

# Metabolic Integration during the Postprandial, Fasting and Feedback Periods

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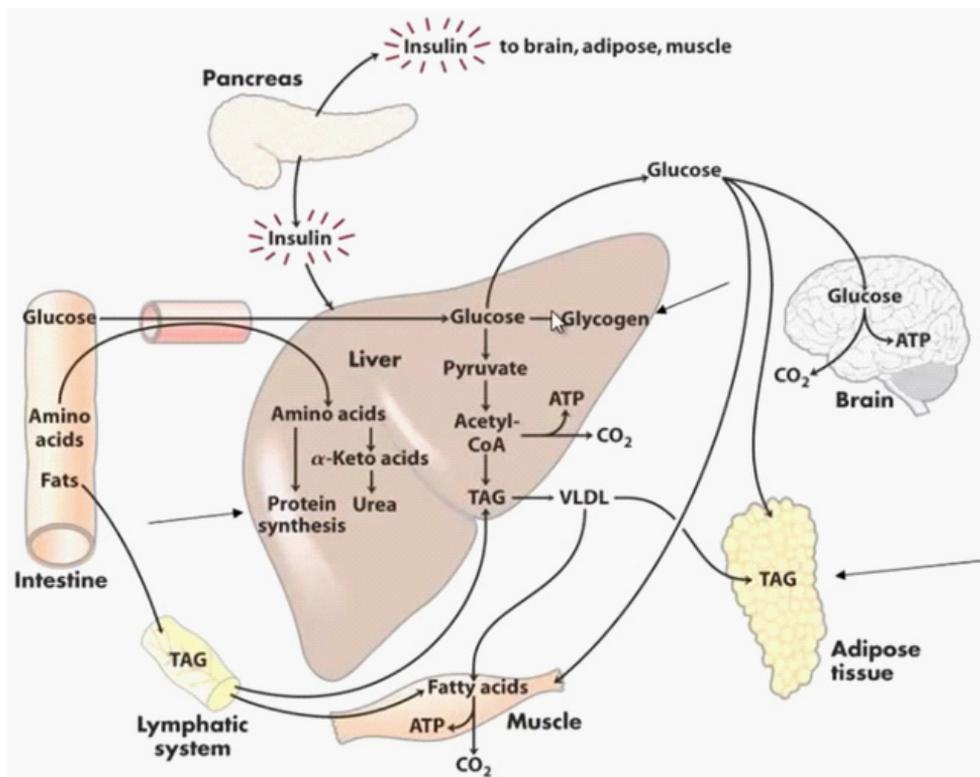
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## ABSTRACT

It is well known that the presence or absence of food can drastically influence the metabolism of carbohydrates, lipids and proteins. Furthermore, it is established that each different tissue has a characteristic metabolic profile. This work reviews the metabolism of main fuels of the cell as in the postprandial, as well as fasting period physiologic and prolonged, considering the metabolic specificity of the following cell or tissues: red blood cell, brain, liver, muscle and fat, focusing the deep metabolic integration that occurs in living organisms. It is also described the metabolic collapse triggered by long fasting and the feedback syndrome associated to the glycemic reestablishment.

## METABOLIC INTEGRATION IN THE POSTPRANDIAL AND FASTING PERIODS

After a feed, most carbohydrates, amino acids and a small part of the triglycerides from the diet are directly taken to the liver by the hepatic portal vein [1-4]. Most triglycerides from the diet, however, travels a different path, they migrate through the lymphatic system, fall into the systemic circulation and can be metabolized by the liver or taken up by tissue adipose [1-4]. In general, the concentration of nutrients in the blood is extremely controlled by the liver, which captures and distributes them. The liver will be the organ responsible to maintenance of homeostasis of carbohydrates, lipids and proteins [1, 2, 4-6]. In the fasting period, glycogen degradation, muscle proteolysis and lipolysis are responsible for maintaining the energy supply in the body (Figure 1). It is need to consider that in every cell or tissue exerting physiological roles specific metabolic pathways have their own characteristics. This chapter analyzes the metabolism of different cells (red blood cells) and tissues (brain, muscles, liver and adipose tissue) focusing on tissue interrelations occurring in the postprandial period and fasting, and also the metabolic characteristics of each tissue.



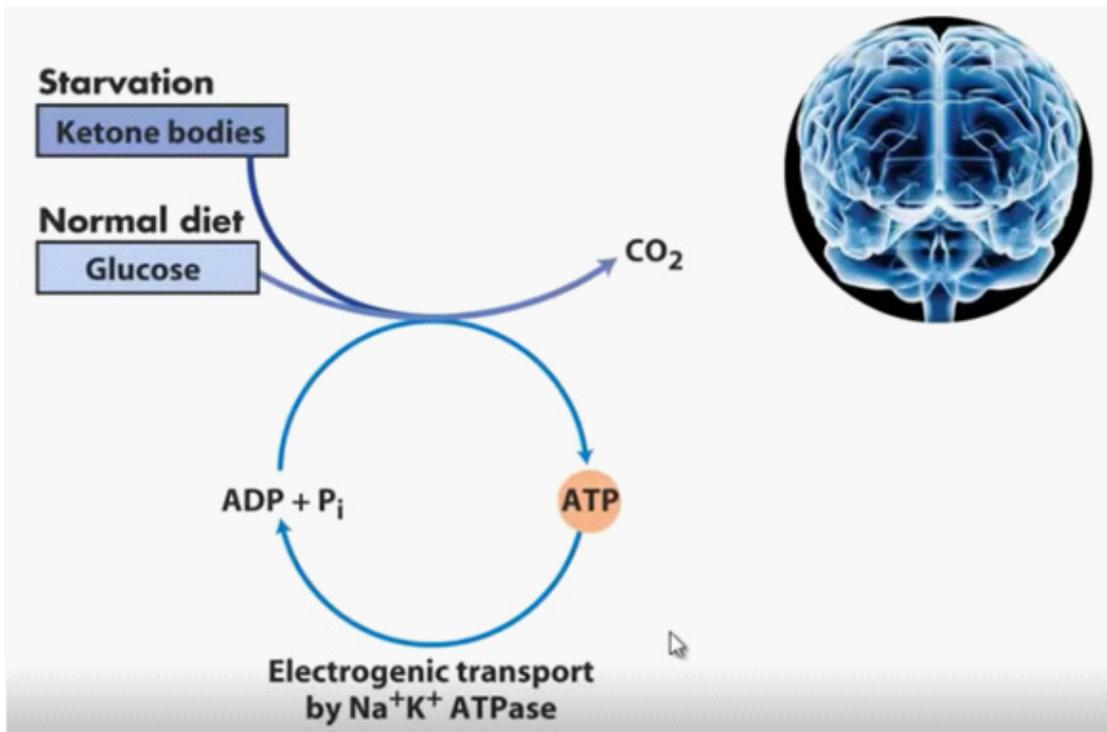
**Figure 1:** Postprandial period in humans living showing all metabolic via after feed. Five organs are the center of metabolism: pancreas, brain, muscle, adipose tissue and mainly the liver that is center of reactions of metabolism.

## THE RED BLOOD CELLS OR HEMACEOUS

The red blood cells, whose main function is the transport of oxygen, would have their extremely impaired function, when transporting the oxygen by long routes, as they do, if they consume the same. Therefore, the metabolism of red blood cells is predominantly anaerobic. Without the mitochondrial apparatus for the oxidation of nutrients, the red blood cells become dependent on the anaerobic glycolytic pathway. The consumption of glucose in these cells occurs in a constant way and independent of the nutritional profile. The uptake of glucose by the GLUT1 is independent of the presence of insulin [1,3,4,7]. In these cells, the glycolytic pathway culminates in the constant production of lactate, which will be captured by the liver. The lactate produced by the red blood cells is converted to glucose by hepatic gluconeogenesis and is one of the sources of maintenance of fasting glycemic [1,3,4,6,8].

## BRAIN TISSUE

The brain has no energy reserves and therefore, regardless of the nutritional status it is necessary that there is a constant glucose supply for brain metabolism. The glucose transporters in the Central Nervous System (**CNS**) are of type GLUT1 and GLUT3, they work independently of the presence of insulin, and together, guarantee high efficiency in glucose uptake in this tissue [3,4,7,9]. In addition to glucose, ketone body can be used as energy substrates in the CNS in long period of fasting (Figure 2). However, the independence of glucose in this tissue, it is never absolute. Situations of hypoglycemia cause disruption in the functioning of the CNS, ranging from headache, speech and motor incoordination, to electroencephalogram and coma [2]. Fatty acids cannot cross the barrier hamate-encephalic and, therefore, cannot supply the energy demand of the CNS. In situation of prolonged fasting, the brain may user ketone body and a small quantities of glucose, around of 40 mg by day to leave glucose for other tissues and the maintenance of glycemic rate and thus the decreasing the proteolysis [3,4,9].



**Figure 2:** Period of starvation and normal diet. Mechanism of consumption of glucose of brain both in normal diet in which consumes 120g by day. However, in starvation period the brain replace and begins the consumes ketone body, but still consumes 40mg of glucose by day.

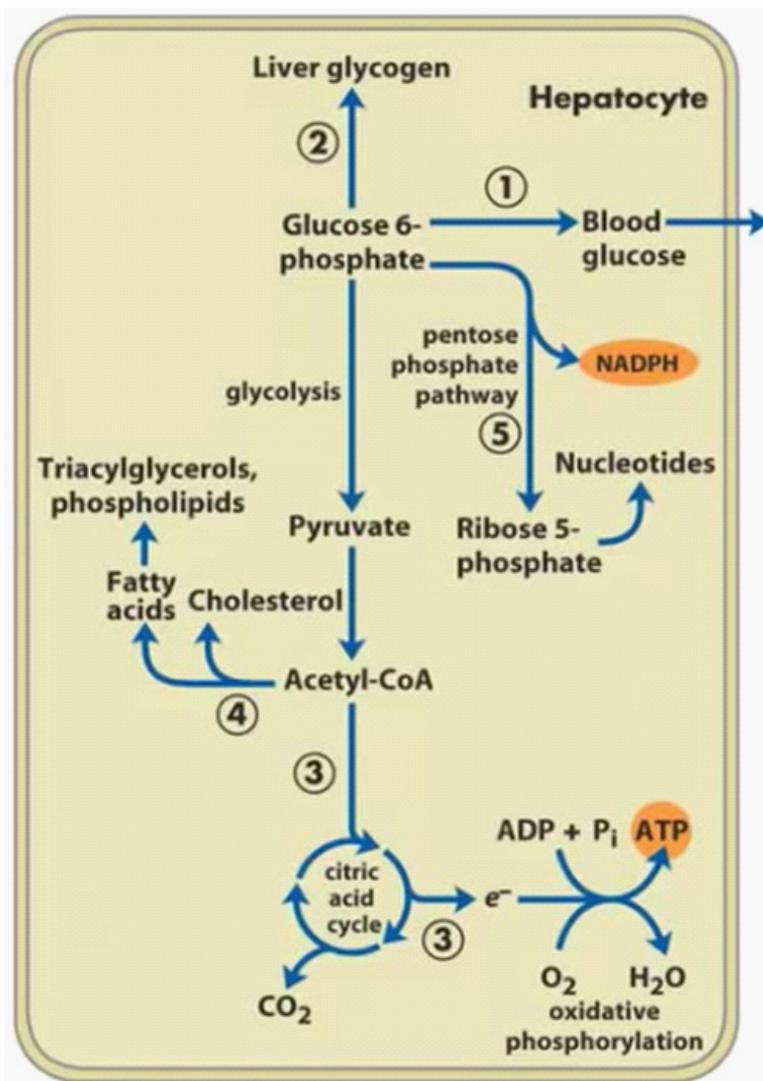
In the physiological situation the consumption of glucose by the CNS reaches 120 g/day, only being lower than the consumption of glucose by the skeletal muscle in physical activity [3]. Most of the energy used by the brain is used in the Na<sup>+</sup> and K<sup>+</sup> ATPase pump [3], responsible for the repolarization of membrane potential in nerve cells. The CNS, even during sleep, maintains a constant glucose 60% of the total glucose consumed by the rest of the body [9], and is the greatest consumer of this nutrient.

## LIVER TISSUE

### The Metabolism of Carbohydrates in the Liver

In the liver, the transport of glucose occurs by GLUT2 transporters, which maintain the concentration of glucose in the hepatocyte in the same proportion that this nutrient exists in the blood circulation by insulin independent manner [1,3,4,7]. However, the glucose can only be used by the hepatic tissue after being phosphorylated. The enzyme responsible for this reaction, a glucokinase, has low affinity for glucose [1,3,7], thus, the liver will only phosphorylate and guarantee the permanence of glucose within of liver cells, since there is a sufficiently high concentration of glucose in circulation. This is because the liver can use other energy substrates

such as fatty acids or amino acids as an energy source. Although insulin does not influence the uptake of glucose in liver cells, it profoundly influences the use of glucose by these cells. Glucose will only be used by the liver as when the insulin/glucagon ratio is high enough to activate the glycolytic pathway [1,3,4,8]. The high glucose supply, together with the presence of insulin will also stimulate glycogen synthesis, and at this time, the liver becomes a store of glucose [1,3,4,8] (Figure 3).

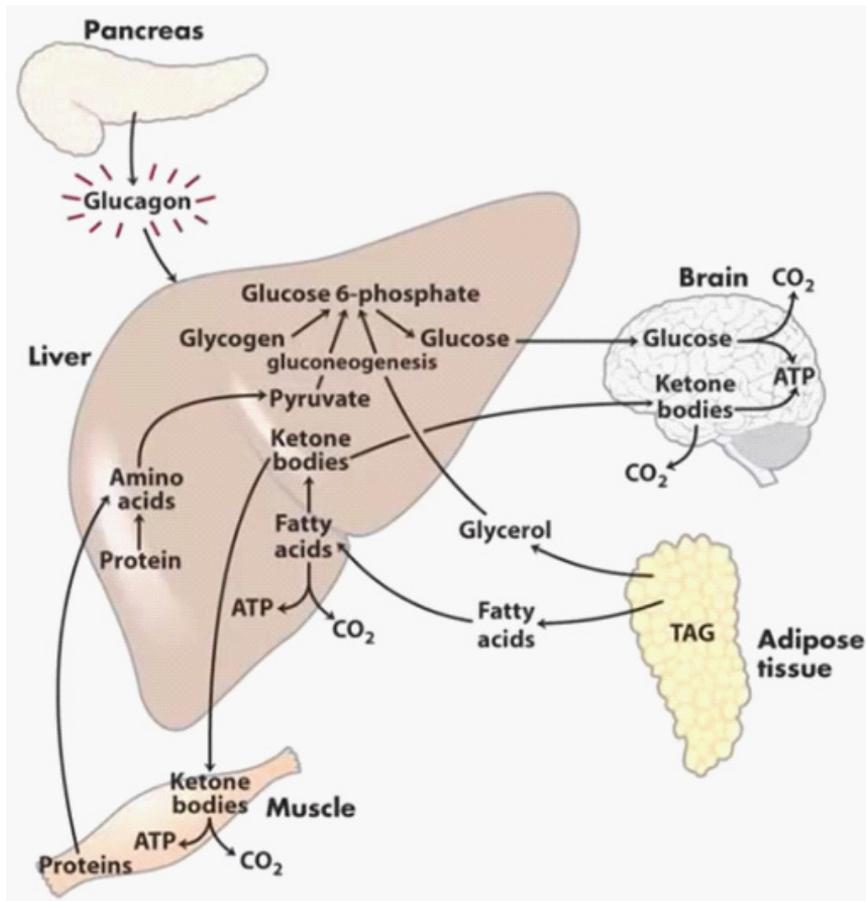


**Figure 3:** Metabolism of glucose of liver tissues. The glucose-6-phosphate here has five destinations as 1) glucose in the blood 2) synthesis of glycogen in the liver 3) pentose-phosphate pathway and/or citric acid cycle and oxidative phosphorylation 4) the final product of glycolysis, the Acetyl-CoA can occur the transformation in cholesterol or fatty acid as triacylglycerol and phospholipids.

Otherwise, the liver will do exactly the opposite, will be a glucose exporter. At the time of fasting, when there is a predominance of glucagon about Insulin, glycogenolysis will be activated and the liver will export the glucose that had stored in the form of glycogen. Since glycogen is a limited reserve and can only supply the glucose demand in the body for a few hours, the liver perform the gluconeogenesis [1,3,6,8].

Gluconeogenesis occurs predominantly in the hepatic tissue by the stimulus of glucagon and is simultaneous to hepatic glycogenolysis in depletion mechanism store by the increasement glucagon levels in the blood [1,3,4,8]. While there is glycogen, the rate of gluconeogenesis is small, however, this pathway will occur in the maximum speed after hepatic glycogen depletion [1,3,4,8]. Therefore, in the prolonged fasting, glycemia is maintained only by gluconeogenesis, which means an important metabolic cost, since this pathway is related to the significant loss of muscle mass and adipose tissue that accompany fasting [1,3,4,6,8]. It is needed to remember that the synthesis of glucose that occurs in the liver during periods of fasting the main precursors are amino acids, skeletal muscle, glycerol, resulting from the mobilization of adipose tissue triglycerides and Lactate, coming from the red blood cells, and having as energy source the intense beta-oxidation of the fatty acids released by the mobilization of triglycerides (Figure 4) [1,4,8]. Gluconeogenesis may continue to occur in the liver for some time even with the arrival of foods the production of glycogen from amino acids from the diet. This is called postprandial gluconeogenesis and occurs to ensure adequate storage of glycogen in the liver [10,11] (Figures 1 and 4).

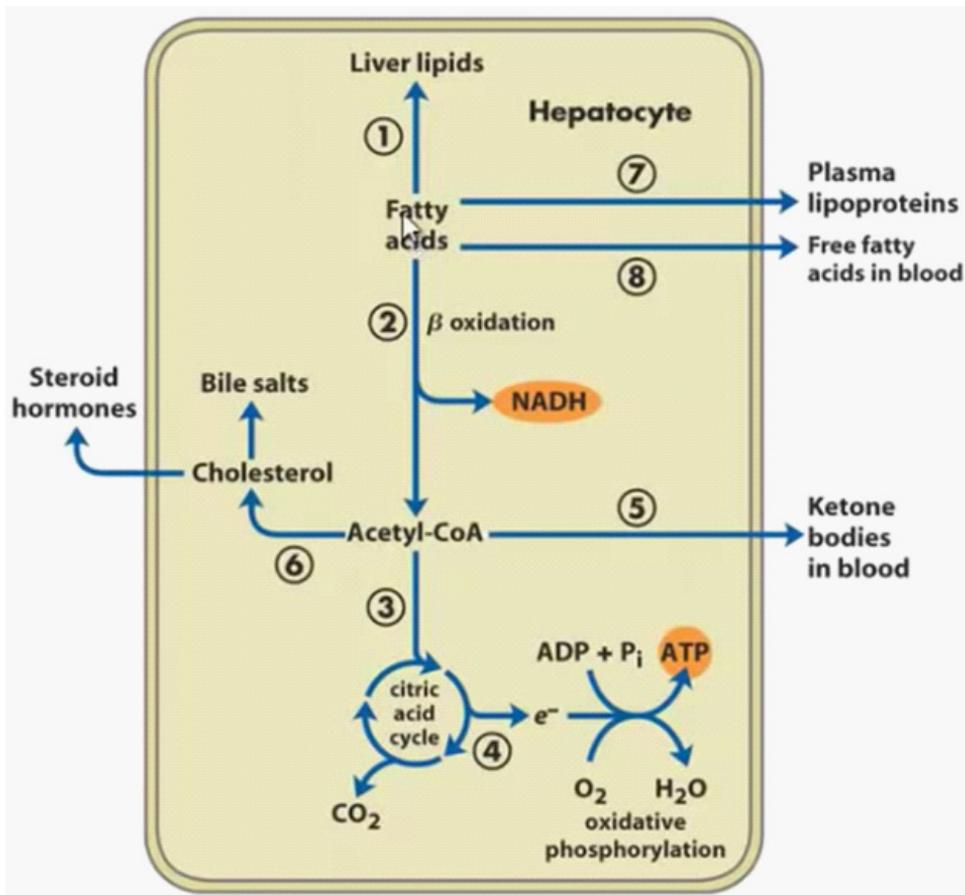
As the fasting period increases, hormones like adrenaline and cortisol are secreted, developing the chronically maintenance of glucose homeostasis. These hormones increase the lipolysis, providing fatty acids and glycerol necessary to gluconeogenesis and ketone bodies synthesis [4,6,8,12]. In addition, the body decreases its metabolism i.e. reduces the basal metabolic rate, this effect is promoted by the lower release of thyroid hormones (T3 and T4) [13,14]. With this the body consumes less energetic substrates but the consumption of glucose by some tissues is greatly diminished as for example the skeletal muscle. This type of adaptation favors the availability of glucose for tissues that use it exclusively as for example erythrocytes and brain [15].



**Figure 4:** Metabolism of liver during fast physiologic and prolonged. Show the several reactions that involve four tissues main: liver, brain, muscle and adipose tissue and the liver as center of reactions.

## Lipid Metabolism in the Liver

In the postprandial period, stimulated by insulin, fatty acids can be synthesized at high speed by the liver from acetyl-coA molecules [1,3,4,8]. The fatty acids synthesized by the liver will be exported through lipoproteins VLDL carriers to the adipose tissue, where they will be stored [1,3,4,9]. Every time food consumption exceeds energy demand, we will have the accumulation of reserves (glycogen and triglycerides) [1,3,4,8]. However, the glycogen storage is quite limited when compared to triglycerides (Figure 1). See that the total capacity of the liver to store glycogen is around of 70 g and skeletal muscle 120 g [3,9,16], but adipose tissue may contain tens of kilograms of triglyceride. The ability to transform excess lipids is practically unlimited and every time there is an imbalance in this process and we will have obesity (Figure 5).



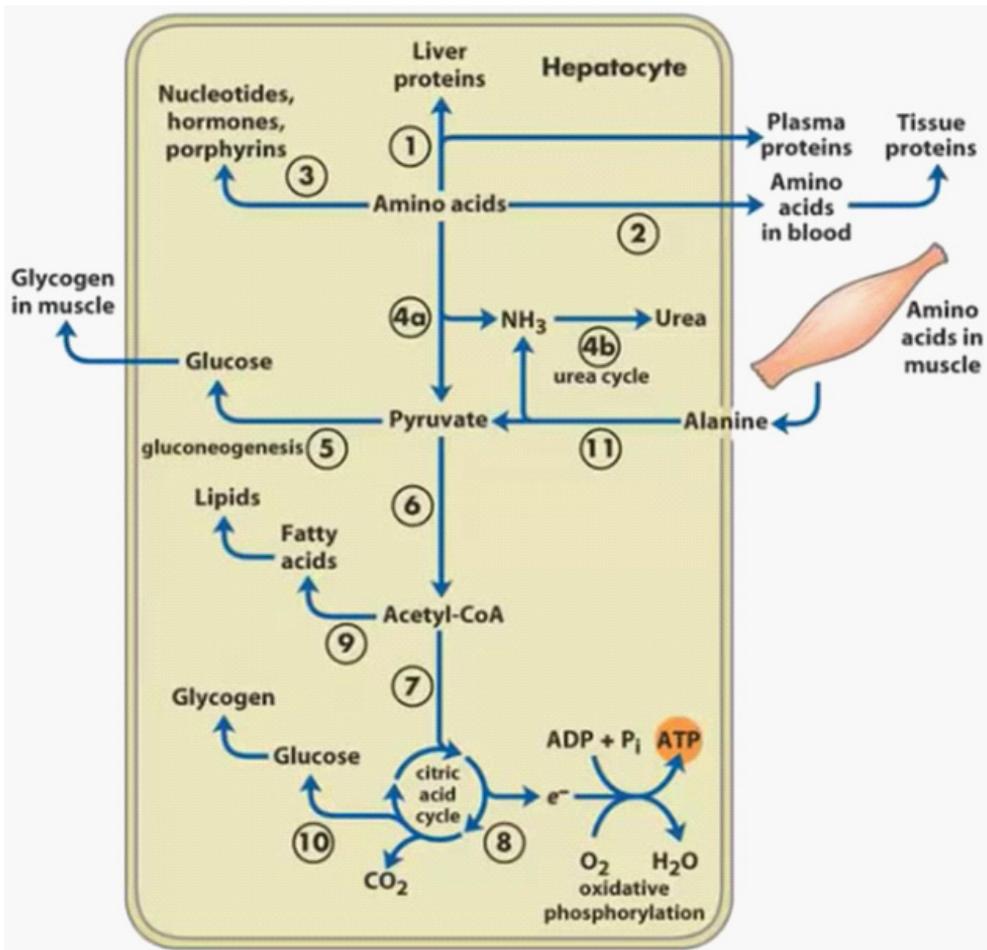
**Figure 5:** Metabolism of liver lipids. The fatty acids can undergo transformation in 8 products: 1) liver lipids, 2) beta-oxidation, 3) can enter the citric acid cycle through Acetyl-CoA, 4) oxidative phosphorylation, 5) ketone bodies in blood, 6) through Acetyl-CoA can undergo cholesterol synthesis and be transformed into bile salts or steroid hormones, 7) lipoproteins or 8) free fatty acids in blood.

In a fasting situation, however, the liver picks up fatty acids released by the mobilization of adipose tissue triglycerides, which will be used for the synthesis of ketone bodies [1,3,8,12]. Ketone bodies are favored because the other pathway possible for the use of fatty acids, beta-oxidation, is inhibited in the liver. At this time, since there is a deviation of the oxaloacetate to gluconeogenesis, decreasing the speed of the citric acid cycle [1,3,6,8,12]. The production of ketone bodies by the liver has the main objective that provides an alternative nutrient to glucose for extrahepatic tissues. The CNS, for example, the prolonged fasting of the new nutrient gradually adapts and after some of their nutritional preference from being glucose (120g/day) to a preferential consumer of ketone bodies (100g/day) although, is always dependent on glucose, even if in a

small proportion (40mg/day) [7]. The deep adaptation of the CNS to the energy source is due to the fact that in the fasting, the continued maintenance of gluconeogenesis means depletion of skeletal muscle proteins, thus, if gluconeogenesis was the only form of energy supply, there would be a proteic collapse in the organism [3,4,6,7]. On the other hand, the maintenance of ketosis implies an important loss of adipose tissue lipids, a reservoir immensely larger than proteins and, therefore, more quantitatively available. It is maintaining a gluconeogenesis moderate and intensifying ketosis that the body can endure a prolonged fast for quite long periods of time, from 30 to 60 days [8,9]. The role of the liver as an energetic supplier of fasting, whether short or glucose or ketone bodies to the rest of the body, essential to maintain proper functioning of the CNS and other cells and consequently, for the maintenance of life.

## Protein Metabolism in the Liver

In the postprandial period, when the concentration of amino acids in the current is high, the complete oxidation of amino acids provides an amount of significant energy for the liver tissue. Amino acids can be completely oxidized by the liver, or converted into glucose or ketone bodies [1,5,6,8,12]. The production of glycogen from amino acids from the diet (postprandial gluconeogenesis) is particularly stimulated by diets rich in protein and may persist for some time even after the end of a meal [10,11]. In fasting times, the liver starts to receive amino acids from the tissue muscle prioritizing gluconeogenesis [4,6]. The liver participates actively in catabolism protein, since the urea cycle is exclusively performed by hepatic tissue, and that it means the preferential way of nitrogen excretion from proteolysis [1,5,6,8,12]. On the other hand, the liver is responsible for the synthesis of all serum proteins [1,8] with the exception of the immunoglobulins which are synthesized by lymphocytes [2,17]. The maintenance of the concentration of circulating proteins in the 6-8 g / dL requires an intense work of hepatic protein synthesis [2] (Figure 6).

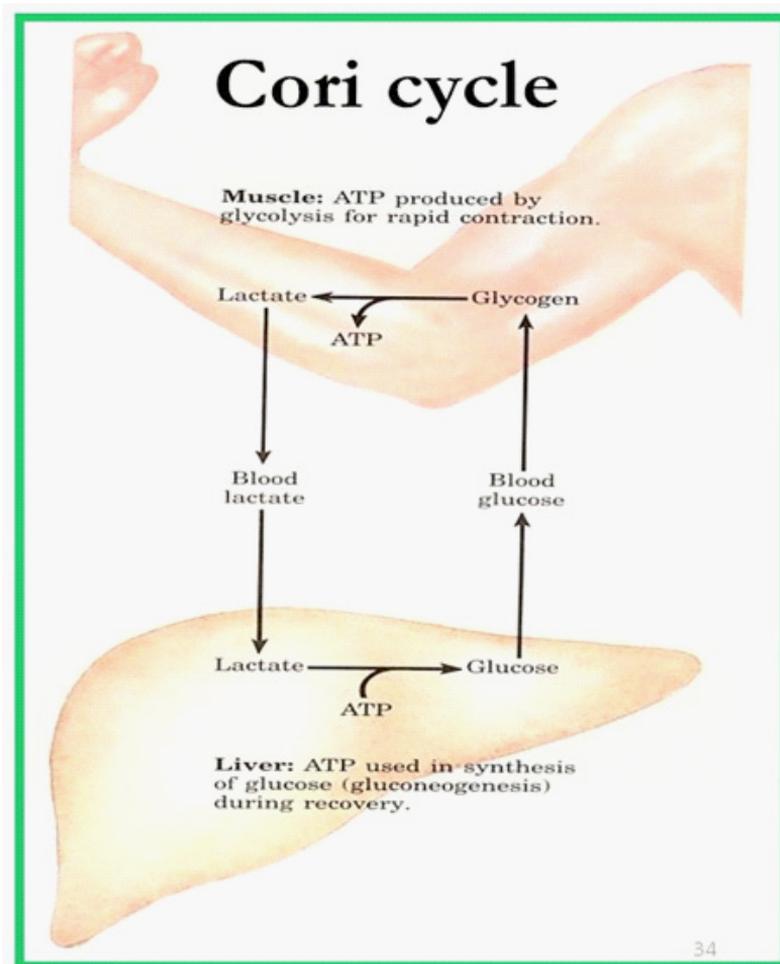


**Figure 6:** Metabolism of protein of liver. The figure show 8 destinations: 1) liver proteins, 2) amino acid in blood to tissue proteins, 3) for productions of hormones, porphyries and nucleotides, 4) released of NH<sub>3</sub> for the urea cycle in eliminate in form the urea.

## MUSCLE TISSUE

In muscle, the use of ketone bodies and free fatty acids may replace the glucose in fasting. However, in situations of intense physical activity, the anaerobic metabolism is favored [1,3,4,8]. The contribution of glycogen stored in the muscle is fundamental to ensure the efficiency of muscular work, especially when it is required of the intense physical activity in a very short time [18], as for example, in explosive exercises, 400-meter races or swimming events of 100 meters, or in strength exercises (bodybuilding). Glucose uptake into muscle occurs by GLUT4 transporters, the adipose tissue is extremely dependent on the insulin [3,4,7,19]. Insulin increases the number of GLUT4 receptors in muscle and adipose tissue membranes, because it stimulates

the mobilization of this carrier from the storage sites and their migration to the membrane plasma [3,4,7,19]. Another action of insulin in muscle tissue is the inhibition of protein degradation with favor of protein synthesis [4,6,20,21], thereby, adequate diets in amino acids and carbohydrates become important for muscular hypertrophy induced by physical exercise [21]. In skeletal muscle in high activity, the glycolysis velocity is greater than that of the citric acid cycle, then a large part of pyruvate will be converted to lactate, which is captured by the liver, becoming a substrate for gluconeogenesis [1,3,4,8,18]. In this situation liver and muscle establish a relationship of interdependence, the muscle consumes glucose in an important way, producing lactate is taken to the liver by the circulatory chain and there it is again converted into glucose [1,3,4,8,12,18], this cycle of reactions is known as the Cori, as shown in figure 7.



**Figure 7:** Cori cycle. After of an exercise of burst, Acetyl-CoA from glycogen does not enter the citric acid cycle due to lack of oxygen in muscle and is converted directly into lactate and transported through the blood to liver and after transformed in glucose that back to muscle for production of power.

Part of the pyruvate produced in the muscle is converted to alanine by transamination, and this alanine, will also fuel the hepatic gluconeogenesis pathway and. This cycle is called as alanine cycle [1,3,6,8]. During periods of intense muscle work, or during prolonged fasting, important proteolysis occurs, and release of the amino acid alanine that functions as an important substrate for gluconeogenesis in these situations [1,3,4,6,8]. In the first days of fasting, muscle proteolysis is intense, about 75 g/day, and after 3 or 4 days of fasting, it occurs on a smaller scale, about 20g /day. Muscle proteins should be spared after few days of fasting because the protein reserve is limited, corresponding to 6 kg of muscle mass, for an adult individual of 70 kg, and would be insufficient to maintain glycemia for periods longer than two weeks [9]. Thus, after a period of 3 or 4 days of fasting, the CNS is replaced the use of glucose by ketone bodies, which allows a slower rate of muscle proteolysis and consequently gluconeogenesis [9] (Figure 2). In any case, the muscle is the main source of amino acids during starvation and will be the great feeder of gluconeogenesis in prolonged periods of fasting.

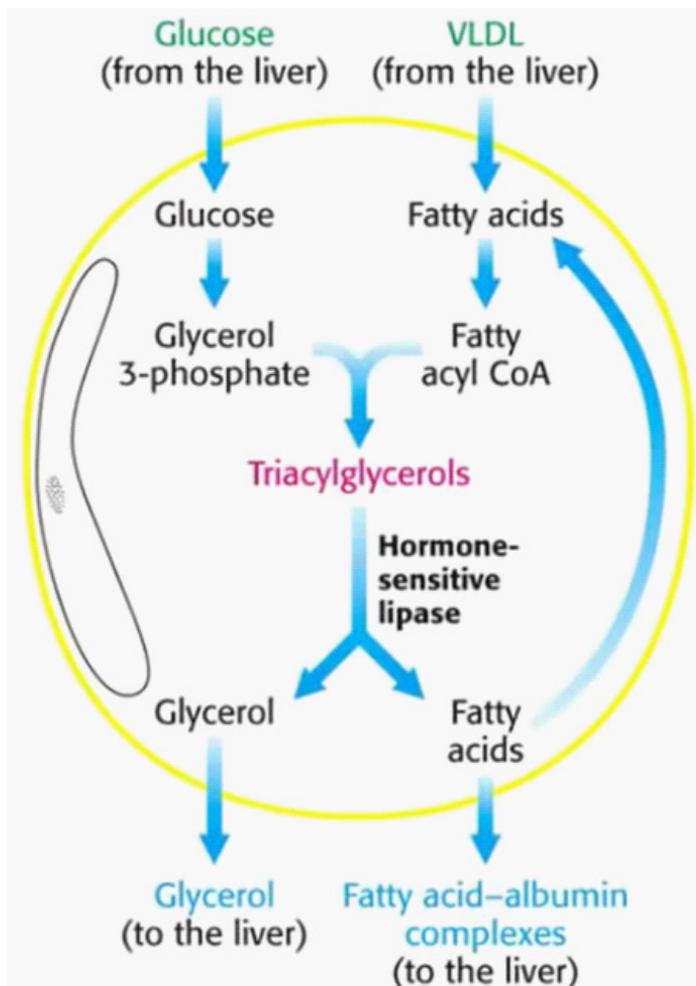
In periods of moderate and long-term physical exercise, the main fuel for muscle tissue becomes lipids, and in this sense, the triglyceride deposits from the muscle itself are of particular importance [12,18,22,23]. In any case, the heart muscle seems to prioritize the ketones bodies, preferring them to glucose [4,7]. As discussed above (Figure 6), muscle tissue can utilize various energetic substrates to ensure the efficiency of muscle work. The type of energy substrate used by the muscle is primarily determined by the intensity and duration of exercise, but may be influenced by the level of training, diet and external factors that could modify the metabolic response to exercise [18,22]. This does not mean that whatever fuel is preferentially used excludes the others, but there is a combination of different energy sources for the same metabolism.

## ADIPOSE TISSUE

The adipose tissue is distributed under the subcutaneous tissue, but with a tendency to accumulate in the abdominal cavity and skeletal muscle, and reaches about 15%, the weight of a normal subject, i.e., about 15 kg for an adult 70 kg [3,9]. This large lipid volume is undoubtedly the largest reserve

of the body, and is characterized by the accumulation of large amounts of

triglycerides (**TG**) in adipose cells [1,3,4,8]. The great part of the fatty acids molecules reach the adipose tissue transported by lipoproteins [1-3] (Figure 8).



**Figure 8:** Metabolism of the adipose tissue arrived from of VLDL and/or glucose. Both glucose and fatty acids on entering of adipose tissue is transformed in triacylglycerols in the biosynthesis. If the organism with low glucose an enzyme called hormone-sensitive lipase break the triacylglycerols in glycerol and fatty acid is transported in albumin complexes.

The synthesis of TG, from glycerol-3-phosphate and fatty acids or the hydrolysis of the TG molecule are regulated processes by the availability of glucose in adipose tissue cells [3,4,9]. The entry of glucose in adipose tissue is made by GLUT4 receptors dependent on the action of Insulin ratio [3,4,7], and thus, when the insulin/glucagon ratio is high, glycerol-3-phosphate is produced in adipose tissue by the reduction of dihydroxyacetone phosphate, intermediate of the glycolytic pathway and new TG molecules can be stored [9]. The small pathway called glyceroneogenesis that is a metabolic pathway which synthesizes glycerol 3-phosphate or triglyceride from precursors other than glucose [1,6]. Usually glycerol 3-phosphate is generated from glucose by

glycolysis, but when glucose concentration drops in the cytosol, it is generated by another pathway called glyceroneogenesis. The Glyceroneogenesis uses pyruvate, alanine, glutamine or any substances from the TCA cycle as precursors for glycerol 3-phosphate and phosphoenolpyruvate carboxykinase [8,12]. However, when the insulin/glucagon ratio decreases, the availability of glucose decreases. With the decrease of the production of glycerol-3-phosphate, the synthesis of TG in the adipose tissue will be hampered. On the other hand, when the presence of insulin is lowered and increased glucagon, lipase enzymes that promote TG in fatty acid and glycerol, will be activated, and thus, both fatty acids and glycerol, will be released into the circulatory system and will be picked up by the liver [3,4,8,12].

In general, we can say that the supply of nutrients guarantees a series of conditions that culminate in the activation of the anabolic pathways, is suitable for storage. However, in the fasting period the cells have a predominantly catabolic metabolism. There is an enzyme that controls the biosynthesis and degradation of TG: Acetyl-CoA Carboxylase (**ACC**). The high glucose in blood increase the insulin, a phosphatase dephosphorylates the ACC. Thus, the ACC activate the production of malonyl-CoA, a precursor of the biosynthesis of AG. Moreover, the malonyl-CoA inactive the carnitine acyl-transferase I, that is a transporter of the acyl-carnitine for beta-oxidation that is inactivated. However, a decrease of glucose, the glucagon is increased, the ACC is phosphorylated that become active the carnitine acyl-transferase I, that is taken to the beta-oxidation of AG [1].

The energy reservoirs such as glycogen, triglycerides and proteins will be mobilized to meet the body energy needs. We have also seen that in cases of prolonged fasting, a number of metabolic adaptations occur to ensure the functioning of the body, and the production and use of ketone bodies is of paramount importance in the maintenance of life.

## THE FEEDBACK SYNDROME

In severely malnutrition, there occur a lethal condition which includes electrolytic changes associated with metabolic abnormalities as a result of oral, enteral or parenteral nutritional support [24-26]. In starvation there is a reduction in insulin secretion as a consequence of reduced carbohydrate intake, with prevalence of glucagon, adrenalin and cortisol hormones, which result in an important lipid and proteic catabolic state in order to improve gluconeogenesis [4,8]. Associated with the intense catabolic state of starvation and the reduction of absorptive capacity, an intracellular loss of electrolytes, especially phosphate, is expected [24-26]. In severe nutritional depletion, atrophy of the gut mucosa and impairment of pancreatic function may predispose to severe diarrhea following oral or enteral refeeding, precipitating further electrolyte and mineral imbalance [26].

In the early feedback, shift occurs in glucose and lipid metabolism, as the sudden availability of glucose leads to insulin surge and inhibition of catabolic actions and gluconeogenesis. Although insulin promotes glucose to intracellular migration and potentially adjust energy metabolism and

protein synthesis, there will be simultaneous influx of potassium, phosphate, magnesium and water [25]. The rapid influx of potassium, magnesium, and phosphate intracellularly result in an expressive decrease of these electrolytes serum levels [27]. During starvation, phosphate and potassium are lost from the cell in proportion to the breakdown of glycogen and protein, potassium being the main intracellular cation balancing the negative charges on proteins [26].

Although phosphate is just one of the components affected, hyphosphatemia associated with the feedback syndrome implies a severe clinical condition. In addition to being a component of ATP, other molecules associated with cellular energy storage and production depend on adequate levels of phosphate, including creatine phosphate, among others. Phosphate is still important for mineralization and bone structure, collagen synthesis, calcium homeostasis and vital importance for acid-base balance. Not to mention the action of potassium as an enzymatic cofactor associated with the metabolism of carbohydrates, lipids and proteins [28]. In refeeding acute thiamine deficiency may be precipitated, especially in patients suffering from chronic alcoholism, since diminished thiamine reserves are rapidly used up, as thiamine is used during carbohydrate metabolism. Excessive infusion of glucose may also cause hyperglycemia leading to osmotic diuresis, dehydration and hyperosmolar nonketotic coma [26,29]. The production of fat from glucose due to lipogenesis can result in hypertriglyceridemia and/or a fatty liver [26,29]. Too rapid refeeding, particularly with carbohydrate may precipitate a number of metabolic and pathophysiological complications, which may adversely affect the cardiac, respiratory, hematological, hepatic and neuromuscular systems leading to clinical complications and even death [26]. The feedback syndrome is clinically characterized by neurological and respiratory symptoms, arrhythmias and heart failure, few days after refeeding [24-26].

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