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Biochemistry, Glycogenolysis

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Introduction

Glycogenolysis is the biochemical pathway in which glycogen breaks down into glucose-1-phosphate and glucose. The reaction takes place in the hepatocytes and the myocytes. The process is under the regulation of two key enzymes: phosphorylase kinase and glycogen phosphorylase.

Blood glucose is a source of energy for the entire human body. During the fasting state, to maintain normal blood glucose levels, the liver plays a central role in producing glucose via glycogenolysis and gluconeogenesis.[1]

Glycogen is a branched polysaccharide consisting of glucose units. In humans, it is the principal storage form of glucose. During times of need, the body breaks down glycogen to produce glucose.[2]

Fundamentals

Glycogenolysis, along with glycolysis, plays a central role in carbohydrate metabolism. It is the principal route of glycogen utilization.[3]

Molecular

Glycogen is a storage polysaccharide consisting of D-glucose residues. The glucose residues are joined by α-1,4, which represents most of the linkages, and α-1,6 linkages, which constitute the branch points. Together, they give the molecule a branched structure. The advantages of the highly branched nature are the increased solubility and the ability to concentrate a larger molecule in a shorter space.[4]

Function

The liver breaks down glycogen to maintain adequate blood glucose levels, whereas, muscles break down glycogen to maintain energy for contraction.

Glycogen debranching enzyme is one of the few known proteins possessing two independent catalytic activities that occur at separate sites on a single polypeptide chain. The two activities are transferase and amylo-1,6-glucosidase. Both the debranching enzyme and phosphorylase enzyme are necessary for the complete degradation of glycogen.[5]

Adrenal hormones, such as catecholamines and glucocorticoids, regulate hepatic glycogenolysis. Adenosine stimulates hepatic glycogenolysis through the secretion of corticosterone from the adrenal glands.[1]

By responding to norepinephrine, via a cAMP-dependent mechanism, glycogenolysis contributes to stability maintenance during hypoglycemia. Glycogenolysis generates energy in the form of ATP, NADH, and lactate production.[6]

Glycogenolysis is stimulated by glucagon, which is mediated by an intracellular increase of cAMP and Ca+2, which is mediated either by the adenylate cyclase or phospholipase C pathway. Glucagon activates adenylate cyclase via GR2 receptors. Adenylate cyclase converts ATP to cAMP, which activates PKA, which activates glycogenolysis enzymes via ATP-dependent phosphorylation.[7]

Mechanism

The key regulatory enzymes of glycogenolysis are phosphorylase kinase and glycogen phosphorylase, both activated by phosphorylation. These will predominantly express in the liver, muscle, and brain.[8]

The process of glycogenolysis starts in the muscle due to the activity of the enzyme adenyl cyclase and cAMP. cAMP then binds to phosphorylase kinase and converts it to its active form, which then converts phosphorylase b to phosphorylase a, which finally catalyzes the breakdown of glycogen.[9]

The process of glycogen breakdown can occur either in the cytosol or in the lysosomes. In the cytosol, the enzyme glycogen phosphorylase catalyzes the release of glucose-1-phosphate from the ends of glycogen branches with the use of inorganic phosphate to cleave α-1,4 bonds.[2] After that, glucose-1-phosphate can convert to glucose-6-phosphate. In the lysosome, the enzyme acid α-glucosidase degrades lysosomal glycogen via an autophagy-dependent pathway. It is known that the latter process serves as an immediate source of energy in the newborn period.[2]

Since the enzyme phosphorylase can only cleave until it is four units from a branch point, when glycogen phosphorylase reaches a branch point that is four glucose residues away, the enzyme glycogen debranching enzyme transfers one of the branches to another chain, forming a new α-1,4 bond and leaving a single glucose unit at the branch point, which is later hydrolyzed by α-1,6-glucosidase, forming free glucose.[9]

Clinical Significance

Von Gierke disease, also known as glycogen storage disease type 1A, is an autosomal recessive disorder in which the enzyme glucose-6-phosphatase is deficient, leading to an inability to break down glycogen into glucose. It has an incidence of 1 in 100,000 live births. The clinical presentation is characteristically an infant, usually at the age of three to six months (although the age of presentation is variable), presenting with hypoglycemia and hepatomegaly, frequently accompanied by hyperlipidemia, hyperuricemia, and lactic acidosis. An enzyme assay and liver biopsy confirm the diagnosis. It is manageable through adequate dietary therapy for preventing long-term complications.[10]

Pompe disease, also known as glycogen storage disease type II or acid maltase deficiency, is an autosomal recessive disorder resulting from mutations in the GAA gene on chromosome 17q25, coding for acid alpha-glucosidase, leading to lysosomal accumulation of glycogen in various tissues, but mostly affecting cardiac and skeletal muscles. The clinical presentation depends on the specific mutation and the resulting level of residual acid alpha-glucosidase activity. It is

classified depending on the timing of presentation: classic infantile-onset Pompe disease, with an age of onset ≤ 12 months, and late-onset Pompe disease, which manifests any time after 12 months of age. The classic type characteristically demonstrates a rapidly progressive hypertrophic cardiomyopathy and left ventricular outflow obstruction, accompanied by muscle weakness, hypotonia, and respiratory distress. Motor development is delayed. The main cause of death is cardiac and respiratory failure, most commonly occurring before one year of age. The late-onset type usually lacks cardiac involvement; it presents with muscle weakness progressing to profound weakness and wasting, eventually requiring a wheelchair. Respiratory failure due to the involvement of the diaphragm is a common complication.[11][12]

Cori Disease: also known as glycogen storage disease type III or limit dextrinosis, is a genetic disease caused by a mutation in the AGL gene located in chromosome 1p21 encoding for glycogen debranching enzyme (amylo-1,6-glucosidase), leading to a deficient activity in the key enzyme responsible for glycogen degradation. The characteristic clinical presentation is hypoglycemia, hyperlipidemia, growth retardation, and hepatomegaly. It can subdivide into type IIIa, which present with hepatic and muscle involvement, which can develop myopathy and cardiomyopathy, and type IIIb, which primarily presents with liver disease.[13][5]

McArdle disease: also known as glycogen storage disease type V or myophosphorylase deficiency, is an autosomal recessive inborn error of skeletal muscle metabolism in which glycogen phosphorylase activity is affected, resulting in an inability to break down glycogen. It results from nonsense mutations in the PYGM-gene on chromosome 11, which codes for muscle glycogen-phosphorylase (myophosphorylase). Since muscle glycogen-derived glucose is unavailable during exercise, and glycogen is the primary fuel in exercise, exercise intolerance characterizes the clinical scenario. Vigorous exercise will often cause contractures and rhabdomyolysis accompanied by myoglobinuria.[14][15]

Glycogenolysis activated by catecholamines, such as norepinephrine, has been implicated in memory consolidation. Researchers have proposed that it is an important factor in the development of Alzheimer disease due to chronic atrophy.[6]

Review Questions

- Access free multiple choice questions on this topic.
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