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Glucose Homeostasis and Diabetes

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Glucose is a hexose sugar vital as a substrate for energy metabolism. Glucose represents an essential energy substrate for many tissues and in the brain, it is an obligatory energy source.

It is found in its monosaccharide form in some citrus fruits, and in the disaccharides maltose, lactose and sucrose, and in the polysaccharide starch. Within the body glucose is stored as glycogen; occasionally, other compounds may be modified to create glucose e.g. in starvation.

Glucose is under the regulation of a homeostatic control system which aims to keep the fasting plasma concentration within narrow limits. Insulin-dependent diabetics are prone to fluctuations out of range: hyperglycaemia and hypoglycaemia following treatment.

Glucose and fatty acids: Major metabolic fuels

The existence of an organism depends on the continuous provision of energy for metabolic processes. The most important metabolic fuels are glucose and fatty acids. The maintenance of narrow-controlled blood glucose concentrations (glucose homeostasis) is central for a constant provision of glucose to the brain. Glucose homeostasis is a physiologically well-balanced mechanism depending on three coordinated and simultaneously ongoing processes involving insulin secretion by the pancreas, hepatic glucose output and glucose uptake by splanchnic (liver and gut) and peripheral tissues (muscle and fat). In normal circumstances, glucose is the only fuel the brain can use. Glucose is also preferentially utilized by muscle during the initial stages of exercise. The amount of glucose present in the extracellular fluid is minute – only about 20 g. To ensure the continuous provision of glucose to the brain and other tissues, metabolic fuels are stored for use in times of need. Carbohydrates are stored as glycogen. The amount of available glycogen stored is not large; approximately 75 g in the liver and 400 g in the muscles. Liver glycogen can remain the main supplier of glucose for no longer than 16 h. To safeguard the continuous supply of glucose over longer periods, the body transforms noncarbohydrate compounds into glucose during gluconeogenesis. [1]

Long-chain fatty acids: Storage fuel

The caloric value of fats is higher than that of either carbohydrates or proteins, and therefore long-chain fatty acids are an ideal storage fuel. The body has a virtually unlimited capacity for the accumulation of fats. [1]

Amino acids: Fuel during fasting, illness, or injury

Amino acids normally serve as substrates for the synthesis of the body's own proteins, rather than as a source of energy. However, during a prolonged fast, or after illness or injury, proteins are degraded and the constituent amino acids are converted into glucose. Excess amino acids provided with food are normally converted to carbohydrates either for storage or for energy metabolism. [1,2]

Glucose homeostasis

Glucose metabolism centres around the maintenance of blood glucose levels within a standard range and the co-ordination of fuel utilization with other reserves e.g. lipids and ketone bodies.

Essentially, blood glucose levels are dependent on the balance between output - breakdown for energy - and input - dietary absorption and release either from storage or by interconversion from other compounds.

Glucose storage predominantly occurs in the liver as glycogen. The biochemical pathways of the liver are adapted to release glucose in response to reductions in the plasma glucose concentration and modulation by various hormones. Pathways include glycogenolysis and gluconeogenesis. [1,3]

Gluconeogenesis

It is the formation of glucose, especially in the liver, from noncarbohydrate sources, such as amino acids and the glycerol portion of fats.

When the glucose content of the extracellular fluid decreases, glycogen is mobilized immediately, providing a short-term supply of endogenous glucose. Subsequently, this supply is complemented by gluconeogenesis, the other source of endogenous glucose. Gluconeogenesis

takes place primarily in the liver, with the kidneys contributing during a prolonged fast. The substrates for gluconeogenesis originate from anaerobic glycolysis (lactate) and the breakdown of either muscle protein (alanine) or adipose tissue triglycerides (glycerol). Muscle handles carbohydrate quite differently in contrast to the liver, as it does not have glucose-6-phosphatase (G-6-Pase) and hence cannot release glucose into the circulation. Instead, it uses glycogen for its own energy needs. However muscle contributes to endogenous glucose production by releasing lactate, a product of anaerobic glycolysis, which is transported to the liver, where it enters gluconeogenesis. Muscle can use both glucose and fatty acids as energy sources. During intensive exercise, glucose is the preferred fuel. Fatty acids are the main energy source at rest and during prolonged exercise. [1-4]

Glycogenolysis

It is the catabolism of glycogen by removal of a glucose monomer and addition of phosphate to produce glucose-1-phosphate. This derivative of glucose is then converted to glucose-6-phosphate, an intermediate in glycolysis.

The hormones glucagon and epinephrine stimulate glycogenolysis. Glycogenolysis transpires in the muscle and liver tissue, where glycogen is stored, as a hormonal response to epinephrine (e.g., adrenergic stimulation) and/or glucagon, a pancreatic peptide triggered by low blood glucose concentrations.

Liver (hepatic) cells can consume the glucose-6-phosphate in glycolysis, or remove the phosphate group using the enzyme glucose-6-phosphatase and release the free glucose into the bloodstream for uptake by other cells. Muscle cells will not release glucose, but instead use the glucose-6-phosphate in glycolysis. [1-4]

Regulation of plasma glucose levels

Glucose homeostasis is controlled primarily by the anabolic hormone insulin and also by several insulin-like growth factors. Several catabolic hormones (glucagon, catecholamines, cortisol, and growth hormone) oppose the action of insulin; they are known as anti-insulin or counter-regulatory hormones. [1-5]

Insulin

It is secreted in response to the increase in plasma glucose following a meal. Insulin decreases the plasma glucose concentration by promoting the uptake of glucose into tissues, intracellular glucose metabolism, and glycogen synthesis. Insulin is secreted from the beta cells of pancreatic islets of Langerhans. Glucose stimulates the secretion of insulin.

Glucagon

It is synthesized by the alpha cells of the pancreatic islet of Langerhans. Its secretion is stimulated by low and inhibited by high concentrations of glucose and fatty acids in the plasma. Glucagon stimulates glycogen breakdown and gluconeogenesis and inhibits glycogen synthesis and glucose oxidation. Its metabolic actions on target tissues are thus the opposite of those of insulin.

The fine balance between insulin and glucagon action is a key factor in the control of fuel metabolism.The glucose level acts as a signal that initiates the islet hormonal response.[1,5, 8]

The metabolic effects of insulin

Insulin promotes storage of carbohydrate and lipids, and synthesis of protein. It acts on three main target tissues – the liver, muscle, and adipose tissue. In the liver, insulin stimulates both glycolysis and glycogen synthesis. It also suppresses lipolysis and promotes the synthesis of long-chain fatty acids (lipogenesis). The lipids are then packaged into very-low-density lipoproteins (VLDL), which are secreted into the blood. In the peripheral tissues, insulin induces lipoprotein lipase, an enzyme that offloads triglycerides from either hepatic VLDL or dietary chylomicrons by hydrolyzing them into glycerol and fatty acids. Insulin also stimulates triglyceride synthesis from glycerol and fatty acids in adipose tissue. In muscle, insulin increases glucose transport, glucose metabolism, and glycogen synthesis. Insulin also increases cellular uptake of amino acids and stimulates protein synthesis. [1,6,7,9]

Stimulation of insulin secretion by glucose

The glucose concentration in the vicinity of the beta-cell is sensed by the beta-cell glucose transporter GLUT-2. Glucose is carried into the cell by GLUT-2, where it is phosphorylated into

glucose 6-phosphate (G-6-P) by glucokinase which also is a part of the glucose-sensing mechanism. Increased availability of G-6-P increases the rate of glucose utilization and ATP production in the beta-cell. This changes the flux of ions across the cell membrane, depolarizes the cell and increases the concentration of cytoplasmic free calcium (see Chapter 36). The final result is insulin exocytosis. Insulin secretion from the beta-cell after glucose stimulation is biphasic. The first phase of insulin secretion occurs within 10–15 min of stimulation and is the release of preformed insulin. The second phase, which lasts up to 2 hours, is the release of newly synthesized insulin (Fig. 20.5). Insulin secretion is also stimulated by gastrointestinal hormones and some amino acids, such as leucine, arginine, and lysine. Gastrointestinal hormones, such as glucosedependent insulinotropic peptide (GIP), cholecystokinin, glucagon-like peptide-1 (GLP-1) and vasoactive intestinal peptide (VIP), are secreted following ingestion of foods and potentiate insulin secretion. [7,9]

Diabetes mellitus: Impaired fuel metabolism

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia leading to long-term complications. It is a chronic metabolic disorder, which affects 4% of world population. There are two main forms of diabetes. Of all diabetic patients, 10% have type 1 and 90% have type 2. Type 1 patients are unable to produce insulin and must receive exogenous insulin to survive. On the other hand, type 2 patients have at least partially preserved insulin secretion, but are often insulin resistant. Some patients may have no clinical symptoms at all, with the diagnosis made exclusively on the basis of laboratory results. [1,3,9]

Metabolism in diabetes

Persons with type 1 diabetes do not have any, or have only trace amounts of, insulin in plasma. They also have an increased plasma glucagon concentration. Lack of insulin results in the inability of glucose to enter insulin-dependent tissues, such as adipose tissue and muscle. It also contributes to the relative excess of glucagon. As a consequence, glycolysis and lipogenesis are inhibited, and glycogenolysis, lipolysis, ketogenesis, and gluconeogenesis are stimulated. The key event in diabetes is that the liver becomes a producer of glucose. Increased endogenous glucose production, together with impaired glucose transport, lead to fasting hyperglycemia. Simultaneously, unopposed lipolysis produces an excess of acetyl CoA. Ketogenesis is stimulated. In a grossly decompensated patient, ketonemia and ketonuria develop.

Overproduction of acetoacetic and beta-hydroxybutyric acids decrease the pH of blood, which is normally between 7.37 and 7.44 and causes metabolic acidosis. In a type 1 diabetic patient, ketoacidosis can develop very quickly, even after missing a single insulin dose. In type 2 diabetes, ketoacidosis is relatively rare but may be precipitated by a major stress, such as myocardial infarction. As glucose is osmotically active, renal excretion of a large amount of glucose leads to osmotic diuresis. Poorly controlled diabetic patients complain of having polydypsia and of polyuria. The resulting fluid loss eventually leads to dehydration. Diabetic ketoacidosis is a life-threatening condition. [1,2,9]

Conclusion:

This article has described the glucose homeostasis in normal and diabetic individuals. Also the metabolic inter-relationships between key tissues and organs – liver, adipose tissue, and skeletal muscle are discussed. These interactions preserve glucose homeostasis and, in healthy persons, maintain blood glucose concentration within a narrow range. Thus glucose homeostasis is a essential mechanism in regulating normal metabolic activities in an healthy individual. Disruption of this homeostatic system results in potentially life-threatening conditions – hypoglycemia and diabetes mellitus. [1]

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