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ORIGIN OF THE VIOLATION OF THE STORAGE OF GLYCOGEN IN THE BODY

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Annotation: The brain, red blood cells, and inner portion of the adrenal gland (adrenal medulla) depend on a constant supply of glucose for their metabolic functions. This supply begins in the small intestine, where transport proteins mediate the uptake of glucose into cells lining the gut. Glucose subsequently passes into the bloodstream and then the liver, where it is stored as glycogen. In times of starvation or fasting or when the body requires a sudden energy supply, glycogen is broken down into glucose, which is then released into the blood. Muscle tissue also has its own glycogen stores, which may be degraded during exercise.

Key words: Enzymes, glycogen, glucose,maltose,protein, gierke disease.

If enzymes responsible for glycogen degradation are blocked so that glycogen remains in the liver or muscle, a number of conditions known as glycogen storage disorders (GSD) can arise. Depending upon which enzyme is affected, these conditions may affect the liver, muscles, or both. In GSD type I (von Gierke disease), the last step in glucose release from the liver is defective, leading to hypoglycemia. Therapy consists of supplying continuous glucose to the digestive tract (e.g., by continuous drip feedings) during infancy and early childhood. As the child grows, an improvement in symptoms tends to occur. Adequate glucose is supplied by frequent feedings of carbohydrates and slow-release glucose (uncooked cornstarch) before bedtime. Liver transplantation may also be curative, but this drastic measure is reserved for the small percentage of patients who do not respond to the usual treatment or who develop liver cancer. For the muscular forms of the disease, avoidance of strenuous exercise is the usual therapy. Defects in earlier steps in glycogen breakdown in the liver cause GSD types III, IV, VI, and IX, which usually lead to milder versions of type I disease. Pompe disease (GSD type II) is discussed in the section Lysosomal storage disorders.

In addition to glycogen degradation, glucose may be manufactured from amino acids and pyruvate in the process of gluconeogenesis. Key enzymes in the gluconeogenic pathway include carboxylase, phosphoenolpyruvate carboxykinase, and fructose-1,6-diphosphatase. Persons with defects in these enzymes develop conditions including fasting hypoglycemia, lactic acidemia, and liver enlargement. Thus, gluconeogenesis disorders may be difficult to distinguish from glycogen storage disorders at first presentation.

Congenital disorders of glycosylation

Congenital disorders of glycosylation (CDG; formerly known as carbohydrate-deficient glycoprotein syndrome) are recently described diseases that affect the brain and many other organs. The primary biochemical defects of CDG are in the N-glycosylation pathway that occurs in the cytoplasm and endoplasmic reticulum, cellular organelles involved in the synthesis of proteins and lipids. A defect in a mannose-processing enzyme, phosphomannomutase 2, causes the most common form of CDG (type I). Other enzymatic defects have been identified, but the biochemical bases of some CDG subtypes have not yet been determined. The classic form of

CDG (type Ia) is characterized by low muscle tone in infancy, severe developmental delay, and brain abnormalities. Children with type Ia also have inverted nipples and an unusual distribution of fat, especially in the suprapubic region and buttocks. Other features include hypoglycemia, seizures, stroke-like episodes, retinal damage, impaired heart contractility, vomiting, liver disease, diarrhea, and a bleeding tendency. No effective therapy exists for CDG, except for the rare type Ib disease (phosphomannose isomerase deficiency), in which oral administration of mannose may reverse symptoms in some cases.

Lipids are large, water-insoluble molecules that have a variety of biological functions, including storing energy and serving as components of cellular membranes and lipoproteins. Cells that line the small intestine absorb dietary lipids and process them into lipoprotein particles that enter the circulation via the lymphatic system for eventual uptake by the liver. Triglycerides, cholesterol, and fat-soluble vitamins are transported through the blood by these lipoprotein particles.

Lipoprotein disorders

The major classes of lipoproteins are chylomicrons, very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). Disorders that affect lipid metabolism may be caused by defects in the structural proteins of lipoprotein particles, in the cell receptors that recognize the various types of lipoproteins, or in the enzymes that break down fats. As a result of such defects, lipids may become deposited in the walls of blood vessels, which can lead to atherosclerosis (a disease characterized by abnormal thickening and hardening of the walls of the arteries).

Familial hypercholesterolemia is an autosomal dominant disease that is caused by the deficiency of the LDL receptor on the surface of cells in the liver and other organs. As a result, cholesterol is not moved into the cells. Under normal conditions, when enough cholesterol is present in the cell, feedback mechanisms signal enzymes to cease cholesterol synthesis. In familial hypercholesterolemia, these enzymes are relieved of feedback inhibition, thus inducing the production of still more cholesterol. The disease is characterized by early coronary vascular disease, strokes, and fatty deposits on the tendons. Blood cholesterol levels are very high from birth, and LDL cholesterol is also elevated. Treatment is by a low-cholesterol diet and drugs that inhibit cholesterol synthesis or increase its excretion in the gastrointestinal tract.

If a person with familial hypercholesterolemia is homozygous for the condition, severe vascular disease starts in early childhood, and heart attacks are usual by the age of 20. Similar symptoms are present in familial dysbetalipoproteinemia (hyperlipoproteinemia type III), which may be inherited as an autosomal recessive or autosomal dominant condition (that is, if the trait has been inherited from both parents). In this disorder, which manifests in adulthood, increased blood cholesterol and triglycerides are present due to an abnormality of a constituent of lipoproteins called apoprotein E. Treatment is similar to that required for familial hypercholesterolemia.

A deficiency of microsomal transfer protein causes abetalipoproteinemia, an autosomal recessive condition characterized by the virtual absence of VLDL and LDL. Triglycerides accumulate in the gastrointestinal tract and liver, and there are low blood levels of cholesterol, HDL cholesterol, and triglycerides. Persons with abetalipoproteinemia have severe fat malabsorption and develop neurological symptoms including unsteady gait, retinal defects, and nerve damage due to the deficiency of vitamin E. During prolonged starvation, the metabolism of fats stored in adipose

tissue is needed for energy production. After the glycogen stores have been depleted, both gluconeogenesis and the production of ketone bodies by liver fatty acid beta-oxidation (or β-oxidation) are essential for providing energy for the brain. The oxidation of fatty acids for energy occurs in the mitochondria of liver cells and requires a carrier molecule, carnitine, which is synthesized in the body and is also obtained from the dietary intake of animal products such as meat, milk, and eggs. Some fatty acid oxidation disorders arise through dysfunction of carnitine transport enzymes, although most of these conditions are caused by fat-degrading enzymes directly involved in the beta-oxidation cycle itself. In individuals with inherited disorders of carnitine transport, a deficiency of carnitine may cause severe brain, liver, and heart damage. Treatment with carnitine is partially effective. Fatty acid oxidation disorders are relatively common and as a group may account for approximately 5 to 10 percent of cases of sudden infant death syndrome (SIDS). The disorders commonly manifest with hypoglycemia, liver disease, decreased muscle tone, and heart failure (cardiomyopathy).

Children with medium-chain acyl-CoA dehydrogenase deficiency (MCAD) appear completely normal, unless they fast for a prolonged period or are faced by other metabolically stressful conditions, such as a severe viral illness. During periods of metabolic stress, affected individuals may develop hypoglycemia, lethargy, vomiting, seizures, and liver dysfunction. Intravenous hydration and glucose must be given in a timely fashion, otherwise the disease can be fatal. However, if hydration and nutrition are monitored closely, children with MCAD lead a relatively normal life. Therapy consists of carnitine administration and avoidance of excessive fat intake. Other fatty acid oxidation disorders may respond to similar therapy, but in general, their prognosis is not as good.

Long-chain 3-hydroxy-acyl-CoA dehydrogenase (LCHAD) deficiency may present with heart failure, hypoglycemia, multi-organ system failure, and retinal pigmentary changes. A fetus with LCHAD deficiency can induce liver disease during pregnancy in a mother who is a heterozygous carrier for the condition. This appears to be due to a combination of the metabolic demands of pregnancy, the lack of enzyme activity in the fetus, and the reduced activity of the enzyme in the mother, causing enough of an imbalance in the usual energy pathways to result in the storage of fat in the maternal liver.

Mitochondrial disorders

The mitochondrial respiratory chain consists of five multi-subunit protein complexes that produce the majority of energy driving cellular reactions. Dysfunction of the respiratory chain leads to decreased energy production and to an increase in the production of toxic reactive oxygen species. In addition, damaged mitochondria release apoptotic factors, which act as signals to induce cell death. Respiratory chain proteins are formed by the concerted action of both nuclear and mitochondrial genes. Therefore, mitochondrial disorders may be inherited in either a Mendelian (autosomal recessive, autosomal dominant, or X-linked) or maternal (mitochondrial) fashion, because mutations may occur in either the nuclear or mitochondrial genome.

The signs and symptoms of mitochondrial disorders are dependent on the severity of the mutation, the percentage of dysfunctional mitochondria, and the energy requirements of the affected tissues. Patients with mitochondrial disorders may present with a bewildering array of symptoms, because any tissue in the body may be affected at any point in an individual's lifetime.

However, prominent involvement of the nervous and muscular systems is common because these tissues are highly dependent on mitochondrial metabolism. Patients often have biochemical markers of underlying disease (for example, an elevated blood lactate level or unusual organic acids in the urine), but some patients have completely normal metabolic screens. Often the diagnosis of mitochondrial disorders requires demonstration of respiratory chain dysfunction by the measurement of complex activities in muscle tissue obtained from a biopsy. So-called muscle ragged red fibres may be seen on microscopic examination and are suggestive of mitochondrial disease, but often are not present and may be seen in other muscle disorders. Sometimes a diagnosis can be made by identifying an mtDNA mutation through molecular diagnostic techniques. However, not all mutations are known, and it is impractical to perform a complete analysis of an individual's mtDNA. Furthermore, because some mitochondrial disorders may be caused by mutations present in the nuclear DNA, screening of nuclear genes that code for mitochondrial respiratory gene subunits ultimately may be necessary to pinpoint the underlying cause of a patient's symptoms; however, such an exhaustive search is not practical.

Defective mitochondrial membrane ion transporters, transmembrane carrier proteins, and intramitochondrial metal homeostasis may also cause mitochondrial disorders. Neurodegenerative disorders including Friedreich ataxia and Wilson disease have been associated with aberrant mitochondrial metal metabolism; impaired iron homeostasis is present in Friedreich ataxia, while copper metabolism is abnormal in Wilson disease. The respiratory chain is affected secondarily in these conditions. Mitochondrial respiratory chain dysfunction also has been theorized to play a role in more common neurodegenerative diseases such as Alzheimer disease, Parkinson disease, Huntington disease, and amyotrophic lateral sclerosis (ALS, or Lou Gehrig disease), as well as in normal aging. However, evidence of the role of mitochondrial dysfunction in these conditions and in normal aging is inconclusive. There is no proven therapy for patients with respiratory chain disorders, though various dietary supplements and cofactors have been tried, and experiments have begun in the area of gene therapy.

Lysosomal storage disorders

Lysosomes are cytoplasmic organelles in which a variety of macromolecules are degraded by different acid hydrolase enzymes. Lysosomal enzymes are coded for by nuclear DNA and are targeted to lysosomes by specific recognition markers. If a lysosomal enzyme is absent or has reduced activity or if enzymes are not correctly targeted to lysosomes, the macromolecules normally degraded by lysosomes will accumulate, causing abnormal storage of various complex compounds including glycolipids, glycosaminoglycans, oligosaccharides, and glycoproteins. Lysosomal storage disorders are autosomal recessive, except for Fabry disease and Hunter syndrome, which are X-linked. Abnormal macromolecule storage leads to a variety of signs and symptoms, depending on where the storage occurs. Some diseases (e.g., Gaucher disease type I) usually affect only peripheral tissues such as the liver, spleen, or bone, others affect only the central nervous system (e.g., Tay-Sachs disease), while yet others affect both brain and systemic organs (e.g., Niemann-Pick disease).

Characteristics of many lysosomal storage disorders include coarsening of facial features, eye abnormalities, enlarged liver and spleen, and bone disease. As a group, these conditions cause severe neurological impairment, often starting in infancy. However, each disease often has a spectrum of severity depending on the degree of enzymatic compromise. For example, although Tay-Sachs disease is often fatal in early childhood, some forms do not present until adulthood.

Most lysosomal storage disorders have no therapy, except for supportive care. The difficulty with most therapies is that they do not enter the brain, because of the presence of the so-called blood-brain barrier. Bone marrow transplantation has been attempted in individuals with lysosomal storage disorders, but overall results have been disappointing. Successful therapy for disorders without central nervous system involvement has been accomplished; Gaucher disease type I, for example, is responsive to enzyme replacement therapy, that is, frequent intravenous infusions of the specific enzyme that is missing in the disorder, and encouraging results have been reported in Fabry disease and Pompe disease (GSD type II). Peroxisomes are cytoplasmic organelles that play a central role in the catabolism of very-long-chain fatty acids and other compounds through the process of beta-oxidation. They also are critical in the biosynthesis of important cellular membrane constituents (plasmalogens), cholesterol, and bile acids. Unlike mitochondria, peroxisomes do not contain DNA, therefore all of the components of their enzyme systems and membrane proteins are coded for by the nucleus. Most peroxisomal disorders exhibit autosomal recessive inheritance, with the exception of the X-linked form of adrenoleukodystrophy. They usually present with severe neurological compromise, but other organ systems—for example, bone and kidneys—may also be affected. No specific treatment exists for these disorders, and nearly all are lethal early in their course.

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