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Biochemistry and molecular genetics of human glycogenoses

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Abstract: Most of the glycogen metabolism disorders that affect skeletal muscle involve enzymes of glycogenolysis (myophosphorylase (PYGM), glycogen debranching enzyme (AGL), phosphorylase b -kinase (PHKB)) and glycolysis (phosphofructokinase (PFK), phosphoglyceromutase (PGAM 2), aldolase A (ALDOA), β -enolase (ENO 3)); however, 3 of them involve glycogen synthesis (glycogenin-1 (GYG 1), glycogen synthase (GSE), and debranching enzyme (GBE 1)). Many present with exercise-induced cramps and rhabdomyolysis with more intense exercise (ie, PYGM , PFK , PGAM 2), while others present with muscle wasting and weakness (GYG 1, AGL , GBE 1). Failure of serum lactate to rise with exercise, with an exaggerated response to ammonia, is a common but not invariant feature. Serum creatine kinase (CK) levels are often elevated in myopathic forms and PYGM deficiency , but may be normal and elevated only in rhabdomyolysis (PGAM 2, PFK , ENO 3). Therapy for glycogen storage diseases that result in exercise-induced symptoms involves lifestyle adaptations and carefully selected exercises. Immediate carbohydrate ingestion before exercise improves symptoms in glycogenolytic defects (i.e., PYGM), but may worsen symptoms in glycolytic defects (i.e., PFK). Low-dose creatine monohydrate may provide modest improvement in PYGM mutations.

Keywords: Glycolysis, glycogenosis, forearm stress test, myogenic hyperuricemia, glycogenolytic.

Introduction: Glucose metabolism myopathies are a heterogeneous group of disorders characterized by skeletal muscle dysfunction due to defects in glucose handling processes. These disorders can be roughly divided into three main categories:

disorders of glycolysis (breakdown of glucose), glycogenolysis (breakdown of glycogen, a storage form of glucose) and glycogen synthesis (formation of glycogen). The manifestation of symptoms of these myopathies is closely related to the energy needs of the muscles. During normal activity, symptoms may be minimal or absent altogether. However, during physical exertion that requires significant energy expenditure, defects in glucose metabolism become obvious, manifesting themselves in the form of muscle weakness, pain, cramps and other symptoms. This is explained by the fact that under conditions of increased energy demand, muscles are unable to effectively use glucose as a fuel source. It is interesting to note that some of these disorders can manifest themselves not only as metabolic myopathies, with symptoms appearing during exertion, but also as fixed myopathies. In this case, muscle weakness and atrophy are present constantly, regardless of the level of physical activity, mimicking the clinical picture of diseases such as muscular dystrophy or various congenital myopathies.

Differential diagnosis in such cases is very complex and requires specialized studies. In this chapter, we will consider in detail the process of glucose metabolism in skeletal muscle, its role in muscle performance, and its relationship with physical exercise . We will analyze the main stages of glucose metabolism - from its uptake by cells to the final formation of ATP, the energy currency of the cell. The key enzymes and proteins involved in each step, as well as the mechanisms of their regulation, will be described. Particular attention will be paid to the role of insulin and muscle activity in the regulation of glucose uptake. After a detailed description of the metabolic pathways, we will move on to consider specific disorders of glucose metabolism caused by genetic defects. For each myopathy, the genetic defects underlying the disease, clinical manifestations, diagnostic criteria, and available treatments will be described.

It is worth noting that Pompe disease, although associated with glycogen accumulation, is different from other glycogenoses. Its mechanism is not a defect in the enzymes involved in metabolizing glucose for energy, but a defect in the lysosomal enzyme acid alpha-glucosidase (GAA). The accumulated glycogen in the lysosomes disrupts normal cell function, leading to muscle weakness and other symptoms. Because of this specific mechanism, Pompe disease is often classified as a lysosomal storage disease rather than a metabolic myopathy and is treated separately.

Now let's talk about glucose uptake by muscles in more detail. Glucose enters muscle cells via special carrier proteins, the main ones being GLUT4 and GLUT1. GLUT4 is an insulin-stimulated carrier. At rest, most GLUT4 is located intracellularly, in special vesicles. When the insulin level in the blood increases (for example, after eating), insulin binds to its receptor on the surface of the muscle cell, which triggers a cascade of intracellular signaling events that lead to the movement of vesicles with GLUT4 to the cell membrane (sarcolemma). This dramatically increases the number of glucose carriers on the cell surface and, consequently, the rate of glucose uptake.

In addition to insulin, muscle activity also stimulates the translocation of GLUT4 to the sarcolemma, providing muscles with an additional source of energy during exercise. GLUT1, unlike GLUT4, is a constitutive transporter; its activity is independent of insulin and is not regulated by vesicle translocation. It provides the basal level of glucose uptake. Thus, the coordinated work of GLUT4 and GLUT1 ensures the adaptation of glucose uptake to changing muscle needs. Disturbances in the work of these transporters may underlie some forms of myopathies.

The source of free fatty acids during exercise is both plasma and intramyocellular lipids (IMCL). Given that FFAs are more reduced than glucose, the amount of oxygen required for oxidation is higher and thus when carbohydrate stores are depleted the runner must slow down, which is experienced during a long run such as a marathon as "hitting a wall".

Energy crises in glycolytic and glycogenolytic defects and the development of rhabdomyolysis. Rhabdomyolysis is a syndrome that represents an extreme degree of myopathy and is characterized by the destruction of muscle tissue cells, a sharp increase in creatine levels. People suffering from glycogenolytic or glycolytic defects experience significant problems in energy production, especially during prolonged or intense physical activity. These metabolic myopathies arise from inherited deficiencies in enzymes that are critical for carbohydrate metabolism, affecting the body's ability to produce ATP, the main energy currency of cells. The consequences of these deficiencies are most pronounced during prolonged isometric contractions (eg, holding a heavy weight) or high-intensity repetitive movements. The underlying mechanism is impaired efficient conversion of glucose and glycogen into usable energy. During exercise, skeletal muscles rely heavily on glucose and glycogen as their primary fuel sources.

Glycogen stored in muscle cells undergoes glycogenolysis, a breakdown process that produces

glucose-6-phosphate, an important intermediate metabolite. This metabolite then enters glycolysis, a series of enzymatic reactions that further break down glucose, generating ATP and pyruvate. Pyruvate then enters the mitochondria, the cell's powerhouses, where it fuels oxidative phosphorylation, a highly efficient process that generates large amounts of ATP. In people with glycolytic or glycogenolytic defects, this pathway is impaired. Deficiencies in either enzyme involved in glycogenolysis or glycolysis result in decreased pyruvate production, limiting the capacity for oxidative phosphorylation and, ultimately, ATP synthesis.

This energy deficit is further exacerbated by the increased energy demands of exercising muscles. The impact of these deficits goes beyond simple fatigue. Decreased ATP availability during exercise disrupts critical cellular processes. For example, the sodium-potassium pump, responsible for maintaining ion gradients across the cell membrane, becomes less efficient, leading to ionic imbalances. This, in turn, can cause muscle cramping and pain, a warning sign of an impending metabolic crisis. In addition, decreased ATP production leads to a buildup of reactive oxygen species (ROS), highly reactive molecules that damage cellular components including proteins and DNA. Calcium homeostasis is also significantly disrupted; insufficient ATP levels reduce the ability of the sarcoplasmic reticulum to sequester calcium ions, leading to calcium overload within the muscle cell. This calcium overload activates numerous calcium-dependent enzymes that contribute to further cellular damage. Impaired energy production directly impacts V-O2-peak, the maximum rate of oxygen consumption during exercise. Patients with these defects exhibit lower V-O2-peak compared to healthy individuals and experience limitations in exercise performance even at relatively low intensities. This reflects the body's inability to meet the oxygen demands of exercising muscles due to impaired substrate utilization.

Some individuals may experience a "second wind" phenomenon, whereby an initial exercise load causes a rapid increase in perceived exertion, heart rate, and ventilation, followed by a temporary relief of symptoms when exercise intensity is reduced. This temporary improvement is likely due to increased capillary dilation, improved oxygen and substrate delivery to the muscles, and the mobilization of alternative energy substrates from the liver (via glycogenolysis) and adipose tissue (via lipolysis). However, if the energy crisis is severe or prolonged, or if the individual overcomes the warning signs of muscle pain and cramping, the consequences may be much more severe, leading to rhabdomyolysis.

Rhabdomyolysis is a severe condition characterized by the breakdown of skeletal muscle fibers, releasing their contents into the bloodstream. The hallmark of rhabdomyolysis is a sharp increase in plasma creatine kinase (CK), often exceeding 10 times the upper limit of normal (~200 IU/L). CK is an enzyme found primarily in skeletal muscle; its release into the blood indicates muscle damage. However, rhabdomyolysis is not determined solely by elevated CK; other muscle-specific enzymes such as aspartate aminotransferase (AST), aldolase, and myoglobin are also released.

Myoglobin, the protein that carries oxygen in muscle tissue, can cause kidney damage if its concentration becomes high enough. Muscle damage in rhabdomyolysis associated with metabolic myopathies is a consequence of the previously mentioned energy-deficit-mediated processes: ROS accumulation, calcium overload, and ion imbalance. Together, these processes contribute to the breakdown of the sarcolemma (the muscle cell membrane), allowing the release of intracellular contents and triggering an inflammatory response. The inflammatory response further exacerbates muscle damage and can contribute to acute kidney injury, a life-threatening complication of rhabdomyolysis.

Diagnosis of glycogen storage disease type V

The diagnosis of glycogen storage disease type V (GSD V) is suggested by history, blood tests showing elevated creatine kinase (CK) activity and often high urate levels.

A forearm stress test, which involves measuring lactate and ammonia levels in the cubital vein before and after repeated isometric contraction exercise, is used to confirm the diagnosis. Unlike healthy individuals, patients with GSD V show a lack of normal lactate elevation and an exaggerated ammonia elevation.

The forearm test is an adjunct to the history and physical examination. It helps interpret the results of genetic tests, especially in cases with non-classical GSD V presentations. A normal rise in lactate and ammonia on exercise testing eliminates most metabolic GSDs from further consideration.

Muscle biopsy in patients with GSD V can be misleading, especially after an acute attack of rhabdomyolysis when nonspecific necrosis and inflammation are observed.

Molecular diagnosis of GSD V has traditionally involved analysis of a mutation panel of the PYGM gene. Many groups have now moved to sequencing the entire PYGM gene. Next-generation sequencing-based "myopathy panels" including genes associated with GSD and

structural myopathies are also being used for diagnosis.

It is important to note that the clinical manifestations of GSD V may resemble other glycogenolytic and glycolytic defects.

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Myopathies Related to Glycogen Metabolism Disorders

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Links

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