GLYCOGEN METABOLISM & THE OTHER SUGARS

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BIOMEDICAL IMPORTANCE

- Glucose is the highly preferred energy source for the brain, and the mandatory energy source for cells with few or no mitochondria, such as mature erythrocytes.
- **Blood glucose** can be obtained from three primary sources: **the diet**, **degradation of glycogen**, and **gluconeogenesis**.
- **Glycogen** is the major storage form of carbohydrate in animals, corresponding to starch in plants; it **is a branched polymer of a-D-glucose**.
- It occurs mainly in liver and muscle, with limited amounts in the brain.
- Muscle glycogen provides a readily available source of glucose-6-phosphate for glycolysis within the muscle itself.
- Liver glycogen functions as a reserve to maintain the **blood glucose** concentration in the fasting state.

STRUCTURE AND FUNCTION OF GLYCOGEN

- The main stores of glycogen in the body are found in skeletal muscle and liver, although most other cells store small amounts of glycogen for their own use.
- The function of muscle glycogen is to serve as a fuel reserve for the synthesis of adenosine triphosphate (ATP) during muscle contraction.
- That of liver glycogen is to maintain the blood glucose concentration, particularly during the early stages of a fast.
- Glycogen is a branched-chain polysaccharide made exclusively from a-D-glucose.
- The primary glycosidic bond is an a(1→4) linkage. After an average of eight to ten glucosyl residues, there is a branch containing an a(1→6) linkage.

SYNTHESIS OF GLYCOGEN (GLYCOGENESIS)

- Glycogen is synthesized from molecules of a-D-glucose.
- The process occurs in the cytosol, and requires energy supplied by ATP (for the phosphorylation of glucose) and uridine triphosphate (UTP).
- a-D-Glucose attached to uridine diphosphate (UDP) is the source of all the glucosyl residues that are added to the growing glycogen molecule.
- UDP-glucose is synthesized from glucose 1-phosphate and UTP by UDP-glucose pyrophosphorylase (glucose-1-phosphate uridylyltransferase).
- Glucose 1-phosphate is produced from glucose 6-phosphate by phosphoglucomutase.

Synthesis of a primer is needed to initiate glycogen synthesis

- Glycogen synthase is responsible for making the α(1→4) linkages in glycogen.
- This enzyme can only elongate already existing chains of glucose.
- In the absence of a glycogen fragment, a protein, called **glycogenin (priming glucosyltransferase)**, can serve as an acceptor of glucose residues from UDP-glucose.
- The side chain hydroxyl group of a specific **tyrosine** serves as the site at which the initial glucosyl unit is attached.
- The reaction is catalyzed by glycogenin itself via autoglucosylation.
- Glycogenin then catalyzes the transfer of the next few molecules of glucose from UDP-glucose, producing a short, α(1→4)-linked glucosyl chain.

Elongation of glycogen chains is performed by glycogen synthase

- Elongation of a glycogen chain involves the transfer of glucose from UDP-glucose to the non-reducing end of the growing chain, forming a new glycosidic bond between the anomeric hydroxyl of carbon 1 of the activated glucose and carbon 4 of the accepting glucosyl residue.
- The enzyme responsible for making the a(1→4) linkages in glycogen is **glycogen synthase**.
- *The **non-reducing end** of a carbohydrate chain is one in which the anomeric carbon of the terminal sugar is linked by a glycosidic bond to another compound, making the terminal sugar non-reducing.*

Formation of branches in glycogen molecule

- Branches are made by the action of the branching enzyme, amylo-α(1→4) → α(1→6)-transglucosidase.
- This enzyme removes a chain of six to eight glucosyl residues from the non-reducing end of the glycogen chain, breaking an α(1→4) bond to another residue on the chain, and attaches it to a non-terminal glucosyl residue by an α(1→6) linkage (4:6 transferase).
- After elongation of these two ends has been accomplished by glycogen synthase, their terminal six to eight glucosyl residues can be removed and used to make additional branches.

DEGRADATION OF GLYCOGEN (GLYCOGENOLYSIS)

- The degradative pathway that mobilizes stored glycogen in liver and skeletal muscle is not a reversal of the synthetic reactions.
- Instead, a separate set of cytosolic enzymes is required.
- When glycogen is degraded, the primary product is glucose 1-phosphate, obtained by breaking a(1→4) glycosidic bonds.
- In addition, free glucose is released from each a(1→6)-linked glucosyl residue.

Shortening of chains is performed by glycogen phosphorylase

- **Glycogen phosphorylase** sequentially cleaves the a(1→4) glycosidic bonds between the glucosyl residues at the non-reducing ends of the glycogen chains by simple phosphorolysis (**producing glucose 1-phosphate**) until four glucosyl units remain on each chain before a branch point.
- The resulting structure is called a limit dextrin, and phosphorylase cannot degrade it any further.
- This enzyme contains a molecule of covalently bound **pyridoxal phosphate** (PLP) that is required as a coenzyme.

Removal of branches

- Branches are removed by the two enzymic activities of a single bifunctional protein, **the debranching enzyme**.
- First, oligo-a(1→4)→a(1→4)-**glucan transferase activity** removes the outer three of the four glucosyl residues attached at a branch.
- It next transfers them to the non-reducing end of another chain, lengthening it accordingly.
- Therefore, an a(1→4) bond is broken and an a(1→4) bond is made, and the enzyme functions as a 4:4 transferase.
- Next, the remaining single glucose residue attached in an a(1→6) linkage is removed hydrolytically by **amylo-a(1→6)-glucosidase** activity, releasing **free glucose**.
- The glucosyl chain is now available again for degradation by glycogen phosphorylase until four glucosyl units from the next branch are reached.

Conversion of glucose 1-phosphate to glucose 6-phosphate by phosphoglucomutase

- Glucose 1-phosphate, produced by glycogen phosphorylase, is converted in the cytosol to glucose 6-phosphate by phosphoglucomutase.
- In the liver, glucose 6-phosphate is transported into the endoplasmic reticulum (ER) by glucose 6-phosphate translocase.
- There it is converted to glucose by **glucose 6-phosphatase**.
- The glucose then moves from the ER to the cytosol.
- Hepatocytes release glycogen-derived glucose into the blood to help maintain blood glucose levels until the gluconeogenic pathway is actively producing glucose.
- **In the muscle, glucose 6-phosphate cannot be dephosphorylated because of a lack of glucose 6-phosphatase.** Instead, it enters glycolysis, providing energy needed for muscle contraction.

Lysosomal degradation of glycogen

- A small amount (1–3%) of glycogen is continuously degraded by the lysosomal enzyme, α(1→4)-glucosidase (**acid maltase**).
- This may be especially important in glucose homeostasis in neonates.
- However, a deficiency of this enzyme causes accumulation of glycogen in vacuoles in the lysosomes, resulting in the serious glycogen storage disease Type II: **Pompe disease**.
- *Type II: Pompe disease is the only glycogen storage disease that is a lysosomal storage disease.*

REGULATION OF GLYCOGEN SYNTHESIS AND DEGRADATION

- In the liver, glycogenesis accelerates during periods when the body has been well fed, whereas glycogenolysis accelerates during periods of fasting.
- In skeletal muscle, glycogenolysis occurs during active exercise, and glycogenesis begins as soon as the muscle is again at rest.
- Regulation of glycogen synthesis and degradation is accomplished on two levels.
  - First, glycogen synthase and glycogen phosphorylase are **hormonally** regulated to meet the needs of the body as a whole.
  - Second, the pathways of glycogen synthesis and degradation are **allosterically** controlled to meet the needs of a particular tissue (liver/muscle).

Activation of glycogen degradation by cAMP-directed pathway through hormones

- The binding of hormones, such as **glucagon or epinephrine**, to plasma membrane G protein-coupled receptors signals the need for glycogen to be degraded—either to **elevate blood glucose levels** or to **provide energy for exercising muscle**.
- Activation of protein kinase A
- Activation of phosphorylase kinase
  - Phosphorylase kinase exists in two forms: an inactive "b" form and an active "a" form.
- Activation of glycogen phosphorylase
  - Glycogen phosphorylase also exists in two forms: the dephosphorylated, inactive "b" form and the phosphorylated, active "a" form.
- The cascade of reactions listed above results in **glycogenolysis**.
- The large number of sequential steps serves to **amplify the effect of the hormonal signal**.

Inhibition of glycogen synthesis by a cAMP-directed pathway

- The regulated enzyme in glycogenesis is glycogen synthase.
- It also exists in two forms, the active "a" form and the inactive "b" form.
- However, for glycogen synthase, *in contrast to phosphorylase kinase and glycogen phosphorylase*, **the active form is dephosphorylated whereas the inactive form is phosphorylated**.
- Glycogen synthase a is converted to the inactive "b" form by phosphorylation at several sites on the enzyme, with the level of inactivation proportional to its degree of phosphorylation.
- This conversion process is catalyzed by several different protein kinases that are regulated by cAMP or other signaling mechanisms.

Allosteric regulation of glycogen synthesis and degradation

- Glycogenesis is stimulated when substrate availability and energy levels are high, whereas glycogenolysis is increased when glucose and energy levels are low.
- In the well-fed state, glycogen synthase b in both liver and muscle is allosterically activated by glucose 6-phosphate which is present in elevated concentrations.
- In contrast, glycogen phosphorylase a is allosterically inhibited by glucose 6-phosphate, as well as by ATP, a high-energy signal in the cell.
- In liver, *but not muscle*, free glucose is also an allosteric inhibitor of glycogen phosphorylase a, making it a better substrate for protein phosphatase-1.

Activation of glycogen degradation by calcium ions

- Ca^{2+} is released into the cytoplasm in muscle in response to neural stimulation and in liver in response to epinephrine binding to a1-adrenergic receptors.
  - In **muscle**, during contraction nerve impulses cause membrane depolarization, which promotes Ca^{2+} release from the sarcoplasmic reticulum into the sarcoplasm of myocytes.
  - The Ca^{2+} binds calmodulin and the complex activates muscle phosphorylase kinase b.
  - Binding of epinephrine to **hepatocyte** a-adrenergic G protein-coupled receptors activates a phospholipid-dependent cascade that results in movement of Ca^{2+} from the ER into the cytoplasm.
  - A Ca^{2+}-calmodulin complex forms and activates hepatic phosphorylase kinase b.

Activation of glycogen degradation in muscle by AMP

- Muscle glycogen phosphorylase is active in the presence of the high AMP concentrations that occur in the muscle under extreme conditions of anoxia and ATP depletion.
- AMP binds to glycogen phosphorylase b, causing its activation without phosphorylation.

GLYCOGEN STORAGE DISEASES

- These are a group of genetic diseases that result from a defect in an enzyme required for glycogen synthesis or degradation.
- They result either in formation of glycogen that has an abnormal structure, or in the accumulation of excessive amounts of normal glycogen in specific tissues as a result of impaired degradation.
- The severity of the glycogen storage diseases ranges from fatal in infancy to mild disorders that are not life-threatening.
- Glycogen storage diseases (GSD) are listed in the table given in the next slide.

GLYCOGEN STORAGE DISEASES

Type	Name	Enzyme Deficiency	Clinical Features
0	—	Glycogen synthase	Hypoglycemia; hyperketonemia; early death
Ia	Von Gierke's disease	Glucose 6-phosphatase	Glycogen accumulation in liver and renal tubule cells; hypoglycemia; lactic acidemia; ketosis; hyperlipemia
Ib	—	Endoplasmic reticulum glucose 6-phosphate transporter	As type Ia; neutropenia and impaired neutrophil function leading to recurrent infections
II	Pompe's disease	Lysosomal $\alpha_1 \rightarrow 4$ and $\alpha_1 \rightarrow 6$ glucosidase (acid maltase)	Accumulation of glycogen in lysosomes: juvenile onset variant, muscle hypotonia, death from heart failure by age 2; adult onset variant, muscle dystrophy
IIIa	Limit dextrinosis, Forbe's or Cori's disease	Liver and muscle debranching enzyme	Fasting hypoglycemia; hepatomegaly in infancy; accumulation of characteristic branched polysaccharide (limit dextrin); muscle weakness
IIIb	Limit dextrinosis	Liver debranching enzyme	As type IIIa, but no muscle weakness
IV	Amylopectinosis, Andersen's disease	Branching enzyme	Hepatosplenomegaly; accumulation of polysaccharide with few branch points; death from heart or liver failure before age 5
V	Myophosphorylase deficiency, McArdle's syndrome	Muscle phosphorylase	Poor exercise tolerance; muscle glycogen abnormally high (2.5%–4%); blood lactate very low after exercise
VI	Hers' disease	Liver phosphorylase	Hepatomegaly; accumulation of glycogen in liver; mild hypoglycemia; generally good prognosis
VII	Tarui's disease	Muscle and erythrocyte phosphofructokinase 1	Poor exercise tolerance; muscle glycogen abnormally high (2.5%–4%); blood lactate very low after exercise; also hemolytic anemia
VIII		Liver phosphorylase kinase	Hepatomegaly; accumulation of glycogen in liver; mild hypoglycemia; generally good prognosis
IX		Liver and muscle phosphorylase kinase	Hepatomegaly; accumulation of glycogen in liver and muscle; mild hypoglycemia; generally good prognosis
X		cAMP-dependent protein kinase A	Hepatomegaly; accumulation of glycogen in liver

Harper's Illustrated Biochemistry, 29e

OTHER HEXOSES METABOLISM

- Glucose, fructose, and galactose are the main hexoses absorbed from the gastrointestinal tract, derived from dietary starch, sucrose, and lactose, respectively.
- Fructose and galactose can be converted to glucose, mainly in the liver.

FRUCTOSE METABOLISM

- About 10% of the calories contained in the Western diet are supplied by fructose (approximately 55 g/day).
- The major source of fructose is the disaccharide sucrose, which, when cleaved in the intestine, releases equimolar amounts of fructose and glucose.
- Fructose is also found as a free monosaccharide in many fruits, in honey, and in high-fructose corn syrup (55% fructose/45% glucose typically), which is used to sweeten soft drinks and many foods.
- Entry of fructose into cells is not insulin dependent (unlike that of glucose into certain tissues like muscle and adipose tissue), and, in contrast to glucose, fructose does not promote the secretion of insulin.

- For fructose to enter the pathways of intermediary metabolism, it must first be phosphorylated.
- This can be accomplished by either hexokinase or **fructokinase**.
- Hexokinase phosphorylates glucose in most cells of the body, and several additional hexoses can serve as substrates for this enzyme.
- However, it has a low affinity (that is, a high Km) for fructose.
- Fructokinase provides the primary mechanism for fructose phosphorylation.
- It is found in the liver (which processes most of the dietary fructose), kidney, and the small intestinal mucosa, and converts fructose to fructose 1-phosphate, using ATP as the phosphate donor.

- Fructose 1-phosphate is cleaved by *aldolase B* (also called *fructose 1-phosphate aldolase*) to dihydroxyacetone phosphate (DHAP) and glyceraldehyde.
- DHAP can directly enter glycolysis or gluconeogenesis, whereas glyceraldehyde can be metabolized by a number of pathways.
- The rate of fructose metabolism is more rapid than that of glucose because the trioses formed from fructose 1-phosphate bypass phosphofructokinase-1 step.

Conversion of mannose to fructose 6-phosphate

- Mannose, the C-2 epimer of glucose, is an important component of glycoproteins.
- *Hexokinase* phosphorylates mannose, producing mannose 6-phosphate, which, in turn, is (reversibly) isomerized to fructose 6-phosphate by *phosphomannose isomerase*.

Conversion of glucose to fructose via sorbitol

- Most sugars are rapidly phosphorylated following their entry into cells.
- They are thereby trapped within the cells, because organic phosphates cannot freely cross membranes without specific transporters.
- An alternative mechanism for metabolizing a monosaccharide is to convert it to a polyol (sugar alcohol) by the reduction of an aldehyde group, by that producing an additional hydroxyl group.

Synthesis of sorbitol

- **Aldose reductase** reduces glucose, producing sorbitol.
- This enzyme is found in many tissues, including the lens, retina, Schwann cells of peripheral nerves, liver, kidney, placenta, red blood cells, and in cells of the ovaries and seminal vesicles.
- In cells of the liver, ovaries, and seminal vesicles, there is a second enzyme, **sorbitol dehydrogenase**, which can oxidize the sorbitol to produce fructose.

The effect of hyperglycemia on sorbitol metabolism

- Elevated intracellular glucose concentrations and an adequate supply of NADPH cause aldose reductase to produce a significant increase in the amount of sorbitol, which cannot pass efficiently through cell membranes and, thus, remains trapped inside the cell.
- This is aggravated when sorbitol dehydrogenase is low or absent, for example, in retina, lens, kidney, and nerve cells.
- As a result, sorbitol accumulates in these cells, causing strong osmotic effects and, therefore, cell swelling as a result of water retention.

GALACTOSE METABOLISM

- The major dietary source of galactose is lactose (galactosyl β-1,4-glucose) obtained from milk and milk products.
- Some galactose can also be obtained by lysosomal degradation of complex carbohydrates, such as glycoproteins and glycolipids, which are important membrane components.
- Like fructose, the entry of galactose into cells is not insulin-dependent.
- Like other hexoses, galactose must be phosphorylated before it can be further metabolized.
- Most tissues have a specific enzyme for this purpose, called **galactokinase**, which produces galactose 1-phosphate.
- As with other kinases, ATP is the phosphate donor.

LACTOSE SYNTHESIS

- Lactose is a disaccharide that consists of a molecule of β-galactose attached by a β(1→4) linkage to glucose.
- Lactose is synthesized in the Golgi (in **lactating mammary glands**) by **lactose synthase** (UDP-galactose:glucose galactosyltransferase), which transfers galactose from UDP-galactose to glucose, releasing UDP.

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