# Metabolism of Monosaccharides and Disaccharides

## Overview:

- Glucose is the most common monosaccharide consumed.
- Galactose and lactose are found in significant amounts in the diet.
- Galactose is an important component of the cell structural carbohydrates.

## Fructose Metabolism

- ✓ 10% of the western diet is supplied by fructose (55g/day)
- ✓ Sucrose is the major source for fructose, it is cleaved into glucose + fructose (a1-2 linkage)
- ✓ It is found in fruits, honey and corn syrup
- ✓ Entry of fructose into the cells is NOT insulin-dependent, it also does NOT promote insulin secretion. (unlike glucose)

## Phosphorylation of fructose

It can be phosphorylated by 2 enzymes

1) Fructokinase, which is the primary enzyme for phosphorylation of fructose, it is found in the liver and uses ATP as a donor.

Fructose $\longrightarrow$ Fructose 1-Phosphate

2) Hexokinase, which is found in most tissues of the body. It has a high Km (low affinity) for fructose, therefore little amount of fructose is converted at normal concentration of fructose found in the body.

Fructose $\longrightarrow$ Fructose 6-Phosphate

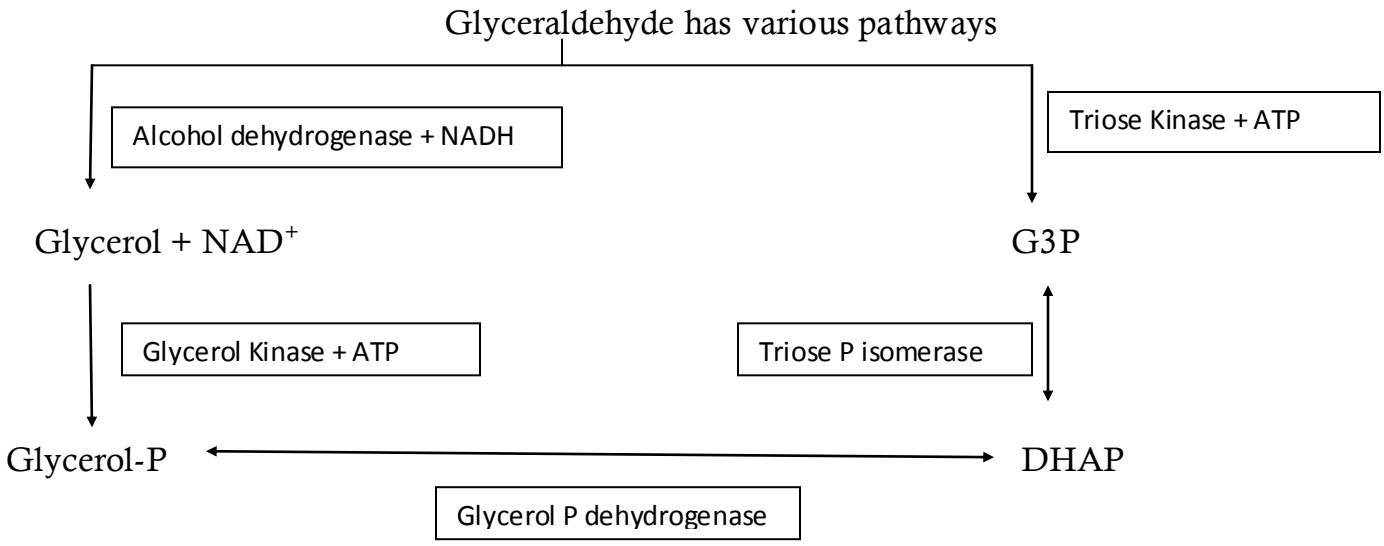
Cleavage of fructose 1-Phosphate

Aldolase B cleaves fructose 1-phosphate into dihydroxtacetone phosphate (DHAP) and Glyceraldehyde.

- ✓ Aldolase A: found in most tissues
- ✓ Aldolase B: found in the liver
- ✓ Aldolase C: found in the brain

All 3 of these aldolases cleave fructose 1,6-biphosphate during glycolysis into DHAP and G3P. but only aldolase B cleaves fructose 1-phopshate.

DHAP produced from this cleavage can directly enter either glycolysis or gluconeogensis.




Rate of fructose metabolism is more rapid than that of glucose as trioses formed from fructose 1-phosphate bypass **PFK1** (the rate limiting enzyme of glycolysis)

## Disorders of Fructose Metabolism

### **Frutosuria:**

- Fructokinase deficiency
- Autosomal recessive
- Benign
- Fructose accumulates in urine

### **Hereditary Fructose Intolerance**

- Disturbance of liver and kidney metabolism due to "fructose poisoning"
- Autosomal recessive disease

- Aldolase B deficiency which leads to intracellular trapping of fructose 1-phosphate
- Inorganic phosphate concentration drops, hence ATP levels drop too increasing AMP concentration
- Degradation of AMP results in hyperuricemia and lactic acidosis
- Hypoglycemia occurs as less gluconeogensis
- Vomiting
- Hemorrhage as protein synthesis decreases, less blood clotting factors
- Renal dysfunction or hepatomegaly
- Fructose in urine
- Sucrose + sorbitol + fructose must be removed from diet
- Absence of dental caries

## Conversion of Mannose to fructose 6-Phosphate

Mannose is a C2 epimer of glucose, it is an important component of glycoproteins

Mannose ⟶ Mannose 6-Phosphate ⟷ Fructose 6-Phosphate

Hexokinase +ATP

Phosphomannose isomerase

## Conversion of glucose to fructose via sorbitol

The enzyme which catalyses the following reaction can be found in the lens, retina, Schwann cells, liver, kidney, placenta, RBCS, ovaries and seminal vesicles.

Glucose ⟶ Sorbitol

Aldolase reductase

In the liver, ovaries and seminal vesicles, we have a second enzyme **sorbitol dehydrogenase**, it *oxidizes sorbitol into fructose*.

NOTE: this benefits sperm cells which use fructose as a major carbohydrate energy source.

During hyperglycemia, glucose can still enter these cells (e.g. uncontrolled diabetes). Elevated amounts of glucose with an adequate supply of NADPH causes *aldolase*

*reductase* to produce a significant increase in the amount of sorbitol, which gets trapped in the cell.

This effect is **exacerbated when sorbitol dehydrogenase is low in concentration or deficient.**

Accumulation of sorbitol causes osmotic effects which results in water retention and cell swelling.

This disruption may lead to **nephropathy or retinopathy**.

# Galactose Metabolism

- ✓ Lactose has a B-glycosidic bond between galactose and glucose, consumption of lactose is the major source for the galactose found in the body. (from milk and milk products)
- ✓ It is not insulin dependent
- ✓ Galactose is the c4 epimer of Glucose

Galactose is converted to galactose 1-phosphate by galactokinase found in most tissues.

GALT (galactose 1-phosphate uridyltransferase) is an enzyme which converts galactose 1-phosphate to UDP-galactose by adding it to UDP-Glucose.

Galactose $\xrightarrow{\text{Galactokinase}}$ Galactose 1-Phosphate $\xrightarrow{\text{GALT + UDP-Glucose}}$ UDP-Galactose

UDP-hexose 4-epimerase interconverts between UDP-galactose and UDP-glucose in order for the monosaccharides to be used in different pathways.

e.g. UDP-galactose is used in the synthesis of lactose, glycoproteins, lipids or GAGS

Galactose $\xrightarrow{\text{Aldolase reductase + NADPH}}$ Galacitol + $NADP^+$ (physiologically unimportant reaction)

## Disorders of Galactose Metabolism

## Galactokinase Deficiency

- ✓ Rate autosomal recessive disease
- ✓ Galactosemia ( high galactose concentration in blood)
- ✓ Galactosuria (high galactose concentration in urine)
- ✓ Galacitol accumulation if galactose is present in diet

## Classic Galactosemia

- ✓ GALT deficiency
- ✓ Autosomal recessive
- ✓ Galactose 1-P and galacitol accumulate in nerve, lens, liver and kidney cells, which causes liver damage, mental retardation or contracts
- ✓ Antenatal diagnosis is possible by chronic virus sampling (rapid diagnosis is very important)
- ✓ Therapy: remove galactose + lactose from diet
- ✓ Premature ovarian failure risk and developmental delays risk can occur despite treatment.

# Lactose synthesis

Lactose is synthesized in the Golgi apparatus by Lactose synthase enzyme, by transferring the galactose from UDP-Galactose to Glucose forming Lactose

UDP galactose + Glucose $\xrightarrow{\text{Lactose Synthase}}$ UDP + Lactose

This enzyme is **composed of 2 proteins; A and B**

Protein A is present in many tissues, it is a B-D-Galactosyl transferase, it transfers galactose from NAG ( N-acetyl-D-glucosamine) to NAL (N-acetyl-lactosamine).

NAL is an important component of the linkage of glycoproteins.

Protein B is found ONLY in lactating mammary glands, its synthesis is stimulated by prolactin.

Protein B forms a complex with the enzyme Protein A, changing its specificity of the transferase so that lactose, rather than NAL is produced.