BIOCHEMICAL MECHANISM OF GLUCONEOGENESIS PROCESS

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Abstract. *In this article we will discuss in detail the process of gluconeogenesis and its biochemical mechanism. gluconeogenesis refers to reactions in the mitochondria and cytosol that normalize blood glucose levels during fasting. the process of gluconeogenesis is controlled locally or centrally (insulin, glucagon and cortisol). the balance between stimulating and inhibiting hormones regulates the rate of gluconeogenesis. liver and kidneys are the organs that supply various tissues with circulating blood glucose. different tissues have many mechanisms to generate glucose during fasting to maintain sufficient energy levels for their proper functioning.*

Keywords: *glycogen, glycogenolysis, triglyceride, hepatocyte, alanine, mitochondria, cytosol.*

Introduction. Gluconeogenesis occurs in animals, plants, fungi and microorganisms. Its reactions are the same for all tissues and biological species. Important precursors of glucose in animals are three-carbon compounds such as lactate, pyruvate, glycerol, and some amino acids. In mammals, gluconeogenesis occurs primarily in the liver and, to a lesser extent, in the renal cortex and epithelial cells lining the small intestine. The glucose formed during gluconeogenesis goes into the blood, from where it is delivered to other tissues. After intense physical activity, lactate, formed during anaerobic glycolysis in skeletal muscles, returns to the liver and is converted there into glucose, which again enters the muscles or is converted into glycogen (this cycle is known as the corey cycle). In plant seedlings, the fats and proteins stored in the seed are converted, including through gluconeogenesis, into the disaccharide sucrose, which is transported throughout the developing plant. Glucose and its derivatives serve as precursors for the synthesis of the plant cell wall, nucleotides, coenzymes, and many other vital metabolites. In many microorganisms, gluconeogenesis begins with simple organic compounds containing two or three carbon atoms, such as acetate, lactate and propionate, which are found in the nutrient medium.

Although the reactions of gluconeogenesis are the same in all organisms, the adjacent metabolic pathways and the ways in which gluconeogenesis is regulated differ between species and tissues. During exercise, several tissues such as the brain, erythrocytes, renal medulla and cornea, testis, and skeletal muscle require a continuous supply of glucose. The brain uses glucose only in sated and fasting states, with the exception of long-term starvation, which uses ketones. It is noteworthy that the daily amount of glucose used by the brain is 70% of the total glucose produced by the liver in a normal fasting person.

Initially, during the first hours of starvation, liver glycogenolysis is the main source of glucose. Glucose stored as glycogen can cover energy needs for about a day; the amount of glucose provided by glycogen reserves is 190 g, and the daily requirement for glucose is 160 g. After

several hours of fasting, gluconeogenesis and glycogenolysis contribute equally to blood glucose. The amount of glucose provided by glycogen decreases rapidly, and the increase in the fraction of glucose added by gluconeogenesis leads to a constant maintenance of the total amount of glucose produced. It is estimated that 54% of glucose comes from gluconeogenesis after 14 hours of fasting, and this contribution increases to 64% after 22 hours and 84% after 42 hours. However, when glycogen stores are depleted, the body uses lactate, glycerol, glucogenic amino acids, and odd-chain fatty acids as sources of glucose. Long-term starvation increases the participation of the kidneys in gluconeogenesis and accounts for about 40% of total gluconeogenesis.

Alanine produced by protein catabolism and subsequent transamination reactions in skeletal muscle is released into the blood and absorbed by the liver. Inside hepatocytes, alanine undergoes transamination to pyruvate, which is used for gluconeogenesis. Glucose produced in the liver is released into the circulation and taken up by muscle cells for use in the production of atf. Other gluconeogenic amino acids (ex. Methionine, histidine, valine) and gluconeogenic and ketogenic (ex. Phenylalanine, isoleucine, threonine, tryptophan) are transaminated to various intermediates of the gluconeogenic pathway.

In red blood cells and other tissues without mitochondria, and in muscle tissue that supports anaerobic metabolism, glucose is converted to pyruvate and then to lactate. Lactate is released into the plasma and taken up by the liver to be converted to glucose by a redox reaction catalyzed by lactate dehydrogenase.

Fatty acids are stored as triglycerides and mobilized by hormone-sensitive lipase (hsl); from the triglyceride structure, glycerol is released into the blood for absorption by the liver, phosphorylated by glycerol kinase, and oxidized by glycerol phosphate dehydrogenase to dihydroxyacetone phosphate, an intermediate of the gluconeogenesis/glycolysis pathway. Unlike ketogenic double-chain fatty acids, odd-chain fatty acids are converted to propionyl coa by beta-oxidation. After several steps, propionyl coa is converted to methylmalonyl coa. Methylmalonyl coa mutase/b12 catalyzes the conversion of the latter to succinyl-coa. Succinyl-coa is an intermediate of the tca cycle that is ultimately converted to oxaloacetic acid and enters the gluconeogenesis pathway. Pure ketogenic amino acids (leucine, lysine) converted to double-chain fatty acids and acetyl-coa cannot enter gluconeogenesis, because this step is catalyzed by pyruvate dehydrogenase (pdh).

After entering the glyconeogenesis cycle, the sequence of reactions in the picture occurs. The last irreversible reaction involves glucose-6 phosphatase, which catalyzes the hydrolysis of glucose-6 phosphate to glucose. This enzyme is mainly present in the liver, kidneys and intestinal epithelium, and the reaction takes place in the endoplasmic reticulum of cells. Muscle cells do not secrete this enzyme because they use glucose for energy.

In certain conditions, such as ischemic stroke and brain tumor development, astrocytes increase the activity of gluconeogenic enzymes and they use lactate, alanine, aspartate and glutamate as substrates.

Conclusion. *Overall, the net reaction of gluconeogenesis is the synthesis of glucose from non-carbohydrate precursors, involving the consumption of atp, gtp, and nadh, with the production of nad+ and pyruvate. The process is important to maintain blood glucose levels during periods of fasting or high energy demand.*

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