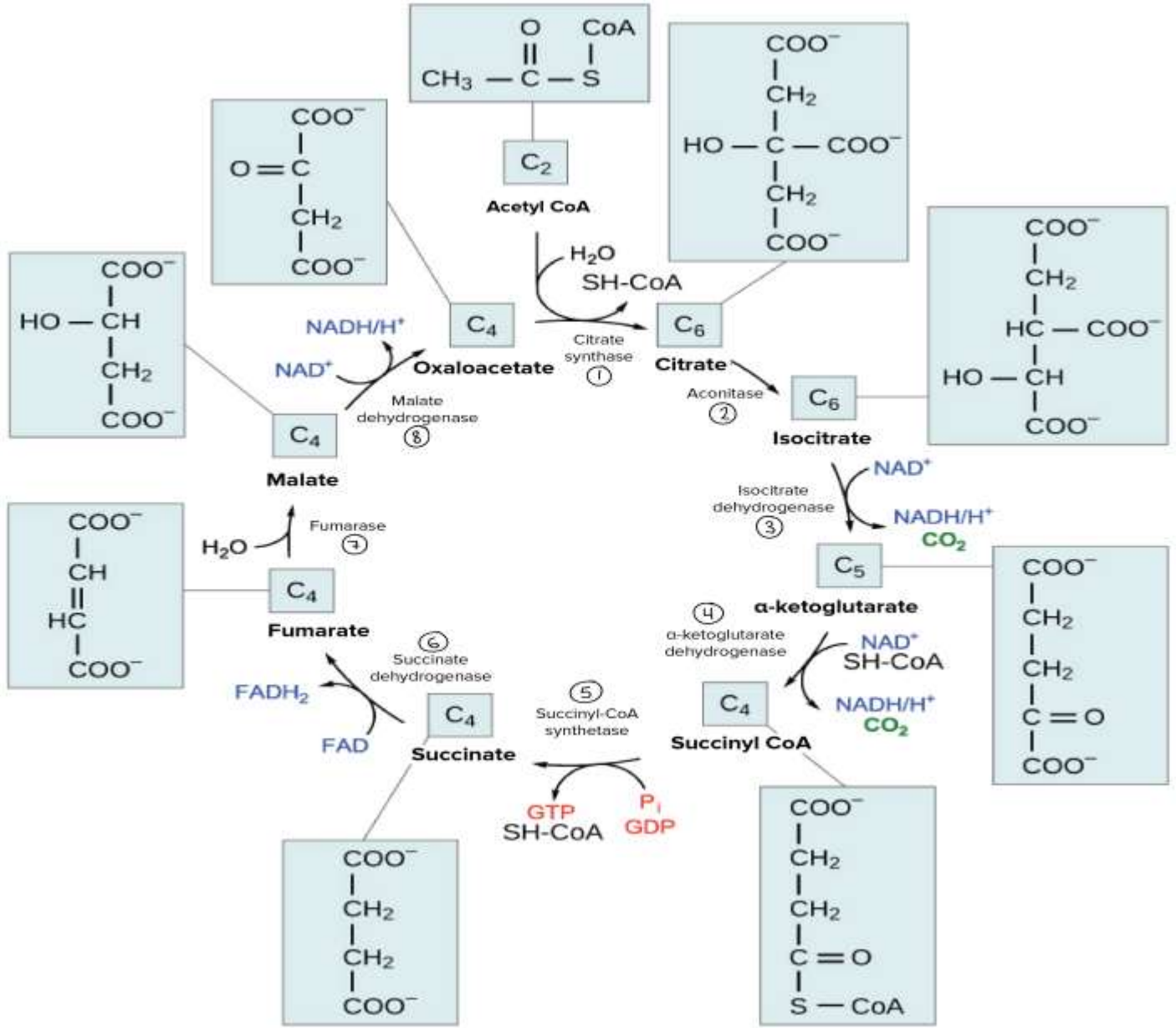
- Gluconeogenesis: Non-carbohydrate precursors of glucose; Reactions and the Key enzymes of gluconeogenesis (Pyruvate carboxylase, PEP carboxykinase, Fructose-1,6-bisphosphatase and Glucose-6 phosphatase); Regulation of gluconeogenesis and Cori cycle
- Gluconeogenesis occurs in all animals, plants, fungi, and microorganism
- In mammals, the major site of Gluconeogenesis is the Liver (90% glucose synthesis) and minor site is kidney (10%).
- It helps to maintain the blood glucose level during prolonged starvation.
- The major noncarbohydrate precursors are pyruvate, lactate, alanine, oxaloacetate, dihydroxyacetone phosphate. , glycerol and several glucogenic amino acids.
- Gluconeogenesis is not the reversal of glycolysis

Regulation of Gluconeogenesis:

- **Acetyl CoA's Dual Role:** Acetyl CoA plays a pivotal role in the regulation of gluconeogenesis. It has both stimulatory and inhibitory effects on the pathway:
- **Positive Regulation:** Acetyl CoA enhances the activity of the enzyme pyruvate carboxylase, leading to increased production of oxaloacetate, a key intermediate in gluconeogenesis.
- **Negative Regulation:** Conversely, acetyl CoA inhibits pyruvate dehydrogenase, reducing the conversion rate of pyruvate to acetyl CoA.
- **Glucagon's Influence:** Glucagon, a hormone secreted from the α-cells of the pancreas, plays a crucial role in glucose homeostasis. It regulates gluconeogenesis in two primary ways:
- By mediating cyclic AMP, glucagon inactivates pyruvate kinase, decreasing the conversion rate of phosphoenolpyruvate (PEP) to pyruvate.
- It inhibits phosphofructokinase while activating fructose 1,6-bisphosphatase, promoting glucose synthesis.
- **Glucogenic Amino Acids:** During periods of decreased insulin levels, glucogenic amino acids regulate the conversion rate of glucose 6-phosphate to glucose, further emphasizing their role in glucose production.

CITRIC ACID CYCLE:

- The citric acid cycle, also known as the tricarboxylic acid cycle and the Krebs cycle, completes the oxidation of glucose by taking the pyruvates from glycolysis.
- CO_2 andH_2O generating ATP by oxidative phosphorylation.
- In prokaryotic cells, the citric acid cycle occurs in the cytoplasm; in eukaryotic cells the citric acid cycle takes place in the matrix of the



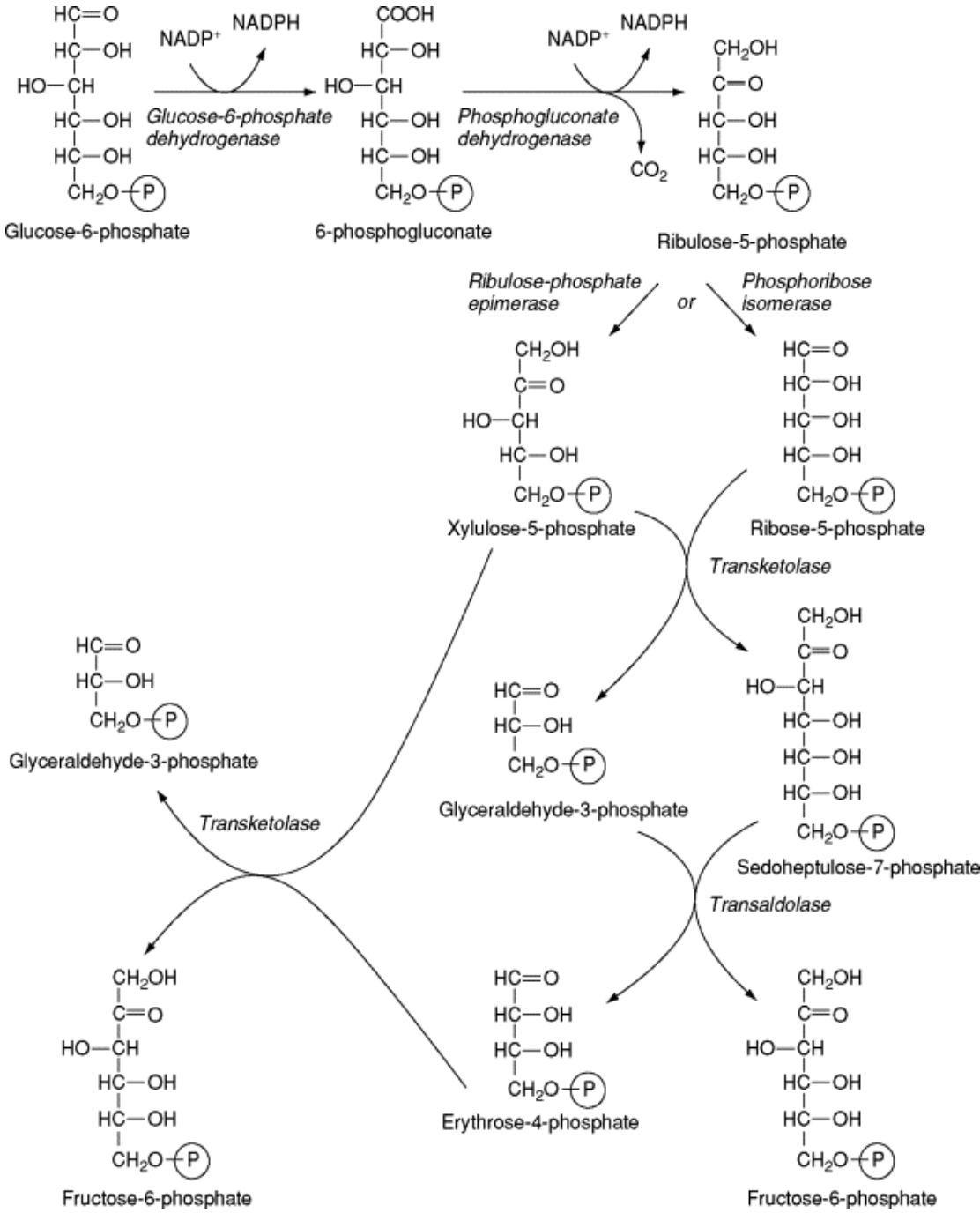
Source:https://www.nursinghero.com/study-guides/ivytech-bio1-1/reading-citric-acid-cycle

Regulation of citric acid cycle

- Substrate availability: The availability of substrates like acetyl-CoA and oxaloacetate affects the rate of citrate formation.
- Product inhibition: Accumulated products, like NADH, inhibit regulatory enzymes.
- Calcium: Calcium ions activate enzymes that increase the rate of reactions in the cycle.
- Transcriptional regulation: Intermediates of the citric acid cycle regulate hypoxia-inducible factors (HIF), which regulate oxygen homeostasis.
- Allosteric regulation: Citrate inhibits phosphofructokinase, an enzyme involved in glycolysis.
- ATP/ADP ratio: The ratio of mitochondrial NAD+/NADH is influenced by the ratio of ATP/ADP.

PENTOSE PHOSPHATE PATHWAY

- The pentose phosphate pathway (PPP) is an alternative way of glucose use.
- It consists of an aerobic and an anaerobic part.
- In aerobic pathway ribulose-5-phosphate, carbon dioxide (CO2), and reduced nicotinamide adenine dinucleotide phosphate (NADPH).
- One molecule of ribulose-5-phosphate and two molecules of NADPH are produced out of one molecule of glucose.
- In anaerobic transformation of ribulose-5-phosphate delivers no energy but new glucose-6-phosphate.



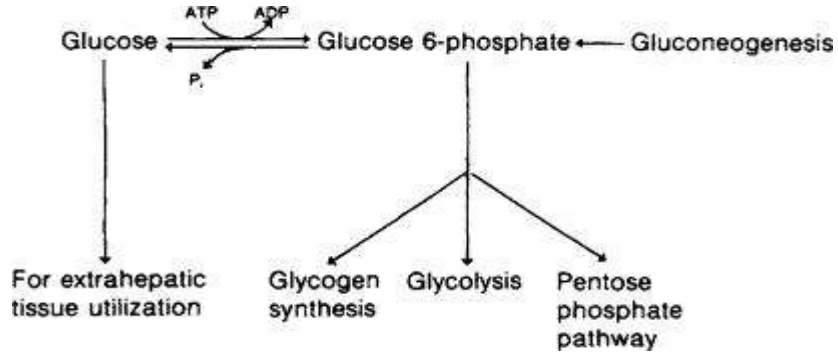
Source:https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/pentose-phosphate-pathway

REGULATION:

- Glucose-6-phosphate dehydrogenase (G6PD): The rate-limiting enzyme of the PPP, G6PD is regulated by the redox state of the NADP couple. NADPH production is tightly coupled to utilization, as NADPH competes with NADP for binding to the enzyme.
- p53: The tumor suppressor p53 negatively regulates G6PD activity by directly binding to it. However, cancer-associated mutations of p53 can cause G6PD to be liberated, increasing PPP flux and glycolysis.
- CARKL: CARKL is important for regulating the flux through the PPP by generating high levels of S7P. This restricts the reversible reaction in the non-oxidative PPP.
- Metabolite levels: Metabolite levels determine the reaction thermodynamics and flux direction of the non-oxidative PPP.
- Adrenaline and cyclic adenosine monophosphate (cAMP): These can inhibit G6PD activity through PKA-mediated phosphorylation.
- Aldosterone: Aldosterone decreases the expression and activity of endothelial G6PD

Key Junctions in Metabolism:

- Points where various metabolic pathways **intersect**
- Enable efficient **regulation** and **coordination** of cellular processes.



GLUCOSE 6 PHOSPHATE:

The **regulation** of **glucose-6-phosphate** refers to the **control mechanisms** that dictate the **levels** and **flux** of **glucose-6-phosphate** within **cells**, ensuring that its **metabolism** is finely tuned to **meet** the **cellular demands** for **energy production, biosynthesis, and redox balance**

source :https://www.sciencedirect.com/topics/immunology-and-microbiology/gluconeogenesis

In terms of **regulation**, the fate of **glucose-6-phosphate** is tightly **controlled** to ensure proper **energy production** and **biosynthesis** according to the **cell's needs**.

Glycolysis Regulation:

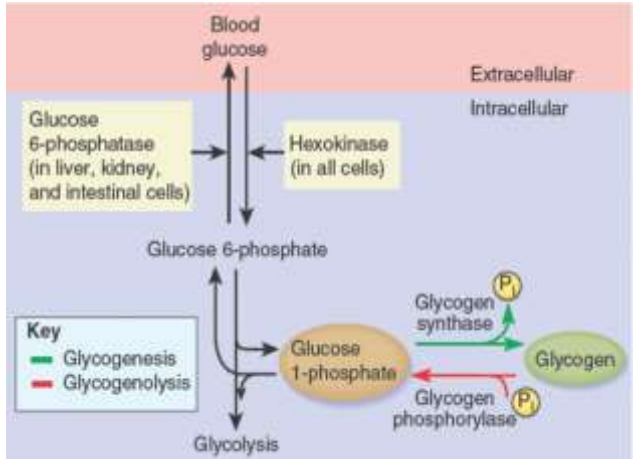
Enzyme Regulation:

- **Hexokinase** or **glucokinase** catalyzes the conversion of glucose to glucose-6-phosphate
- Feedback inhibition and allosteric regulation control enzyme activity.
- High glucose-6-phosphate levels inhibit hexokinase to prevent excessive glucose uptake.

Substrate Availability:

- Glucose concentration influences glucose uptake and conversion to glucose-6-phosphate
- Hormonal regulation, like insulin signaling, modulates glucose transporter activity.

Pentose Phosphate Pathway Regulation:



Rate-limiting Enzyme:

- **Glucose-6-phosphate dehydrogenase (G6PD)** is the rate-limiting enzyme
- Its activity is regulated by substrate availability, product inhibition (NADPH), and allosteric regulation by metabolites.

NADPH/NADP+ Ratio

- Balance between NADPH and NADP+ is crucial for redox balance and biosynthesis
- High NADPH levels inhibit G6PD activity, while low ratios stimulate activity for biosynthesis and antioxidant defense
- Overall, tight regulation of glucose-6-phosphate metabolism allows cells to adjust energy production and biosynthetic capacity according to metabolic demands, maintaining cellular homeostasis and preventing metabolic imbalances associated with diseases like diabetes and metabolic syndrome.

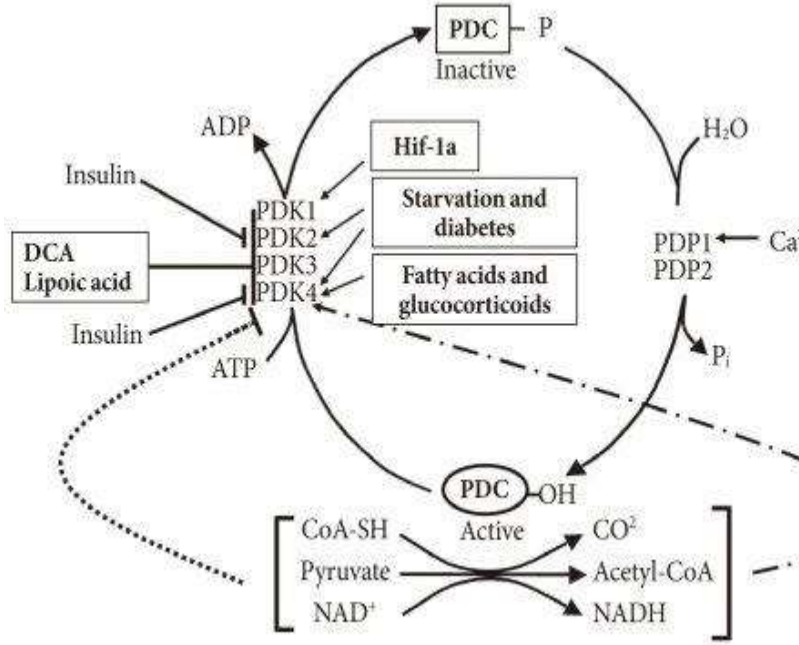
Pyruvate:

Pyruvate serves as a key junction in cellular metabolism, connecting glycolysis, the citric acid cycle (also known as the Krebs cycle or TCA cycle), and various biosynthetic pathways.

At this junction, pyruvate can be directed towards different metabolic pathways based on the cell's energy needs and the availability of substrates.

Regulation:

- - Pyruvate is a critical intermediate in glycolysis.
-
- - Its fate is regulated by cellular conditions:
-
- **Aerobic conditions:** Converted to acetyl-CoA for the citric acid cycle.
-
- - **Anaerobic conditions: Converted to lactate to sustain glycolysis.**
- -Pyruvate is also a substrate for gluconeogenesis to synthesize glucose.
- **Regulation factors** include:
- - Oxygen availability.
- - **Enzyme activity (**e.g., pyruvate dehydrogenase).
- - **Hormonal signals (**e.g., insulin, glucagon).
- - Overall, pyruvate metabolism is finely tuned to meet energy demands and maintain cellular homeostasis .

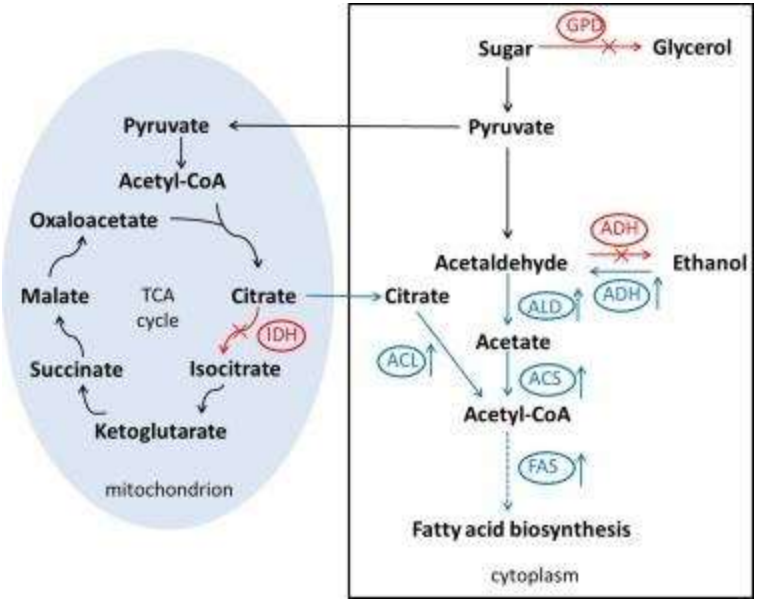


Source :www.researchgate.net

Acetyl-CoA :

- Acetyl-CoA is a metabolic hub, regulating pathways and cellular processes essential for energy production and molecular synthesis.
- Its control is vital for maintaining cellular function and metabolic balance.

Acetyl-CoA plays a central role in metabolism and is tightly regulated to ensure metabolic homeostasis. Regulation occurs at multiple levels



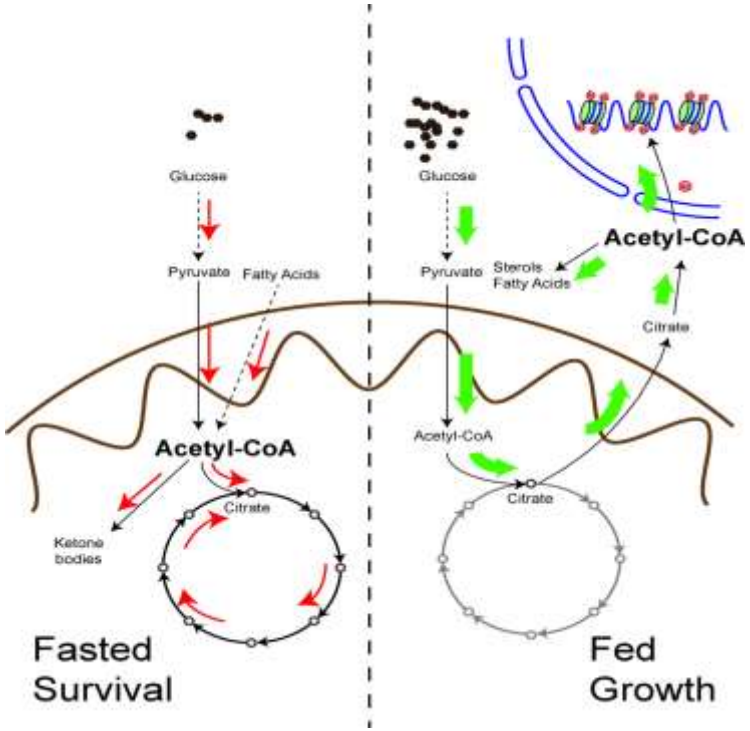
Formation Sources: Acetyl-CoA is derived from glucose breakdown (glycolysis), fatty acid breakdown (beta-oxidation), and certain amino acids

Utilization Pathways: It's used in fatty acid and cholesterol synthesis, as well as in the citric acid cycle for ATP production.

Regulation Points:
Enzyme activity is controlled by factors like substrate availability, hormonal signals, and allosteric regulation.

Source :www.sciencedirect.com

- **Feedback inhibition:** Acetyl-CoA inhibits its own formation enzymes like pyruvate dehydrogenase
- .**Substrate availabilit**y is influenced by hormones like insulin and glucagon
- Cellular energy status modulates enzyme activity in the citric acid cycle
- Acetyl-CoA metabolism is tightly regulated to maintain energy balance and metabolic homeostasis.



In a well-fed state:

Nutrient abundance prevails, with elevated levels of glucose, fatty acids, and amino acids.
Acetyl-CoA levels are high, stemming from the breakdown of carbohydrates, lipids, and proteins.
Acetyl-CoA serves as a key substrate, driving metabolic pathways such as the citric acid cycle, fatty acid synthesis, and cholesterol synthesis.

Source :https://images.app.goo.gl/3TphgHeLaF1K7yhYA

Regulation of acetyl-CoA metabolism is finely tuned to efficiently utilize and store excess nutrients.

Maintaining cellular energy homeostasis and metabolic equilibrium is prioritized.

In a starved state:

Nutrient scarcity prevails, leading to reduced levels of glucose, fatty acids, and amino acids.

Acetyl-CoA levels decline due to decreased influx from external sources and increased reliance on internal reserves.

Metabolic pathways adapt to prioritize energy conservation and utilize alternative fuel sources such as ketone bodies and gluconeogenic precursors.

GLUCOSE HOMEOSTASIS

- Balances glucose production by the liver and glucose uptake/utilization by the body's tissues.
- **INSULIN** is the important regulator for this metabolic glucose equilibrium.
- Blood glucose level maintained within 70-100 mg/dl.

    Levels above the range : *HYPERGLYCEMIA*

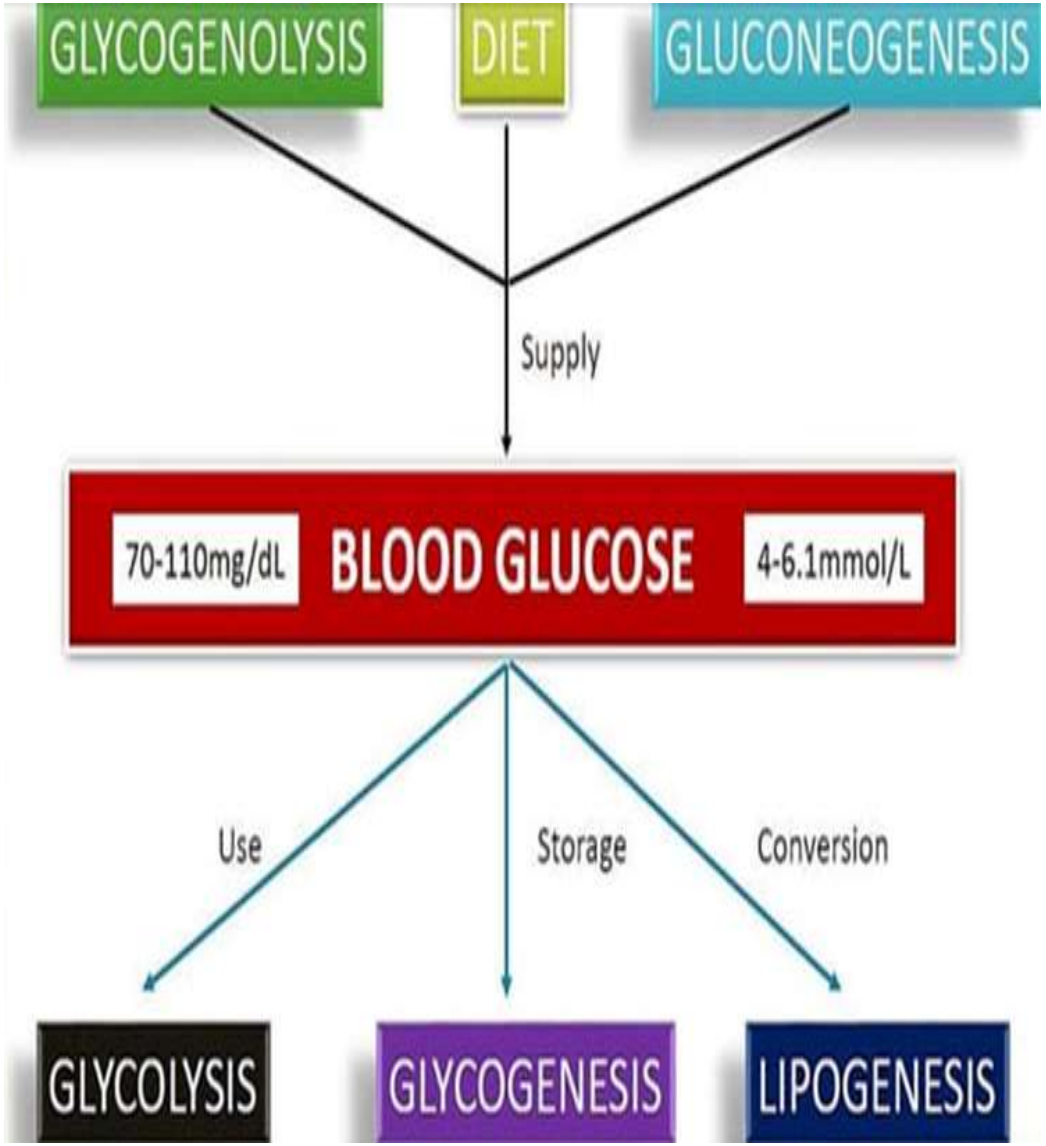
    Levels below the range : *HYPOGYLCEMIA*

Fasting level 100-125 mg/dl

Postprandial level <140 mg/dl

Factors involved in the blood glucose homeostasis :

1. HORMONES
2. METABOLIC PROCESSES
3. RENAL MECHANISM



Source:https://images.app.goo.gl/jcXmsro1xddcEi9k7

HORMONES FEATURES

- Source : Pancreatic α cells.
- Functions :

    High Glucose : By Gluconeogenesis & Glycogenolysis.

    High Ketons : By ketogenesis & Lipolysis.

- Gluconeogenesis : Indirectly increases plasma urea by transaminase (which converts Alanine to Pyruvate and Urea is released)
- Target Tissue : Liver,NOT skeletal muscles (muscles are indirectly affected by the release of Insulin)
- Increased by : Hypoglycemia & Fasting.
- Decreased by : Insulin, Hyperglycemia, and Somatostatin.

HORMONES

- Hypoglycemic hormones
  - Insulin
- Hyperglycemic hormones
  - Glucagon
  - Cortisol
  - Growth hormone
  - Epinephrine

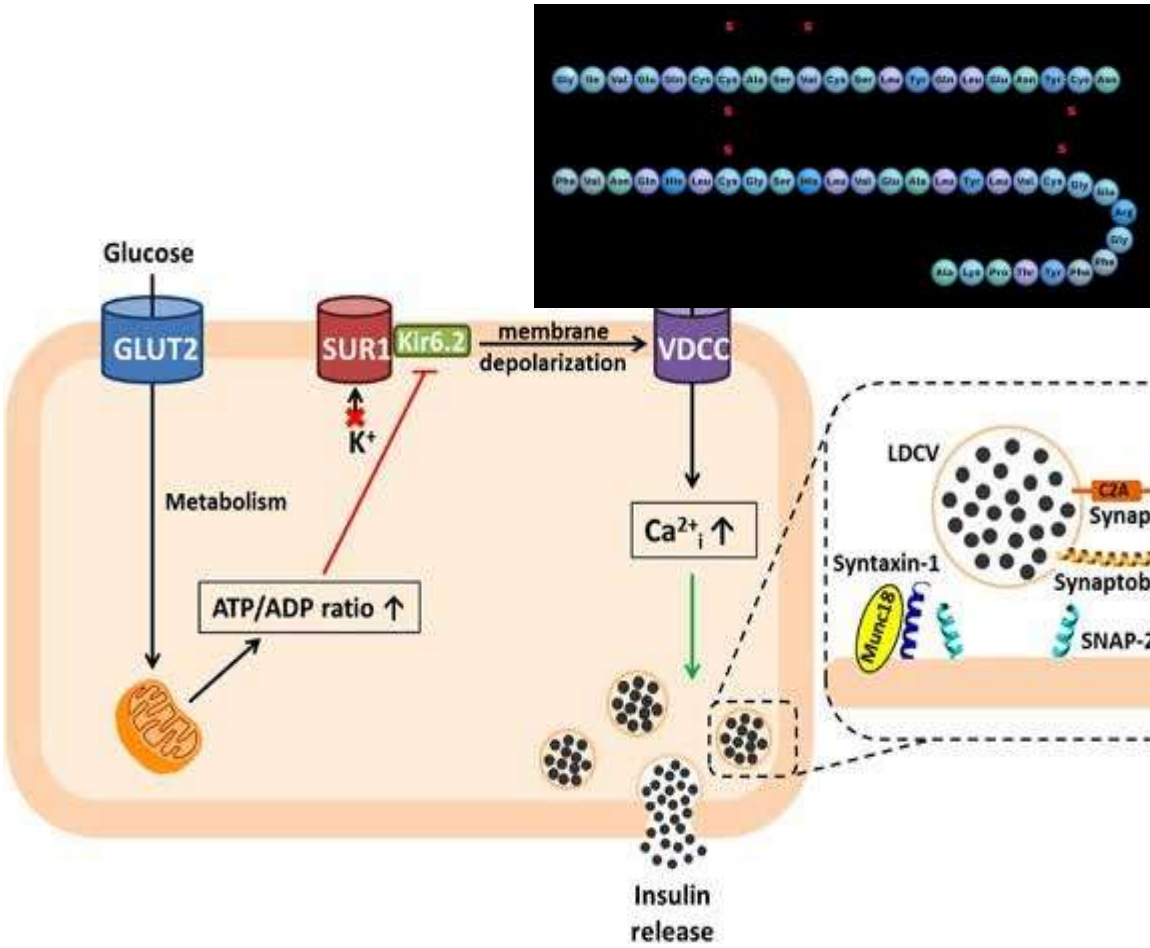
INSULIN

- Insulin is the polypeptide hormone produced by the β cells of langerhans.
- Insulin is composed of 51 amino acids arranged in two polypeptide chains, designated A and B, which are linked together by two disulfide bridges.
- Regulation of Insulin secretion

  Stimulated by Glucose, Amino Acids,

  Gastrointestinal hormones.

  Regulated by Epinephrine.



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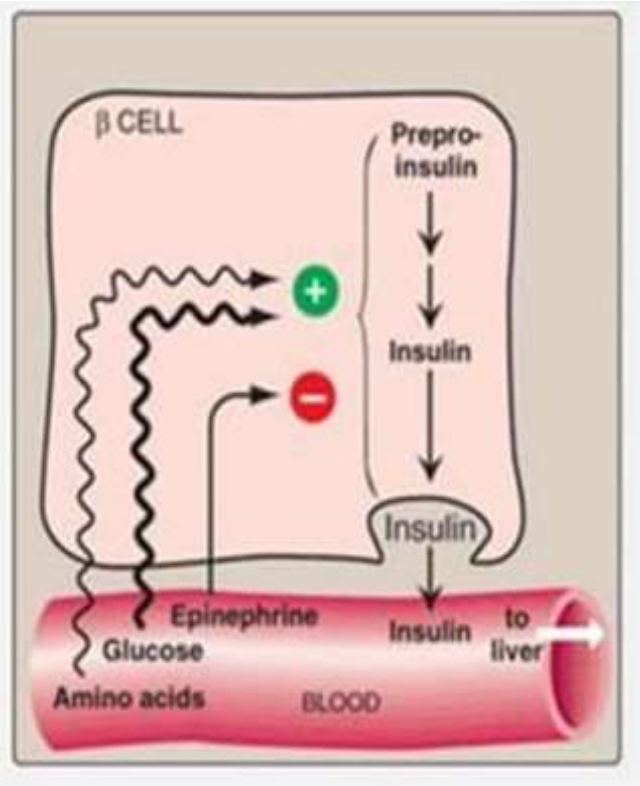

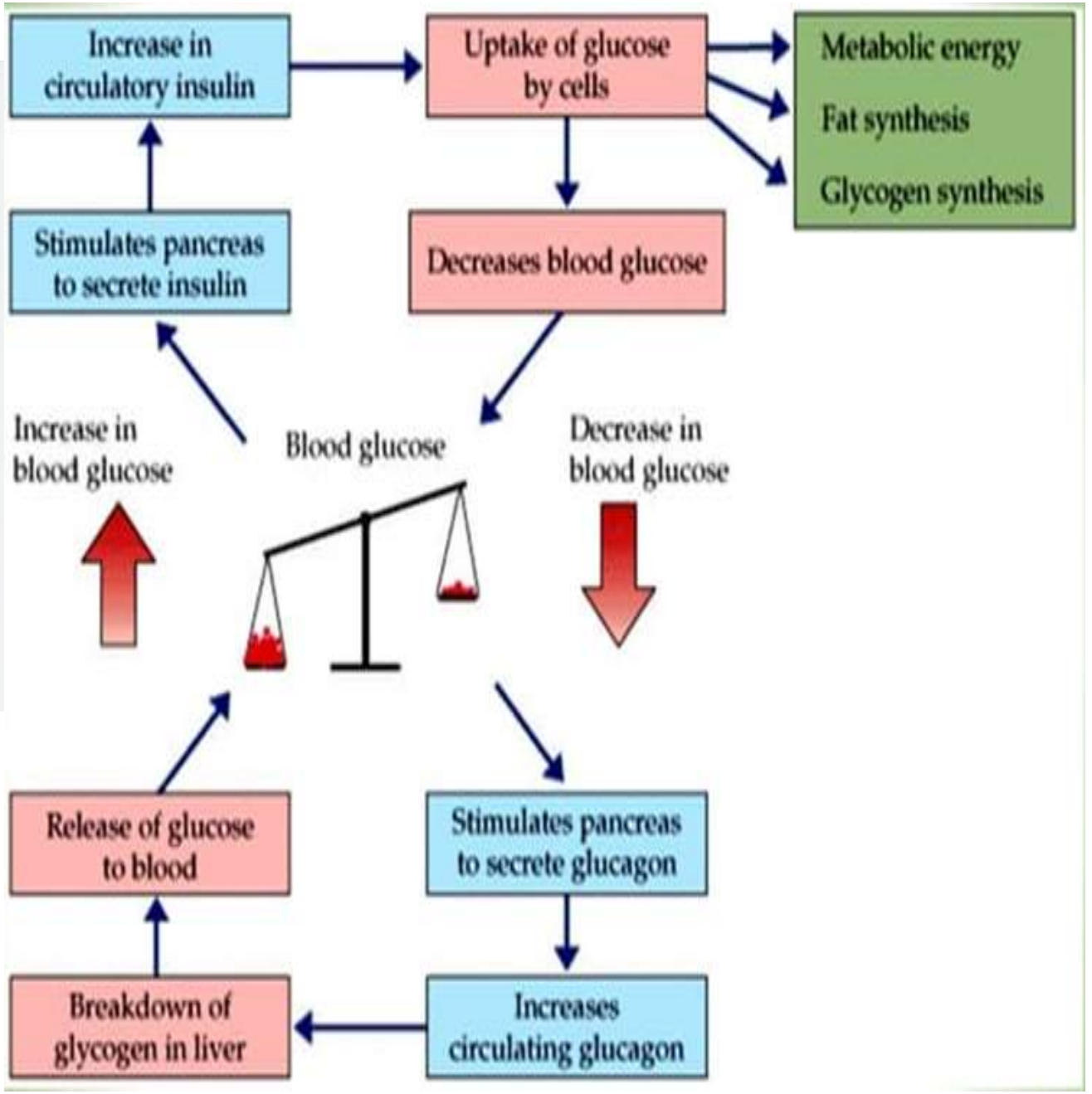

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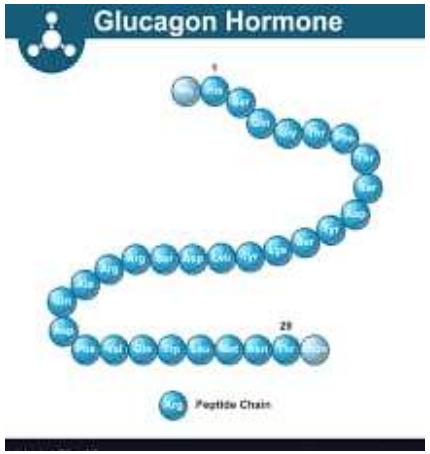
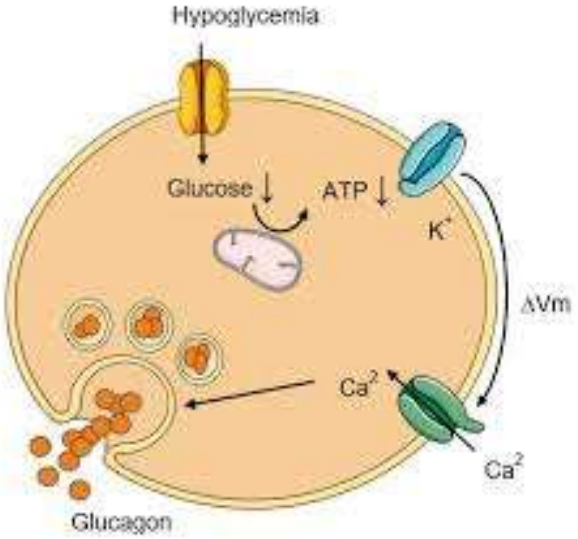
Role of other hormones

- Glucagon:

1. Glucagon secreted from pancreatic alpha cells in the islet of Langerhans plays an important role in maintaining glucose homeostasis
2. Glucagon activates enzymes in liver cells that break down glycogen into glucose.
3. Glucagon also acitvates enzymes that are invovled in the formation of glucose from glycerol and amino acids.
4. Glucagon also decreases the rate of respiration of glucose in cells.

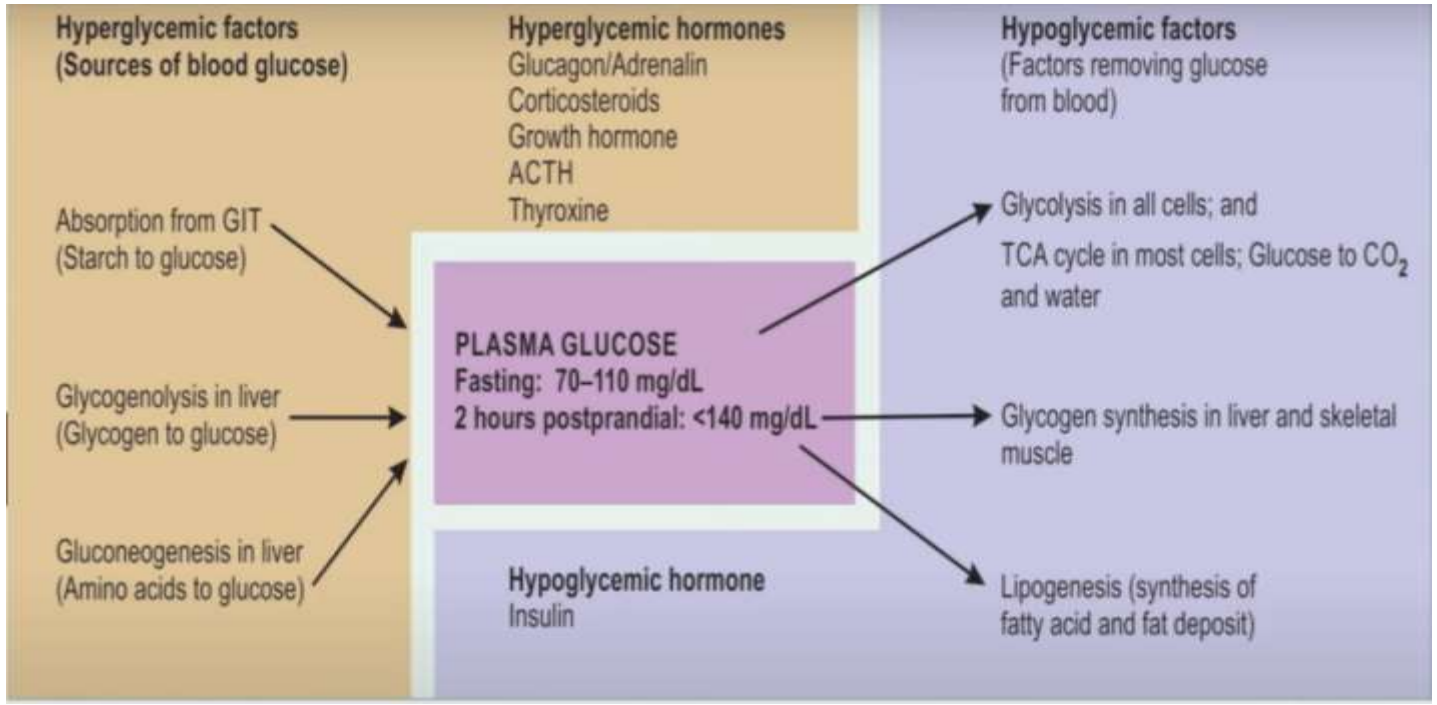




Source:https://images.app.goo.gl/MB8QKgZmefhLJn1P7 ,https://images.app.goo.gl/fiFyViMVWQju9mAbA.

- Epinephrine:
    - Secreted by adrenal medulla.
    - Acts both on muscle and liver to bring glycogenolysis by increasing phosphorylase activity
    - Secreted in response to stress, trauma, or extreme exercise.
    - Epinephrine has a direct effect on energy metabolism, causing a rapid mobilization of energy-yielding fuels, including glucose from the liver (produced by glycogenolysis or gluconeogenesis)
- Glucorticoids :
    - Hormones of adrenal cortex.
    - Stimulate protein metabolism and increase gluconeogenesis
    - Inhibits glucose utilization by extrahepatic tissues
    - Increases blood glucose level

- Growth Hormone and adrenocorticotropic hormone (ACTH):
    - Hormones of anterior pituitary gland causing hyperglycemia
    - Glucose uptake by certain tissues decreased by GH
    - ACTH decreases glucose utilization



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Glucose homeostasis in fasting state

- Stimulation of ***Glycogenolysis*** **-**Breakdown of glycogen in the liver that releases the glucose.
- Stimulation of ***Gluconeogenesis*** **–** Synthesis of glucose from non carbohydrate sources
- Stimulation of ***Lipolysis*** – Breakdown of Fatty acids.

Glucose homeostasis in Postprandial condition:

- Stimulation of ***Glycolysis*** **-** The process in which glucose is broken down to produce energy.
- Stimulation of ***Glycogenesis*** **-** when blood glucose levels are sufficiently high to allow excess glucose to be stored in liver and muscle cells as Glycogen.
- Stimulation of ***Lipogenesis*** **-** Synthesis of fatty acids from non lipid precursor.

RENAL CONTROL MECHANISM

- If the blood glucose level is raised above 180mg/dl complete tubular reabsorption of glucose does not occur and the extra amount is appears in the urine causing ***Glycosuria*****.**

ROLE OF ORGANS IN BLOOD GLUCOSE HOMEOSTASIS:

	LIVER	ADIPOSE TISSUE	MUSCLE
Increased by Insulin	Fatty acid synthesis Glycogen synthesis Protein synthesis	Glucose uptake Fatty acid synthesis	Glucose uptake Glycogen synthesis Protein synthesis
Decreased by Insulin	Ketogenesis Gluconeogenesis	Lipolysis	
Increased by Glucagon	Glycogenolysis Gluconeogenesis Ketogenesis	Lipolysis	