Carbohydrate Metabolism

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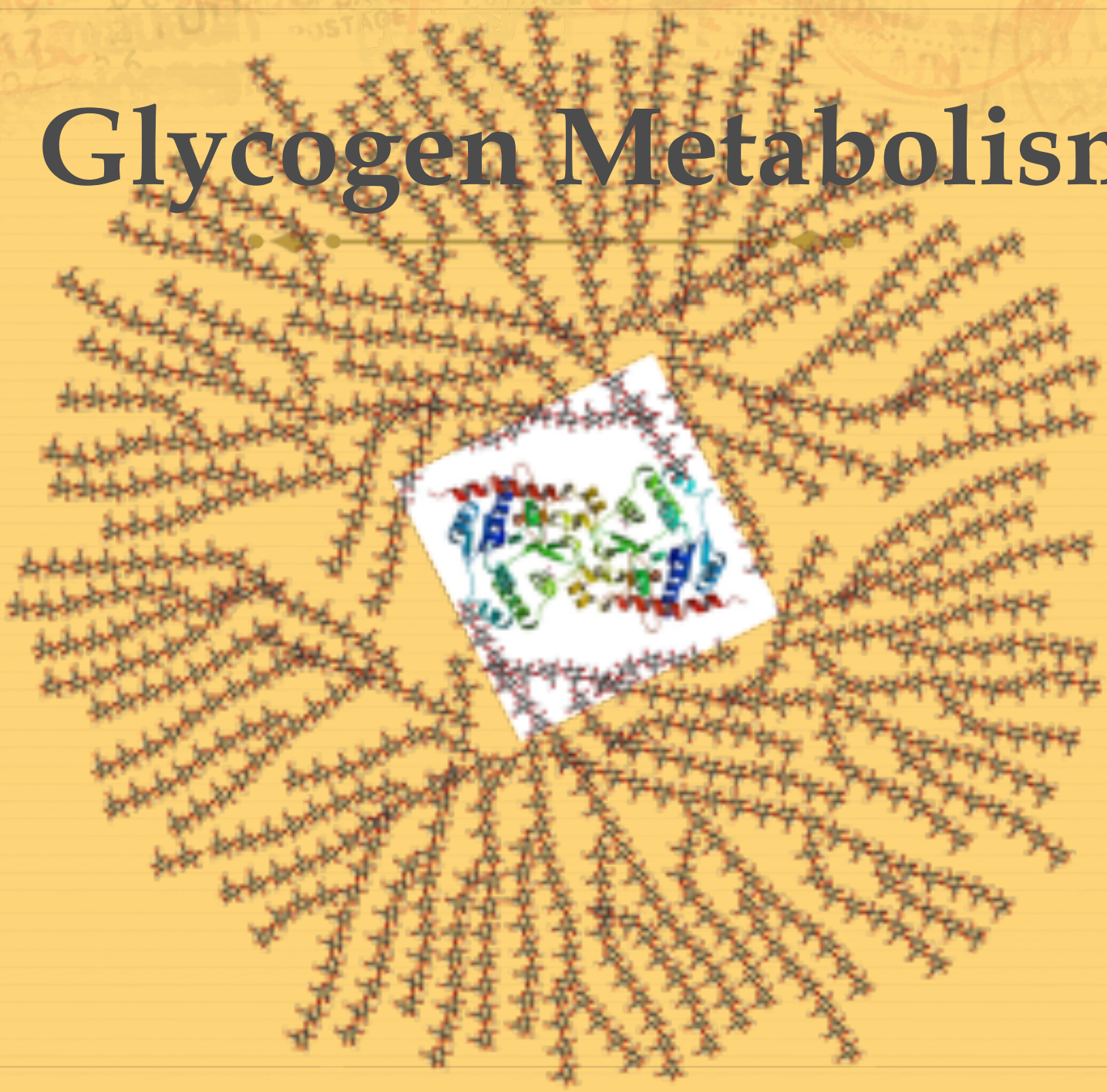
Glycogen Metabolism



Glycogen Metabolism

- A constant source of blood glucose is an absolute requirement for human life.
- Glucose is the greatly preferred energy source for the brain, and the required energy source for cells with few or no mitochondria, such as mature erythrocytes.
- Glucose is also essential as an energy source for exercising muscle, where it is the substrate for anaerobic glycolysis.

Glycogen Metabolism

- Blood glucose can be obtained from three primary sources:
  - ✓ the diet,
  - ✓ degradation of glycogen
  - ✓ gluconeogenesis.

Glycogen Metabolism

- **Diet**

Dietary intake of glucose and glucose precursors, such as starch, monosaccharides, and disaccharides, is sporadic and, depending on the diet, is not always a reliable source of blood glucose.

- **Gluconeogenesis**

In contrast, gluconeogenesis can provide sustained synthesis of glucose, but it is somewhat slow in responding to a falling blood glucose level.

Therefore, the body has developed mechanisms for storing a supply of glucose in a rapidly mobilizable form, namely, glycogen.

Glycogen Metabolism

- **Glycogen degradation**

In the absence of a dietary source of glucose, this sugar is rapidly released from liver and kidney glycogen.

Similarly, muscle glycogen is extensively degraded in exercising muscle to provide that tissue with an important energy source.

WHAT IS THE 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.
- The function of liver glycogen is to maintain the blood glucose concentration, particularly during the early stages of a fast.

A. Amounts of liver and muscle glycogen

- 400 g of glycogen make up 1–2% of the fresh weight of resting muscle,
- 100 g of glycogen make up to 10% of the fresh weight of a well-fed adult liver.
- What limits the production of glycogen at these levels is not clear.
- However, in some glycogen storage diseases, the amount of glycogen in the liver and/or muscle can be significantly higher.

B. Structure of glycogen

- Glycogen is a branched-chain polysaccharide made exclusively from α-D-glucose.
- The primary glycosidic bond is an α(1→4) linkage.
- After an average of eight to ten glucosyl residues, there is a branch containing an α(1→6) linkage.
- A single molecule of glycogen can have a molecular mass of up to 108 daltons.
- These molecules exist in discrete cytoplasmic granules that also contain most of the enzymes necessary for glycogen synthesis and degrada- tion.

C. Fluctuation of glycogen stores

- During the well-fed state liver glycogen stores ↑, and are depleted ↓ during a fast.
- Muscle glycogen is not affected by short periods of fasting (a few days) and is only moderately decreased in prolonged fasting (weeks).
- Muscle glycogen is synthesized to replenish muscle stores after they have been depleted following strenuous exercise.

!!!!!

- Glycogen synthesis and degradation are cytosolic processes that go on continuously.
- The differences between the rates of these two processes determine the levels of stored glycogen during specific physiologic states.

GLYCOGENESIS (SYNTHESIS OF GLYCOGEN)

- Glycogen is synthesized from molecules of α-D-glucose !!!
- The process occurs in the cytosol, and requires energy supplied by ATP (for the phosphorylation of glucose) and uridine triphosphate (UTP).

A. Synthesis of UDP-glucose

- α-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 .

B. Synthesis of a primer to initiate glycogen synthesis

- Glycogen synthase is responsible for making the $\alpha(1\rightarrow4)$ linkages in glycogen.
- This enzyme can not initiate chain synthesis using free glucose as an acceptor of a molecule of glucose from UDP-glucose. Instead, it can only elongate already existing chains of glucose.
- Therefore, a fragment of glycogen can serve as a **primer** in cells whose glycogen stores are not totally depleted.

B. Synthesis of a primer to initiate glycogen synthesis

- In the absence of a glycogen fragment, a protein, called glycogenin, 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; thus, glycogenin is an enzyme. Glycogenin then catalyzes the transfer of the next few molecules of glucose from UDP-glucose, producing a short, $\alpha(1\rightarrow4)$- linked glucosyl chain. This short chain serves as a primer that is able to be elongated by glycogen synthase as described below [Note: Glycogenin stays associated with and forms the core of a glycogen granule.]

C. Elongation of glycogen chains by glycogen synthase

- Elongation of a glycogen chain involves the transfer of glucose from UDP-glucose to the nonreducing 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 $\alpha(1\rightarrow4)$ linkages in glycogen is glycogen synthase.

D. Formation of branches in glycogen

- If no other synthetic enzyme acted on the chain, the resulting structure would be a linear (unbranched) molecule of glucosyl residues attached by $\alpha(1\rightarrow4)$ linkages*.
- In contrast, glycogen has branches located, on average, eight glucosyl residues apart, resulting in a highly branched, tree-like structure that is far more soluble than the unbranched amylose. Branching also increases the number of nonreducing ends to which new glucosyl residues can be added, thereby greatly accelerating the rate at which glycogen synthesis can occur, and dramatically increasing the size of the molecule.

D. Formation of branches in glycogen

1. **Synthesis of branches:** Branches are made by the action of the branching enzyme, amylo-$\alpha(1\rightarrow4) \rightarrow \alpha(1\rightarrow6)$-transglucosidase.
   This enzyme removes a chain of six to eight glucosyl residues from the nonreducing end of the glycogen chain, breaking an $\alpha(1\rightarrow4)$ bond to another residue on the chain, and attaches it to a non-terminal glucosyl residue by an $\alpha(1\rightarrow6)$ linkage, thus functioning as a 4:6 transferase.

D. Formation of branches in glycogen

2. Synthesis of additional branches: 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.

GLYCOGENOLYSIS (DEGRADATION OF GLYCOGEN)

- 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 $\alpha(1\rightarrow4)$ glycosidic bonds.
- In addition, free glucose is released from each $\alpha(1\rightarrow6)$-linked glucosyl residue.

A. Shortening of chains

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

B. Removal of branches

- Branches are removed by the two enzymatic activities of a single bifunctional protein, "the debranching enzyme".

1. oligo-α(1→4)→α(1→4)-glucan transferase activity removes the outer three of the four glucosyl residues attached at a branch.

It next transfers them to the nonreducing end of another chain, lengthening it accordingly. Thus, an α(1→4) bond is broken and an α(1→4) bond is made, and the enzyme functions as a 4:4 transferase.

2. The remaining single glucose residue attached in an α(1→6) linkage is removed hydrolytically by amylo-α(1→6)-glucosidase activity, releasing free glucose.

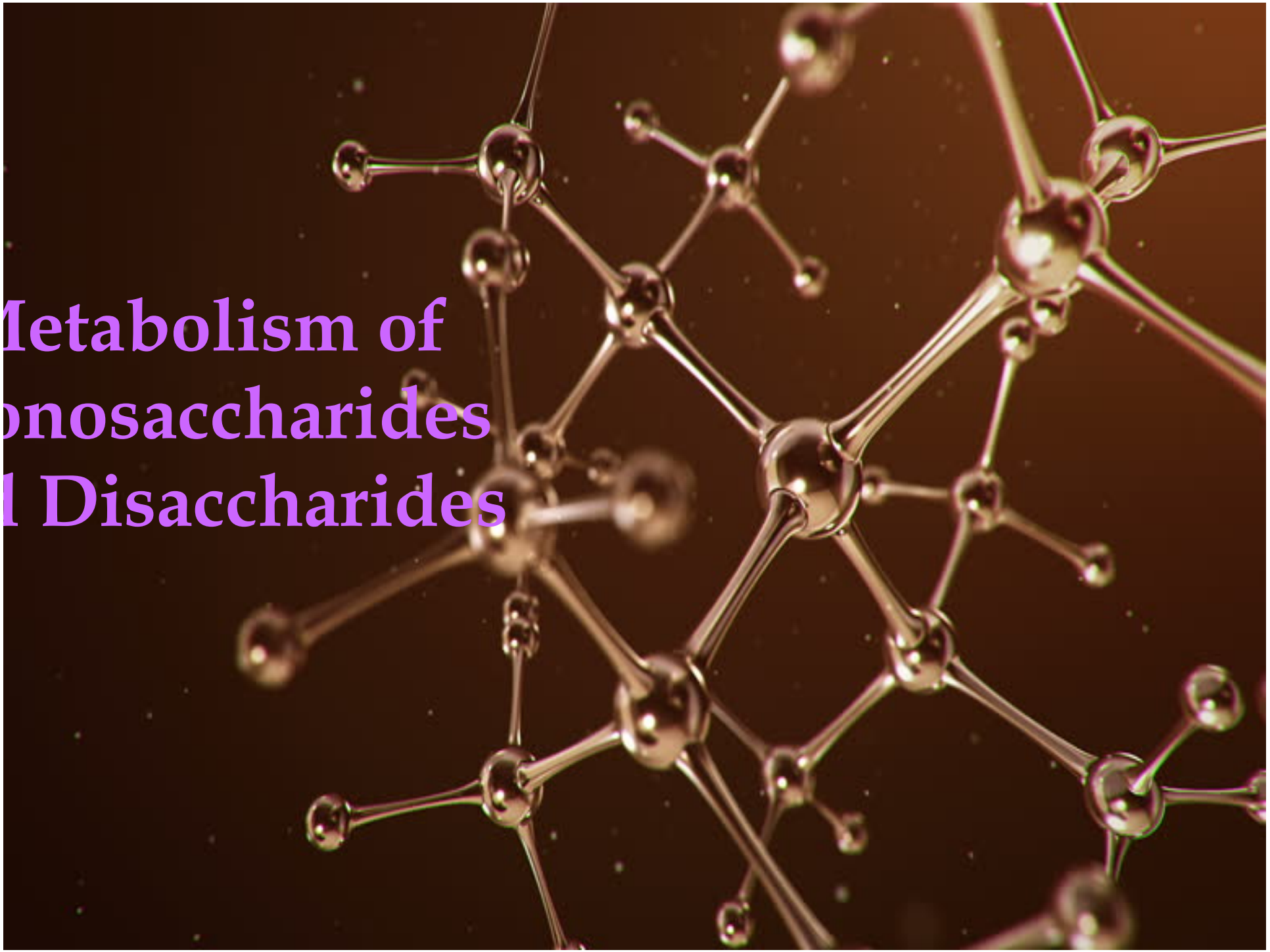
The glucosyl chain is now available again for degradation by glycogen phosphorylase until four glucosyl units from the next branch are reached.

C. Conversion of glucose 1-phosphate to glucose 6-phosphate

- Glucose 1-phosphate, produced by glycogen phosphorylase, is converted in the cytosol to glucose 6-phosphate by phosphogluco-mutase—a reaction that produces glucose 1,6-bisphosphate as a temporary but essential intermediate.
- 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 same enzyme used in the last step of gluconeogenesis.
- 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!!.

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.
- A particular enzyme may be defective in a single tissue, such as liver (resulting in hypoglycemia) or muscle (muscle weakness), or the defect may be more generalized, affecting liver, muscle, kidney, intestine, and myocardium.
- The severity of the glycogen storage diseases (GSDs) ranges from fatal in infancy to mild disorders that are not life-threatening.


Metabolism of
onosaccharides
l Disaccharides

- Glucose is the most common monosaccharide consumed by humans, and we have discussed its metabolism previous.
- However, two other monosaccharides—fructose and galactose—occur in significant amounts in the diet (primarily in disaccharides), and make important contributions to energy metabolism.
- In addition, galactose is an important component of cell structural carbohydrates.

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), and, in contrast to glucose, fructose does not promote the secretion of insulin.

A. Phosphorylation of fructose

- For fructose to enter the pathways of intermediary metabolism, it must first be phosphorylated.
- This can be accomplished by either hexokinase or fructokinase (also called ketohexokinase).
- 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.
- Therefore, unless the intracellular concentration of fructose becomes unusually high, the normal presence of saturating concentrations of glucose means that little fructose is converted to fructose 6-phosphate by hexokinase.
- Fructokinase provides the pri- mary mechanism for fructose phosphorylation. It is found in the liver, kidney, and the small intestinal mucosa, and converts fructose to fructose 1-phosphate, using ATP as the phosphate donor.

B. Cleavage of fructose 1-phosphate

- Fructose 1-phosphate is not phosphorylated to fructose 1,6-bis-phosphate as is fructose 6-phosphate , but is cleaved by *aldolase B* (also called *fructose 1-phosphate aldolase*) to dihydroxyacetone phosphate (DHAP) and glyceraldehyde.

- Humans express 3 *aldolases*, *A*, *B* and *C*, the products of three different genes.

Aldolase A (found in most tissues),
Aldolase B (in liver), and
Aldolase C (in brain) all cleave fructose 1,6-bisphosphate produced during glycolysis to DHAP and glyceraldehyde 3-phosphate.

!!! Only *aldolase B* cleaves fructose 1-phosphate.

DHAP can directly enter glycolysis or gluconeogenesis, whereas glyceraldehyde can be metabolized by a number of pathways.

C. Kinetics of fructose metabolism

- The rate of fructose metabolism is more rapid than that of glucose because the trioses formed from fructose 1-phosphate bypass *phosphofructokinase-1* – the major rate-limiting step in glycolysis.

D. Disorders of fructose metabolism

- A deficiency of one of the key enzymes required for the entry of fructose into intermediary metabolic pathways can result in either a benign condition as a result of;

- ✓ ***fructokinase* deficiency** (essential fructosuria),
- ✓ A severe disturbance of liver and kidney metabolism as a result of ***aldolase B* deficiency** (**hereditary fructose intolerance, HFI**),

III. 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.

III. GALACTOSE METABOLISM

A. Phosphorylation of galactose

- Like fructose, galactose must be phosphorylated before it can be further metabolized.
- Most tissues have a specific enzyme for this purpose, galactokinase, which produces galactose 1-phosphate. As with other kinases, ATP is the phosphate donor.

III. GALACTOSE METABOLISM

B. Formation of UDP-galactose

- Galactose 1-phosphate cannot enter the glycolytic pathway unless it is first converted to UDP-galactose.
- This occurs in an exchange reaction, in which UDP-glucose reacts with galactose 1-phosphate, producing UDP-galactose and glucose 1-phosphate.
- The enzyme that catalyzes this reaction is galactose 1-phosphate uridyltransferase (GALT).

C. Use of UDP-galactose as a carbon source for glycolysis or gluconeogenesis

- For UDP-galactose to enter the mainstream of glucose metabolism, it must first be converted to its C-4 epimer, UDP-glucose, by UDP- hexose 4-epimerase.
- This "new" UDP-glucose (produced from the original UDP-galactose) can then participate in many biosynthetic reactions.

D. Role of UDP-galactose in biosynthetic reactions

- UDP-galactose can serve as the donor of galactose units in a number of synthetic pathways, including synthesis of lactose, glycoproteins, glycolipids, and glycosaminoglycans.
- If galactose is not provided by the diet (for example, when it cannot be released from lactose as a result of a lack of *β-galactosidase* in people who are lactose-intolerant), all tissue requirements for UDP-galactose can be met by the action of *UDP-hexose 4-epimerase* on UDP-glucose, which is efficiently produced from glucose 1-phosphate.

E. Disorders of galactose metabolism

- *GALT* is deficient in individuals with classic galactosemia. In this disorder, galactose 1-phosphate and, therefore, galactose accumulate in cells. Physiologic consequences are similar to those found in hereditary fructose intolerance, but a broader spectrum of tissues is affected. The accumulated galactose is shunted into side pathways such as that of galactitol production.
- This reaction is catalyzed by aldose reductase, the same enzyme that converts glucose to sorbitol.
- A deficiency in galactokinase results in a less severe disorder of galactosemia metabolism, although cataracts are common.

LACTOSE SYNTHESIS

- Lactose is a disaccharide that consists of a molecule of β -galactose attached by a β (1→4) linkage to glucose.
- Lactose, known as the "milk sugar," is produced by the mammary glands of most mammals. Therefore, milk and other dairy products are the dietary sources of lactose.
- Lactose is synthesized in the Golgi by lactose synthase, which transfers galactose from UDP-galactose to glucose, releasing UDP.

Pentose Phosphate Pathway and NADPH

- The pentose phosphate pathway (also called the hexose monophosphate pathway, or 6-phosphogluconate pathway) occurs in the cytosol of the cell.
- It includes two, irreversible oxidative reactions, followed by a series of reversible sugar–phosphate interconversions.
- No ATP is directly consumed or produced in the cycle.
- Carbon 1 of glucose 6-phosphate is released as CO_2, and two NADPH are produced for each glucose 6-phosphate molecule entering the oxidative part of the pathway.

Pentose Phosphate Pathway and NADPH

- The rate and direction of the reversible reactions of the pentose phosphate pathway are determined by the supply of and demand for intermediates of the cycle.

What is The Function of Pentose Phosphate Pathway ??

- ✓ The pathway provides a major portion of the body's NADPH, which functions as a biochemical reductant.
- ✓ It also produces ribose 5-phosphate, required for the biosynthesis of nucleotides,
- ✓ Provides a mechanism for the metabolic use of five-carbon sugars obtained from the diet or the degra- dation of structural carbohydrates in the body.

IRREVERSIBLE OXIDATIVE REACTIONS

- The oxidative portion of the pentose phosphate pathway consists of three reactions that lead to the formation of

1. ribulose 5-phosphate,
2. CO_2
3. 2 molecules of NADPH for each molecule of glucose 6-phosphate oxidized.

- This portion of the pathway is particularly important in the liver, lactating mammary glands, and adipose, which are active in the NADPH-dependent biosynthesis of fatty acids, in the testes, ovaries, placenta and adrenal cortex, which are active in the NADPH-dependent biosynthesis of steroid hormones, and in erythrocytes, which require NADPH to keep glutathione reduced.

Irreversible Oxidative Reactions

A. Dehydrogenation of glucose 6-phosphate

- Glucose 6-phosphate dehydrogenase (G6PD) catalyzes an irreversible oxidation of glucose 6-phosphate to 6-phosphogluconolactone in a reaction that is specific for NADP+ as its coenzyme.
- The pentose phosphate pathway is regulated primarily at the G6PD reaction !!!
- NADPH is a potent competitive inhibitor of the enzyme, and, under most metabolic conditions, the ratio of NADPH/NADP+ is sufficiently high to substantially inhibit enzyme activity.
- However, with increased demand for NADPH, the ratio of NADPH/ NADP+ decreases and flux through the cycle increases in response to the enhanced activity of G6PD.
- Insulin upregulates expression of the gene for G6PD, and flux through the pathway increases in the well-fed state.

Irreversible Oxidative Reactions

B. Formation of ribulose 5-phosphate

- 6-Phosphogluconolactone is hydrolyzed by 6-phosphogluconolactone hydrolase.
- The reaction is irreversible and not rate-limiting.
- The oxidative decarboxylation of the product, 6-phosphogluconate is catalyzed by 6-phosphogluconate dehydrogenase.
- This irreversible reaction produces a pentose sugar–phosphate (ribulose 5-phosphate), CO_2 (from carbon 1 of glucose), and a second molecule of NADPH.

Reversible Nonoxidative Reactions

The nonoxidative reactions of the pentose phosphate pathway occur in all cell types synthesizing nucleotides and nucleic acids.

These reactions catalyze the interconversion of sugars containing three to seven carbons.

These reversible reactions permit ribulose 5-phosphate (produced by the oxidative portion of the pathway) to be converted either to ribose 5-phosphate (needed for nucleotide synthesis) or to intermediates of glycolysis—fructose 6-phosphate and glyceraldehyde 3-phosphate.

Uses of NADPH

- The coenzyme NADP+ differs from NAD+ only by the presence of a phosphate group on one of the ribose units.
- This seemingly small change in structure allows NADP+ to interact with NADP+- specific enzymes that have unique roles in the cell.
- For example, in the cytosol of hepatocytes the steady-state ratio of NADP+/NADPH is approximately 0.1, which favors the use of NADPH in reductive biosynthetic reactions.
- This contrasts with the high ratio of NAD+/NADH (approximately 1000), which favors an oxidative role for NAD+.

Uses of NADPH

- ✓ **A. Reductive biosynthesis**: NADPH can be thought of as a high-energy molecule, much in the same way as NADH.
  However, the electrons of NADPH are destined for use in reductive biosynthesis, rather than for transfer to oxygen as is the case with NADH. Thus, in the metabolic transformations of the pentose phosphate pathway, part of the energy of glucose 6-phosphate is conserved in NADPH—a molecule with a negative reduction potential that, therefore, can be used in reactions requiring an electron donor.
- ✓ **B. Reduction of hydrogen peroxide**
- ✓ **Cytochrome P450 monooxygenase system**
- ✓ **Phagocytosis by white blood cells**
- ✓ **Synthesis of nitric oxide**

THANKS FOR LISTENING, ANY QUESTIONS?

References

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