Energy metabolism: gluconeogenesis and oxidative phosphorylation

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Abstract

Most animal cells are able to meet their energy needs from the oxidation of various types of compounds: sugars, fatty acids, amino acids, but some tissues and cells of our body depend exclusively on glucose and the brain is the largest consumer of all. That is why the body has mechanisms in order to keep glucose levels stable. As it decreases, the degradation of hepatic glycogen occurs, which maintains the appropriate levels of blood glucose allowing its capture continues by those tissues, even in times of absence of food intake. But this reserve is limited, so another metabolic pathway is triggered for glucose production, which occurs in the kidneys and liver and is called gluconeogenesis, which means the synthesis of glucose from non-glucose compounds such as amino acids, lactate, and glycerol. Most stages of glycolysis use the same enzymes as glycolysis, but it makes the opposite sense and differs in three stages or also called deviations: the first is the conversion of pyruvate to oxaloacetate and oxaloacetate to phosphoenolpyruvate. The second deviation is the conversion of fructose 1,6 biphosphate to fructose 6 phosphate and the third and last deviation is the conversion of glucose 6 phosphate to glucose.

Keywords: Gluconeogenesis; Oxidative phosphorylation; Metabolism.

1. Introduction

Most animal cells are able to meet their energy needs from the oxidation of various types of compounds: sugars, fatty acids, amino acids, but some tissues and cells of our body depend exclusively on glucose and the brain is the largest consumer of all. That is why the body has mechanisms in order to keep glucose levels stable. As it decreases, the degradation of hepatic glycogen occurs, which maintains the appropriate levels of blood glucose allowing its capture continues by those tissues, even in times of absence of food intake. But this reserve is limited, so another metabolic pathway is triggered for glucose production, which occurs in the kidneys and liver and is called gluconeogenesis, which means the synthesis of glucose from non-glucose compounds such as amino acids, lactate, and glycerol.

Most stages of glycolysis use the same enzymes as glycolysis, but it makes the opposite sense and differs in three stages or also called deviations: the first is the conversion of pyruvate to oxaloacetate and oxaloacetate to phosphoenolpyruvate. The second deviation is the conversion of fructose 1,6 biphosphate

to fructose 6 phosphate and the third and last deviation is the conversion of glucose 6 phosphate to glucose. The control of gliconeogenesis is done by the glucagon it stimulates and the insulin it inhibits. Glycolysis and gluconeogenesis are regulated reciprocally by allosterism and covalent modifications to prevent unproductive two-way operation at the same time.

Oxidative phosphorylation is the final stage of the respiratory chain and is the phase in which most energy is produced. It is the main source of ATP in heterotrophic organisms under aerobic conditions. All the oxidative stages of degradation converge to this stage in which the energy from oxidation makes the synthesis of ATP.

Phosphorylation occurs in mitochondrial ridges and in the membrane of these ridges has several complexes that involve the reduction of O2 in H2O with electrons coming from NADH and FADH2 and forming a chemotic gradient for the production of ATP. There are four complexes associated with different prosthetic groups and also two mobile components that make the transfer of electrons.

ATP feels that it can be called complex V, it catalyzes ATP synthesis through the energy of the proton gradient.

2. Gliconeogensis

Gliconeogenesis is the liquid synthesis or formation of glucose from substrates other than carbohydrates, it is also called gliconeogenesis. Several amino acids, lactate, pyruvate, propionate and glycerol are sources of carbon for this route. It is important to point out that glucose can be produced from fructose, carbohydrate. The use of glycogen for glucose 6-phosphate synthesis must be distinguished from glycologenesis and is called glycogenolysis. Glucogenolysis refers to the breakdown of glycogen into glucose, and therefore does not correspond to the synthesis of new glucose.

Gliconeogenesis is important at stable levels. For blood glucose levels must be maintained to support the metabolism of tissues that use it as a primary substrate; such as the brain, erythrocytes, kidney, crystal, cornea, and testicles. Gluconeogenesis thus allows blood glucose levels to be maintained long after all the glucose in the diet has been absorbed and completely oxidized, and all the glucose stored as glycogen has been used.

Most neoglycogenesis is developed by the liver under fasting conditions, in which there is no more enough glycogen for glucose lysis (glycolysis). The other organ responsible for glucose synthesis by anglican compounds is the renal cortex.

It is important to remember that glycolysis becomes irreversible, i.e. it prevents your final substrates from being able to follow the paths for the conversion of new glucose. In living beings, this irreversibility occurs in three ways (all using heat released by the carbohydrate energy consumption) and are: the conversion of glucose into glucose 6-phosphate by hexokinase, the phosphorylation of fructose 6-phosphate into fructose 1,6-bisphosphate by phosphofructokinase and the conversion of phosphoenolpyruvate into pyruvate by pyruvate kinase. Thus, neoglycogenesis works with the aid of enzymes that work in other ways.

Several enzymes are used as catalysts, helping to transform substrates of glycolytic metabolism into new glucose. Most of the reactions that synthesize glucose in vivo act with its enzymes inversely to glycolysis, for example, pyruvate carboxylase and phosphoenolpyruvate carboxykinase.

Inside the gliconeogenesis there are two cycles involved between tissues, usually the hepatic glucose synthesis that releases it to peripheral tissues.

They are the cycles: of Cori, also called glycose-lactate cycle, and the cycle of alanine, or glycose-alanine cycle. Both are suppliers of glucose, continuously supplying the tissues that need it as their main energy source. Therefore, it is essential that peripheral tissues supply lactate and alanine as metabolites for energy extraction from glucose.

Also known as the glycose-lactato-glucose route, it uses the lactate produced in the muscles, during the deprivation of oxygen from this tissue, as a substrate for the conversion of glucose.

Intense muscle activity uses the reserved glycogen in the tissue as a source of energy via muscle glycolysis. From muscle glycolysis, glucose provides energy in the form of ATP converting into pyruvate. When the molecular oxygen supply is sufficient for pyruvate oxidation, the product is the release of water and CO2. However, during intense physical activity, the distribution of oxygen to muscle tissue can easily become scarce and there is an independent need for energy (ATP) of oxygen. Thus, the pyruvate to be reduced, uses the catalysis of the enzyme pyruvate dehydrogenase, favoring the formation of lactate. This lactate accumulates in muscle tissue in the form of lactic acid and spreads through the bloodstream to the liver, where it is metabolized into glucose.

An important factor about the conversion of lactate from lactic acid to glucose is that the conversion itself uses the energy of adenosine triphosphate, i.e., oxygen is involved in the oxidative phosphorylation process of ADP into ATP. This is an important factor, since it explains the accelerated respiration after intense physical activity, capturing oxygen for the transformation of lactate into glucose, and then back into glycogen in the muscles, thus via glycose-lactato-glucose.

With the exception of leucine and lysine, all amino acids can provide carbon for glucose synthesis when catabolized in pyruvate and oxaloacetate.

2-Aminopropanoic acid, commonly called alanine, is one of the simplest amino acids as it does not contain benzene rings. It varies from other amino acids by its methyl group bound to carbon α, thus presenting hydrophobic character.

Pyruvic acid is the final product of the glycolysis reaction, and in aqueous medium it dissociates into pyruvate, important in metabolic processes. When an amine group binds to pyruvate, in living beings, the synthesis of alanine occurs.

The pyruvate is easily converted to oxaloacetate by the enzyme pyruvate carboxylase, a catalyst that in the gliconeogece inverts the flow of carbon.

Another possible way for the organism to supply the energetic demand for glucose in its absence is through the lipidic route, in which fatty acids will be converted into glucose depending on a series of factors limiting the reactions that make up this metabolic process.

The first of these limiting factors is due to the fact that most of the fatty acids available in the body are composed of an even number of carbons; in this case their oxidative catabolism will give rise to acetyl CoA which, in turn, may either generate ketonic compounds or follow the path of the citric acid cycle. In both cases, the gliconeogenesis does not form intermediates when its occurrence is impended.

Fatty acids consisting of an odd number of carbons, however, or which have in their branch a methyl grouping are metabolized in a strong intermediate of gliconeogenesis: the propionyl CoA which can be

converted into oxaloacetate producing, at the end of the cycle, ½ glucose molecule.

It is often said, erroneously in a generic way, that "fat" does not enter the gliconeogenesis pathway; however, it is not taken into account in this statement that a good part of the fat present in the organism is stored in the fat tissue in the form of triacylglycerol and that its metabolism produces another absolute intermediary of this pathway: the glycerol itself.

The glycerol generated in the lysis of the fat molecule of fat tissue by the action of glycerol kinase if phosphorylla in glycerol 3-phosphate which, in turn, is dehydrogenated by glycerol 3-phosphate dehydrogenase in dihydroxyacetone phosphate which, depending on the nutritional status of the individual, may be converted into lactate and followed by glycologenesis or cleaved into pyruvate following the oxidative route to CO2 and H2O.

The control of gliconeogenesis can be done by three mechanisms: negative feed back (the products of the reaction inhibiting its start automatically), by alosteric inhibition (programmed inhibitors inactivating the enzymes involved in the process), and by hormonal regulation, the latter being the focus of this work.

The two hormones involved in the regulation of this route are insulin and glucagon. Both produced by the endocrine portion of the pancreas in the beta and alpha pancreatic cells (respectively), are opposite of the energy metabolism pathway being the first catabolic and the second anabolic in the second stanza since it primarily stimulates glycogenolysis.

When the organism is in regular situations in terms of glycemic rate both compete with each other on their actions being secreted in minimum portions. Once this rate is at high levels (indicated high dietary intake) the pancreas is stimulated by a series of chemical, physical and hormonal factors and secreting the insulin which will be responsible for displacing the metabolism for glycolysis by activating the membrane carriers GLUT 4 to capture to the cytosol the glucose available in the bloodstream.

Otherwise – low glycemic rate – these same factors stimulate the pancreas to secrete glucagon. This will be responsible for sequencing the start of glycogenolysis by shifting the energy metabolism to the consumption of the glycogen stored in the liver and muscles; once this muscle and visceral stock is depleted and there is still glycidic demand, it remains circulating in the bloodstream stimulating the glycogenesis from the triacylglycerols stored in the subcutaneous fat tissue. In the last case – individuals with very severe malnutrition – proteolysis can still occur stimulating glycidic neosynthesis from amino acids such as alanine by the Cori cycle.

Excessive alcohol consumption, especially by undernourished people, can cause hypoglycemia. Hypoglycemia is an inhibitory effect of alcohol on hepatic gliconeogenesis, the liver is unable to cope with the reduction equivalents formed by the oxidation of ethanol, and a metabolic disorder occurs. These equivalents, instead of converting lactate to glucose, convert from alanine to lactate, with excessive accumulation of lactate in the blood, and lactic acidosis can develop, although it is usually mild.

Alcohol consumption can lead to a loss of motor and intellectual performance, stupor and anesthesia. Hypoglycemia also contributes to these effects, i.e. the person is really drunk when their blood sugar is low and can lead to irreversible damage to the central nervous system.

- GLICOSE

Glucose is the largest substrate for brain metabolism and the brain is the primary organ in the use of glucose, with brain size being the main determinant of glucose production.

• HIPOGLICEMIA:

Plasma glucose is less than 40 mg% (plasma glucose is approximately 10%-15% higher than blood).

Premature newborns of gestational age are more susceptible to hypoglycemia than children born full-term or of the right size for their age. Children in general are also quite susceptible than adults simply because they have a higher brain/body weight ratio and the brain uses disproportionately higher amounts of glucose than the rest of the body. Newborns have limited ketogenic capacity, apparently because the transport of long chain fatty acids into hepatic mitochondria is underdeveloped. Because the use of ketone bodies by the brain is directly proportional to the concentration of circulating ketone bodies, the newborn is unable to save glucose in significant amounts by using ketone bodies. Thus, the neonate brain depends exclusively on glucose from glycogenolysis and gliconeogenesis.

The liver's ability to synthesize glucose from lactate and alanine is also limited in newborn children because the speed limiting enzyme, phosphoenol pyruvate carboxyl kinase, is present in very small amounts during the first few hours after birth. Its induction at the necessary level to avoid hypoglycemia during fasting stress takes a few hours. Premature and young children for gestational age also have lower glycogen reserves more quickly, making them glycogen-dependent than normal children.

In a more simple way, it would be like saying that the lower the glucose value, the brain becomes deficient, since the brain does not stock glucose and particularly the very low weight RNs have low substrates to maintain the glucose concentration. As glucose falls, there is an increase in fatty acids, and free radicals, with a decrease in the energy substrate for the brain. In hypoglycemia, the transport of ions is impaired and activates the mechanisms of loss of cell membrane integrity, allowing the entry of calcium and sodium into the cell, leading to cell swelling and neuronal death.

3. Therapeutic possibilities

Oxidative phosphorylation is the final stage of energy producing metabolism in aerobic organisms. All oxidative steps in the degradation of carbohydrates, fats and amino acids converge to this final stage of cellular respiration in which the energy from oxidation is responsible for ATP synthesis.

In a simplified way oxidative phosphorylation provides ATP to the cells from the glycolysis co-factors, Krebs cycle and acetyl-CoA converted nutrients that follow the citric acid cycle.

Unlike the Krebs cycle that occurs in the mitochondrial matrix, the respiratory chain or electron transport chain, occurs in the mitochondrial matrix in prokaryotic cells.

In the presence of oxygen, hydrogen electrons released from NADH and FADH2 pass through a cascade system by enzymatic complexes in the membrane of mitochondria and cytochromes, which transport these electrons between one complex and another.

This passage of energy through mitochondrial membrane enzymes is important because it accepts hydrogen electrons, decreasing its energy until it transports them to the oxygen atom forming water. If there were not a transport that would decrease the energy of the hydrogen electrons, all the contained energy would be dissipated in the form of heat, which is not advantageous for the organism. So, there is a system that transports electrons and pumps protons against the membrane electric gradient using this energy for ATP (the cellular chemical energy) synthesis.

(a) Complex I

The first hydrogen electron-accepting enzyme is called NADH-ubiquinone oxido-redutase or simply Complex I. This complex transfers the electrons that were previously carried by NADH to Citochrome.

This enzyme has a component called FMN (flavine mononucleotide), which similar to FAD is capable of receiving 2 protons and 2 electrons. The FMN has a partially reduced form (when it receives 1 proton and 1 electron) called semiquinone or FMNH. The FMNH has a free radical that accepts 1 more proton and 1 electron becoming FMNH2, its totally reduced form.

In addition to the FMN, Complex I has iron-sulfur centers (Fe-S) that are not proton acceptors and carry only electrons, received or donated by the Fe ion, whose valence alternates between Fe 3+ and Fe 2+. The Fe-S centers are still present in Complexes II and III. The S portion of this protein is bound to cysteine residues.

The FMN portion of this enzyme receives the hydrogen from NADH oxidizing it to NAD and reducing to FMNH2. It is important to note that the reduction of FMN implies the removal of a proton from the mitochondrial matrix. The electrons of the FMNH2 formed go to the Fe-S centers until the Coenzyme Q, leaving the Complex I. The protons, as they are not accepted by the iron-sulfur centers, are pumped to the space between the mitochondrial membranes.

(b) Complex II

The complex II also called succinate dehydrogenase or succinateubiquinone oxido-redutase makes up the electron chain in addition to participating in the Krebs cycle, oxidizing the succinate to fumarate.

One of the differences of complex I is the electron acceptor component of the enzyme, using FAD. FAD oxidizes the succinate producing fumarate and FADH2. When NADH2 donates its electrons to the F3+ ion of the Fe-S centers, protons of H are discarded back into the mitochondrial matrix. It is also possible to notice that different from complex I, the energy from the transfer of electrons to the coenzyme Q is not enough to pump protons against the concentration gradient.

(c) Coenzyme Q

Between the path that the electrons travel through the complexes, before reaching the complex III, there is after the complexes I and II the coenzyme Q.

Coenzyme Q functions as a convergence point of NADH from complex I, complex II succinate and other substrates that can be oxidized by donating their electrons through the respiratory chain reducing FAD to FADH2. An example are the products of triacylglycerol metabolism. The electrons from these substrates pass directly from FAD to CoQ.

(d) Complex III

Complex III, ubiquinone-cytochrome c oxido-redutase or cytochrome bc1 transfer electrons from ubiquinone to cytochrome c, accompanied by movement of protons. This enzyme is formed cytochrome bL and bH, cytochrome c1 and a Fe-S protein.

According to the Q cycle, the III complex presents two distinct catalytic sites: one for oxidation of QH2 being part of cytochrome bL and the other for reduction of Q containing cytochrome bH. With the oxidation

of QH2, two protons are thrown in the intermembranous space and when Q is reduced, the protons are removed from the matrix.

Complex III by oxidizing coenzyme Q and reducing cytochrome c, removes two protons from the matrix and pumps four protons outside the mitochondria.

(e) Complex IV

Or cytochrome oxidase, carries two electrons from cytochrome c to molecular oxygen, reducing it to H2O. The IV complex is a large protein of the internal mitochondrial membrane. It is divided into two subunits:

Subunit I: Contains two heme groups designated a and a3 and one copper ion (CuB). The heme a3 and CuB form a second binuclear center that accepts electrons from the heme a and then transfers them to the O2 connected to the a3.

Subunit II: Contains two copper ions complexed with the -SH groups of two cysteine residues in a binuclear center that resemble the proteins of the 2F and 2S centers.

The transfer of electrons through the IV complex occurs from the cytochrome c to the CuA, from the heme a3- CuB center and finally to the O2. For each four H+ substrates of the matrix converting the O2 into 2H2O. The intermediates remain strongly bound to the complex until they are completely converted to water.

In summary the whole process is: NADH Ubiquinone Citochrome b Citochrome c1 Citochrome a3 O2 + 4 hydrogen ions = 2H2O

The translocation of protons through the mitochondrial membrane is done by the complexes I, III and IV. According to Mitchell's 1961 hypothesis, electron transport energy is used to pump protons through the mitochondrial membrane. The consequence of pumping these particles is a difference in potential between the two sides of the membrane, the energy of this gradient is called proton-motor force, composed of two gradients: the pH gradient, derived from the accumulation of H in the space between membranes; and the electrical gradient, because the mitochondrial matrix becomes very electronegative when compared to the intermembranous space.

As the membrane is impermeable to protons, there are active sites that allow the spontaneous passage of protons. The same sites that allow this passage are constituted by the ATP synthesizer complex. ATP synthase catalyzes the formation of ATP when protons pass through the enzyme towards the interior of the mitochondria.

There are two hypotheses that try to explain proton pumping. One model, that of direct coupling, is used to justify the transport of protons through membranes by the Complexes I and III, proposing that the electron transporters, when reduced, capture protons from the mitochondrial matrix, and when transferred to the next component of the chain, release protons in the intermembrane space. This same hypothesis does not seem to be correctly applied to Complex VI, since this enzyme does not have components that present protons in the reduced state.

The other model, the indirect coupling, says the pumping of protons is distinct and not directly related to the transport of electrons. It proposes that the passage of energy promotes a different conformational change in oxidized and reduced states. Thus, changes related to the Bohr effect, after the transfer of electrons, cause a decrease in pKa values, and the side chains are exposed on the outside of the membrane, releasing protons

into the intermembranous space.

The ATP synthase enzyme is formed from an invagination of the internal face of the mitochondrial internal membrane; this membranous portion is made up of microspheres attached to the membrane by stems that allow rotation on their own axis. Studies have shown that the treatment of mitochondria in ultrasound ends up producing fragments of this membrane that form spontaneous vesicles containing the microspheres attached by the stems on the external side of the membrane.

It is also noted that the vesicle devoid of its microspheres perform the function of electron transport and that the uncoupled microspheres of the complex end up promoting ATP hydrolysis. Based on these observations, it is inferred that ATP synthase has two distinct segments, F0 for proton pumping and F1 for ATP synthesis.

The F0 portion is composed of six conjugations of interposed alphas and betas subunits and it is understood that the ADP + Pi = ATP reaction occurs due to a distinct structural conformation, momentary and sequential between the three beta subunits and as there is a transfer of energy from the process is used for the rotation of the enzyme transforming it from electrochemistry to mechanics saving the balance of ATPs produced is still one of the mysteries of biochemistry.

4. Competing Interests

The authors declare no competing interests.

5. References

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