## ii. Carbohydrate chemistry and metabolism...

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## **Carbohydrate Chemistry**

#### **Classification and Structure**

#### 1. Monosaccharides

- **Definition**: Simple sugars with general formula (CH2O)n\mathrm{(CH\_2O)}\_n(CH2O)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.,  $\alpha(1\rightarrow 4)$ ,  $\beta(1\rightarrow 2)$ ).
- Examples:
  - **Sucrose** (glucose–fructose,  $\alpha$ -1 $\rightarrow$ 2 bond).
  - **Lactose** (glucose-galactose, β-1→4 bond).
  - **Maltose** (glucose–glucose,  $\alpha$ -1 $\rightarrow$ 4 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  $\alpha(1\rightarrow 6)$  branch points in addition to  $\alpha(1\rightarrow 4)$  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.
- o 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 $\rightarrow$ 4 linkages) and **branching enzyme** ( $\alpha$ -1 $\rightarrow$ 6). 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)

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- **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.
- o Complete oxidation of acetyl-CoA produces CO<sub>2</sub>, NADH, FADH<sub>2</sub>.
- NADH and FADH<sub>2</sub> 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)

- $\circ$  Autoimmune destruction of pancreatic  $\beta$ -cells  $\rightarrow$  absolute insulin deficiency.
- Clinical Features: Hyperglycemia, ketoacidosis, polyuria, polydipsia, weight loss.
- **Treatment**: Exogenous insulin administration.

#### 2. Type 2 Diabetes (T2DM)

- $\circ\,$  Insulin resistance in peripheral tissues + relative insulin deficiency.
- Clinical Features: Hyperglycemia, often associated with obesity, metabolic syndrome.
- **Complications**: Cardiovascular disease, neuropathy, nephropathy, retinopathy.
- o 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.
  - $\circ$  Inability to release free glucose from the liver  $\rightarrow$  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)
  - o Milder hypoglycemia than Type I, accumulation of limit dextrin-like structures in cytosol.
- 4. **Type V: McArdle Disease** (Muscle glycogen phosphorylase deficiency)
  - $\circ~$  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.

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#### **Disorders of Fructose and Galactose Metabolism**

#### 1. Hereditary Fructose Intolerance (HFI)

- Aldolase B deficiency; fructose-1-phosphate accumulates in liver, causing hypoglycemia, jaundice, vomiting.
- o 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 uridyltransferase deficiency): Accumulation of galactose-1-phosphate, galactose → toxic effects in liver, brain, eyes (cataracts). Early dietary restriction of galactose is essential.
- o 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.

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