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Glucose Homeostasis – Mechanism and Defects

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1. Introduction

Glucose is an essential metabolic substrate of all mammalian cells. D-glucose is the major carbohydrate presented to the cell for energy production and many other anabolic requirements. Glucose and other monosaccharides are transported across the intestinal wall to the hepatic portal vein and then to liver cells and other tissues. There they are converted to fatty acids, amino acids, and glycogen, or are oxidized by the various catabolic pathways of cells.

Most tissues and organs, such as the brain, need glucose constantly, as an important source of energy. The low blood concentrations of glucose can causes seizures, loss of consciousness, and death. On the other hand, long lasting elevation of blood glucose concentrations, can result in blindness, renal failure, vascular disease, and neuropathy. Therefore, blood glucose concentrations need to be maintained within narrow limits. The process of maintaining blood glucose at a steady-state level is called glucose homeostasis. This is accomplished by the finely hormone regulation of peripheral glucose uptake, heaptic glucose production and glucose uptake during carbohydrate ingestion. This maintenance is achieved through a balance of several factors, including the rate of consumption and intestinal absorption of dietary carbohydrate, the rate of utilization of glucose by peripheral tissues and the loss of glucose through the kidney tubule, and the rate of removal or release of glucose by the liver and kidney. To avoid postprandial hyperglycemia (uncontrolled increases in blood glucose levels following meals) and fasting hypoglycemia (decreased in blood glucose levels during periods of fasting), the body can adjust levels by a variety of cellular mechanisms. Important mechanisms are conveyed by hormones, cytokines, and fuel substrates and are sensed through of cellular mechanisms.

Diabetes mellitus is one of the clinical manifestations of long-term metabolic abnormalities involving multiple organs and hormonal pathways that impair the body's ability to maintain glucose homeostasis. As a result of impaired glucose homeostasis is a hyperglycemia. Prolonged elevation of blood glucose concentrations causes a number of complications like blindness, renal failure, cardiac and peripheral vascular disease, neuropathy, foot ulcers, and limb amputation. Vascular complications represent the leading cause of mortality and morbidity in diabetic patients.

Hypoglycemia is abnormally low levels of sugar (glucose) in the blood. Low levels of sugar in the blood interfere with the function of much organ system. A person with hypoglycemia may feel weak, drowsy, confused, hungry, and dizzy. The other signs of low blood sugar are: paleness, headache, irritability, trembling, sweating, rapid heart beat, and a cold. The

most common cause of hypoglycemia is a complication of diabetes. Low level of glucose in the blood occurs most often in people who use insulin to lower their blood sugar. Hypoglycemia can occur as a side effect of some oral diabetes medication that increases insulin production. People with diabetes who reduce food intake to lose weight are more likely to have hypoglycemia.

2. Role of glucose in mammalian cells metabolism

2.1 Glucose as a source of cellular energy

Glucose is rapidly metabolized to produce ATP (adenosine triphosphate), a high energy end product. Glucose is oxidized through a large series of reactions that extract the greatest amount of possible energy from it. If glucose metabolism occurs in the presence of oxygen (aerobically), the net production are 36 molecules of ATP from one molecule of glucose, and 2 molecules of ATP, if glucose metabolism occurs in the absence of oxygen (anaerobically). For details see [Szablewski, 2011].

2.1.1 Glycolysis

Glycolysis is the first pathway which begins the complete oxidation of glucose to pyruvate. It takes place in the cytoplasm of the cell. Glycolysis occurs virtually in all tissues. This pathway is unique in the sense that it can proceed in both aerobic and anaerobic conditions. Glycolysis is the pathway which cleaves the six carbon glucose molecule into two molecules of the three carbon compound pyruvate. The end result of glycolysis is two molecules of ATP and two molecules of $NADH+H^+$ (Nicotinamide adenine dinucleotide – reduced form). NAD is used as an electron acceptor. This cofactor is present only in limited amounts and once reduced to $NADH+H^+$, as in this reaction, it must be re-oxidized to NAD to permit continuation of the pathway. This process occurs by the one of the two methods: aerobic metabolism of glucose or anaerobic glycolysis.

2.1.2 Oxidative decarboxylation

During aerobic metabolism of glucose in the mitochondria, pyruvate is oxidized. During this reaction NAD is uses as an electron and proton acceptor, and pyruvate is converted to acetyl coenzyme-A (abbreviated as "acetyl-CoA"). The carboxyl group of pyruvate leaves the molecule as CO_2 and the remaining two carbons become acetyl-CoA. This reaction occurs twice since each glucose (six carbons) produce 2 pyruvates (three carbons each). Consequently, these processes produce 2 $NADH+H^+$, 2 Acetyl-CoA, and 2 CO_2.

2.1.3 Krebs cycle

Further series of reactions, all which occur inside mitochondria (mitochondrial matrix) of eukaryotic cells, is collectively called "Krebs Cycle", also known as the "Citric Acid Cycle" or the "Tricarboxylic Acid Cycle". In this cycle, acetyl-CoA is oxidized ultimately to CO_2. It is to note, that the molecules that are produced in these reactions can be used as building blocks for a large number of important processes, including the synthesis of fatty acids, steroids, cholesterol, amino acids, and the purines and pyrimidines. Fuel for Krebs cycle comes from lipids, carbohydrates, and proteins, which produce the molecule acetyl-CoA. While the Krebs cycle does produce CO_2, this cycle does not produce significant chemical energy in the form of ATP directly. This cycle produces $NADH+H^+$ and $FADH_2$, which feed

into the respiratory cycle, also located inside mitochondria (inner mitochondrial membrane). It is electron transport chain that is responsible for production of large quantities of ATP. The electron transport chain converts $NADH+H^+$ and $FADH_2$ into reactants that the Krebs cycle requires to function. If oxygen is not present, the electron transport chain cannot function, which halts the Krebs cycle.

2.1.4 Electron transport chain

Oxidative phosphorylation is a series of reactions that utilize the energy from $NADH+H^+$ and $FADH_2$ electron carriers to produce more ATP. Embedded in the inner membrane of the mitochondria are the series of proteins that use the stored energy from $NADH+H^+$ and $FADH_2$ to pump protons into the membrane space. This results in an electrical and chemical gradient of protons. The enzyme ATP synthase (ATPase) uses the proton gradient to drive the reaction of producing ATP from ADP and inorganic phosphate. The electron transport chain consists of a series of proteins (called cytochromes) that are embedded in the inner mitochondria membrane and an enzyme ATP synthase. There are four complexes, namely, I, II, III, and IV. In complex IV, the electrons are combined with protons and oxygen to form water, the final end-product. The oxygen acts as the final electron acceptor and without oxygen, soothe reaction does not proceed and therefore only anaerobic respiration is possible. The end result of electron transport chain is three molecules of ATP, if a donor of protons and electrons is $NADH+H^+$ and one molecule of H_2O. If a donor of protons and electrons is $FADH_2$, the end result of electron transport chain is two molecules of ATP and one molecule of H_2O.

2.1.5 The metabolism of lactate

The anaerobic glycolysis occurs in the absence of oxygen (anaerobically). During anaerobic glycolysis, earlier obtained pyruvate is reduced to a compound called lactate. This reduction of pyruvate to lactate is coupled to the oxidation of $NADH+H^+$ to NAD. Glycolysis and reduction of pyruvate to lactate are coupled to the net production of two molecules of ATP from one molecule of glucose. Accumulation of lactate also causes a reduction in intracellular pH. Therefore lactate is removed to other tissues and dealt with by one of the two mechanisms: 1) Lactate is converted back to pyruvate. This process is enzymatically catalyzed by lactate dehydrogenase. In this reaction, lactate becomes oxidized (loses two electrons) and is converted to pyruvate. The pyruvate then proceeds to be further oxidized by a second mechanism, the aerobic metabolism of glucose. 2) Conversion of lactate to glucose in the process of gluconeogenesis.

2.2 Gluconeogenesis

Gluconeogenesis is a metabolic pathway that results in the generation of glucose from non-carbohydrate carbon substrate such as lactate, glycerol, and glucogenic amino acids. One common substrate is lactic acid formed in the skeletal muscle in the absence of oxygen. It may also come from erythrocytes, which obtain energy solely from glycolysis. The lactic acid is released to the blood stream and transported into liver. Here it is converted to glucose. The glucose is then returned to the blood for use by muscle as an energy source and to replenish glycogen stores. This cycle is termed the "Cori cycle". The gluconeogenesis of the cycle is net consumer energy, costing the body four moles of ATP more than are produced during glycolysis. Therefore, the cycle cannot be sustained indefinitely. The

process of gluconeogenesis uses some of the reactions of glycolysis (in reverse direction) and some reactions unique to this pathway to re-synthesize glucose. This pathway requires an energy input, but has a role of maintaining a circulating glucose concentration in the blood stream even in the absence of dietary supply. Fatty acids cannot be converted into glucose in animals with the exception of odd-chain acids, which yield propionyl-CoA, a precursor of succinyl-CoA. Glycerol, which is a part of all triacylglycerols, can also be used in gluconeogenesis. On the other hand, in humans and other mammals, in which glycerol is derived from glucose, glycerol is sometimes not considered a true gluconeogenic substrate, as it cannot be used to generate new glucose. For details see [Szablewski, 2011].

2.3 Glycogenesis

Glycogenesis is the process of glycogen synthesis in which glucose molecules are added to chains of glycogen to storage in liver and muscle. This process acts during rest periods following the Cori cycle, in the liver, and also activated by insulin in response to high glucose levels. For details see [Szablewski, 2011].

2.4 Glycogenolysis

When the blood sugar levels fall, glycogen stored in the tissue, especially glycogen of muscle and liver may be broken down. This process of breakdown of glycogen is called "Glycogenolysis" (also known as "Glycogenlysis"). Glycogenolysis occurs in the liver and muscle. Hepatocytes can consume glucose-6-phosphate in glycolysis, or remove the phosphate group and release the free glucose into the blood stream for uptake by other cells. Since muscle cells lack enzyme glucose-6-phosphatase, they cannot convert glucose-6-phosphate into glucose and therefore use the glucose-6-phosphate for their own energy demands. For details see [Szablewski, 2011].

2.5 Pentose phosphate pathway

The pentose phosphate pathway (also called "Phosphogluconate pathway" or "Hexose monophosphate shunt") is primarily a cytoplasmic anabolic pathway that converts the six carbons of glucose to five carbons (pentose) sugars and reducing equivalents. The primary functions of this pathways are: 1) To generate reducing equivalents ($NADH+H^+$) for reductive biosynthesis reactions within cells; 2) To provide the cell with ribose-5-phosphate for the synthesis of the nucleotides and nucleic acids; 3) To metabolize dietary pentose sugars derived from the digestion of nucleic acids as well as rearrange the carbon skeleton of dietary carbohydrates into glycolytic/gluconeogenic intermediates. This pathway is an alternative to glycolysis. While it does involve oxidation of glucose, its primary role is anabolic rather than catabolic. It is to note, that 30% of the oxidation of glucose in the liver occurs via the pentose phosphate pathway. For details see [Szablewski, 2011].

2.6 Lipogenesis

Lipogenesis is the process by which simple sugars such as glucose are converted to fatty acids. Lipogenesis starts with acetyl-CoA and builds up by the addition of two carbon units. Fatty acids are subsequently esterified with glycerol to form triglycerides that are packed in very low-density lipoprotein (VLDL) and secreted from the liver. For details see [Szablewski, 2011].

3. Glucose homeostasis

3.1 Definition of glucose homeostasis

Most tissues and organs need glucose constantly, as an important source of energy. The low blood concentrations of glucose can cause seizures, loss of consciousness, and death. On the other hand, long lasting elevation of glucose concentrations, can result in blindness, renal failure, vascular disease etc. therefore, blood glucose concentrations need to be maintained within narrow limits. The process of maintaining blood glucose at a steady-state level is called "glucose homeostasis" [DeFronzo, 1988]. This is accomplished by the finely hormone regulation of peripheral glucose uptake, hepatic glucose production, and glucose uptake during carbohydrates ingestion. For details see [Szablewski, 2011].

3.2 Mechanisms of glucose homeostasis

To avoid postprandial hypoglycemia and fasting hypoglycemia, the body can adjust glucose levels by secreting two hormones, insulin and glucagon that work in opposition to each other. During periods of hyperglycemia, the β-cells of the pancreatic islets of Langerhans secrete more insulin. Insulin is synthesized in β-cells of pancreas in response to an elevation in blood glucose and amino acid after a meal. The major function of insulin is to counter the concerned action of a number of hyperglycemia-generating hormones to maintain low blood glucose levels. It also plays an important role in the regulation of glucose metabolism. This hormone regulates glucose metabolism at many sites reducing hepatic glucose output, via decreased gluconeogenesis and glycogenolysis, facilitates the transport of glucose into striated muscle and adipose tissue, and inhibits glucagon secretion. Insulin is not secreted if the blood concentration is ≤ 3 mmol/L, but is secreted in increasing amounts as glucose concentrations increase beyond this threshold [Gerich, 1993]. When blood glucose levels increase over about 5 mmol/L the β-cells increase their output of insulin. The glucagon producing α-cells of the pancreatic islets of Langerhans remain quiet, and hold on their hormone. It is to note, that postprandially, the secretion of insulin occurs in two phases. An initial rapid release of preformed insulin, followed by increased insulin synthesis and release in response to blood glucose. Long-term release of insulin occurs if glucose concentrations remain high [Aronoff et al., 2004; Cryer, 1992]. On the other hand, during periods of hypoglycemia, the α-cells of the pancreatic islets of Langerhans secrete more glucagon. It is the principal hormone responsible for maintaining plasma glucose at appropriate levels during periods of increased functional demand [Cryer, 2002]. This hormone counteracts hypoglycemia and opposes insulin actions by stimulating hepatic glucose production. It induces a catabolic effect, mainly by activating liver glycogenolysis and gluconeogenesis, which results in the release of glucose to the bloodstream, thereby increasing blood glucose levels. The digestion and absorption of nutrients are associated also with increased secretion of multiple gut hormones that act on distal targets. There are more than 50 gut hormones and peptides synthesized and released from the gastrointestinal tract. These hormones are synthesized by specialized enteroendocrine cells located in the epithelium of the stomach, small bowel, and large bowel. It was demonstrated that ingest food caused a more potent release of insulin than glucose infused intravenously [Perley & Kipnis, 1967]. This effect, termed the "incretin effect" suggests that signals from the gut are important in the hormonal regulation of glucose disappearance. Incretin hormones are peptide hormones secreted from the gut and specific criteria have to be fulfilled for an agent to be called an incretin. They have a number of important biological effects, as for example,

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