"Monosaccharide and Disaccharide Metabolism"

I. Overview

- Glucose is the most common monosaccharide consumed by humans.
- Fructose and Galactose:
    - Also occur in significant amounts in the diet.
    - Primarily found in disaccharides.
    - Make important contributions to energy metabolism.
- Galactose:
    - An important component of glycosylated proteins.

II. Fructose Metabolism

- Dietary Contribution:
    - ~10% of calories in the typical Western diet are supplied by fructose (~55 g/day).

- Major Source:
    - Disaccharide sucrose.
        - Cleaved in the intestine.
        - Releases equimolar amounts of fructose and glucose.
- Other Sources:
    - Free monosaccharide form in:
        - Many fruits.
        - Honey.
        - High-fructose corn syrup (typically 55% fructose and 45% glucose).
            - Used to sweeten soft drinks and many foods.
- Cellular Transport:
    - Fructose transport into cells is not insulin dependent.
        - Unlike glucose, whose uptake into certain tissues is insulin dependent.

- Hormonal Response:
    - Fructose does not promote the secretion of insulin, in contrast to glucose.

A. Phosphorylation

- Requirement for Metabolism:
    - For fructose to enter intermediary metabolism, it must first be phosphorylated.
- Enzymes Involved:
    - Hexokinase
        - Phosphorylates glucose in most cells of the body.
        - Can use several additional hexoses as substrates.
        - Has low affinity (high Km) for fructose.
        - Due to saturating concentrations of glucose, little fructose is phosphorylated by hexokinase unless intracellular fructose concentration is unusually high.
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- Fructokinase
    - Provides the primary mechanism for fructose phosphorylation.
    - Has a low Km for fructose.
    - Has a high Vmax (maximal velocity).
    - Found in the liver, kidneys, and small intestine.
    - Converts fructose to fructose 1-phosphate, using ATP as the phosphate donor.
    - (Note: These three tissues also contain aldolase B)

B. Fructose 1-phosphate Cleavage

- Pathway Difference:
    - Fructose 1-phosphate is not phosphorylated to fructose 1,6-bisphosphate like fructose 6-phosphate.
    - Instead, it is cleaved by aldolase B (also called fructose 1-phosphate aldolase).

- Cleavage Products:
    - Yields two trioses:
        - Dihydroxyacetone phosphate (DHAP)
        - Glyceraldehyde

- Aldolase Isoenzymes in Humans:
    - Three distinct isoenzymes, each from a different gene:
        - Aldolase A – present in most tissues
        - Aldolase B – present in liver, kidneys, and small intestine
        - Aldolase C – present in the brain
    - All three:
        - Cleave fructose 1,6-bisphosphate (from glycolysis) to:
            - DHAP
            - Glyceraldehyde 3-phosphate
    - Only aldolase B:
        - Cleaves fructose 1-phosphate

- Fate of Cleavage Products:
    - DHAP:
        - Can enter glycolysis or gluconeogenesis
    - Glyceraldehyde:
        - Can be metabolized by multiple pathway

C. Kinetics

- Fructose metabolism is more rapid than glucose metabolism:
    - Because triose production from fructose 1-phosphate bypasses phosphofructokinase-1 (PFK-1).
    - PFK-1 is the major rate-limiting step in glycolysis.

D. Disorders

- Enzyme Deficiencies Affecting Fructose Metabolism:
    - Can result in:
        - A benign condition due to fructokinase deficiency → Essential fructosuria.

        - A severe disturbance in liver and kidney metabolism due to aldolase B deficiency → Hereditary fructose intolerance (HFI).
            - Occurs in approximately 1:20,000 live births

- HFI Onset:

    - First symptoms appear when a baby is weaned from lactose-containing milk and starts ingesting food containing sucrose or fructose.

- Pathophysiology of HFI:

    - Fructose 1-phosphate accumulates, leading to:
        - Drop in inorganic phosphate (Pi).
        - Decrease in ATP production.
    - As ATP falls, AMP rises.
        - AMP is degraded → causes hyperuricemia and lactic acidemia.
    - Decreased hepatic ATP availability leads to:
        - Decreased gluconeogenesis → causes hypoglycemia with vomiting.
        - Decreased protein synthesis → results in:
            - Decrease in blood-clotting factors.
            - Decrease in other essential proteins.

- Renal reabsorption of Pi is also decreased.
  - (Note: The drop in Pi also inhibits glycogenolysis.)

- Diagnosis of HFI:
  - Based on:
    - Detection of fructose in the urine.
    - Enzyme assay using liver cells.
    - DNA-based testing.

- Management of HFI:
  - Sucrose and fructose must be removed from the diet.
    - To prevent liver failure and possible death.
  - Individuals with HFI tend to display a life-long aversion to sweets.

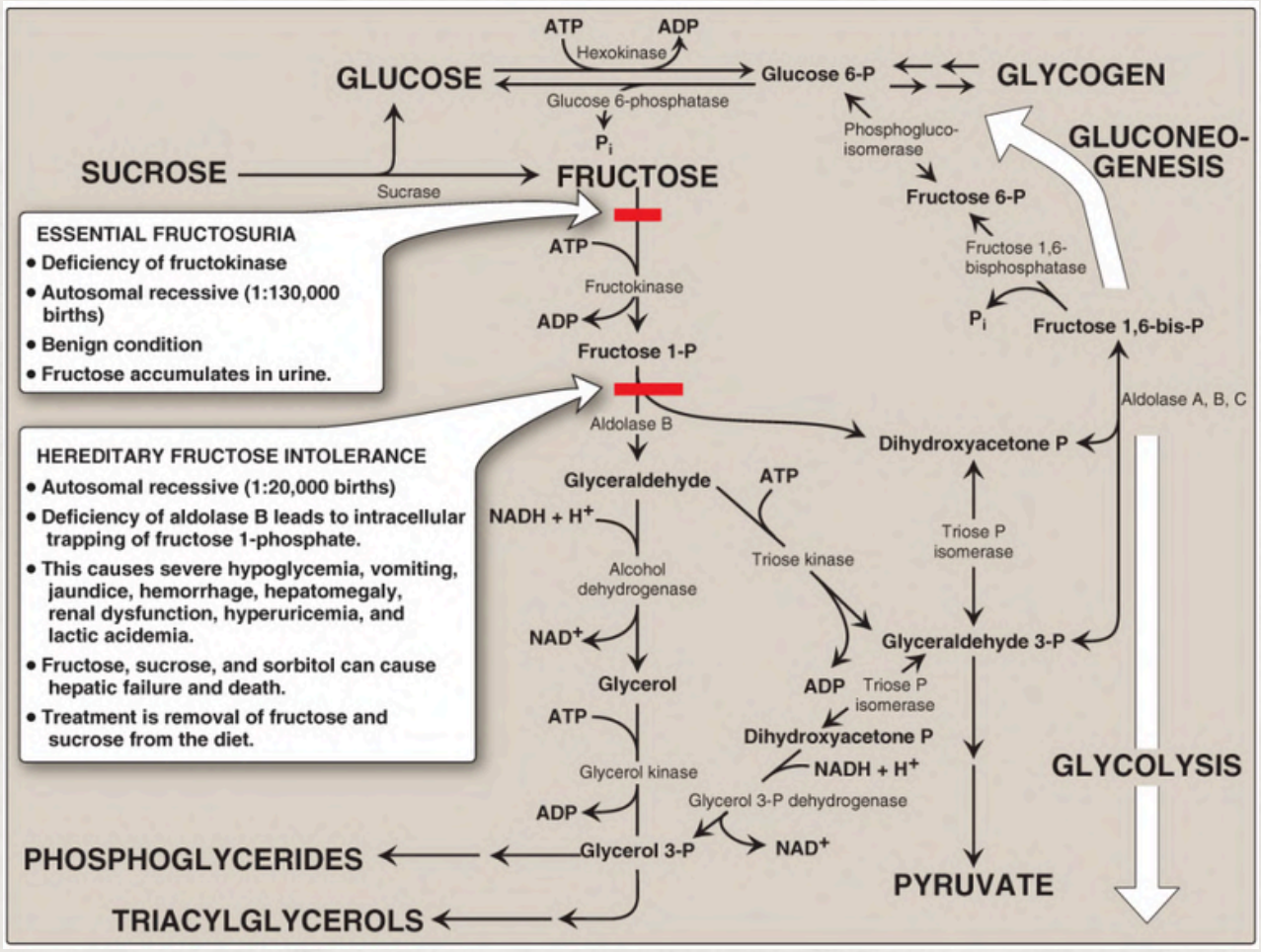
E. Mannose Conversion to Fructose 6-phosphate

- Mannose:
  - The C-2 epimer of glucose.
  - An important component of glycoproteins.

- Metabolism:
    - Hexokinase phosphorylates mannose to form mannose 6-phosphate.
    - Mannose 6-phosphate is then reversibly isomerized to fructose 6-phosphate by phosphomannose isomerase.

- Sources of Intracellular Mannose:
    - Mostly:
        - Synthesized from fructose.
        - Derived from pre-existing mannose produced by glycoprotein degradation, then salvaged by hexokinase.
    - (Note: Dietary carbohydrates contain little mannose.)

Summary of Fructose Metabolism



F. Glucose Conversion to Fructose via Sorbitol

General Concept

- Most sugars are rapidly phosphorylated after entering cells.
    - This traps them inside the cell.

- Organic phosphates cannot freely cross membranes without specific transporters.

- Alternate Mechanism:

  - A monosaccharide can be converted to a polyol (sugar alcohol) by reduction of an aldehyde group.
    - This forms an additional hydroxyl group.

1. Sorbitol Synthesis

- Aldose reductase:

  - Reduces glucose to produce sorbitol (or glucitol).
  - Has a high Km for glucose.
  - Found in many tissues:
    - Retina
    - Lens
    - Kidneys
    - Peripheral nerves
    - Ovaries
    - Seminal vesicles

- Sorbitol dehydrogenase:
    - Oxidizes sorbitol to fructose.
    - Found in:
        - Liver
        - Ovaries
        - Seminal vesicles

- Physiological Roles:
    - In seminal vesicles:
        - Glucose → sorbitol → fructose.
        - Benefits sperm cells, which use fructose as a major carbohydrate energy source.
    - In liver:
        - Converts available sorbitol to fructose.
        - Fructose then enters glycolysis.

2. Hyperglycemia and Sorbitol Metabolism

- Tissue Entry of Glucose Without Insulin:
    - In retina, lens, kidneys, peripheral nerves:
        - Glucose can enter without insulin.

        - In hyperglycemia (e.g., poorly controlled diabetes mellitus):
            - Large amounts of glucose enter these cells.

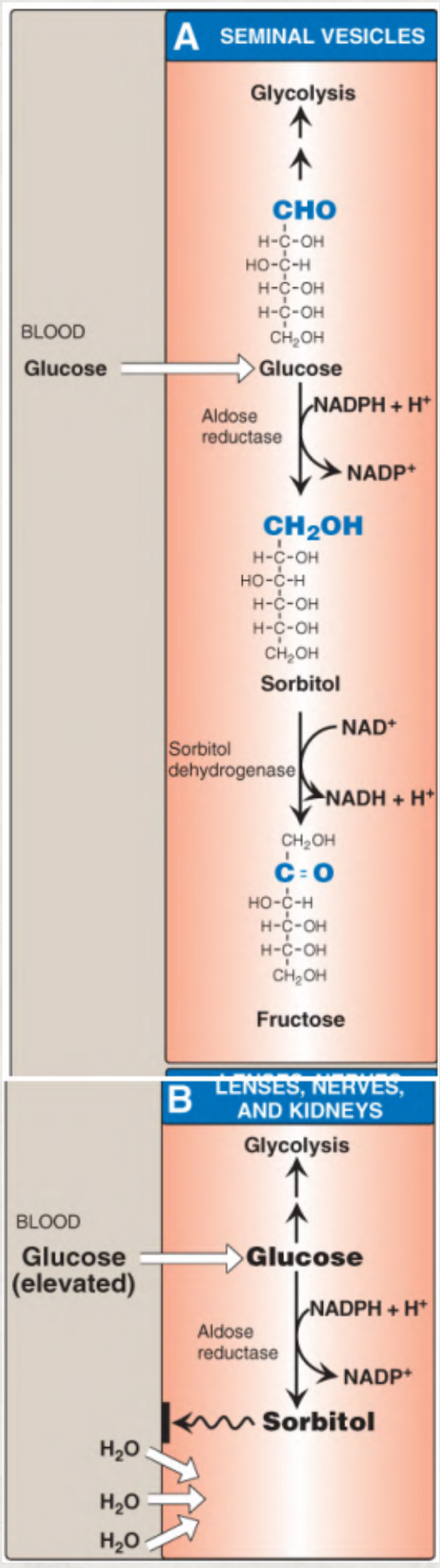
- Effect of High Intracellular Glucose + NADPH:

    - Aldose reductase activity increases.
        - Produces a significant increase in sorbitol.
    - Sorbitol:
        - Cannot pass efficiently through cell membranes.
        - Remains trapped inside the cell.
        - Accumulates further if sorbitol dehydrogenase is low or absent.

- Cellular Consequences:

    - Sorbitol accumulation causes:
        - Strong osmotic effects
        - Cell swelling due to water influx and retention

- Pathologic Consequences (linked to osmotic stress):
    - Cataract formation
    - Peripheral neuropathy
    - Microvascular problems leading to:
        - Nephropathy
        - Retinopathy
- NADPH Depletion:
    - Aldose reductase reaction uses NADPH.
    - Decreases generation of reduced glutathione.
        - An important antioxidant.
    - This may contribute to diabetic complications.



III. Galactose Metabolism

Dietary Sources

- Major dietary source of galactose:
    - Lactose (galactosyl β-1,4-glucose) obtained from milk and milk products.
    - (Note: Digestion of lactose occurs by β-galactosidase, also called lactase)

A. Phosphorylation

- Requirement for metabolism:
    - Like fructose, galactose must be phosphorylated before further metabolism.
- Enzyme involved:
    - Most tissues contain galactokinase.
        - Produces galactose 1-phosphate.
- Phosphate donor:
    - As with other kinases, ATP is the phosphate donor.

- Other sources of galactose:
    - Lysosomal degradation of glycoproteins and glycolipids.
- Transport into cells:
    - Like fructose and mannose, galactose transport into cells is not insulin dependent.

B. Uridine Diphosphate-Galactose Formation

- Conversion of galactose 1-phosphate:
    - Galactose 1-phosphate cannot enter glycolysis unless it is first converted to UDP-galactose.
- Mechanism:
    - An exchange reaction occurs:
        - UDP-glucose reacts with galactose 1-phosphate.
        - Produces:
            - UDP-galactose
            - Glucose 1-phosphate

- Catalyzing enzyme:
    - Reaction is catalyzed by galactose 1-phosphate uridylyltransferase (GALT).
- Note: Glucose 1-phosphate can be isomerized to glucose 6-phosphate, which can then:
    - Enter glycolysis or
    - Be dephosphorylated.

C. UDP-Galactose Conversion to UDP-Glucose

- For UDP-galactose to enter the mainstream of glucose metabolism:
    - It must be isomerized to its C-4 epimer, UDP-glucose.
- Enzyme:
    - UDP-hexose 4-epimerase

- Fate of the "new" UDP-glucose (produced from original UDP-galactose):
    - Can participate in biosynthetic reactions (e.g., glycogenesis)
    - Can participate in the GALT reaction

D. UDP-Galactose in Biosynthetic Reactions

- UDP-galactose serves as the donor of galactose units in several synthetic pathways, including:
    - Lactose synthesis
    - Glycoprotein synthesis
    - Glycolipid synthesis
    - Glycosaminoglycan synthesis

- Note:
    - If dietary galactose is absent (e.g., cannot be released from lactose due to lack of β-galactosidase in lactose-intolerant individuals):
        - All tissue requirements for UDP-galactose can still be met by:
            - UDP-hexose 4-epimerase acting on UDP-glucose

- UDP-glucose is efficiently produced from:
  - Glucose 1-phosphate
  - Uridine triphosphate (UTP)

E. Disorders

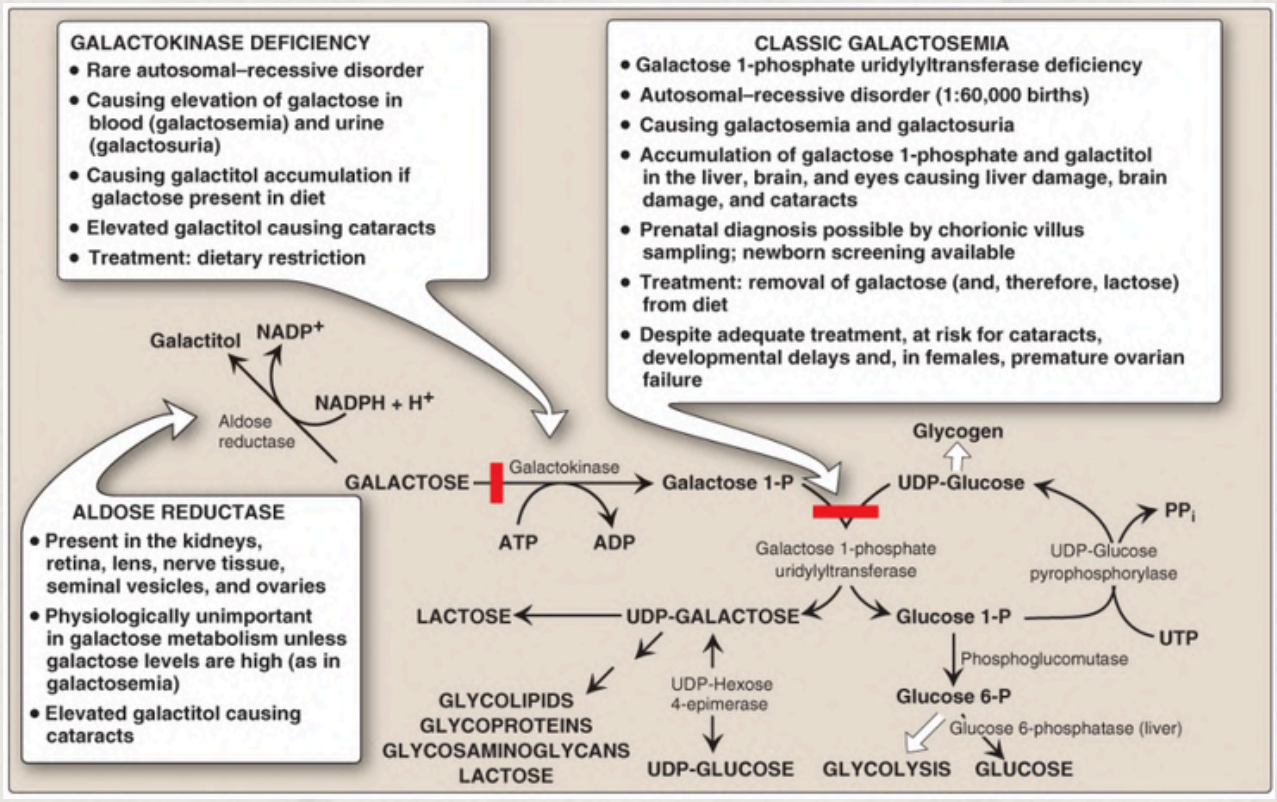
- GALT deficiency:
  - Severely deficient in individuals with classic galactosemia
  - Leads to accumulation of:
    - Galactose 1-phosphate
    - Galactose

- Physiologic consequences:
  - Similar to those seen in hereditary fructose intolerance (HFI)
  - But affect a broader spectrum of tissues

- Shunting of accumulated galactose:
  - Directed into side pathways, such as galactitol production

- Enzyme for galactitol production:
    - Aldose reductase
        - The same enzyme that reduces glucose to sorbitol
- Screening:
    - GALT deficiency is part of the newborn screening panel
- Treatment of galactosemia:
    - Removal of galactose and lactose from the diet
- Other enzyme deficiencies:
    - Galactokinase deficiency
    - UDP-hexose 4-epimerase deficiency
        - Result in less severe disorders
        - Cataracts are common in these conditions

Summary of Galactose Metabolism



IV. Lactose Synthesis

- Lactose:
  - A disaccharide composed of:
    - A molecule of β-galactose
    - Attached by a β(1→4) linkage to glucose
  - Therefore, lactose is galactosyl β(1→4)-glucose

- Source:
    - Lactose, the sugar in milk, is made by:
        - Lactating (milk-producing) mammary glands
    - Dietary sources of lactose:
        - Milk and other dairy products

A. Lactose Synthase

- Enzyme catalyzing lactose synthesis:
    - Lactose synthase (UDP-galactose:glucose galactosyltransferase)

- Location:
    - Functions in the Golgi

- Mechanism:
    - Transfers galactose from UDP-galactose to glucose
    - Releases UDP

- Structure:
    - Composed of A and B proteins

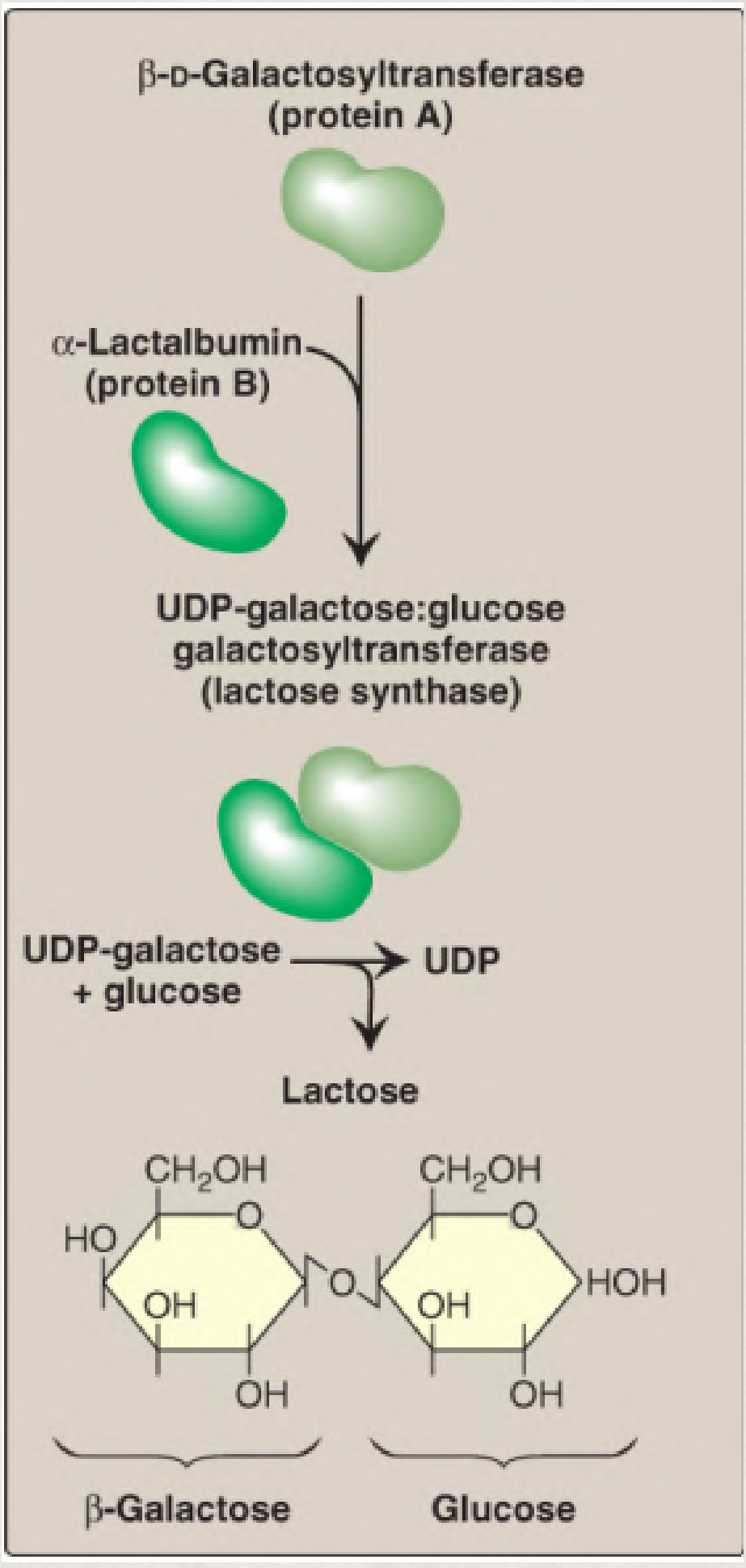
B. Protein A (β-D-galactosyltransferase)

- Found in:
  - A number of body tissues
- Function in non-lactating tissues:
  - Transfers galactose from UDP-galactose to:
    - N-acetyl-D-glucosamine
  - Produces:
    - Same β(1→4) linkage found in lactose
    - N-acetyllactosamine
      - A component of structurally important N-linked glycoproteins

C. Protein B (α-lactalbumin)

- Found only in:
  - Lactating mammary glands
- Nature:
  - α-lactalbumin

- Regulation:
    - Its synthesis is stimulated by the peptide hormone prolactin
- Function:
    - Forms a complex with protein A (β-D-galactosyltransferase)
    - Alters the enzyme's specificity:
        - Decreases the Km for glucose
        - Shifts the enzyme to produce lactose instead of N-acetyllactosamine



Clinical Application: Lactose Intolerance

- Also called:
    - Lactose malabsorption
- Prevalence:
    - Affects up to 60% of adults with ancestries other than Northern European
- Cause:
    - Deficiency of β-galactosidase (also called lactase) in the small intestine
- Pathophysiology:
    - Insufficient lactase → Inability to fully digest dairy products
- Symptoms after consuming dairy:
    - Cramping
    - Diarrhea
    - Bloating

- Management:
    - Use of lactase supplements
    - Avoidance of dairy products