

ii. Carbohydrate chemistry and metabolism...

ii. Carbohydrate chemistry and metabolism, Disorders associated with carbohydrate metabolism

Carbohydrate Chemistry

Classification and Structure

1. Monosaccharides

- **Definition:** Simple sugars with general formula $(\text{CH}_2\text{O})_n$. The most common biologically relevant forms range from 3 to 7 carbons (trioses, tetroses, pentoses, hexoses, heptoses).
- **Examples:** Glucose (aldohexose), fructose (ketohexose), galactose (aldohexose), ribose (aldopentose).
- **Stereochemistry:** Existence of chiral centers leads to D- and L-forms. In nature, **D-configuration** predominates for sugars.
- **Ring Formation:** Hexoses typically cyclize to form **pyranose** rings (6-membered) or **furanose** rings (5-membered) via intramolecular hemiacetal or hemiketal linkages.

2. Disaccharides

- **Definition:** Two monosaccharides linked by a **glycosidic bond** (e.g., $\alpha(1\rightarrow4)$, $\beta(1\rightarrow2)$).
- **Examples:**
 - **Sucrose** (glucose-fructose, $\alpha(1\rightarrow2)$ bond).
 - **Lactose** (glucose-galactose, $\beta(1\rightarrow4)$ bond).
 - **Maltose** (glucose-glucose, $\alpha(1\rightarrow4)$ bond).

3. Polysaccharides

- **Homopolysaccharides:** Composed of one type of monomer (e.g., glycogen, starch, cellulose).
- **Heteropolysaccharides:** Composed of two or more monomeric species (e.g., glycosaminoglycans).
- **Branching:** Glycogen and amylopectin (branched starch) have $\alpha(1\rightarrow6)$ branch points in addition to $\alpha(1\rightarrow4)$ linkages, allowing compact energy storage and rapid mobilization.

4. Glycoconjugates

- **Glycoproteins:** Proteins with oligosaccharide chains covalently attached (N-linked or O-linked).
- **Proteoglycans:** Heavily glycosylated proteins with glycosaminoglycan chains, crucial for extracellular matrix structure.
- **Glycolipids:** Lipids with carbohydrate moieties (e.g., gangliosides in neuronal membranes).

Carbohydrate Metabolism

Overview of Central Pathways

1. Glycolysis

- **Location:** Cytosol of all cells.
- **Function:** Breakdown of 1 glucose (6C) into 2 pyruvate (3C each), net gain of 2 ATP and 2 NADH.
- **Regulation:** Key control points at **hexokinase/glucokinase**, **phosphofructokinase-1 (PFK-1)**, and **pyruvate kinase**. Modulated by ATP/AMP ratios, citrate, and fructose-2,6-bisphosphate.

2. Glycogen Metabolism

- **Glycogenesis:** Synthesizes glycogen from glucose monomers, catalyzed by **glycogen synthase** ($\alpha(1\rightarrow4)$ linkages) and **branching enzyme** ($\alpha(1\rightarrow6)$). Predominant in liver and muscle.
- **Glycogenolysis:** Breaks down glycogen to glucose-1-phosphate via **glycogen phosphorylase** and **debranching enzyme**. The liver contributes glucose to blood; muscle uses glucose-6-phosphate internally for ATP.

3. Gluconeogenesis

- **Location:** Mainly liver (and kidney cortex).
- **Function:** Synthesis of glucose from non-carbohydrate precursors (lactate, glycerol, amino acids).
- **Regulation:** Reciprocal control with glycolysis. Key enzymes include **fructose-1,6-bisphosphatase** (F-1,6-BPase), **PEP carboxykinase** (PEPCK), **pyruvate carboxylase**. Inhibited by AMP, fructose-2,6-bisphosphate; stimulated by glucagon, cortisol.

4. Pentose Phosphate Pathway (PPP)

- **Phases:** Oxidative phase (generates NADPH, ribulose-5-phosphate) and non-oxidative phase (interconverts sugars for nucleotide biosynthesis, glycolysis intermediates).
- **Importance:** NADPH for reductive biosynthesis (fatty acids, cholesterol), protection against oxidative stress (glutathione reduction). Ribose-5-phosphate for nucleotide synthesis.

5. TCA Cycle and Oxidative Phosphorylation

- Pyruvate from glycolysis is decarboxylated to acetyl-CoA (link reaction), entering the **TCA cycle** in mitochondria.
- Complete oxidation of acetyl-CoA produces CO₂, NADH, FADH₂.
- NADH and FADH₂ feed electrons into the **electron transport chain**, generating a proton gradient that drives ATP synthesis.

Hormonal and Allosteric Regulation

- **Insulin:** Anabolic hormone secreted by pancreatic β-cells; promotes glucose uptake in muscle/adipose, stimulates glycogenesis and glycolysis, inhibits gluconeogenesis.
- **Glucagon:** Catabolic hormone secreted by pancreatic α-cells; stimulates glycogenolysis, gluconeogenesis, inhibits glycolysis in the liver.
- **Epinephrine:** Adrenal hormone that activates glycogenolysis (muscle, liver) for rapid energy release during stress.
- **Cortisol:** Enhances gluconeogenesis, long-term metabolic adaptations to stress or fasting.

Disorders Associated with Carbohydrate Metabolism

Diabetes Mellitus

1. Type 1 Diabetes (T1DM)

- Autoimmune destruction of pancreatic β-cells → absolute insulin deficiency.
- **Clinical Features:** Hyperglycemia, ketoacidosis, polyuria, polydipsia, weight loss.
- **Treatment:** Exogenous insulin administration.

2. Type 2 Diabetes (T2DM)

- Insulin resistance in peripheral tissues + relative insulin deficiency.
- **Clinical Features:** Hyperglycemia, often associated with obesity, metabolic syndrome.
- **Complications:** Cardiovascular disease, neuropathy, nephropathy, retinopathy.
- **Management:** Lifestyle interventions, oral hypoglycemics (e.g., metformin), or insulin when needed.

3. Gestational Diabetes

- Hyperglycemia arising during pregnancy; increases fetal/macrosomia risk. Often resolves postpartum but raises later T2DM risk.

Glycogen Storage Diseases (GSDs)

1. Type I: Von Gierke's Disease (Glucose-6-phosphatase deficiency)

- Severe fasting hypoglycemia, lactic acidosis, hyperuricemia, hyperlipidemia.
- Inability to release free glucose from the liver → accumulation of G6P, increased glycolysis, lactate production.

2. Type II: Pompe Disease (Lysosomal α-1,4-glucosidase deficiency)

- Glycogen accumulates in lysosomes, affecting muscle/cardiac function; cardiomyopathy, hypotonia in infancy.
- Enzyme replacement therapy available.

3. Type III: Cori Disease (Debranching enzyme deficiency)

- Milder hypoglycemia than Type I, accumulation of limit dextrin-like structures in cytosol.

4. Type V: McArdle Disease (Muscle glycogen phosphorylase deficiency)

- Exercise intolerance, muscle cramps, myoglobinuria, no rise in blood lactate during exercise.

5. Type VI: Hers Disease (Liver glycogen phosphorylase deficiency)

- Mild fasting hypoglycemia, mild hepatomegaly.

Disorders of Fructose and Galactose Metabolism

1. Hereditary Fructose Intolerance (HFI)

- **Aldolase B deficiency**; fructose-1-phosphate accumulates in liver, causing hypoglycemia, jaundice, vomiting.
- Dietary fructose/sucrose/sorbitol must be restricted.

2. Essential Fructosuria

- Benign, due to deficiency in **fructokinase**; fructose appears in urine.

3. Galactosemia

- **Classic Galactosemia** (Galactose-1-phosphate uridylyltransferase deficiency): Accumulation of galactose-1-phosphate, galactose → toxic effects in liver, brain, eyes (cataracts). Early dietary restriction of galactose is essential.
- **Galactokinase deficiency**: Milder, primarily causes cataracts due to galactitol accumulation.

Lactose Intolerance

- **Primary Lactase Deficiency**: Common in adults of certain ethnicities; reduced lactase enzyme leads to bloating, diarrhea upon lactose ingestion.
- **Secondary Lactase Deficiency**: Due to intestinal damage (infections, celiac disease).

Pyruvate Metabolism Disorders

1. Pyruvate Dehydrogenase Complex Deficiency

- Causes lactic acidosis, neurological defects, congenital forms of Leigh syndrome.
- Impaired aerobic oxidation of pyruvate → shifts towards lactate production.

2. Lactic Acidosis

- Elevated lactate due to hypoxia, mitochondrial disorders, or enzyme deficiencies.
- Symptoms include muscle weakness, rapid breathing, organ dysfunction.

Integrative Perspective

- **Energy Homeostasis**: Carbohydrates are the primary quick energy source; the body finely regulates glucose availability (glycogen stores, gluconeogenesis) to meet demands.
- **Lipid and Protein Interplay**: In prolonged fasting or diabetes, inadequate carbohydrate metabolism leads to increased lipolysis, ketone body production, and potential ketoacidosis. Proteins can be mobilized to provide gluconeogenic substrates.
- **Gene-Environment Interactions**: Modern dietary patterns (high sugar intake) plus genetic susceptibilities can lead to metabolic syndrome and T2DM.
- **Biotechnology and Therapeutics**: Advances in insulin analogues, enzyme replacement therapy (Pompe disease), or gene therapy for certain GSDs showcase the applications of understanding carbohydrate biochemistry.

Concluding Remarks

Carbohydrates serve dual roles in **structural** (cell walls, extracellular matrix) and **metabolic** (energy) functions. Their pathways—ranging from **glycolysis** and **glycogenesis** to **gluconeogenesis** and **pentose phosphate**—are tightly regulated by **enzymes** and **hormones** to maintain **glucose homeostasis**. Dysfunction in these pathways—whether due to enzyme deficiencies, dysregulated hormones, or genetic mutations—causes clinically significant **disorders** (e.g., **diabetes mellitus**, **glycogen storage diseases**, **fructose/galactose metabolic disorders**).

Understanding **carbohydrate chemistry and metabolism** is thus central to **clinical diagnostics** (e.g., blood glucose tests, GTT), **therapeutic interventions** (insulin, dietary management), and **biochemical research** aimed at dissecting metabolic flux, enzyme regulation, and novel treatments for metabolic diseases.