1. Metabolism

The term metabolism describes the interconversion of chemical compounds in the body, the pathways used by different molecules, their interrelationships, and the mechanisms that control the flow of metabolites through these pathways. Normal metabolism includes adaptation to periods of starvation, exercise, gestation, and lactation. Abnormal metabolism can be caused by a nutritional or enzyme deficiency, abnormal hormone secretion, or the action of drugs or toxins.

Metabolic pathways are divided into three categories:

(1) Anabolic pathways: These pathways are involved in the synthesis of larger and more complex compounds from smaller precursors, for example, the synthesis of proteins from amino acids and the synthesis of triacylglycerol and glycogen stores. Anabolic pathways are endothermic.

(2) Catabolic pathways: which serve to destroy large molecules, generally involve oxidation processes; they are exothermic, produce reducing equivalents and ATP, mainly via the respiratory chain.

(3) Amphibolic pathways: such as the citric acid cycle, appear at the crossroads of metabolism and serve as links between anabolic and catabolic pathways.

2. Glycolysis or Embden-Meyeroff-Parnas pathway

2.1. Introduction

Most tissues have a minimal need for glucose. In the brain, this need is significant. Glycolysis, the main pathway for glucose metabolism, takes place in the cytosol of all cells. It is a unique process because it can be aerobic or anaerobic depending on the availability of oxygen and an electron transport chain. Glucose's ability to provide ATP in the absence of oxygen is crucial because it allows skeletal muscle to function at very high levels when oxygen supply is insufficient, and enables tissues to survive episodes of anoxia.

2.2. Entry of glucose into the cell

The main dietary polysaccharides, starch and glycogen, which are a glucose is a storage form of glucose from plants and animals, respectively. After food intake, the digestion of these plant and animal polysaccharides begins in the mouth, where they are broken down by salivary amylase, leading to the formation of oligosaccharides. Then, in the upper part of the small intestine, the pancreas and the digestive tract, through hydrolytic enzymes (such as pancreatic amylases and oligosaccharidases), break down these oligosaccharides into simple monosaccharides (glucose, fructose, and galactose).(Figure1) Subsequently, these monosaccharides enter enterocytes via membrane transporters. Glucose molecules enter enterocytes via protein transporters, as they are impermeable to the cell membrane, (the membrane is lipophilic).

Glucose absorption through the intestinal lumen occurs via membrane cotransporters coupled to ions(Figure 2),The sodium-glucose cotransporter type 1, or sodium-glucose linked transporter (SGLT-1), carries out active transport (requires ATP). Glucose transporters (GLUTs) are sodium-independent membrane transport proteins that transport monosaccharides, including glucose, fructose, and galactose, and facilitate diffusion (do not require ATP).

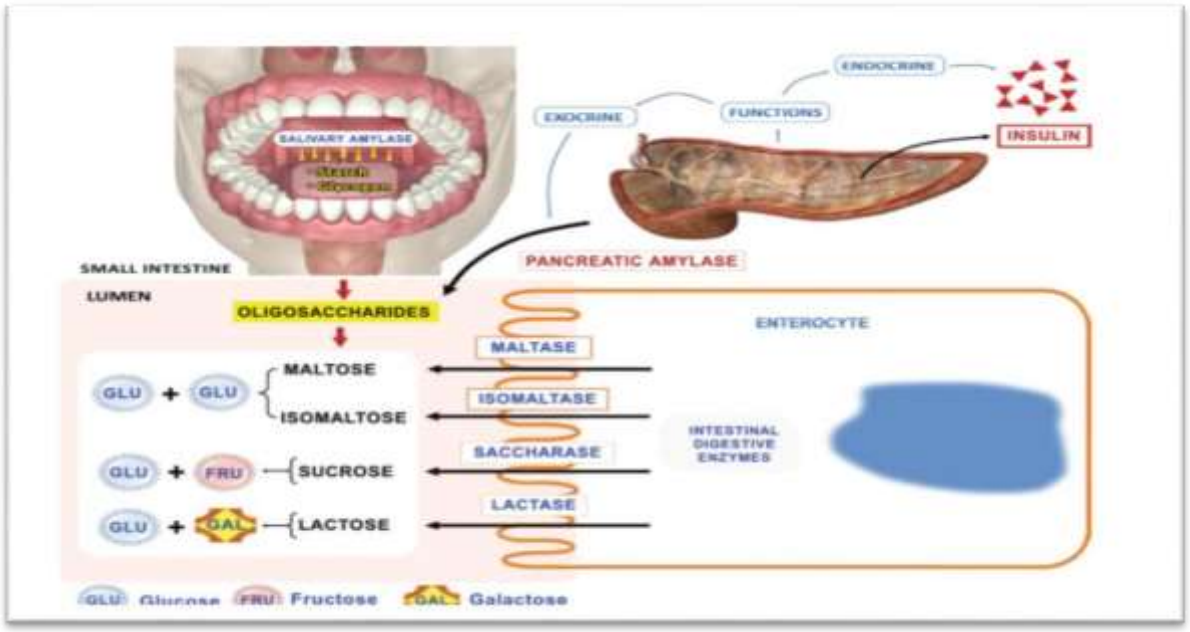


Figure 1: Breakdown of carbohydrates by pancreatic and intestinal enzymes.

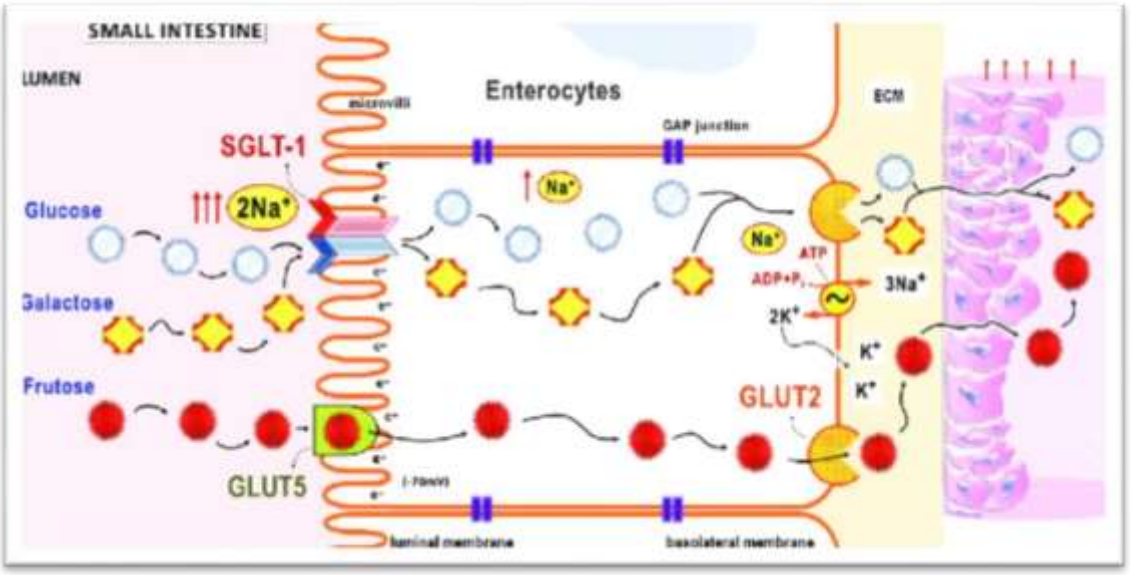


Figure 2: Glucose absorption by enterocytes.

2.3. Stages of glycolysis

2.3.1. Enzymatic steps of the first phase

2.3.1.1. Phosphorylation of glucose by ATP

All the enzymes of glycolysis are located in the cytosol. Glucose enters the glycolytic pathway through its phosphorylation to glucose 6-phosphate, catalyzed by hexokinase, which uses ATP as a phosphate donor. Under physiological conditions, the phosphorylation of glucose to glucose 6-phosphate can be considered irreversible.

2.3.1.2. Transformation of glucose 6-phosphate into fructose 6-phosphate

Glucose 6-phosphate is converted to fructose 6-phosphate by a phosphohexose isomerase, which involves an aldose-ketose isomerization.

2.3.1.3. Phosphorylation of F-6-P to fructose 1,6-bisphosphate

This reaction is followed by another phosphorylation catalyzed by phosphofructokinase (phosphofructokinase-1), yielding fructose 1,6-bisphosphate. The phosphofructokinase-catalyzed reaction can be considered irreversible.

2.3.1.4. Fructose 1,6-bisphosphate cleavage

Fructose 1,6-bisphosphate is cleaved by an aldolase (fructose 1,6-bisphosphate aldolase) into two triose phosphates: glyceraldehyde 3-phosphate and dihydroxyacetone phosphate.

2.3.1.5. Triose phosphate interconversion

Glyceraldehyde 3-phosphate and dihydroxyacetone phosphate are interconverted by an enzyme, phosphotriose isomerase.

2.3.2. Enzymatic steps of the second phase

2.3.2.1.Oxidation of 3-phosphoglyceraldehyde to 1,3-bisphosphoglycerate

Glycolysis continues with the oxidation of glyceraldehyde 3-phosphate to 1,3-bisphosphoglycerate. The enzyme that catalyzes this reaction, glyceraldehyde 3- phosphate dehydrogenase, is NAD-dependent.

2.3.2.2.Phosphate transfer on ADP

In the following reaction, catalyzed by phosphoglycerate kinase, phosphate is transferred from 1,3-bisphosphoglycerate to ADP to form ATP (substrate-level phosphorylation) and 3-phosphoglycerate.

2.3.2.3.Isomerization of 3-phosphoglycerate to 2-phosphoglycerate

3-Phosphoglycerate is isomerized to 2-phosphoglycerate by phosphoglycerate mutase.

2.3.2.4.Dehydration of 2-Phosphoglycerate to phosphoenolpyruvate

The next step is catalyzed by enolase and involves dehydration to form phosphoenolpyruvate.

2.3.2.5.Transfer of phosphate from phosphoenolpyruvate to ADP

Phosphate from phosphoenolpyruvate is transferred to ADP by pyruvate kinase, to generate two ATP molecules per glucose molecule oxidized.

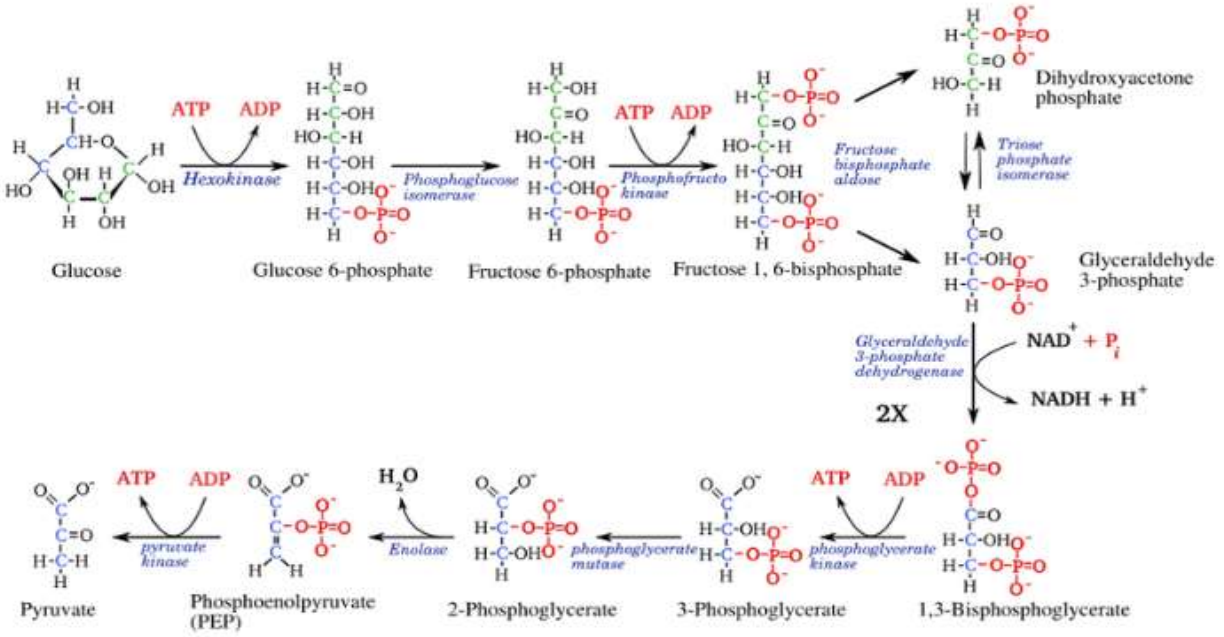


Figure 3: Stages of glycolysis.

2.4.Energy balance of glycolysis

2.5.NAD^+ cytosolic regeneration

Pyruvate is then reduced to lactate using $NADH_2$. This reaction is catalyzed by lactate dehydrogenase. The reoxidation of $NADH_2$ via the formation of lactate allows Glycolysis can continue in the absence of oxygen by regenerating sufficient NAD^+ for another reaction cycle catalyzed by glyceraldehyde 3-phosphate dehydrogenase.

2.6. Shuttles systems of glycolytic NADH transportation

Under aerobic conditions, pyruvate is used in the mitochondria and, after conversion to acetyl CoA, is oxidized to CO_2 through the citric acid cycle. $NADH_2$ is continuously produced in the cytosol by glyceraldehyde 3-phosphate dehydrogenase, an enzyme of the glycolytic pathway. However, under aerobic conditions, $NADH_2$ extramitochondrial molecules do not accumulate and are used in the mitochondria for oxidation by the respiratory chain via shuttles because they cannot penetrate the mitochondrial membrane. The transfer mechanism using the shuttle system:

2.6.1. Glycerol 3-phosphate shuttle

The transfer of reducing equivalents across the mitochondrial membrane occurs via pairs of substrates linked by appropriate dehydrogenases present on both sides of the mitochondrial membrane. The glycerol 3-phosphate shuttle is composed of two enzymes, cytosolic glycerol 3-phosphate dehydrogenase and mitochondrial glycerol 3-phosphate dehydrogenase (cGPDH and mGPDH, respectively). Electrons are transferred from NAD^+ When dihydroxyacetone phosphate is reduced to glycerol 3-phosphate by cGPDH. On the outer surface of the inner mitochondrial membrane, glycerol 3-phosphate is reoxidized to dihydroxyacetone phosphate by mGPDH, by binding to a prosthetic FAD group (Figure 4).

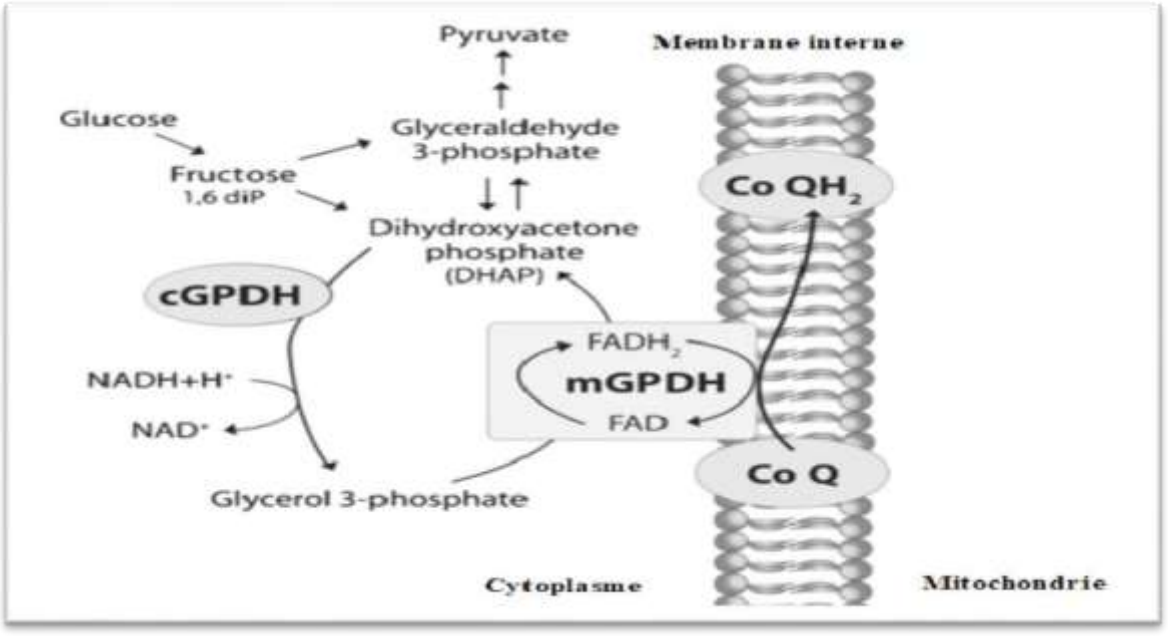


Figure 4: Glycerol 3-phosphate shuttle.

2.6.1. Malate-Aspartate Shuttle

The malate-aspartate shuttle is composed of two antiporter transporters (aspartate glutamate) and (malate-α-ketoglutarate), which are used for the transfer of the reducing equivalents NADH, H^+ products of glycolysis inside the mitochondria (they do not cross the mitochondrial membrane) (Figure 5). The complexity of this system is due to the impermeability of the mitochondrial membrane to oxaloacetate, which must react with glutamate for transamination into aspartate and α-ketoglutarate before transport across the mitochondrial membrane.

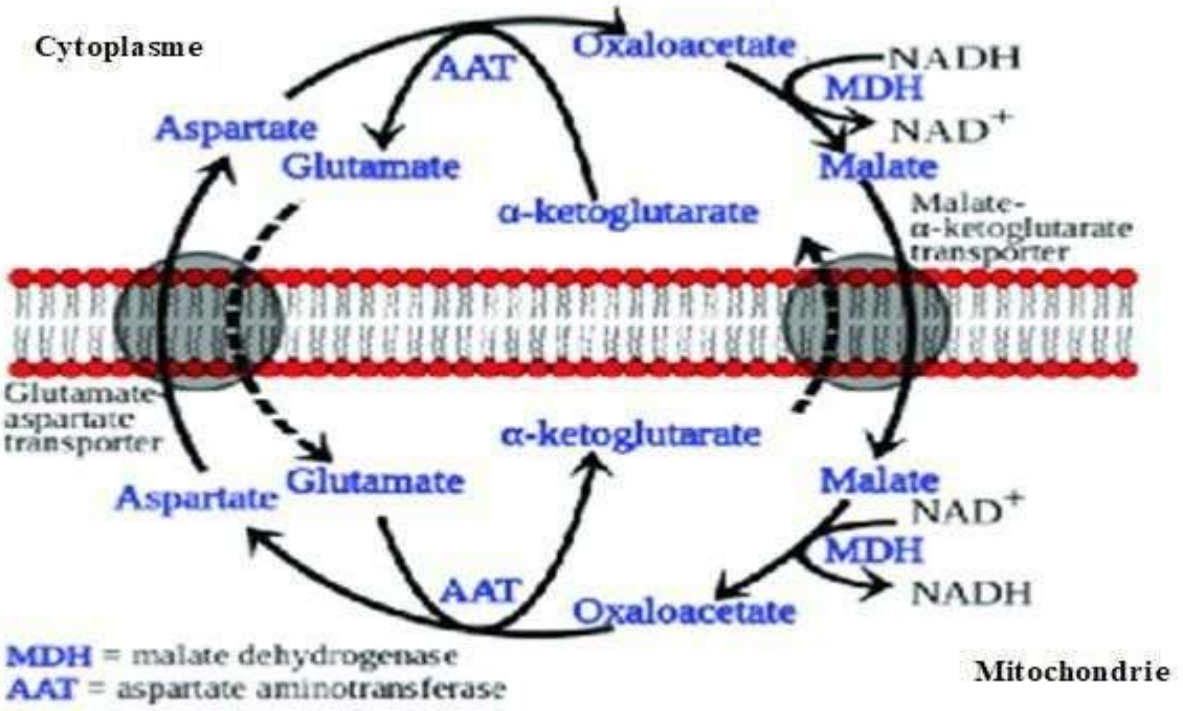


Figure 5: Malate-Aspartate Shuttle.

2.7. Glycolysis is a source of biosynthetic precursors

- **Glucose 6-phosphate**

Glucose 6-phosphate is an important compound found at the junction of several metabolic pathways: glycolysis, gluconeogenesis, the pentose phosphate pathway (glucuronate synthesis), glycogenesis, glycogenolysis, and ribose synthesis. Thus, in muscle, glucose-6-phosphate can also be formed from glucose-1-phosphate derived from glycogen; finally, it can come from other sugars such as galactose or mannose. In muscle glucose-6 P is degraded via the glycolytic pathway, while in the liver it essentially gives glucose under the action of glucose-6 phosphatase, a microsomal enzyme involved in gluconeogenesis or gluconeogenesis.

- **Pyruvate**

Pyruvate can give rise to other molecules depending on the availability of oxygen (presence or absence), energy requirements, and cellular enzymatic equipment.

- Oxidation of pyruvate to CO_2 and H_2O.
- Reduction of pyruvate to lactate (lactic acid fermentation) by lactate dehydrogenase (Figure 6).
- Transformation of pyruvate to acetaldehyde by pyruvate decarboxylase, followed by the transformation of acetaldehyde to ethanol by alcohol dehydrogenase (alcoholic fermentation) (Figure 6).
- Carboxylation of pyruvate to oxaloacetate (gluconeogenesis reaction).
- Acetyl CoA formation (synthesis of fatty acids and lipids).
- Synthesis of alanine (transamination).

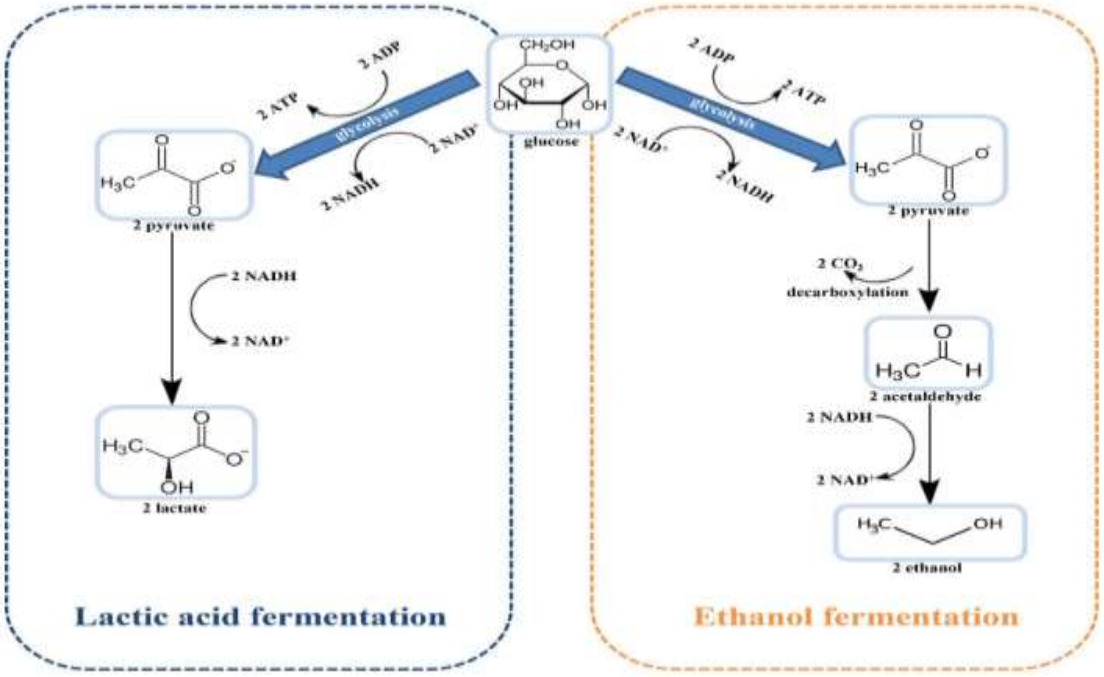


Figure 6: Lactic and alcoholic fermentation.

- **Phosphoenolpyruvate**

- Synthesis of phenylalanine, tyrosine, tryptophan (amino acid synthesis).

- **Dihydroxyacetone phosphate**

- Glycerol-3-phosphate synthesis (synthesis of triglycerides and phospholipids).

2.8. Entry of other carbohydrates into glycolysis

Food provides an abundance of glycogen and dietary starch (polysaccharides), which are acted upon by hydrolytic enzymes, releasing glucose, which is then phosphorylated into glucose 6-phosphate. Disaccharides (sucrose, lactose, maltose) contain, respectively, a fructose unit, a galactose unit, or a glucose unit linked to a glucose molecule (under the action of specific enzymes secreted by the intestinal mucosa (Figure 7).

The galactose resulting from the hydrolysis of lactose is converted into glucose-6P by a series of three reactions:

- It is phosphorylated by ATP to galactose-1P by the action of galactokinase.
- Phosphogalactose-uridyl transferase catalyzes the transfer of galactosyl from galactose-1P to UDP-glucose with the release of glucose-1P.
- The third reaction, catalyzed by UDP-galactose-4 epimerase, is an epimerization of galactosyl to glucosyl by inversion of the configuration of the hydroxyl in position 4.

Fructose from the hydrolysis of sucrose is converted into glyceraldehyde 3-phosphate through a series of four reactions:

- It is phosphorylated by ATP to fructose-1P under the action of fructokinase.
- Fructose 1 phosphate is cleaved by aldolase 2 (fructose-1-phosphate aldolase) into two triose phosphates: glyceraldehyde and 3-dihydroxyacetone phosphate.
- Phosphorylation of glyceraldehyde to glyceraldehyde-3 phosphate by glyceraldehyde kinase
- Isomerization of 3-dihydroxyacetone phosphate to glyceraldehyde-3-phosphate by phosphotriose isomerase).

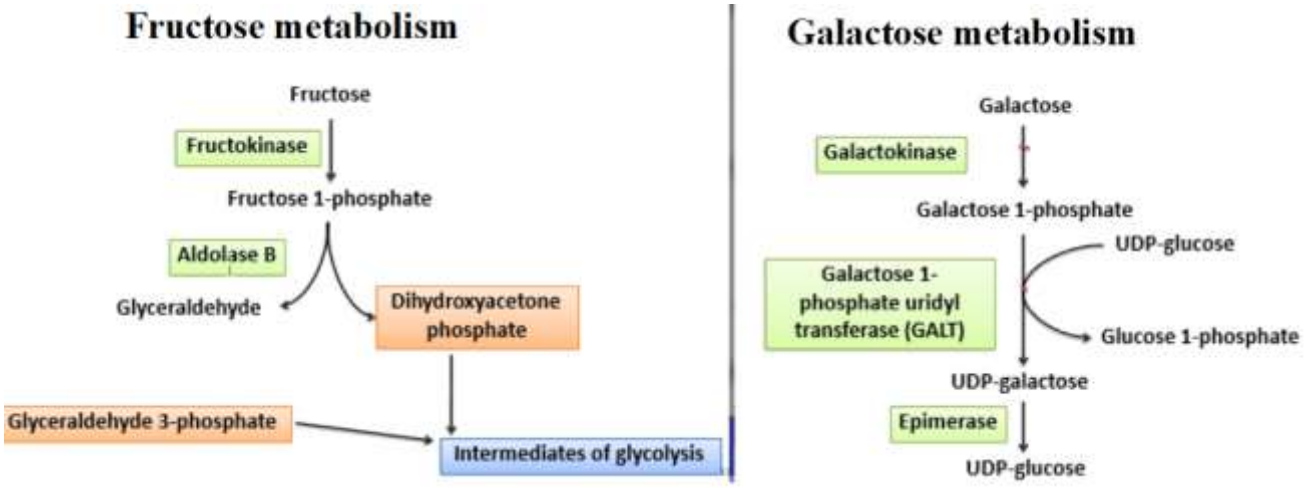


Figure 7: Entry of other carbohydrates into glycolysis

2.9. Regulation of glycolysis

Two types of mechanisms regulate glycolysis: allosteric regulation and hormonal regulation.

2.9.1. Allosteric regulation

In metabolic pathways, the enzymes that catalyze essentially irreversible reactions are potential control sites. Irreversible reactions in glycolysis occur at the level of three enzymes: hexokinase, phosphofructokinase, and pyruvate kinase.

- **Hexokinase**

Hexokinase is allosterically inhibited by its product, glucose 6- phosphate.

- **Glucokinase**

Liver cells also contain an isoenzyme of hexokinase, glucokinase, which has a Km much higher than the normal intracellular concentration of glucose.

- **Phosphofructokinase-1**

Under physiological conditions, it is both inducible and subject to allosteric control. It plays an important role in regulating the rate of glycolysis. PFK1 is an enzyme allosteric. Its activity is inhibited by high concentrations of ATP. The protein has two types of ATP binding sites: the active site and a regulatory site (allosteric site). Inhibition occurs through excess substrate and also through a final product of the reaction (or feedback inhibition), since ATP is a product of glycolysis.

The citrate an intermediate in the Krebs cycle, which can be considered an indicator of energy status, also inhibits this reaction. Conversely, ADP and AMP, phosphate acceptors, are activator of the enzyme. Fructose 2,6-bisphosphate (F 2, 6 bi P) is produced by the phosphorylation of fructose 6-

phosphate by the active phosphofructokinase 2 (PKF2) PFK1(Figure 8).

- **Pyruvate kinase**

The liver enzyme is tightly regulated; as an allosteric enzyme, it is stimulated by fructose-1,6-bisphosphate. The activity of liver pyruvate kinase is inhibited by ATP and alanine (an amino acid involved in gluconeogenesis).

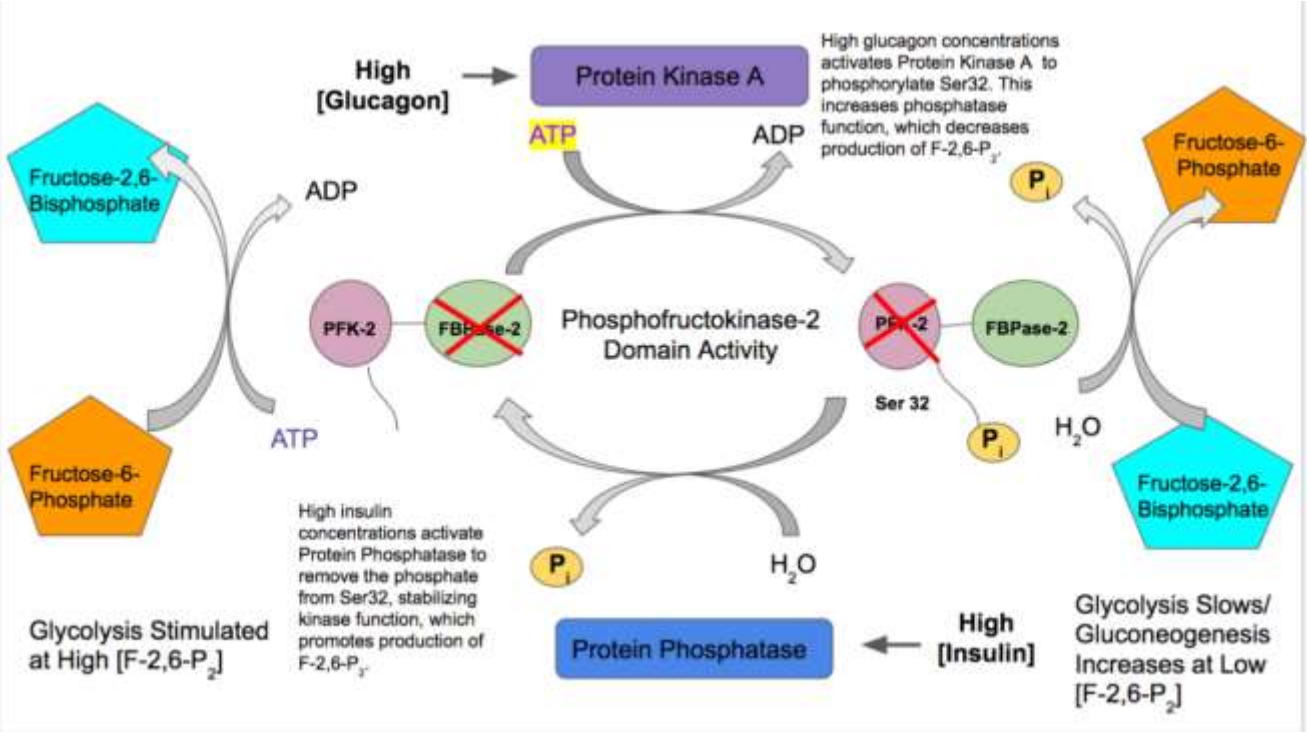


Figure 8:PFK1 regulation

2.9.2.Hormonal regulation

- **Phosphofructokinase-1**

It has been shown that, in the liver, glycolysis is regulated by insulin.fructose-2,6 bisphosphate glucagon stimulates phosphofructokinase 1. The phosphorylation of fructose-6-phosphate to fructose-2,6-bisphosphate by phosphofructokinase 2 (PFK2) and the hydrolysis of fructose-2,6- bisphosphate to fructose-6-phosphate by fructose-2,6-bisphosphatase 2 (FBP2) are carried out by the same peptide chain. Thus, in the liver, glucagon, via cAMP-dependent protein kinase, induces the phosphorylation of this protein, which stimulates FBP2 activity and inhibits PFK2. Consequently, glucagon has a negative effect on glycolysis (Figure 8).

- **Pyruvate Kinase**

Several pyruvate kinase isoenzymes, which are distributed differently in tissues, have been characterized in mammals. The hepatic pyruvate kinase enzyme (L-form) is phosphorylated by a cAMP-dependent protein kinase and dephosphorylated by a phosphatase.

Phosphorylation inhibits glycolysis.

2.10. Cori Cycle

During skeletal muscle exercise, where anaerobic glycolysis predominates, rapid catalysis occurs, driven by lactate dehydrogenase. Lactate is rapidly excreted and enters the bloodstream, where it is largely converted back to pyruvate in the liver via lactate dehydrogenase. The pyruvate not catalyzed to acetyl-CoA can be converted to oxaloacetate, which then enters the gluconeogenesis pathway. This cycle is called the Cori cycle (Figure 9).

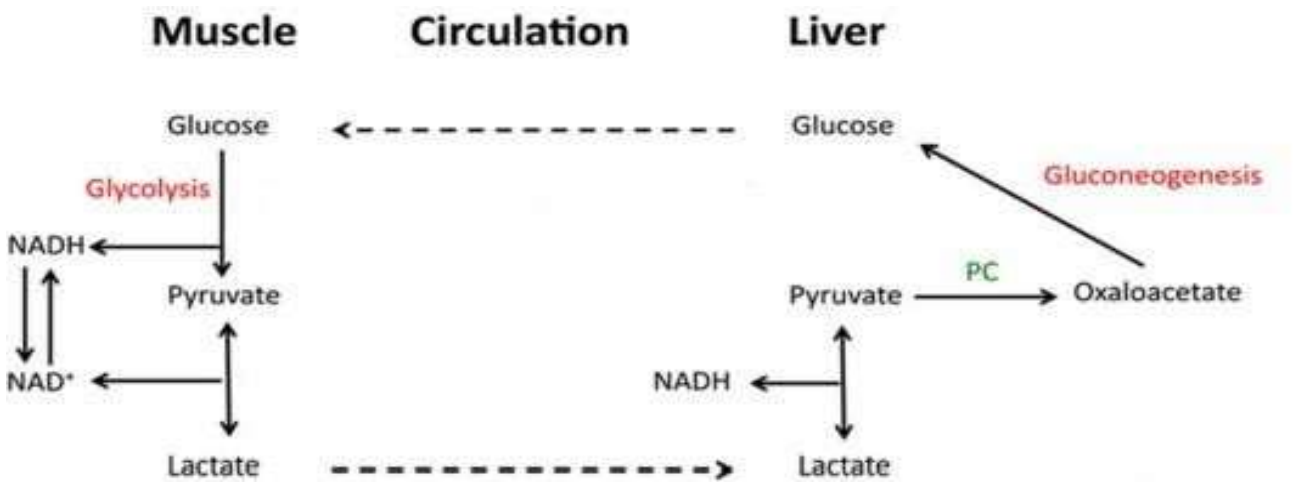


Figure 9 : Cori cycle. **PC** : pyruvate carboxylase.

2.11. Anaerobic glycolysis

- **Erythrocytes**

Erythrocytes, which lack mitochondria, are entirely dependent on glucose as a metabolic fuel, which they metabolize via anaerobic glycolysis. However, the oxidation of glucose beyond pyruvate, the final stage of glycolysis, requires molecular oxygen and mitochondrial enzyme systems such as the pyruvate dehydrogenase complex, the citric acid cycle, and the respiratory chain.

- **Muscles**

Muscle can contract in an anaerobic environment when deprived of oxygen; glycogen is depleted and

lactate is released. The presence of oxygen restores aerobic conditions, and the lactate disappears. However, if the contraction occurs under aerobic conditions, lactate does not accumulate, and pyruvate becomes the primary end product of glycolysis. Pyruvate is oxidized to CO_2 and water. If oxygen becomes scarce, mitochondrial reoxidation of NADH formed during glycolysis does not occur; NADH is then reoxidized by reduction of pyruvate to lactate to promote the continuation of glycolysis.

The overall equation for glycolysis, from glucose to lactate, is as follows:

Glucose + 2 ADP + 2 Pi ⟷ Lactate + 2 ATP + 2 H_2O

2.12. Pathologies related to glycolysis

2. 12.1. Hemolytic anemia

The example of pyruvate kinase deficiency: Red blood cells do not possess mitochondria and depend exclusively on glycolysis for their ATP supply. This leads to impaired glycolysis and insufficient ATP production, necessary for maintaining their function and membrane structure. The membrane becomes deformed, and the red blood cells are prematurely phagocytosed by macrophages, resulting in hemolytic anemia..

2.12.2. Lactic acidosis

Anaerobic glycolysis is the first step in glucose metabolism and occurs in the cytoplasm of all cells. Under anaerobic conditions, such as during hypoxia, cells are forced to use anaerobic glycolysis as their sole source of energy production. Intracellular lactate concentration increases. If cellular hypoxia is generalized, lactate cannot be converted into pyruvate or glucose (by gluconeogenesis). It then accumulates in the blood with hydrogen ions, leading to the development of lactacidemia.

3. Pentose phosphate (PP) pathway

The pentose phosphate (PP) pathway, also called the hexose monophosphate shunt. Compared to energy production pathways such as glycolysis and citric acid; The pentose-phosphate cycle is not used as a source of ATP, but mainly as a means to obtain reducing power (NADPH) and intermediate metabolites such as ribose 5 phosphate (nucleotides) and erythrose 4 phosphate (amino acids).One glucose molecule catalyzes the net production of two NADPH molecules (Figure 10). NADPH is used in the synthesis of reducing agents (fatty acids, cholesterol, steroid hormones). NADPH can also be used to maintain redox status and combat

oxidative stress via

the regeneration of reduced glutathione (GSH) by the action of glutathione reductase (red blood cells and neurons).

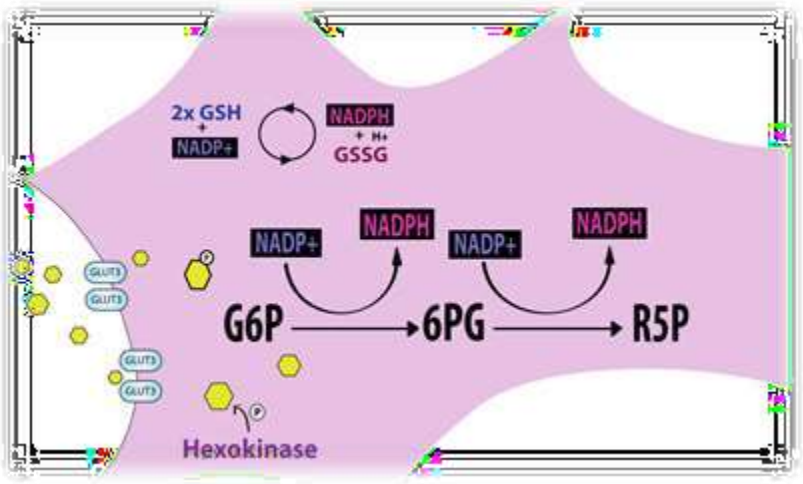


Figure 10: Simplified diagram of glucose metabolism via the pentose phosphate pathway. **GLUT3**: carrier 3, **G6P**: glucose-6-phosphate, **6PG**: 6-phosphogluconate, **R5P**: ribose-phosphate, **GSH**: reduced glutathione, **GSSG**: oxidized glutathione.

3.1. Steps

The PP reaction is a network of seven enzymes that interconvert sugars to phosphates (Figure 11), occurring in two steps: (i) an oxidative phase and (ii) a non-oxidative phase (regeneration of 5 molecules of Glucose-6-P (G6P) from 6 molecules of ribulose-5-P). Two key enzymes control this step: glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase (steps 1 and 3).

- ***Oxidative pathway***

The oxidative pathway is a part consisting of reactions catalyzed by glucose-enzymes. 6-phosphate dehydrogenase (G6PDH), 6-phosphogluconolactonase (6PGL) and 6-phosphogluconate dehydrogenase (6PGDH). These enzymes oxidize glucose-6-phosphate to 6-phosphogluconolactone, hydrolyze lactone to 6-phosphogluconate and oxidize 6-phosphogluconate to ribulose-6-phosphate, respectively. The overall reaction catalyzed by the oxidative pathway of PP is the oxidation of glucose-6-phosphate to ribulose-5-phosphate and $CO_2$2During oxidation, G6P degrades NADPH (Figure 11).

- ***Non-oxidative pathway***

The non-oxidative portion of PP pathway consists of reactions catalyzed by the enzymes ribulose-5-phosphate isomerase (R5PI), ribulose-5-phosphate-3-epimerase (R5PE), transaldolase (TA), and transketolase (TC). R5PI and R5PE convert ribulose-5-phosphate to ribose-5-phosphate and xylulose-5-phosphate, respectively. The reactions catalyzed by transaldolase (TA) and transketolase (TC) interconvert a range of phosphorylated aldoses (ribose-5-phosphate, erythrose-4-phosphate, glyceraldehyde-3-phosphate) and ketoses (xylulose-5-phosphate, fructose-6-phosphate, sedoheptulose-7-phosphate). This network of phosphorylated sugars is linked to glycolysis through their common intermediates glyceraldehyde-3-phosphate and fructose-6-phosphate.

3.1. Regulation

The flow through the PP is specifically modulated in each tissue according to the Physiological parameters. Tissues with biosynthetic functions, such as the liver or adipose tissue, have a high capacity to accelerate PP flux, while other cells, such as muscle cells, lack this capacity. Flux is modulated by the activity of G6PD, the main regulator of PP. This enzyme controls the entry of glucose-6-phosphate into PPP. G6PD is inhibited by a high concentration of NADPH and by intermediates of fatty acid biosynthesis.

The regulation of the pentose phosphate pathway depends on cellular needs. The main modes of pentose phosphate pathways are illustrated in Figure 12.

- **Mode 1:** This mode dominates when the demand for R5P is greater than that for NADPH, for example in cases of cell proliferation. In this situation, the glycolytic metabolites 3GP and F6P can be converted to R5P via reversible PP through a non-oxidative pathway.

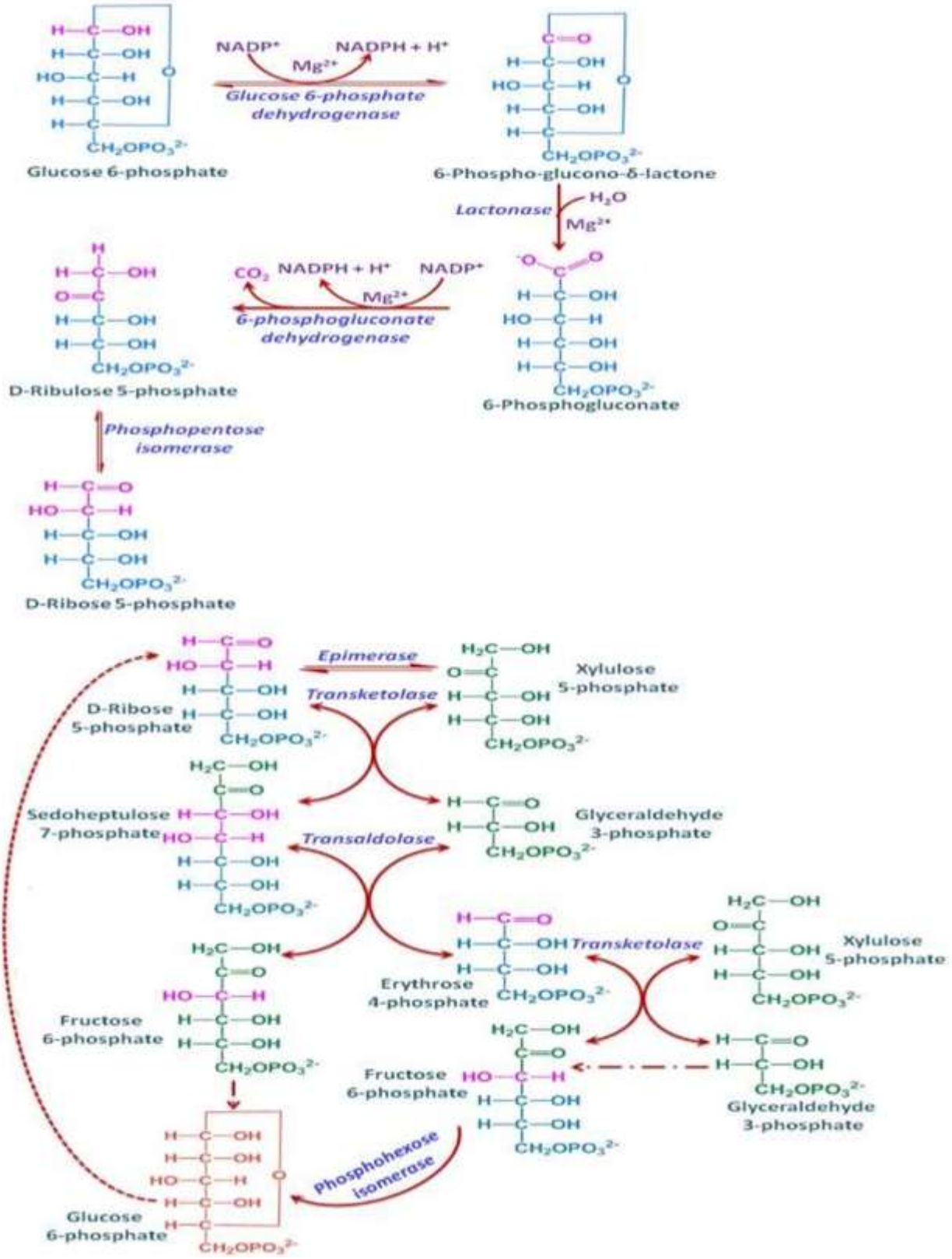


Figure 12: Pentose-phosphate pathway.

- **Mode 2**: This mode occurs when the requirements for NADPH and R5P are balanced. Then, from one molecule of G6P, two molecules of NADPH and one molecule of R5P can be obtained without the generation of glycolytic metabolites.

- **Mode 3**: This pathway is adopted when the cellular need for NADPH exceeds that of R5P and ATP, for example, during fatty acid synthesis in adipocytes. The non- oxidative phase of the pathway leads to the conversion of ribulose 5-phosphate to fructose 6-phosphate (F6P) and glyceraldehyde 3-phosphate (G3P). Subsequently, these glycolytic metabolites, through gluconeogenesis, form G6P, which can re- enter PPP to produce more NADPH.

- **Mode 4**: The cellular requirement for NADPH and ATP is greater than that for R5P. As described in mode 3, ribulose 5-P is transformed into G3P and F5P via the non-oxidative process; however, in mode 4, these molecules are metabolized into pyruvate via glycolysis, which is associated with ATP formation.

4. Citric acid cycle

The Krebs cycle, or tricarboxylic acid cycle, takes place in the mitochondrial matrix. But before reaching the matrix, pyruvate is oxidized and decarboxylated by pyruvate dehydrogenase to form NADH and acetyl-CoA. Acetyl-CoA then enters the cycle via citrate synthase, which transfers the acetyl group to oxaloacetic acid to synthesize citric acid. This is followed by a series of reactions leading to the regeneration of oxaloacetic acid while releasing energy in the form of a phosphorylated compound (GTP) and reducing power (NADH).2and FADH2) (Figure 13).

4.1. Regulation

The regulation of the TCA cycle, like that of glycolysis, occurs both at the level of substrate entry into the cycle and at key reactions of the cycle.

- ***ATP Availability and Cellular Need***

  When the cell's energy charge is low, the cycle operates at a rate faster.

- ***Pyruvate dehydrogenase***

The generation of acetyl-CoA from carbohydrates is a major checkpoint in the cycle. This is the reaction catalyzed by the pyruvate dehydrogenase complex. The pyruvate dehydrogenase complex is inhibited by acetyl-CoA and NADH and activated by coenzyme A

(CoA-SH) and NAD^+.

- ***Citrate and citrate synthase***

The formation of citrate from oxaloacetate and acetyl CoA constitutes an element Important for control. ATP acts as an allosteric inhibitor of citrate synthase. Citrate inhibits PFK (a key enzyme in glycolysis).

- ***Isocitrate dehydrogenase***

ADP acts as a positive modifier, enhancing substrate binding. NADH is an inhibitor.

- ***Alpha ketoglutarate dehydrogenase***

It is inhibited by succinyl-CoA and NADH.

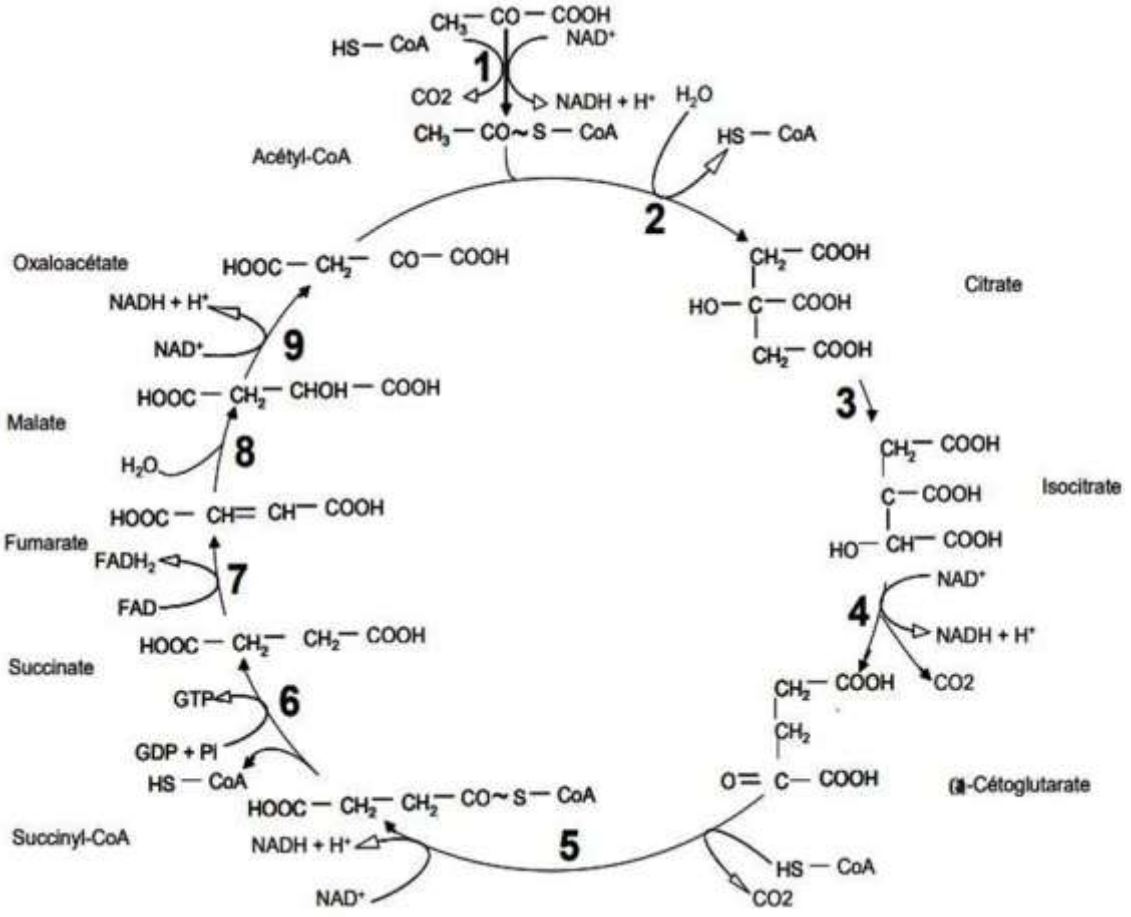


Figure 13: Krebs cycle.

1:pyruvate deshydrogenase (enzyme complex);**2**: citrate synthase;**3**: aconitase;**4**: isocitrate deshydrogenase;**5**: α-ketoglutarate deshydrogenase (enzyme complex);**6**:succinyl-CoA synthetase;**7:**succinate deshydrogenase;**8**: fumarase;**9**: malate deshydrogenase.

5. Glycogen metabolism

A constant source of blood glucose is essential for human life. Glucose is the preferred energy substrate for the brain, and a fundamental energy source cells without mitochondria, such as red blood cells. Skeletal muscles, which contract rapidly, require a significant supply of glucose, which alone, through glycolysis, provides the necessary energy. Blood glucose comes from three sources:

- Dietary glucose ingested with meals,
- Gluconeogenesis,
- Glycogen (glucose polymer) from the liver

The source of dietary glucose (disaccharides, starch, and glycogen) is sporadic and unreliable. Gluconeogenesis is often too slow to meet immediate demand. In contrast, the animal body has developed a rapid mobilization process in the liver and striated muscles in response to immediate demand in the absence of dietary glucose. This process is glycogenolysis, or glycogen breakdown.

While hepatic glycogen is mobilized to maintain blood glucose levels and supply peripheral tissues, glycogen stored in muscles is mobilized and consumed locally for muscle function. Liver glycogen stores increase when animals are well fed and can decrease during prolonged fasting until depleted. Muscle glycogen stores are minimally affected by prolonged fasting and can be replenished after activity that has depleted some of them. Whether in the liver or muscles, glycogen is synthesized from glucose 6-phosphate as a precursor. Glycogen synthesis is called glycogenesis.

5.1. Glycogenolysis

5.1.1 Sequences of enzymatic reactions

The main enzyme in the breakdown of endogenous glycogen (hepatic and muscular) is glycogen phosphorylase, which releases glucose-1-phosphate and limiting dextrin. Two other enzymes, a glycosyltransferase and an α(1-6) glucosidase, are involved in the complete conversion of glycogen to glucose-6-phosphate. Only the liver can convert glucose-6-phosphate into glucose, which is then excreted into the bloodstream.

- **Glycogen phosphorolysis**

Phosphorolysis itself is catalyzed by glycogen phosphorylase. This enzyme cleaves the α(1-4) bond from the non-reducing end and attaches a phosphate group, supplied by ATP, to carbon 1 of the released glucose, yielding glucose 1-phosphate. Phosphorolysis is repeated sequentially on glycogen up to four

glycolytic residues on each chain before the α(1-6) bond. The residual structure is called limit dextrin, which resists further action by phosphorylase (Figure 14).

- **Debranching enzyme**

Debranching enzyme acts on limit dextrin by removing an oligosyl group of three glucose residues from each limit dextrin chain. This oligosyl group is then used to extend another limit dextrin chain, thus allowing phosphorolysis to resume on that chain. After the action of this enzyme, a glucose linked by the α (1-6) bond remains in place of the side chain.

- **α(1-6) Glucosidase**

Finally, α-glucosidase hydrolyzes the glucose residues linked by the α (1-6) bond and releases the glucose. After the action of these three enzymes, glycogen releases primarily glucose 1-phosphate (via phosphorolysis) and a small amount of glucose (via hydrolysis). Glucose 1-phosphate is isomerized to glucose 6-phosphate by phosphoglucomutase. Glucose 6-phosphate can enter glycolysis in the liver and muscle. However, the primary objective of hepatic glycogen degradation is to maintain blood glucose levels. To achieve this, only the liver, after glycogen degradation, possesses glucose 6-phosphatase, which hydrolyzes glucose 6-phosphate into glucose and excretes the latter into the bloodstream. The two catalyzed reactions are as follows:

Glucose 1-P → Glucose 6-P (Phosphoglucomutase)

Glucose 6-P + H_2O → Glucose + Pi (Glucose 6-phosphatase)

The entire sequence of glycogen degradation reactions is summarized in Figure 14.

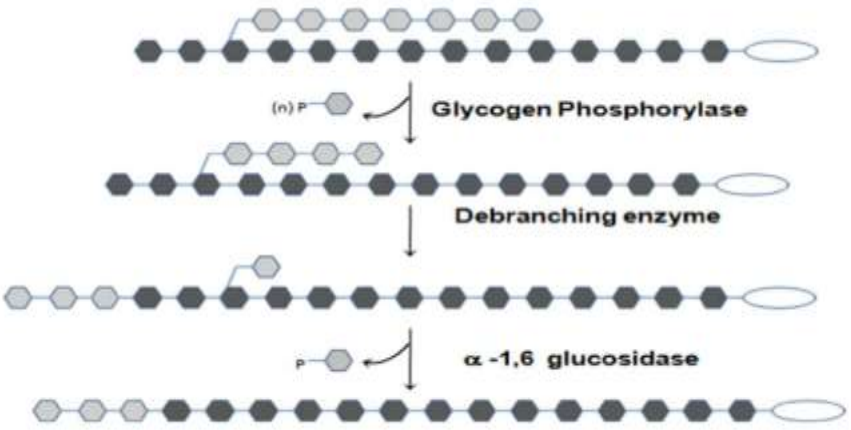


Figure 14: Glycogenolysis steps.

5.1.2. Glycogenolysis regulation

Glycogen metabolism is an integral part of energy metabolism. It is under hormonal control. Adrenaline and glucagon direct catabolism and energy production; insulin controls anabolism, which is oriented towards energy storage. The effects of these two groups of hormones are antagonistic, which necessitates coordinated regulation, as we will see later. Regarding glycogen breakdown, we will distinguish between hormonal regulation and regulation by calcium ions.

5. 1.2.1. Hormonal regulation

Glucagon and adrenaline (epinephrine) are the two main hormones that control the breakdown or mobilization of glycogen. There are two glycogen phosphorylases, one muscular and the other hepatic. Each exists in two forms: the α form (active) and the β form (inactive). The inactive form (β) can be converted to the active form (α) by phosphorylation. The two forms, whether in muscle or in the liver, interconvert into one another through the action of two enzymes: phosphorylase kinase (transition from the inactive form to the active form by phosphorylation) and phosphorylase phosphatase (hydrolysis of the phosphate group) Figure 15.

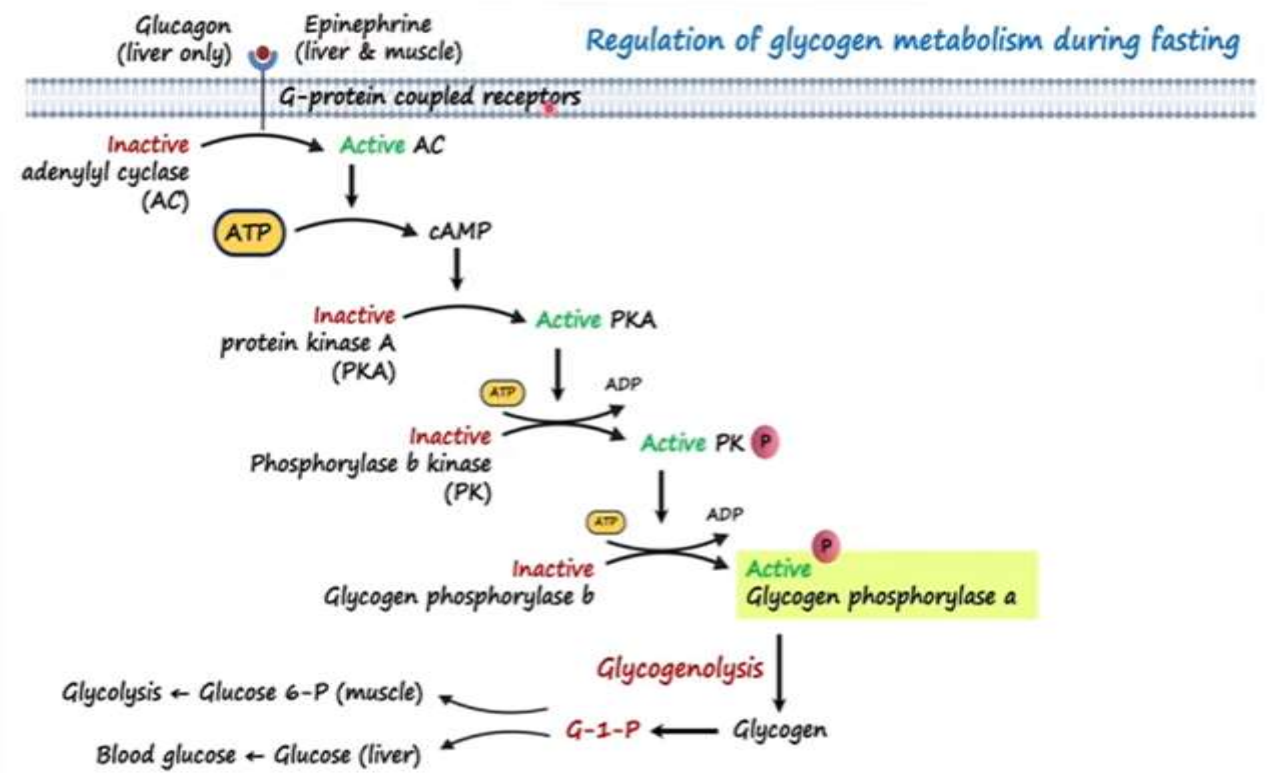


Figure 15: Hormonal regulation of glycogenolysis.

- Phosphorylase kinase, which phosphorylates hepatic or muscle phosphorylase, also exists in two forms: one active (phosphorylated) and the other inactive (dephosphorylated). The interconversion between the inactive and active forms is mediated by a protein kinase.
- Protein kinase is composed of two subunits, one catalytic (active) and the other regulatory. The inactive form is the assembly of the two subunits, with the regulatory subunit masking the catalytic site of the active subunit. Activation of protein kinase is mediated by cAMP (cyclic AMP), which, by combining with the regulatory subunit, releases the catalytic site of the active subunit.
- cAMP is produced in the cytosol from ATP by membrane adenylate cyclase, which is activated by two main hormones: adrenaline (epinephrine) or glucagon.

Hormonal regulation is actually the result of the transduction of a chemical signal leading to intracellular effects, which in this case corresponds to the mobilization of glycogen. The mechanisms of action of adrenaline and glucagon are similar, once each of these hormones binds to its specific membrane receptor.

- The binding of each hormone to its specific membrane receptor leads to the activation of a membrane adenylate cyclase.
- Activated adenylate cyclase catalyzes, through ATP hydrolysis, the formation of cyclic AMP (cAMP), considered a second messenger.
- c AMP binds to protein kinase A (cAMP-dependent) and combines with the regulatory subunit to release the catalytic subunit (active protein kinase A).
- Active protein kinase A phosphorylates, in the presence of ATP, glycogen phosphorylase kinase, which becomes active in its phosphorylated form.
- Finally, this phosphorylase kinase phosphorylates glycogen phosphorylase, converting it from the β form to the α form, which catalyzes the phosphorolysis of glycogen.

5.2.Glycogenesis

The purpose of glycogen synthesis is to store, in the liver, a portion of the excess glucose following a diet rich in carbohydrates and proteins, and in the muscles to regenerate glycogen stores, a fraction of which has been depleted by physical activity. Glycogen synthesis occurs primarily in the liver and muscles. The main enzyme is glycogen synthase. The precursor is glucose 6-phosphate.

5.2.1. Sequences of enzymatic reactions

- **Isomerization of glucose 6-phosphate to glucose 1-phosphate**

The enzyme that catalyzes this reaction is phosphoglucomutase.

Glucose 6-phosphate → glucose 1-phosphate

- Transfer of the glucosyl group onto UTP (formation of UDP-glucose).

The donor of the glucose group in the polymerization of glucose into glycogen is UDP-glucose. Its formation is ensured by UDP-glucose pyrophosphorylase, which transfers the glucosyl group onto UDP, releasing pyrophosphate (PPi). Hydrolysis of PPi by pyrophosphatase further promotes the reaction.

UTP + glucose → UDP-glucose + PPi

- **Synthesis of a primer to initiate glycogen synthesis**

Glycogen synthase, which is responsible for the formation of the α (1-4) linkage, is an elongation enzyme and cannot initiate de novo glycogen synthesis from glucose. A primer is required, which can be obtained in several ways:

- ✓ using a glycogen fragment in the form of dextrin
- ✓ In the absence of this fragment, a specific protein, glycogenin. It possesses a tyrosine side chain that acts as an acceptor, thanks to its -OH group, for the first glucosyl residue from UDP-glucose. The formation of the first glycosidic bond is catalyzed by an initiating glycogen synthase. Glycogenin itself can add a few glucose units linked by α (1-4) bond to complete the primer (8 glucose units) Figure 16.

- **Glycogen synthase chain elongation**

The glycogen chain is elongated by glycogen synthase, which transfers the glucosyl residue of UDP-glucose to the non-reducing end of the primer or elongating glycogen chain and sequentially forms the α (1-4) linkage according to the reaction:

Glycogen (n glucose) + UDP-glucose → glycogen [(n+1)] glucose + UDP

UDP is then converted back to UTP by a nucleoside diphosphate kinase in the presence of ATP.

ATP + UDP → UTP + ADP

- **Side chain formation**

At every 8 glucose residues on the linear chain synthesized by glycogen synthase, a branch forms, giving glycogen a highly branched structure. This increases the number of non-reducing ends, which are favorable to the activity of glycogen phosphorylase during the mobilization of glycogen reserves. This branching also ensures its much higher solubility compared to amylose, which has a purely linear structure. The branching is carried out by a branching enzyme r glycosyl transferase. It takes an oligosaccharide of 5 to 8 glucose residues from the non-reducing end of the elongating chain and attaches it to a glucosyl residue on the main chain via an (1-6) bond.

5.2.2. Regulation of glycogenesis

The regulation of glycogen synthesis is ensured by the ability of glycogen synthase to exist in two forms: an active (dephosphorylated) form and an inactive (phosphorylated) form. The interconversion between the two forms is controlled by an insulin-dependent protein phosphatase and protein kinase A. The activation of glycogen synthase results from a series of cascade reactions triggered by insulin, a polypeptide hormone secreted by the β cells of the islets of langerhans in the pancreas. The molecules essential to this mechanism are:

• A protein phosphatase: it becomes active through phosphorylation catalyzed by an insulin-dependent protein kinase.

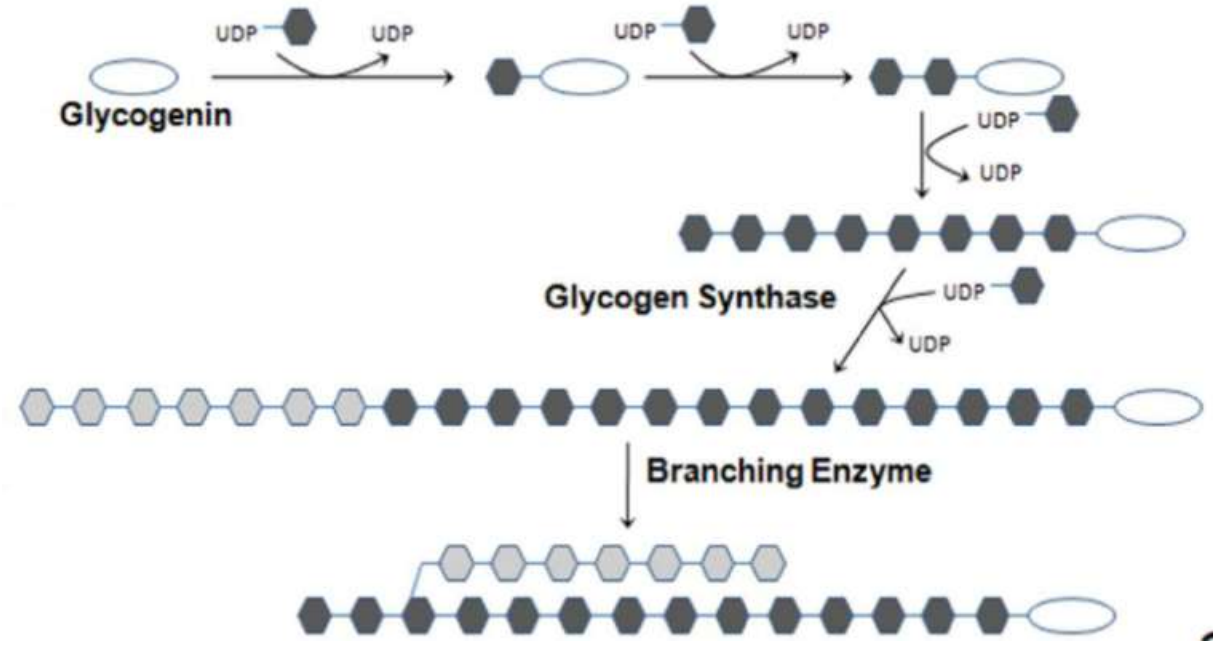


Figure 16: Glycogenesis steps.

• The phosphatase kinase mentioned above: it is the penultimate step in a series of phosphorylation reactions initiated by the tyrosine kinase of the catalytic receptor of insulin.

The insulin receptor, composed of four protein subunits embedded in the target cell membrane. The α2 dimer forms the hormone-binding domain. The β2 dimer has a tyrosine kinase on each subunit, on the inner face of the membrane.

• The mechanism of glycogen synthase activation can be summarized as follows:

- Insulin binds to its receptor and forms an insulin receptor-receptor complex. The receptor's tyrosine kinase phosphorylates a specific tyrosine residue on each β subunit (autophosphorylation).
- The tyrosine kinase then phosphorylates the tyrosine residue on a first protein substrate called IRS-1 (Insulin Receptor Substrate 1). IRS-1-P will initiate a series of cascade phosphorylation reactions, the last step of which is the activation, by phosphorylation, of a protein phosphatase (called insulin-dependent).
- This protein dephosphorylates glycogen synthase (which is inactivated by phosphorylation by protein kinase A) and restores its activity. Glycogen synthesis is thus initiated or restarted. Figure 17 below shows the mechanism of protein phosphatase activation by insulin.

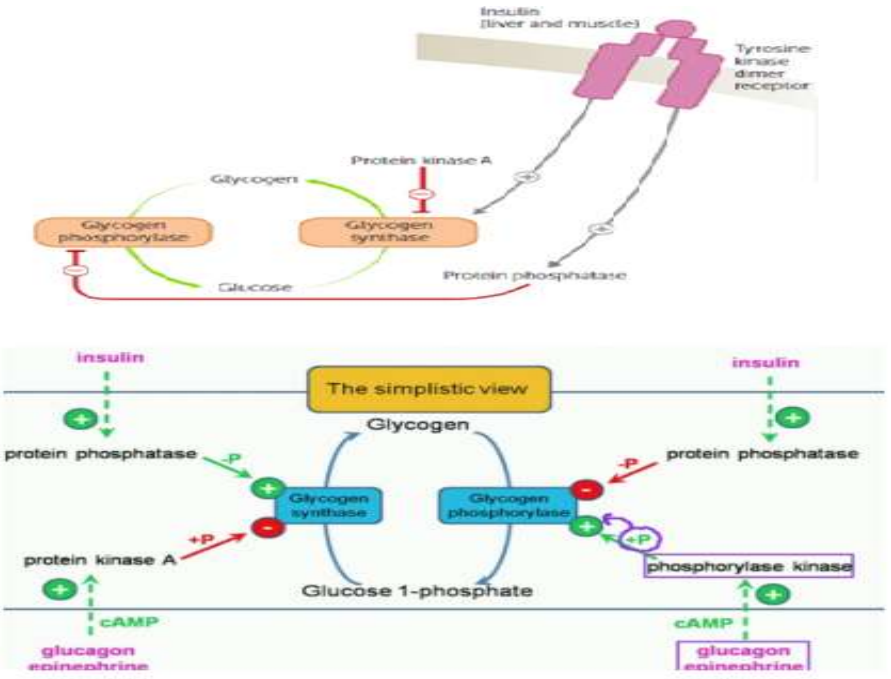


Figure 17: Hormonal regulation of glycogen synthase by insulin and glucagon.

6. Gluconeogenesis pathway

Gluconeogenesis is an endogenous metabolic pathway in which non carbohydrate substances are converted to glucose. The term gluconeogenesis means the generation (genesis) of new (neo) glucose. This biochemical pathway occurs principally in the liver and is essential for survival during prolonged starvation. This process is essential for long-term muscle work, and when the body consumes more fats and proteins than carbohydrates. It also plays a major role in the disposal of lactate and the maintenance of glucose during exercise. The liver plays the central role in this process, while it is believed that the kidneys contribute to 25 % of total glucose synthesis at most.

The production of glucose from other metabolites is necessary to maintain the glucose level in the blood as a fuel source by the brain, erythrocytes, kidney medulla and testes, since glucose is the sole energy source for these organs (Figure18). During starvation, pancreatic -cells release glucagon in response to low levels of glucose. Glucagon stimulates fat mobilization from adipose tissue to skeletal muscle for β-oxidation to release energy. Glycerol released from lipolysis, amino acids from muscle protein breakdown, and lactate generated from muscle and red blood cells are transported through the circulation to the liver where they serve as substrates for gluconeogenesis and production of glucose. The glucose produced provides fuel for erythrocytes and the brain. The adipose tissue needs glucose, which is also necessary for the synthesis of triacylglycerls.

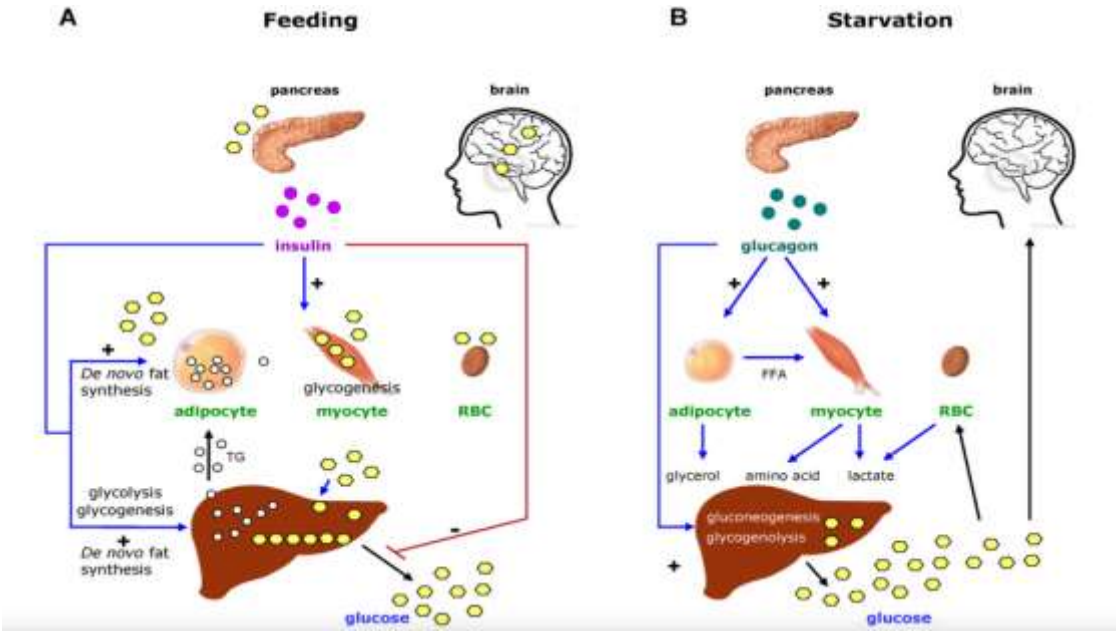


Figure 18: Hormonal regulation of fuel during starvation and feeding.

FFA: free fatty acids; **RBC**: red blood cell; **TG**: triglycerides.

6.1. Enzymes of Gluconeogenesis

Seven reversible steps in gluconeogenesis are catalyzed by the same enzymes used in glycolysis. Gluconeogenesis requires four additional enzymes which bypass the three irreversible reactions catalyzed by the glycolytic enzymes pyruvate kinase, phosphofructokinase and hexokinase. These four gluconeogenic enzymes are pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose-1, 6-bisphosphatase and glucose-6-phosphatase. The gluconeogenic pathway needs to:

- Conversion of pyruvate to PEP by the enzymes: pyruvate carboxylase (PC), mitochondrial malate deshydrogenase, cytosolic malate deshydrogenase and phosphoenolpyruvate carboxykinase (PCK),
- Dephosphorylation of fructose 1, 6-bisphosphate by Fructose 1, 6 biphosphatase,
- Dephosphorylation of glucose 6-phosphate by Glucose 6 phosphatase

The first two reactions occur in the mitochondrial matrix, whereas the following reactions take place in the cytosol. The reactions of gluconeogenesis are presented in Figure 19.

6.1.1. Conversion of pyruvate to PEP

6.1.1.1. Pyruvate carboxylase

Pyruvate carboxylase (PC) is a mitochondrial enzyme in the ligase class that catalyzes the irreversible carboxylation of pyruvate to oxaloacetate in the metabolic pathway of gluconeogenesis. The reaction is dependent on biotin, adenosine triphosphate (ATP) and magnesium. Acetyl-CoA is the allosteric effector of PC in humans. PC catalyzes the following reaction:

6.1.1.2. Mitochondrial malate deshydrogenase

Oxaloacetate is not able to cross the inner mitochondrial membrane; however, malate can permeate it, which influences the manner in which gluconeogenesis takes place. Oxaloacetate is reduced to malate by using NADH and mitochondrial malate dehydrogenase. Mitochondrial malate deshydrogenase catalyzes the following reaction:

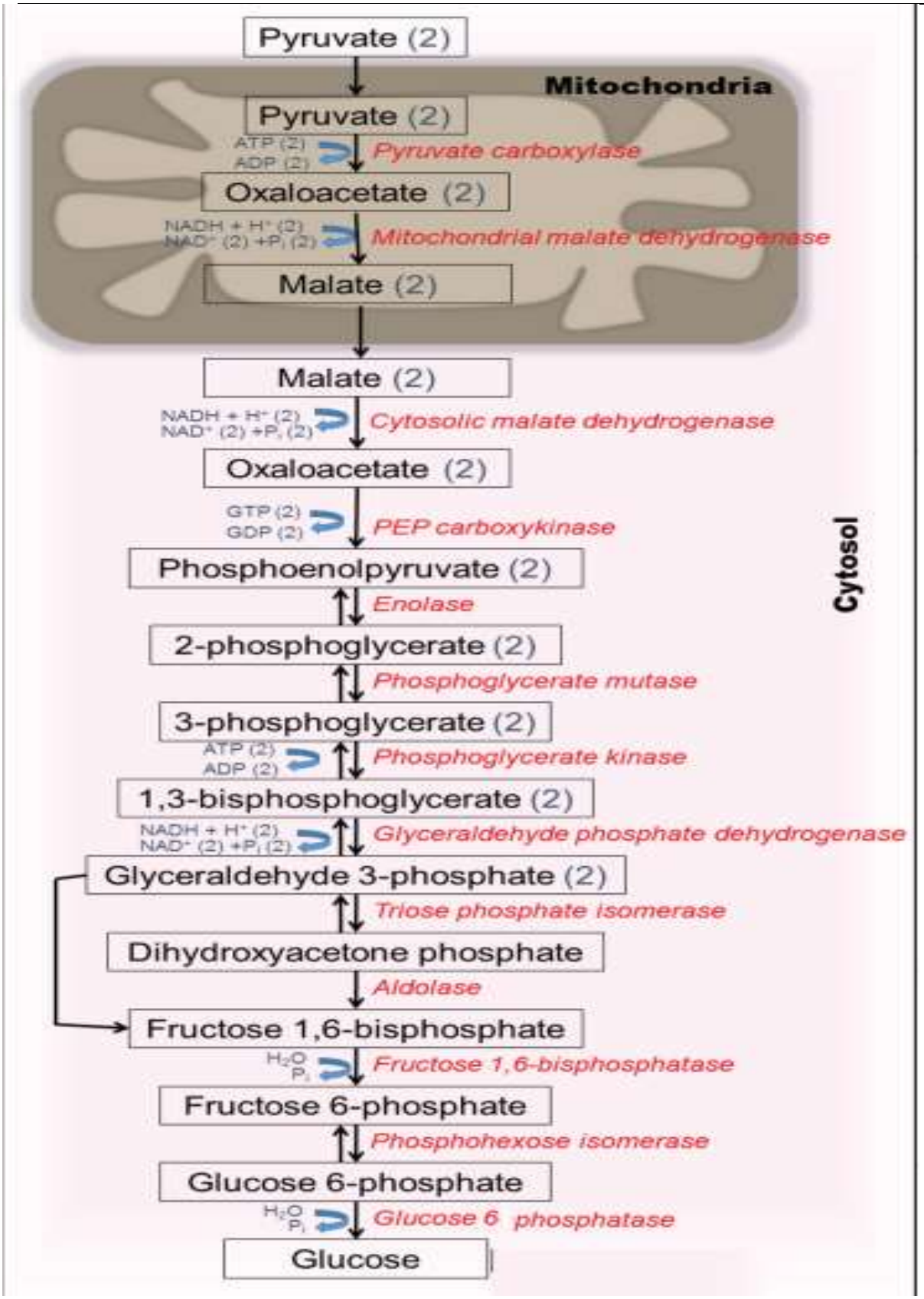


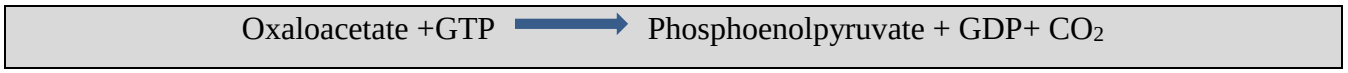
Figure 19: Stages of gluconeogenesis.

6.1.1.3. Cytosolic malate deshydrogenase

After this step, the remaining steps of gluconeogenesis process occur in the cytosol. In the next step, malate is oxidized to oxaloacetate using NAD^+ and the cytosolic isozyme of malate dehydrogenase. Cytosolic malate deshydrogenase catalyzes the following reaction:

6.1.1.4. Pyruvate carboxykinase

Pyruvate carboxykinase (PCK) is an enzyme in the lyase family that converts oxaloacetate into phosphoenolpyruvate and carbon dioxide. (PCK) catalyzes the following reaction:



6.1.2. Dephosphorylation of fructose 1, 6-bisphosphate

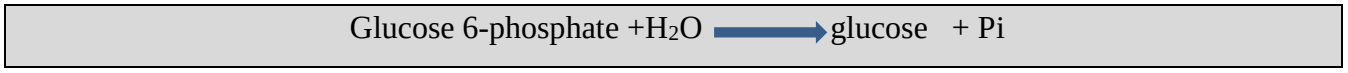
6.1.2.1. Fructose 1, 6 biphosphatase

Fructose 1, 6 biphosphatase (FBPase) is a cytosolic enzyme that catalyzes the dephosphorylation of fructose 1, 6-bisphosphate to fructose 6-phosphate and inorganic phosphate in gluconeogenesis. Fructose 1, 6 biphosphatase catalyzes the following reaction:

6.1.3. Dephosphorylation of glucose 6-phosphate

6.1.3.1. Glucose 6 phosphatase

Glucose 6 phosphatase is an enzyme situated in the endoplasmic reticulum and hydrolyzes glucose 6-phosphate to produce glucose and inorganic phosphate. Only the liver and kidney contain all the enzymes necessary for gluconeogenesis, including glucose-6-phosphatase, which enables the release of glucose. Glucose 6 phosphatase catalyzes the following reaction:



6.2. Precursors

The major substrates for gluconeogenesis are lactate, glycerol, and gluconeogenic amino acids (Figure 20).

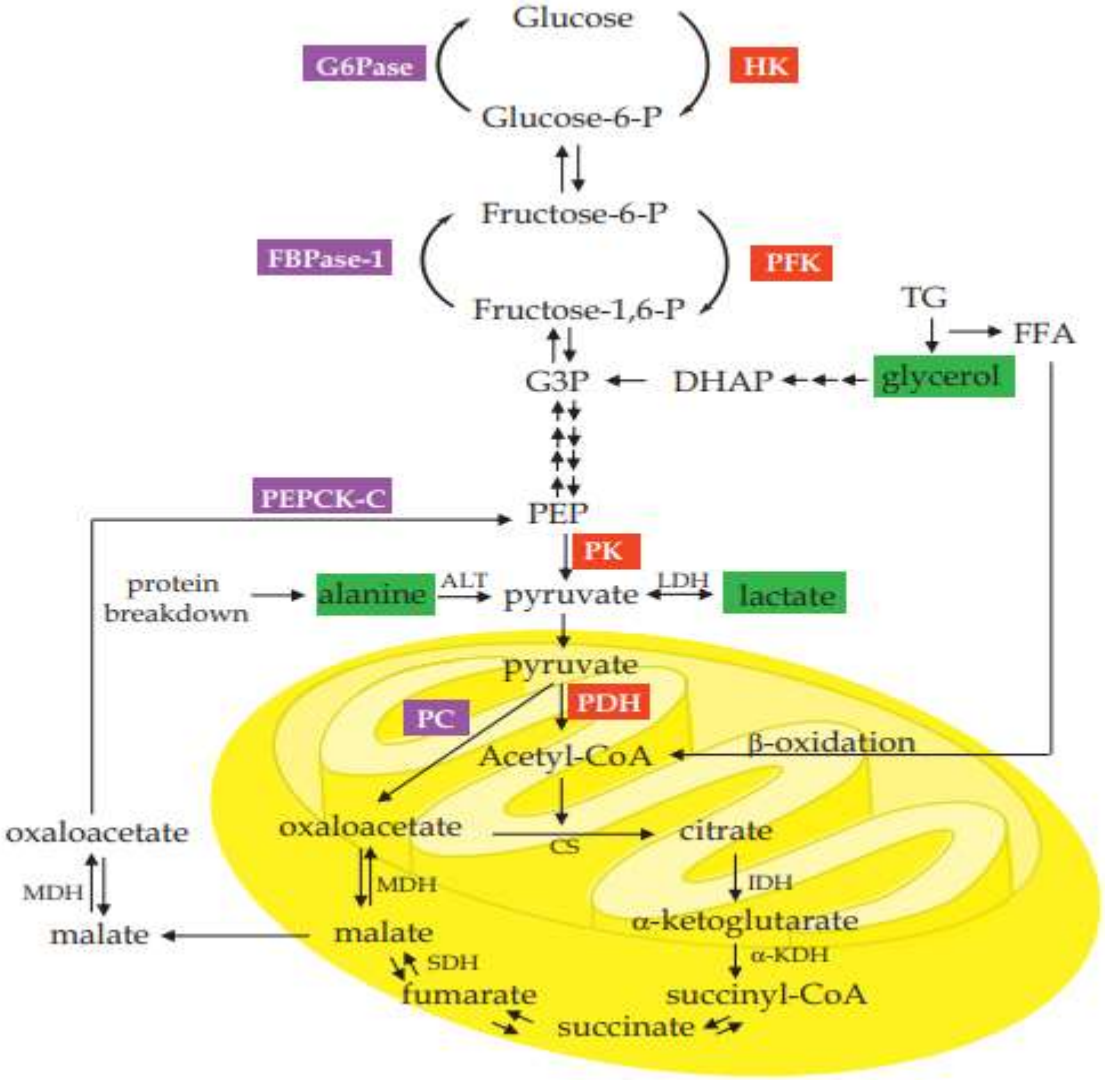


Figure 20: Main precursors for gluconeogenesis**.**

MDH: mitochondrial malatedehydrogenase; **PEP**: phosphoenolpyruvate; **PEPCK**: phosphoenolpyruvate carboxykinase; **FBPase**: fructose-1, 6-bisphosphatase; **G6Pase**: glucose-6-phosphatase; **PFK**: phosphofructokinase; **HK**: hexokinase. **TG**: triglycerides; **DHAP**: dihydroxyacetonephosphate; **ALT**: alanine aminotransferase; **CS**: citrate synthase; **G3P**: glyceraldehyde-3-phosphate; **IDH**: isocitrate dehydrogenase; **KDH**: α-ketoglutarate dehydrogenase; **LDH**: lactate dehydrogenase; **PDH**: pyruvate dehydrogenase complex; **PK**: pyruvate kinase; **SDH**: succinate dehydrogenase.

6.2.1. Lactate and Cori cycle

The main source of lactate is anaerobic glycolysis of red blood cells and the skeletal muscle. This cycle (glucose → pyruvate → lactate → pyruvate → glucose) is known as the Cori cycle (Figure 21). Lactate, formed by the oxidation of glucose in skeletal muscles and by erythrocytes through the proceses of anaerobic glycolysis, is transported to the liver and kidney, where it reforms glucose, which again become available via the circulation for oxidation in the tissues.

The conversion of lactate to glucose begins with the oxidation of lactate, by the action of *lactate dehydrogenase*, to pyruvate. In the presence of ATP, pyruvate carboxylase and CO_2 convert pyruvate

to oxaloacetate. The enzyme, phosphoenolpyruvate carboxykinase transfers oxaloacetate to phosphoenolpyruvate in the presence of GTP and by elimination of CO_2.

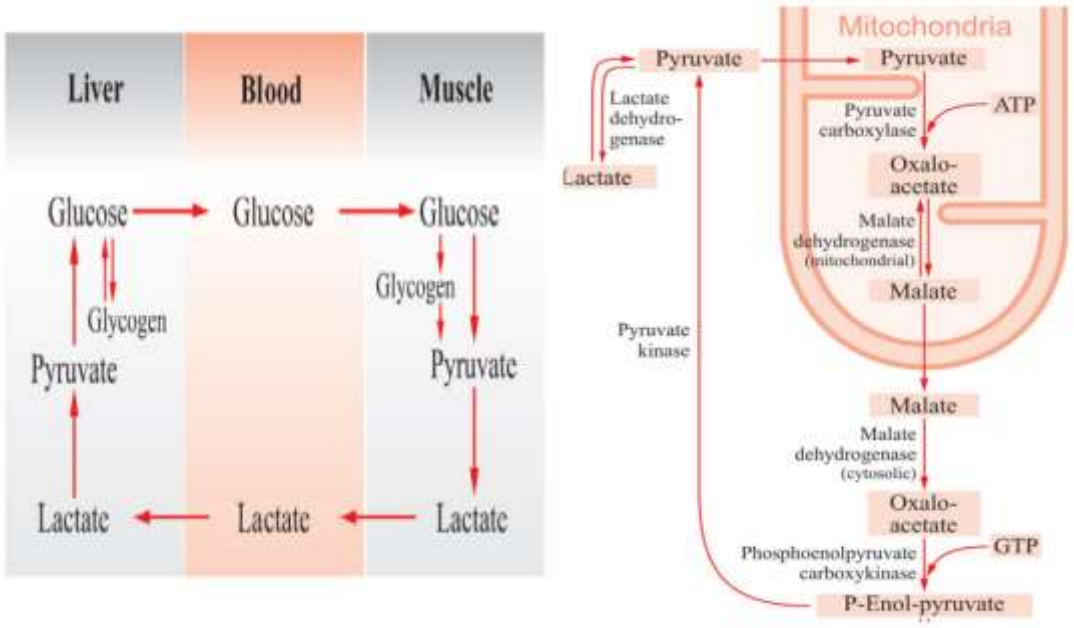


Figure 21: Cori cycle

6.2.2. Glycerol

The contribution of glycerol to gluconeogenesis is directly correlated with its release from the adipose tissue together with fatty acids. Glycerol, a product of the continual lipolysis, diffuses out of the tissue into the blood. It is converted back to glucose by gluconeogenic mechanisms in the liver and kidney. Thus, a continuous cycle exists in which glucose is transported from the liver to adipose tissue and, hence, glycerol is returned to be synthesized into glucose by the liver. Glycerokinase, which requires ATP, catalyzes the conversion of glycerol to glycerol phosphate. Glycerokinase is present in liver and kidney. The enzyme glycerol phosphate dehydrogenase oxidizes glycerol phosphate to the dihydroxacetone phosphate, the component of glycolysis, which enters the glycolytic pathway as a substrate for triose phosphate isomerase (Figure 22).

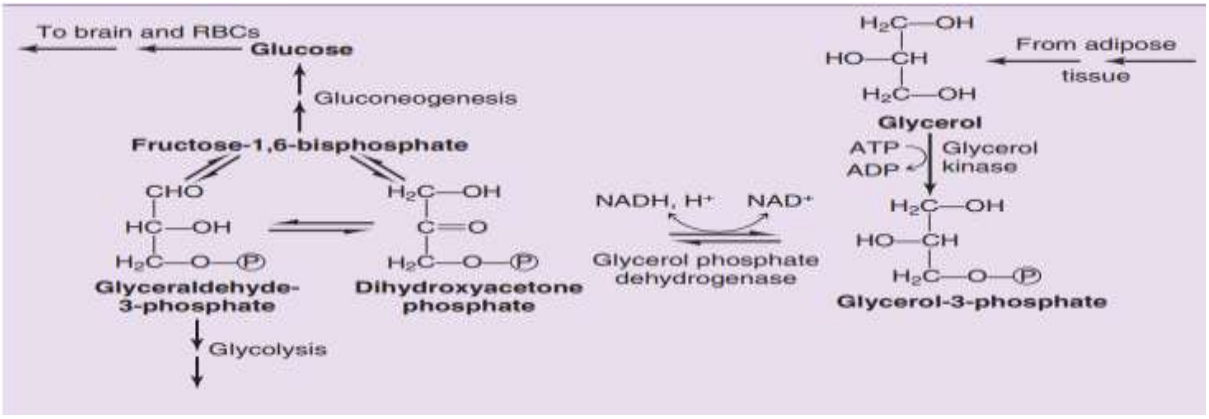


Figure 22: Glycerol enters gluconeogenesis (and glycolysis) at the level of the triose phosphates.
RBC: Red blood cell

6.2.3. Gluconeogenic amino acids

Gluconeogenic amino acids are mostly those that can be converted via pyruvate or intermediates of citric-acid cycle to oxaloacetate, which is the initial substrate of gluconeogenesis. The most important amino acids are alanine and glutamine, which are released from muscles during starvation, exercise. As most of the nitrogen produced during amino acid catabolism is converted into ammonia.

6.2.3.1. Alanine

Glucose-alanine cycle (Figure 23) represents a cycling glucose from the liver to the muscles and alanine from muscles to liver, effecting a net transfer of amino nitrogen from muscle to liver and free energy from liver to muscle. At the level of muscles, pyruvate, formed by glycolysis, transforms to alanine by the action of alanine transaminase (ALT) or glutamate pyruvate transaminase (GPT). The reaction is freely reversible. At the level of hepatocytes alanine transfers to pyruvate by the action of the same enzyme.

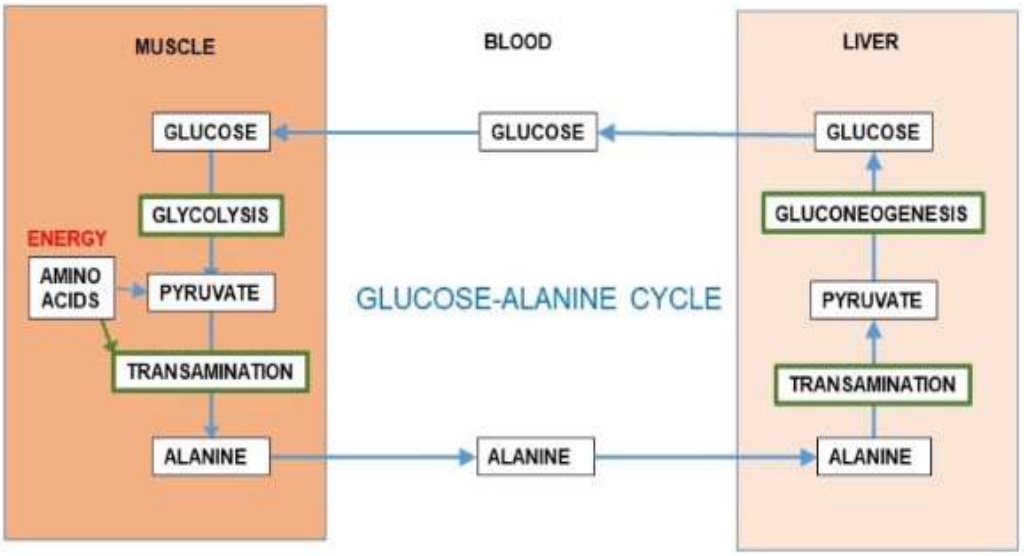


Figure 22 3: Glucose-alanine cycle.

6.2.3.1. Glutamate

The synthesis of glucose in the kidney cortex is directly related to the loss of ketone bodies in the urine. During periods of fasting, the kidney excretes large amounts of ketone bodies (weak acids), but produces urine that is near neutrality. The relative acidity of the tubular urine is maintained at about pH 6.0 by the generation of ammonia from the metabolism of glutamine that has been mobilized from the muscle during starvation. Glutamine is converted into glutamate by glutaminase and glutamate to a-ketoglutarate by glutamate dehydrogenase; this generates two molecules of ammonia that are released into the urine to maintain the neutrality of the urine. The a-ketoglutarate, produced by the removal of

the two amino groups of glutamine, enters the citric acid cycle, is oxidized to malate, and then proceeds to glucose via gluconeogenesis. Thus, ammoniagenesis in the kidney is linked to gluconeogenesis (Figure 24).

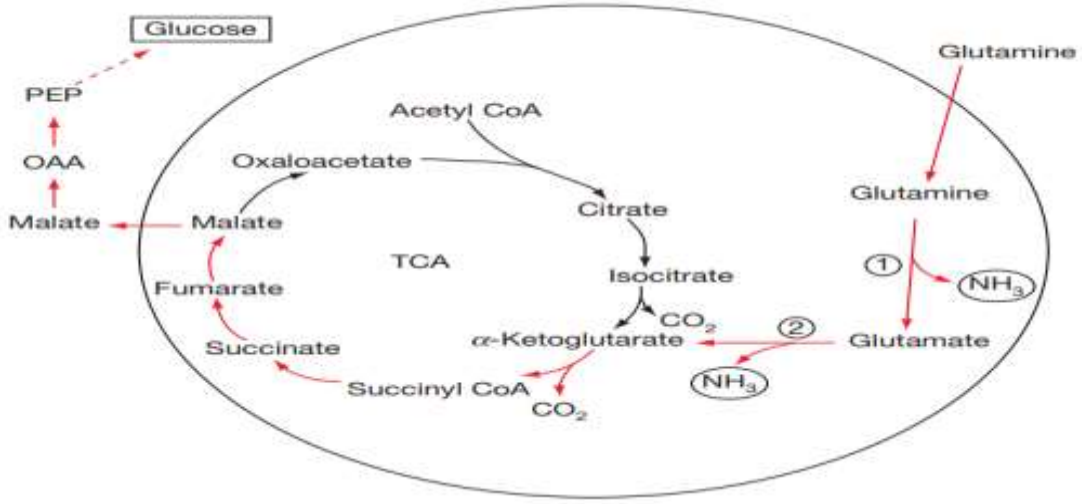


Figure 24: Gluconeogenesis from glutamine in the kidney

6.2.4. Propionate

Propionate is a major hepatic gluconeogenic substrate. Certain glucogenic amino acids (namely isoleucine, valine, threonine, and methionine), the terminal 3 carbons of odd-chain fatty acids undergoing mitochondrial b-oxidation can also enter hepatic gluconeogenesis at the level of propionyl-CoA.

6.4. Regulation

6.4.1. Allosteric regulation

PC from most sources is allosterically activated by acetyl-CoA and competitively inhibited by ADP. Fructose 1, 6-bisphosphatase is activated by high cytoplasmic ATP and citrate levels. This reaction bypasses the regulatory reaction of glycolysis catalyzed by phosphofructokinase, which is inhibited by glucagon, ATP, and citrate. Fructose 1, 6-bisphosphatase (FBPase) is mainly expressed in the liver and is allosterically inhibited by fructose 2, 6-bisphosphate, which is produced by the bifunctional enzyme phosphofructokinase 2/fructose-2, 6-bisphosphatase (PFK 2 / FBPase 2). fructose 2, 6-bisphosphate is a powerful allosteric activator of phosphofructokinase 1 (PFK-1), the enzyme that controls one of the most critical steps of glycolysis (Figure 25).

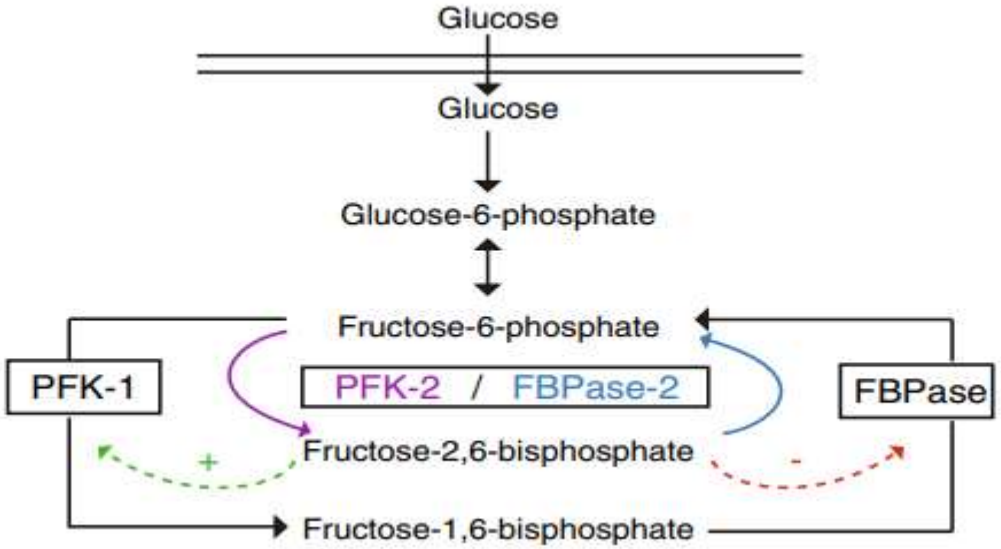


Figure 25: Allosteric regulation of glycolysis and gluconeogenesis.

6.4.2. Covalent modification or hormonal regulation

Insulin and glucagon are the most important hormones regulating hepatic gluconeogenesis. The activity of bifunctional enzyme phosphofructokinase 2/fructose-2, 6-bisphosphatase 2 is a key mechanism for regulating glycolysis and gluconeogenesis through synthesis or hydrolysis of fructose-2, 6-bisphosphate.

Fructose-2, 6-bisphosphate is both synthesized and degraded by the bifunctional enzyme phosphofructokinase 2/fructose-2,6-bisphosphatase, which can act as a kinase (it synthesizes fructose-2,6-bisphosphate using ATP as a source of phosphate) or as a phosphatase (it converts fructose 2,6-bisphosphate into fructose-6-phospahte plus inorganic phosphate).

- High glucagon/insulin ratio (fasting state): Glucagon triggers the production of cAMP, which activates protein kinase A (PKA). PKA phosphorylates the enzyme, which inhibits its kinase domain and activates its phosphatase domain (Fructose 2,6 biphosphatase 2). This leads to the breakdown of fructose 2, 6 biphosphate, this results in a decrease in the concentration of fructose-2, 6-bisphosphate, thereby inhibiting the activity of phosphofructokinase (inhibiting glycolysis) and simulating the activity of fructose-1, 6-bisphosphatase (stimulating gluconeogenesis) (Figure 26).

- Low glucagon/insulin ratio (fed state): insulin signaling triggers the dephosphorylation of the enzyme. In its dephosphorylated state, the kinase domain (phosphofructokinase 2) becomes active while the phosphatase domain is inhibited. This promotes the synthesis of fructose 2, 6

biphosphate from fructose-6-phosphate, thereby activating glycolysis and inhibiting gluconeogenesis.

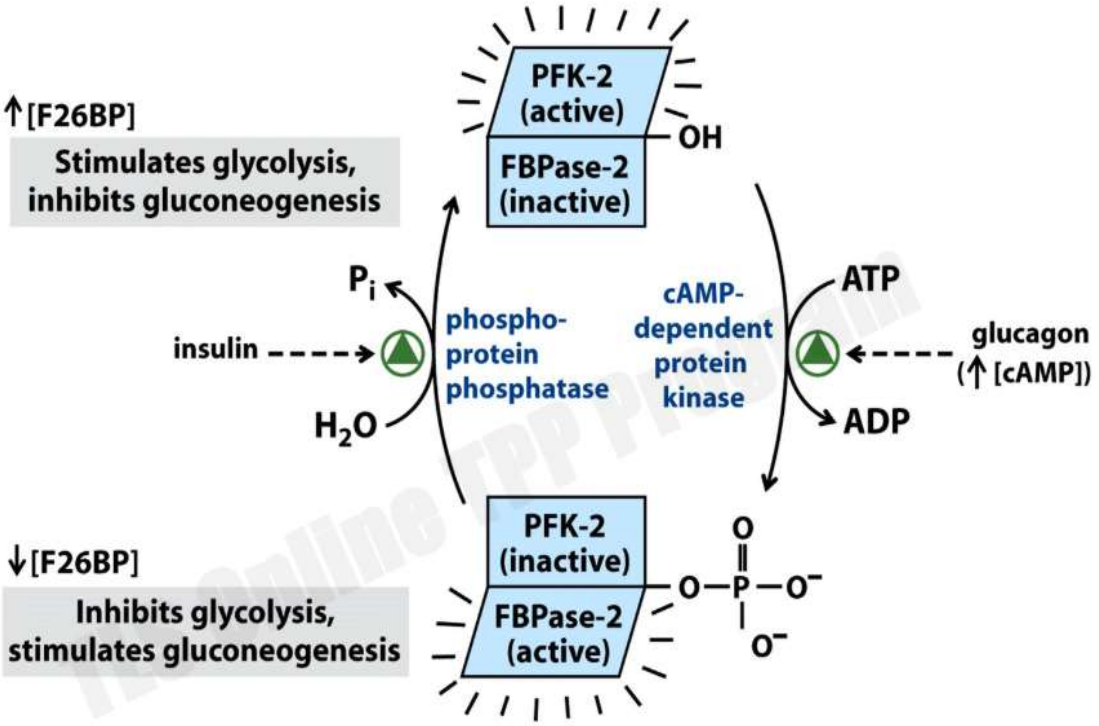


Figure 26: Allosteric regulation of glycolysis and gluconeogenesis.

7. Oxidative phosphorylation

7.1. Mitochondria

Mitochondria generate most of the energy needed for cells to function optimally. Mitochondria are responsible for 95% of ATP production in the cells, and are very numerous in tissues that require large amounts of energy such as the heart, skeletal muscle and neurons. Only mitochondria of the cardiac muscle are responsible for producing approximately six kilos of ATP/day. The double-membrane-bound organelles present an inner matrix and an intermembrane space separated by the inner membrane. The outer membrane completes the structure and separates this cell compartment from the rest of the cytoplasm. The inner and outer membranes differ mainly in their selective permeability to molecules of different sizes.

The outer membrane, a porins that function as voltage-dependent, anion-selective channels, is permeable to ions and small molecules, including NADH and ATP, while proteins and larger molecules cannot pass through porins and need to be imported by translocases. The inner membrane is impermeable to molecules and ions of any size, which can only penetrate through selective proteins channels. Oxidative phosphorylation occurs in the inner membrane through the activity of the electron transport chain complexes incorporated into the membrane along with ATP synthase. The spatial

organization of the internal membrane is essential to the correct functioning of oxidative phosphorylation.

7.2. Electron transport and energy production

Substrates such as glucose, fatty acids and amino acids are converted into energy within the mitochondria in the cycle of Krebs by the electron transport system for the production of ATP.

The Krebs cycle is the major metabolic pathway of energy production in cells providing most of the reduced cofactors, such as NADH and $FADH_2$ that will be oxidized by the electron transport chain complexes to produce energy. Electron transport chain complexes contain multiple polypeptides and various prosthetic groups; their main function is to carry electrons (e^-) from respiratory coenzymes to oxygen, and they are functionally coupled by cytochrome c and coenzyme Q. These complexes including:

- **Complex I** (NADH-ubiquinone oxidoreductase)
- **Complex II** (succinate-ubiquinone oxidoreductase),
- **Complex III** (ubiquinol-cytochrome c oxidoreductase)
- **Complex IV** (cytochrome c oxidase)
- **Complex V** (ATP synthase)

In this manner, the flow of electrons through the electron transfer chain links oxidation to phosphorylation. Electrons enter the electron transfer chain at two primary sites: complex I, where the electron donor is NADH, and complex II, where the electron donor is $FADH_2$. Electrons are passed from complex I and II by coenzyme Q or ubiquinone (CoQ) to complex III. Cytochrome C (cyt c) is the mobile electron carrier from complex III to complex IV where electrons are passed to the terminal electron acceptor, O_2, which is then reduced to water in this step. H^+ are pumped across the inner membrane at complex I, III and IV. ATP synthase, also known as complex V, uses the energy stored in the mitochondrial membrane potential to drive the phosphorylation of ADP to yield ATP, the universal energy currency in cells.

The respiratory chain or electron transport chain uses electron flow to create a proton gradient (proton motive force) that is used to drive adenosine tri-phosphate (ATP) synthesis. Mitchell P, proposed the theory of coupling of phosphorylation to electron and hydrogen transfer by a chemiosmotic type of mechanism.

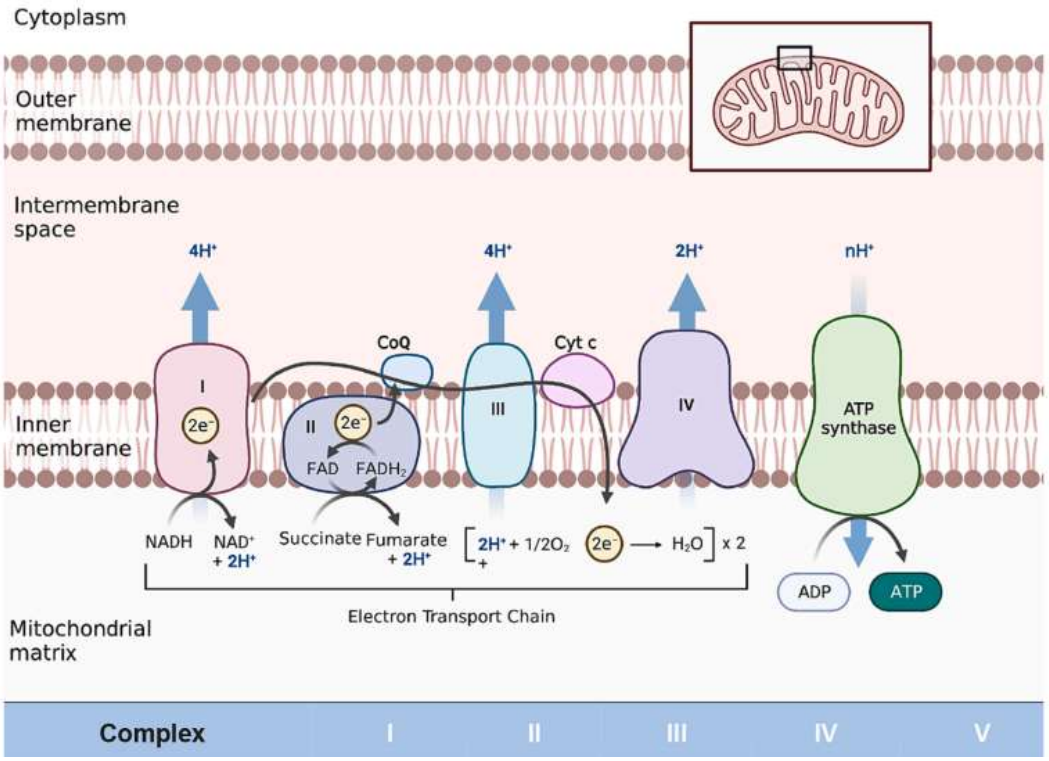


Figure : Oxidative phosphorylation mitochondria.