"Introduction to Carbohydrates"

Overview

- Carbohydrates are the most abundant organic molecules in nature.

- They have a wide range of functions:

    - Provide a significant fraction of the dietary calories for most organisms.
    - Act as a storage form of energy in the body.
    - Serve as cell membrane components that mediate some forms of intercellular communication.

- Carbohydrates also serve as structural components in many organisms:

    - Cell walls of bacteria
    - Exoskeleton of insects
    - Fibrous cellulose of plants

- The empiric formula for many simpler carbohydrates is $(CH_2O)_n$, where $n \geqslant 3$, hence the name "hydrate of carbon."

Classification and Structure

Monosaccharides (Simple Sugars)

- Can be classified by number of carbon atoms.
    - Glucose – primary fuel for most cells
    - Fructose – found in fruits and honey
    - Galactose – part of lactose (milk sugar)
    - Ribose – component of RNA and nucleotides
    - Deoxyribose – component of DNA
    - Mannose – involved in glycoprotein synthesis
- Can also be classified by the type of carbonyl group:
    - Aldehyde carbonyl group → Aldoses
    - Keto carbonyl group → Ketoses
    - Example: Glyceraldehyde is an aldose, Dihydroxyacetone is a ketose.
- Carbohydrates with a free carbonyl group have the suffix -ose.
    - Ketoses have an additional "ul" in their suffix, such as xylulose.
    - Exception to this rule: Fructose

Oligosaccharides and Polysaccharides

- Monosaccharides can be linked by glycosidic bonds to create larger structures.
    - Disaccharides: Contain 2 monosaccharide units
    - Oligosaccharides: Contain 3 to 10 monosaccharide units
    - Polysaccharides: Contain more than 10 monosaccharide units, can be hundreds of sugar units in length

A. Isomers and Epimers

Isomers

- Compounds that have the same chemical formula but different structures are isomers of each other.

- Example: Fructose, glucose, mannose, and galactose all have the same chemical formula $C_6H_{12}O_6$, but different structures.

Epimers

- Carbohydrate isomers that differ in configuration around only one specific carbon atom (with the exception of the carbonyl carbon) are called epimers of each other.

- Example:

    - Glucose and galactose are C-4 epimers because their structures differ only in the position of the -OH (hydroxyl) group at carbon 4.
    - Note: The carbons in sugars are numbered beginning at the end that contains the carbonyl carbon (i.e., the aldehyde or keto group)
    - Glucose and mannose are C-2 epimers.

- Galactose and mannose differ in the position of -OH groups at two carbons (carbons 2 and 4), so they are isomers rather than epimers.

B. Enantiomers

Definition and Identification

- A special type of isomerism is found in pairs of structures that are mirror images of each other.
- These mirror images are called enantiomers, and the two members of the pair are designated as D- and L- sugar

Prevalence in Humans

- The vast majority of sugars in humans are D-isomers.

Structural Difference Between D and L Forms

- In the D-isomeric form, the -OH group on the asymmetric carbon (a carbon linked to four different atoms or groups) farthest from the carbonyl carbon is on the right.
- In the L-isomer, the -OH group is on the left.

Enzyme Specificity

- Most enzymes are specific for either the D or the L form.

- Isomerases are enzymes that are able to interconvert D- and L-isomers.

C. Monosaccharide Cyclization

Acyclic vs Cyclic Forms

- Less than 1% of each of the monosaccharides with five or more carbons exists in the open-chain (acyclic) form in solution.

- They are predominantly found in a ring or cyclic form, in which the aldehyde (or keto) group has reacted with a hydroxyl group on the same sugar, making the carbonyl carbon (carbon 1 for an aldose, carbon 2 for a ketose) asymmetric.

- This asymmetric carbon is referred to as the anomeric carbon.

1. Anomers

Formation and Configuration

- Creation of an anomeric carbon (the former carbonyl carbon) generates a new pair of isomers, the α and β configurations of the sugar (e.g., α-D-glucopyranose and β-D-glucopyranose).

- These α and β forms are anomers of each other.

Structural Differences in Representations

- Note:

    - In the α configuration, the -OH group on the anomeric carbon projects to the same side as the ring in a modified Fischer projection formula.
    - In a Haworth projection formula, it is trans to the CH_2OH group.
    - The α and β forms are not mirror images, and they are referred to as diastereomers.

Enzyme Specificity

- Enzymes are able to distinguish between these two structures and use one or the other preferentially.

- Example:
    - Glycogen is synthesized from α-D-glucopyranose.
    - Cellulose is synthesized from β-D-glucopyranose.

Mutarotation

- The cyclic α and β anomers of a sugar in solution spontaneously (but slowly) form an equilibrium mixture, a process known as mutarotation.

- Note: For glucose, the α form makes up 36% of the mixture.

2. Reducing Sugars

Definition and Mechanism

- If the hydroxyl group on the anomeric carbon of a cyclized sugar is not linked to another compound by a glycosidic bond, the ring can open.

- The sugar can act as a reducing agent and is termed a reducing sugar.

Reaction with Reagents

- Such sugars can react with chromogenic agents (e.g., the Benedict reagent), causing the reagent to be reduced and colored as the aldehyde group of the acyclic sugar is oxidized to a carboxyl group.

Types of Reducing Sugars

- All monosaccharides, but not all disaccharides, are reducing sugars.

- Note: Fructose, a ketose, is a reducing sugar because it can be isomerized to an aldose.

Colorimetric Test for Reducing Sugars

- A colorimetric test can detect a reducing sugar in urine.

- A positive result is indicative of an underlying pathology (because sugars are not normally present in urine).

- It can be followed up by more specific tests to identify the reducing sugar.

D. Monosaccharide Joining

Formation of Complex Carbohydrates

- Monosaccharides can be joined to form:
    - Disaccharides
    - Oligosaccharides
    - Polysaccharides

Examples of Important Disaccharides

- Lactose = Galactose + Glucose
- Sucrose = Glucose + Fructose
- Maltose = Glucose + Glucose

Examples of Important Polysaccharides

- Glycogen (branched; animal source)
- Starch (branched; plant source)
- Cellulose (unbranched; plant source)
- All are polymers of glucose.

E. Glycosidic Bonds

Definition and Enzyme Involvement

- The bonds that link sugars are called glycosidic bonds.
- They are formed by enzymes known as glycosyltransferases.
- These enzymes use nucleotide sugars (activated sugars), such as uridine diphosphate glucose, as substrates.

Naming of Glycosidic Bonds

- Glycosidic bonds are named based on:
    - The numbers of the connected carbons.
    - The position of the anomeric hydroxyl group of the first sugar involved.
- If the anomeric hydroxyl is in the α configuration, it is an α-bond.
- If it is in the β configuration, it is a β-bond.

Example: Lactose

- Lactose is synthesized by forming a glycosidic bond between:
    - Carbon 1 of β-galactose
    - and Carbon 4 of glucose
- This is called a β(1→4) glycosidic bond.
- Note: Because the anomeric end of the glucose residue is not involved in the glycosidic linkage, it (and therefore lactose) remains a reducing sugar.

F. Carbohydrate Linkage to Noncarbohydrates

Types of Linkages

- Carbohydrates can be attached by glycosidic bonds to noncarbohydrate structures, including:
    - Purine and pyrimidine bases in nucleic acids
    - Aromatic rings such as those in steroids
    - Proteins
    - Lipids

- If the group on the noncarbohydrate molecule to which the sugar is attached is an:
    - $-NH_2$ group → the bond is an N-glycosidic link
    - -OH group → the bond is an O-glycosidic link

- Note: All sugar-sugar glycosidic bonds are O-type linkages

III. Dietary Carbohydrate Digestion

General Overview

- Principal sites: Mouth and intestinal lumen.

- Digestion is rapid and catalyzed by enzymes called glycoside hydrolases (glycosidases).

- These enzymes hydrolyze glycosidic bonds.

- Since little monosaccharide is present in typical mixed diets (animal + plant origin), the enzymes primarily include:
    - Endoglycosidases – hydrolyze polysaccharides and oligosaccharides.
    - Disaccharidases – hydrolyze tri- and disaccharides into reducing sugar components.

Specificity of Glycosidases

- Glycosidases are specific for:
    - The structure and configuration of the glycosyl residue.
    - The type of glycosidic bond to be broken.

Final Products of Digestion

- Glucose
- Galactose
- Fructose
- These are absorbed by enterocytes (cells of the small intestine).

A. Salivary α-Amylase

Major Dietary Polysaccharides

- From plants: Starch (composed of amylose and amylopectin).
- From animals: Glycogen.

Action During Mastication (Chewing)

- Salivary α-amylase:
  - Acts briefly on dietary starch and glycogen.
  - Hydrolyzes random α(1→4) bonds.

Note:

- There are both α(1→4)- and β(1→4)-endoglucosidases in nature.
- Humans do not produce β(1→4)-endoglucosidases.
- Hence, humans cannot digest cellulose, a plant carbohydrate with β(1→4) glycosidic bonds between glucose units.

Limitation of α-Amylase

- Cannot hydrolyze α(1→6) bonds found in amylopectin and glycogen.

- Therefore, digestion by α-amylase results in:
  - A mixture of short, branched and unbranched oligosaccharides called dextrins.

Note:

- Disaccharides are also resistant to amylase and thus remain present.

Temporary Halt in Digestion

- In the stomach, high acidity inactivates salivary α-amylase, halting carbohydrate digestion temporarily.

B. Pancreatic α-Amylase

Resumption of Digestion in Small Intestine

- Acidic stomach contents are neutralized by bicarbonate secreted by the pancreas.

- Then, pancreatic α-amylase continues the process of starch digestion.

C. Intestinal Disaccharidases

Site of Final Carbohydrate Digestion

- Occurs primarily at the mucosal lining of the duodenum and upper jejunum.

- Enzymes involved: Disaccharidases located on the brush border (luminal/apical surface) of enterocytes.

- These enzymes are transmembrane proteins.

Examples of Disaccharidases and Their Actions

- Isomaltase
    - Cleaves α(1→6) bonds in isomaltose.
    - Also hydrolyzes most of the maltose.

- Maltase
    - Cleaves α(1→4) bonds in maltose and maltotriose, producing glucose.
- Sucrase
    - Cleaves α(1→2) bond in sucrose, producing glucose and fructose.
- Lactase (β-galactosidase)
    - Cleaves β(1→4) bond in lactose, producing galactose and glucose.
- Trehalase
    - Acts on trehalose, an α(1→1) disaccharide of glucose found in mushrooms and fungi.
    - Cleaves it to yield glucose.

Note: Despite its name, isomaltase hydrolyzes more than just isomaltose and is responsible for the majority of maltose digestion.

Enzyme Complexes and Structures

- Sucrase-Isomaltase (SI) Complex
    - Single protein cleaved into two functional subunits.
    - Subunits remain associated in the cell membrane.
- Maltase-Glucoamylase (MGA) Complex
    - A single membrane protein with two enzymic activities:
        - Maltase activity: Cleaves maltose.
        - Glucoamylase activity: Cleaves α(1→4) bonds in dextrins.
    - Not cleaved into subunits.

D. Intestinal Absorption of Monosaccharides

Site of Absorption

- Upper jejunum is the major site of monosaccharide absorption.

Transport Mechanisms for Different Sugars

- Glucose and Galactose
    - Absorbed by secondary active transport.
    - Requires symport with Na^+ ions.
    - Transporter: Sodium-dependent glucose cotransporter 1 (SGLT-1).

Note:

- The Na^+ gradient is created by the Na^+/K^+ ATPase pump, which:
    - Moves Na^+ out of the enterocyte.
    - Moves K^+ in.
    - This gradient drives the secondary active transport.

- Fructose
    - Absorbed by a facilitated diffusion mechanism.
    - Transporter: GLUT-5.
    - Does not require energy or Na^+.

Exit into Portal Circulation

- All three monosaccharides (glucose, galactose, fructose) exit the enterocyte via:
    - GLUT-2 transporter.
    - Enter portal circulation.

E. Abnormal Degradation of Disaccharides

Normal Efficiency of Carbohydrate Absorption

- In healthy individuals, all digestible carbohydrates are absorbed by the time contents reach the lower jejunum.

- Only monosaccharides (glucose, galactose, fructose) can be absorbed by intestinal mucosa.

Effect of Disaccharidase Deficiency

- Any deficiency (genetic or acquired) in specific disaccharidase enzymes results in:
    - Undigested carbohydrates entering the large intestine.

- No absorption since disaccharides can't be absorbed.

Pathophysiological Consequences

- Osmotically active disaccharides draw water from mucosa into the large intestine → osmotic diarrhea.
- Bacterial fermentation of unabsorbed carbohydrates leads to:
  - Formation of 2- and 3-carbon short-chain fatty acids (also osmotically active).
  - Production of gases: carbon dioxide (CO_2) and hydrogen gas (H_2).
  - Clinical symptoms: abdominal cramps, diarrhea, flatulence.

1. Digestive Enzyme Deficiencies

Genetic Deficiencies

- Inherited enzyme deficiencies result in disaccharide intolerance (e.g., lactase deficiency → lactose intolerance).

Acquired Deficiencies

- Can result from:
    - Intestinal diseases
    - Malnutrition
    - Drugs that damage the small intestinal mucosa

Diarrhea-Associated Loss

- In severe diarrhea, brush border enzymes are rapidly lost → temporary enzyme deficiency.
- Consequence: Patients cannot tolerate lactose or sucrose without worsening diarrhea.
- This intolerance continues during and after recovery from the illness.

2. Lactose Intolerance

Prevalence

- Affects >60% of adults worldwide due to lactase deficiency.
- Northern Europeans:
    - Most likely to retain lactase activity into adulthood.
- African and Asian descent:
    - Up to 90% are lactase deficient.
    - Therefore, reduced ability to digest lactose.

Genetic Basis

- Age-dependent decline in lactase activity begins at ~2 years of age.
- Due to reduced enzyme production, not complete absence.

- Linked to polymorphisms in a regulatory region on chromosome 2:
    - Affects expression of the lactase gene (also on chromosome 2).

Symptoms

- Lactose malabsorption leads to:
    - Osmotic diarrhea
    - Flatulence
    - Abdominal discomfort

Treatment

- Reduce milk intake.
- Consume dairy with less lactose:
    - Yogurt and aged cheeses (lactose partially broken down).

- Ensure calcium intake from:
    - Green vegetables (e.g., broccoli).
- Use lactase-treated milk or oral lactase supplements.
- Rare congenital lactase deficiency also exists (complete absence of enzyme from birth).

3. Sucrase-Isomaltase (SI) Deficiency

Overview

- Results in intolerance to sucrose.
- Previously thought rare; now recognized in up to 9% of European-descended Americans.
- More common in Inuit populations (Alaska and Greenland).

Genetics

- Initially believed to be autosomal recessive.
    - Homozygotes: Congenital SI deficiency.
    - Heterozygotes: May show partial symptoms.

- Over 25 mutations identified in the human sucrase gene.

Symptoms

- Homozygous individuals:
    - Osmotic diarrhea
    - Mild steatorrhea
    - Irritability
    - Vomiting after sucrose ingestion
- Heterozygous carriers:
    - Chronic diarrhea
    - Abdominal pain
    - Bloating

Treatment

- Dietary restriction of sucrose.
- Enzyme replacement therapy.

4. Diagnosis of Enzyme Deficiencies

Diagnostic Tools

- Oral tolerance tests:
    - Use specific disaccharides to identify the enzyme deficiency.
- Hydrogen breath test:
    - Measures H_2 gas in breath.
    - Indicates unabsorbed carbohydrate fermented by intestinal flora.
    - A reliable non-invasive diagnostic method.