NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan-.

Biochemistry, Glycolysis

Authors

Raheel Chaudhry[1]; Matthew Varacallo[2].

Affiliations

[1] Ross University School Of Medicine
[2] Department of Orthopaedic Surgery, University of Kentucky School of Medicine

Last Update: November 13, 2018.

Introduction

Glycolysis is a metabolic pathway and an anaerobic source of energy that has evolved in nearly all types of organisms. The process entails the oxidation of glucose molecules, the single most important organic fuel in plants, mirobes, and animals. Most cells prefer glucose (there are exceptions, such as acetic acid bacteria which prefer ethanol). In glycolysis, per molecule of glucose, 2 ATP molecules are utilized, while 4 ATP, 2 NADH, and 2 pyruvates are produced. The pyruvate can be used in the citric acid cycle, or serve as a precursor for other reactions.

Molecular

Glucose is a hexose sugar, which means that it is a monosaccharide with 6 carbon atoms and 6 oxygen atoms. The first carbon consists of an aldehyde group, and the other 5 carbons have 1 hydroxyl group each. In glycolysis, glucose is broken down ultimately into pyruvate and energy, a total of 2 ATP, is derived in the process (Glucose + 2 NAD+ + 2 ADP + 2 Pi --> 2 Pyruvate + 2 NADH + 2 H+ + 2 ATP + 2 H2O). The hydroxyl groups allow for phosphorylation. The specific form of glucose used in glycolysis is glucose 6-phosphate.

Glucokinase is a subtype of hexokinase found in humans. Glucokinase has a lower affinity for glucose and is found only in the pancreas and liver, whereas hexokinase is found in all cells.

Function

Glycolysis occurs in the cytosol of the cell. It is metabolic pathway which creates ATP without the use of oxygen but can occur in the presence of oxygen as well. In cells which use aerobic respiration as the primary source of energy, the pyruvate formed from the pathway can be used in the citric acid cycle and go through oxidative phosphorylation to be oxidized into carbon dioxide and water. Even if cells primarily use oxidative phosphorylation, glycolysis can serve as an emergency backup for energy or serve as the preparation step before oxidative phosphorylation. In highly oxidative tissue, such as the heart, the production of pyruvate is important for acetyl-CoA synthesis and L-malate synthesis and serves as a precursor to many molecules, such as lactate, alanine, and oxaloacetate.

Glycolysis precedes lactic acid fermentation; the pyruvate made in the former process serves as the prerequisite for the lactate made in the latter process. Lactic acid fermentation is the main source of ATP in animal tissues with low metabolic requirements and with low mitochondrial levels. In erythrocytes, lactic acid fermentation is the sole source of ATP for these cells have no mitochondria, and once mature, the red blood cells have little demand for ATP. Another part of the body which relies entirely or almost entirely on anaerobic glycolysis is the lens of the eye, which is devoid of mitochondria to prevent light scattering.

Though skeletal muscles prefer to catalyze glucose into carbon dioxide and water during heavy exercise where the amount of oxygen is inadequate, the muscles simultaneously undergo anaerobic glycolysis along with oxidative phosphorylation.

Mechanism

Glycolysis Phases

There are two phases of glycolysis: the investment phase and the payoff phase. The investment phase is where energy as ATP is put in, and the payoff phase is where net ATP and NADH molecules are created. A total of 2 ATP is put in the investment phase, and a total of 4 ATP is made in the payoff phase; thus, there is a net total of 2 ATP. The steps with which new ATP are created is called substrate-level phosphorylation.

Investment Phase

In this phase, there are 2 phosphates added to glucose. Glycolysis begins with hexokinase phosphorylating glucose into glucose-6 phosphate (G6P). This is the first transfer of a phosphate group and where the first ATP is used. Also, this step is an irreversible step. This phosphorylation traps the glucose molecule in the cell because it cannot readily pass the cell membrane. From there, phosphoglucose isomerase isomerizes G6P into fructose 6-phosphate (F6P). Then, the second phosphate is added by phosphofructokinase (PFK-1). PFK-1 uses the second ATP and phosphorylates the F6P into fructose 1,6-bisphosphate. This step is also irreversible and is the rate-limiting step. In the following step, fructose 1,6-bisphosphate is lysed into 2. Fructose-bisphosphate aldolase lyses it into dihydroxyacetone phosphate (DHAP) and glyceraldehyde 3-phosphate (G3P). DHAP is turned into G3P by triosephosphate isomerase. DHAP and G3p are in equilibrium with each other, meaning they transform back and forth.

Payoff Phase

It is critical to remember that in this phase there are a total of 2 3-carbon sugars for every 1 glucose in the beginning. The enzyme, glyceraldehyde-3-phosphate dehydrogenase metabolizes the G3P into 1,3-diphosphoglycerate by reducing NAD+ into NADH. Next, the 1,3-diphosphoglycerate loses a phosphate group by way of phosphoglycerate kinase to make 3-phosphoglycerate and creates an ATP through substrate level phosphorylation. At this point, there are 2 ATP created, one from each 3-carbon molecule. The 3-phosphoglycerate turns into 2-phosphoglycerate by phosphoglycerate mutase, and then enolase turns the 2-phosphoglycerate into phosphoenolpyruvate (PEP). In the final step, pyruvate kinase turns PEP into pyruvate and phosphorylates ADP into ATP through substrate-level phosphorylation, thus creating two more ATP. This step is also irreversible. Overall, the input for 1 glucose molecule is 2 ATP, and the output is 4 ATP and 2 NADH and 2 pyruvate molecules.

In cells, it is critical that NADH is recycled back to NAD+ to keep glycolysis running. Without NAD+ the payoff phase will halt and cause a backup in glycolysis. In aerobic cells, NADH is recycled back into NAD+ by way of the oxidative phosphorylation. In aerobic cells, it is done through fermentation. There are 2 types of fermentation: lactic acid and alcohol fermentation.

Regulation

Glucose

Glycolysis can be regulated by the amount of glucose available for the process, which is regulated primarily in 2 ways: regulation of glucose reuptake, or regulation of the breakdown of glycogen. Glucose transporters (GLUT) transport glucose from the outside of the cell to the inside. Cells which contain GLUT can increase the number of GLUT in the plasma membrane of the cell from the intracellular matrix, therefore increasing the uptake of glucose and the supply of glucose available for glycolysis. There are 5 types of GLUTs. GLUT1 is found in RBCs, blood-brain barrier, and blood-placental barrier. GLUT2 is found in the liver, beta-cells of the pancreas, kidney, and gastrointestinal (GI) tract. GLUT3 is found in neurons. GLUT4 is found in adipocytes, heart, and skeletal muscle. GLUT5 transports specifically fructose into cells. Another form of regulation is the breakdown of glycogen. Cells can store extra glucose in the form of glycogen when glucose levels are high in the cell plasma; likewise, when levels are low, the glycogen can be converted back into glucose. Two enzymes control the breakdown of glycogen: glycogen phosphorylase and glycogen synthase. The enzymes can be regulated through feedback loops of glucose or glucose 1-phosphate, or through allosteric regulation by metabolites, or from phosphorylation/dephosphorylation control.

Allosteric Regulators and Oxygen

As described before, many enzymes are involved in the glycolytic pathway by converting one intermediate to another. Control of these enzymes, such as hexokinase, phosphofructokinase, glyceraldehyde-3-phosphate dehydrogenase, and pyruvate kinase can regulate glycolysis by. The amount of oxygen available can also regulate glycolysis. The "Pasteur Effect" describes how the availability of oxygen diminishes the effect of glycolysis, and decreased availability leads to an acceleration of glycolysis, at least initially. The mechanisms responsible for this effect include the involvement of allosteric regulators of glycolysis (enzymes such as hexokinase). The "Pasteur Effect" appears to mostly occur in tissue with high mitochondrial capacities, such as myocytes or hepatocytes, but this effect is not universal in oxidative tissue, such as pancreatic cells.

Enzyme Induction

Another mechanism to control glycolytic rates is transcriptional control of glycolytic enzymes. Altering the concentration of key enzymes allows the cell to change and adapt to alterations in hormonal status. For example, increasing glucose and insulin levels can increase the activity of hexokinase and pyruvate kinase, therefore increasing the production of pyruvate.

PFK-1

Fructose 2,6 bisphosphate is an allosteric regulator of PFK-1. High levels of fructose 2,6 bisphosphate increase the activity of PFK-1. It is produced by phosphofructokinase-2 (PFK-2). PFK-2 has both kinase and phosphorylase activity and can transform fructose 6 phosphates to fructose 2,6 bisphosphate and vice versa. Insulin dephosphorylates PFK-2, and this activates its kinase activity, which increases levels of fructose 2,6 bisphosphate, which goes on to activate PFK-1. Glucagon can also phosphorylate PFK-2, and this activates phosphatase, which transforms fructose 2,6 bisphosphate back to fructose 6 phosphate. This decreases fructose 2,6 bisphosphate levels and decreases PFK-1 activity.

Clinical Significance

Pyruvate kinase deficiency is an autosomal recessive mutation that causes hemolytic anemia. There is an inability to form ATP and causes cell damage. Cells become swollen and are taken up by the spleen, causing splenomegaly. Signs and symptoms include jaundice, icterus, elevated bilirubin, and splenomegaly.

Arsenic poisoning also prevents ATP synthesis because arsenic takes the place of phosphate in the steps of glycolysis.

Questions

To access free multiple choice questions on this topic, click here.

References

1. Naifeh J, Varacallo M. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Nov 13, 2018. Biochemistry, Aerobic Glycolysis.
2. Jois T, Sleeman MW. The regulation and role of carbohydrate response element-binding protein in metabolic homeostasis and disease. J. Neuroendocrinol. 2017 Oct;29(10) [PubMed: 28370553]
3. Shyh-Chang N. Metabolic Changes During Cancer Cachexia Pathogenesis. Adv. Exp. Med. Biol. 2017;1026:233-249. [PubMed: 29282687]
4. Ahmad S, Akhter F, Shahab U, Rafi Z, Khan MS, Nabi R, Khan MS, Ahmad K, Ashraf JM, Moinuddin Do all roads lead to the Rome? The glycation perspective! Semin. Cancer Biol. 2018 Apr;49:9-19. [PubMed: 29113952]

Copyright © 2018, StatPearls Publishing LLC.

This book is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits use, duplication, adaptation, distribution, and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, a link is provided to the Creative Commons license, and any changes made are indicated.

Bookshelf ID: NBK482303 PMID: 29493928