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 (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., α(1→4), β(1→2)).
    - **Examples**:
        - **Sucrose** (glucose–fructose, α-1→2 bond).
        - **Lactose** (glucose–galactose, β-1→4 bond).
        - **Maltose** (glucose–glucose, α-1→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 α(1→6) branch points in addition to α(1→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.
    - **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** (α-1→4 linkages) and **branching enzyme** (α-1→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)**

- **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 CO_2, NADH, $FADH_2$.
    - NADH and $FADH_2$ 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 uridyltransferase 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.