Uronic acid pathway Fructose & Galactose metabolism

By

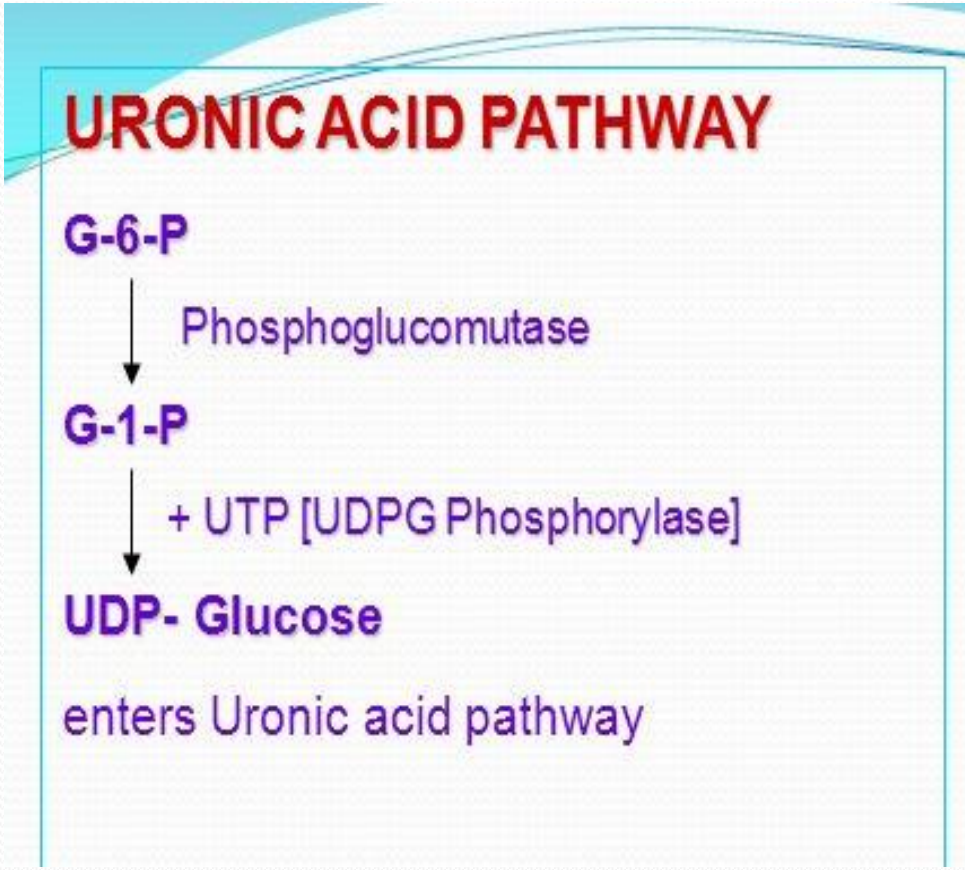
Dr Gulnaz Begum

URONIC ACID PATHWAY

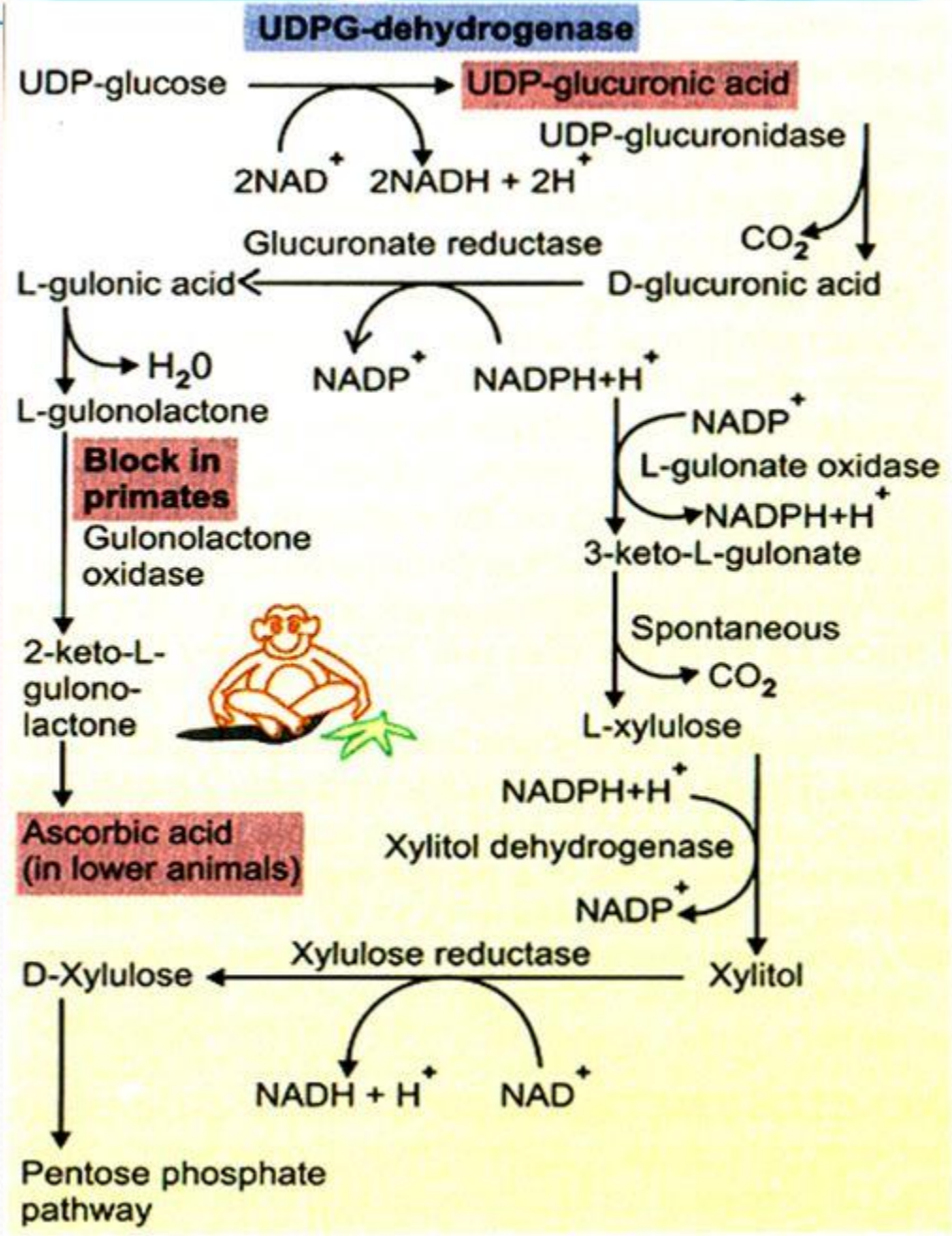
- Alternative pathway for glucose oxidation
- EXAMPLE: gluconic, glucuronic, glucaric

- In liver converts glucose to glucuronic acid,pentoses and ascorbic acid in animals but not in humans.
- No formation of ATP.

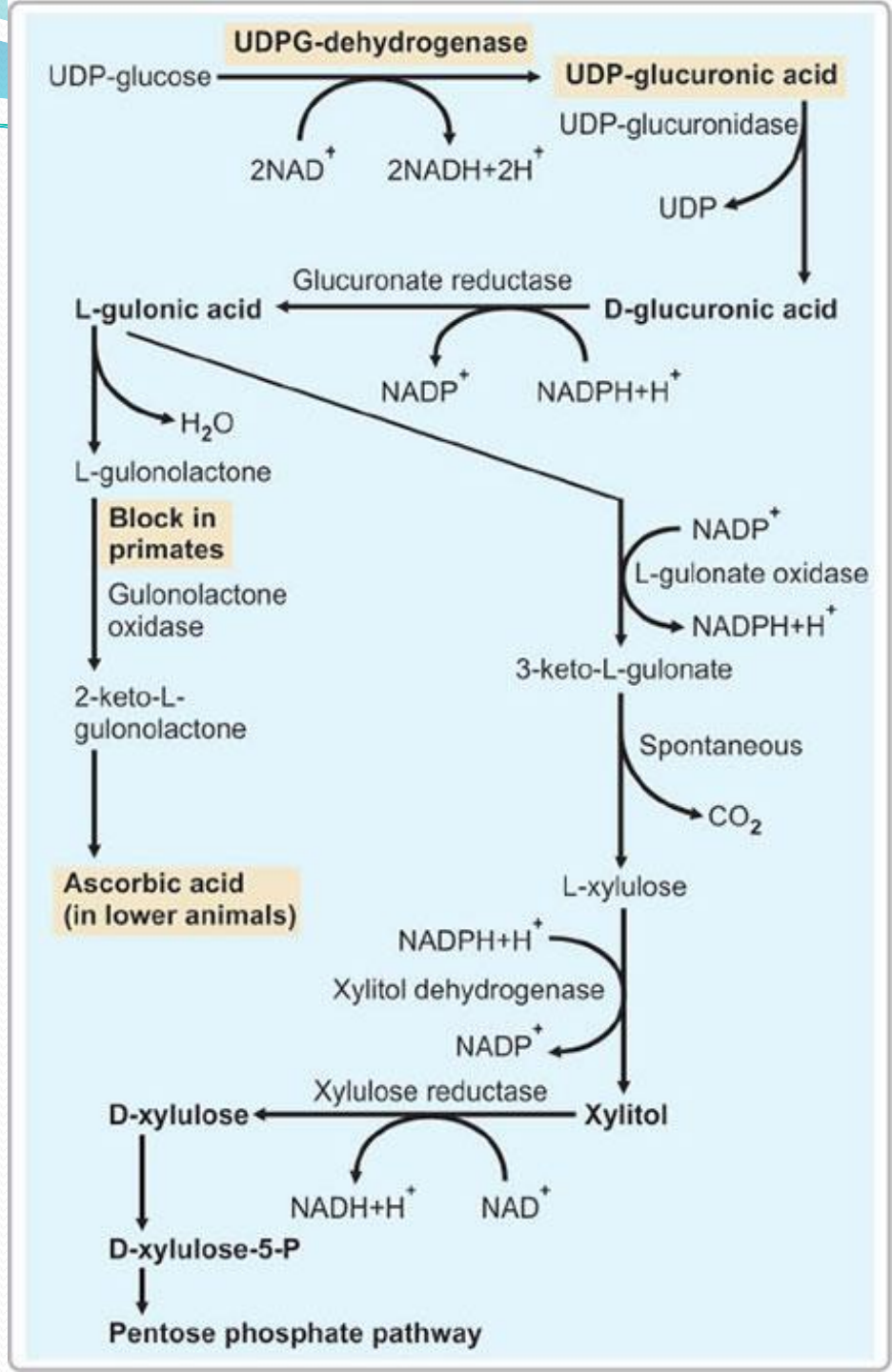
- Formation of UDP-G:
- Glucose-6-P is converted to glucose-I-P by enzyme phosphoglucomutase.
- Glucose-1-P then reacts with UTP to form active nucleotide"uridine-diphosphate glucose".
- Enzyme is UDP-G pyrophosphorylase.



- Formation of D-glucoronic acid:
- UDP-G is oxidized by enzyme UDP-G dehydrogenase. Enzyme require NAD as H acceptor.
- UDP-glucoronic acid is hydrolyzed to form D-glucoronic acid.
- The UDP-glucoronic acid is active form, involved in conjugation forming glucoronoids, or proteoglycons.

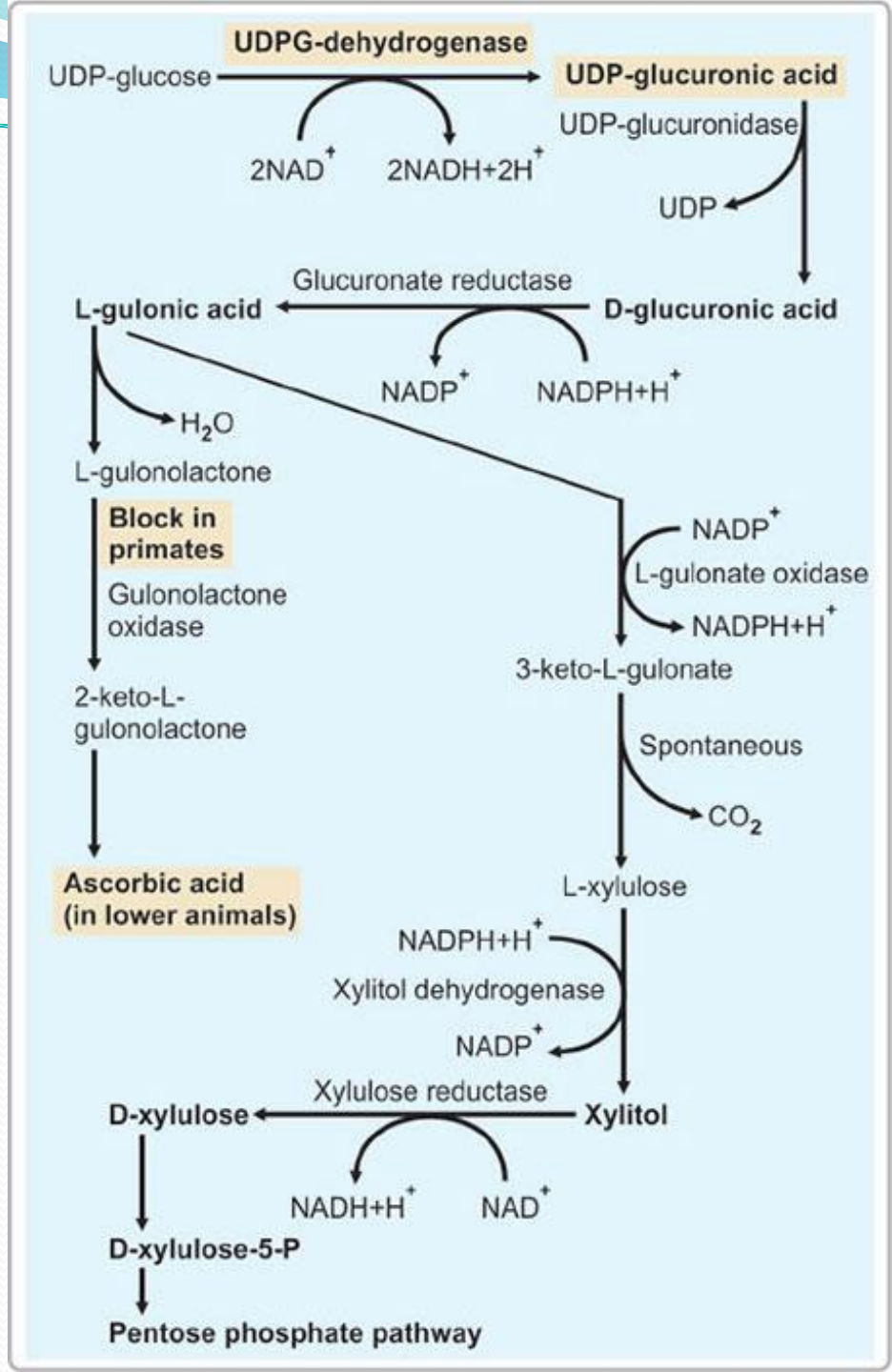


- D-glucoronic acid is converted to L-gulonic acid by NADPH dependant enzyme.
- L-gulonic acid forms ascorbic acid in some animals.
- In man L-Gulonic acid is oxidized to 3-keto-L-gulonic acid which is decarboxylated to L-Xylulose.



Functions of glucoronic acid

- Glucuronic acid is formed in the body is of great physiological importance because it is used in the process of detoxifying many substances like bilirubin , benzoic acid ,steroid hormones & various drugs.
- Synthesis of muco polysacchrides.



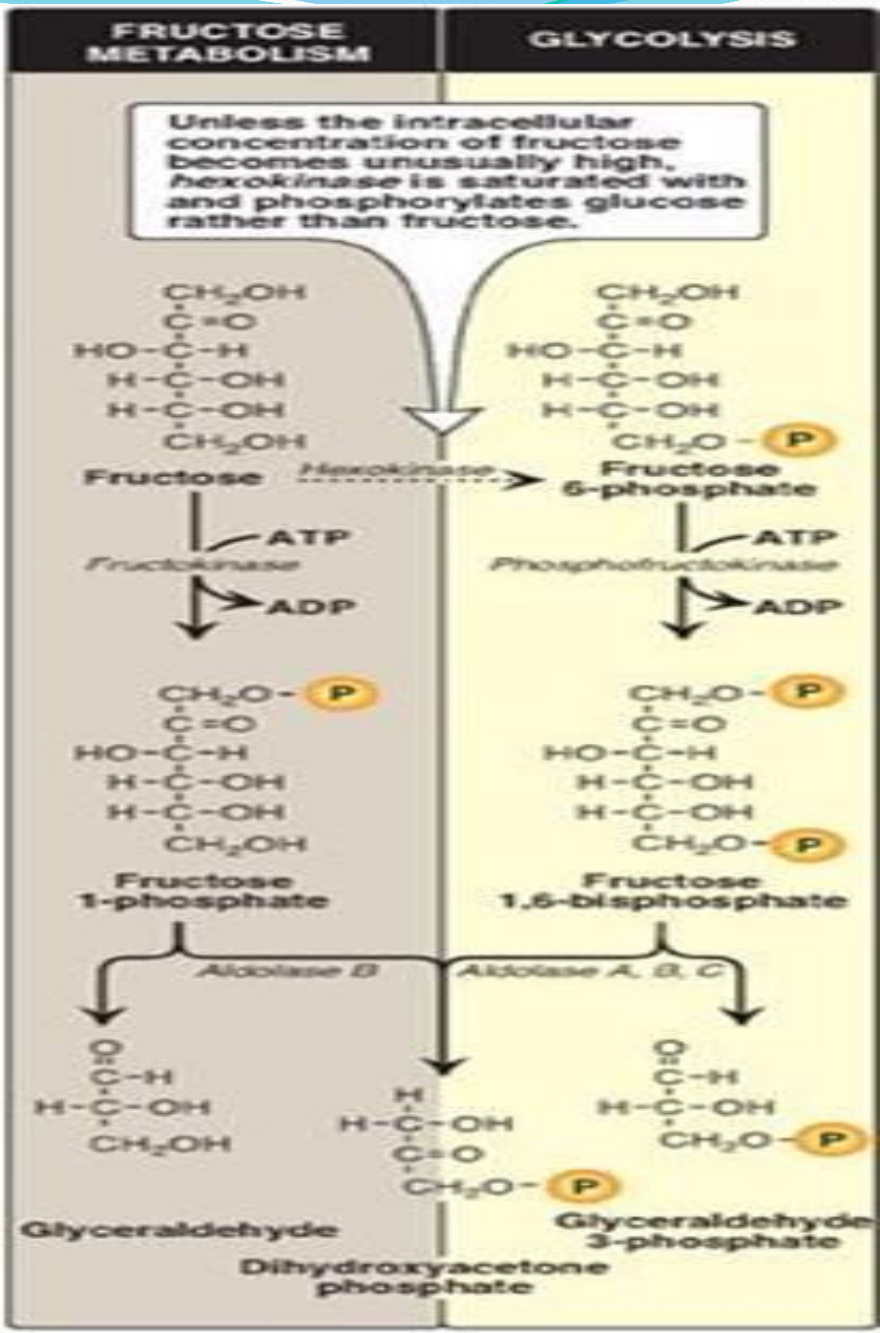
Disorder of uronic acid pathway

- Essential pentosuria :
- Autosomal recessive inherited disorder,
- Enzyme deficient : L-Xylitol dehydrogenase.
- L-xylulose cannot be converted to xylitol.
- L- xylulose is excreated in urine.

FRUCTOSE METABOLISM

- Major source of fructose is disaccharide SUCROSE
- Sucrose is cleaved in the intestines to form GLUCOSE & FRUCTOSE
- Found in many fruits , HONEY & high fructose corn syrup
- Entry into cells is not insulin dependent.

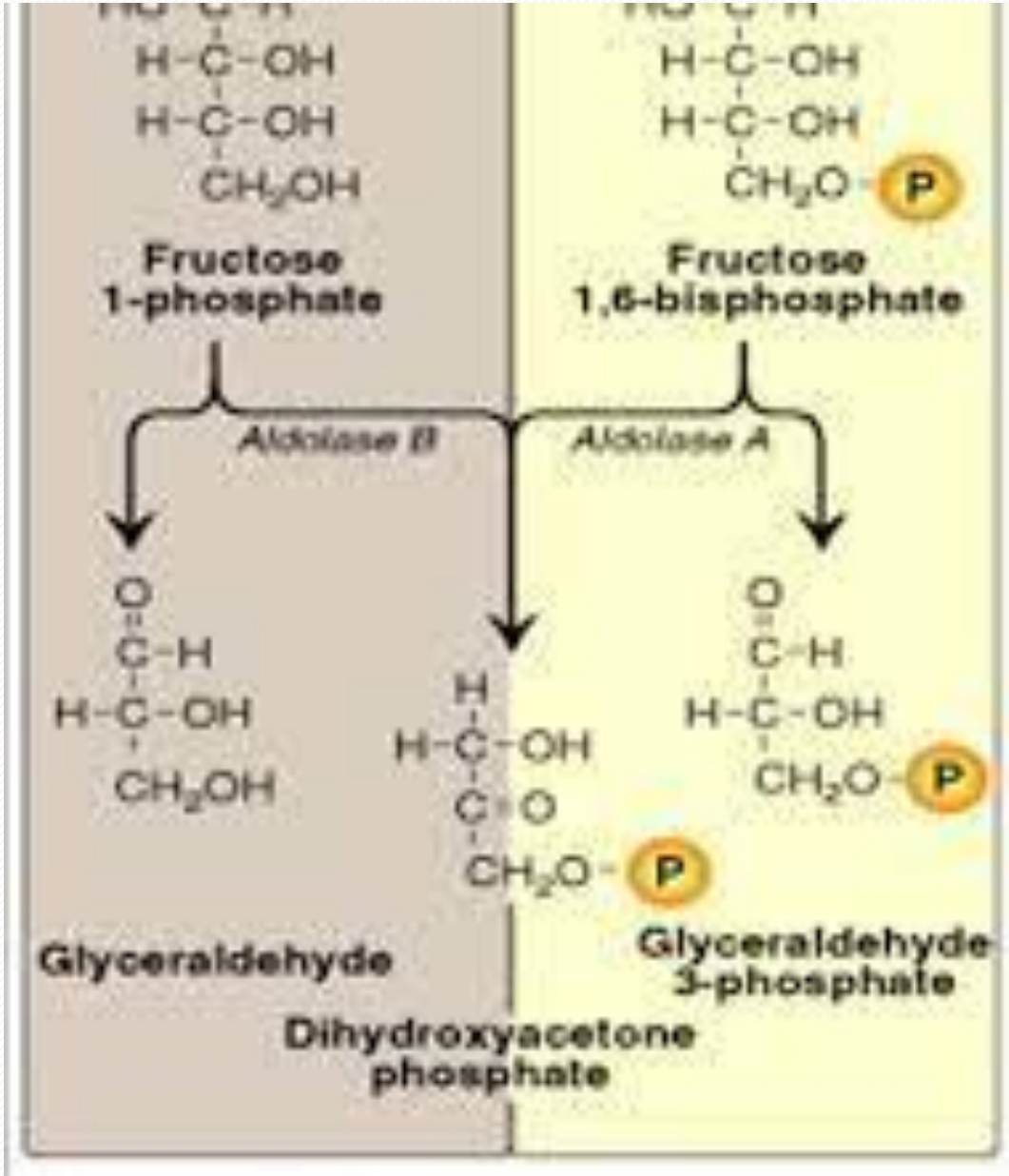
- Fructose is mostly phosphorylated by fructokinase to fructose - 1-phosphates, present in liver,muscles , kidneys & intestine.

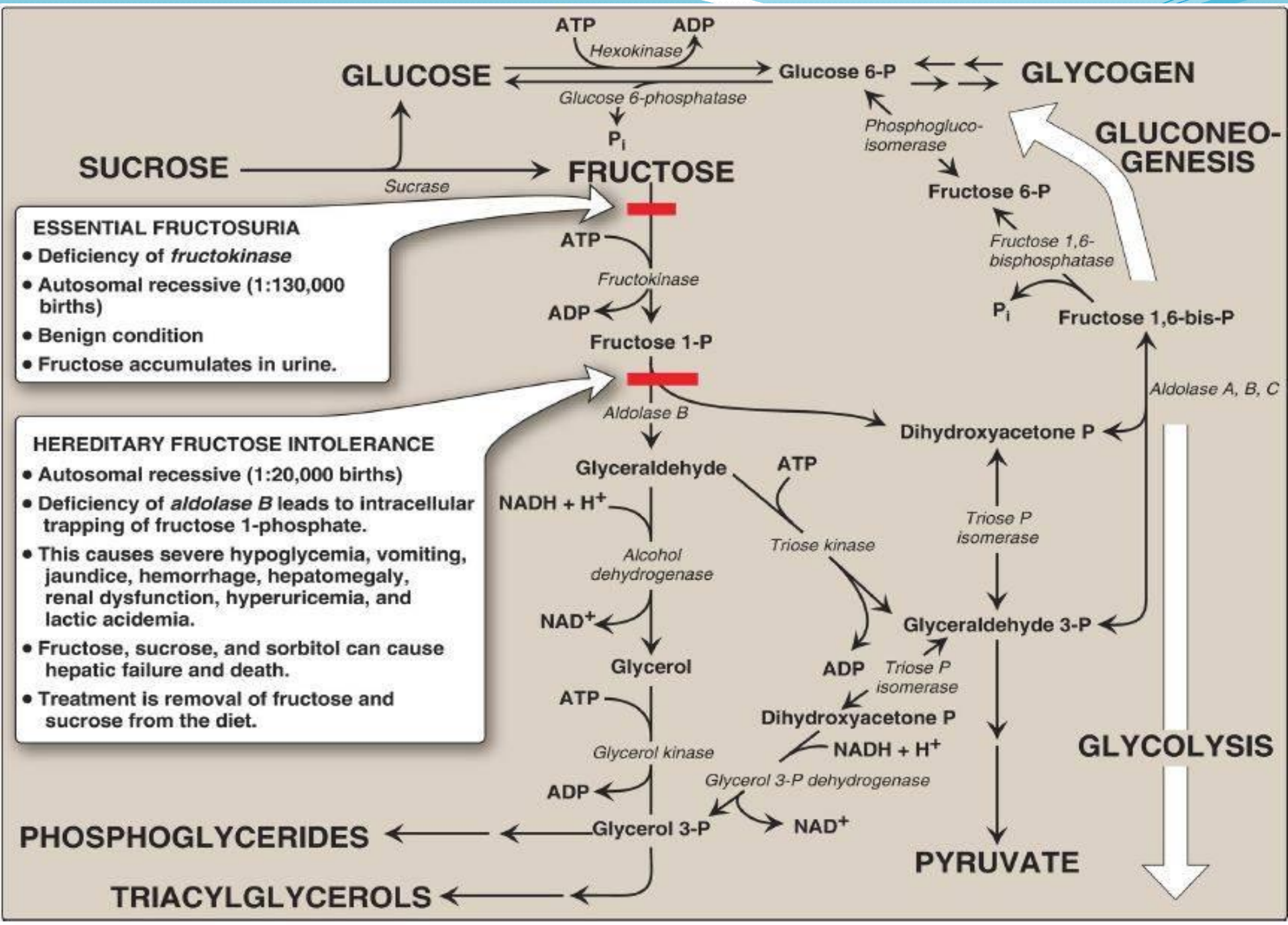


This enzyme cannot phosphorylates glucose.

Its activity is Insulin independent.

This is the major pathway for fructose phosphorylation.



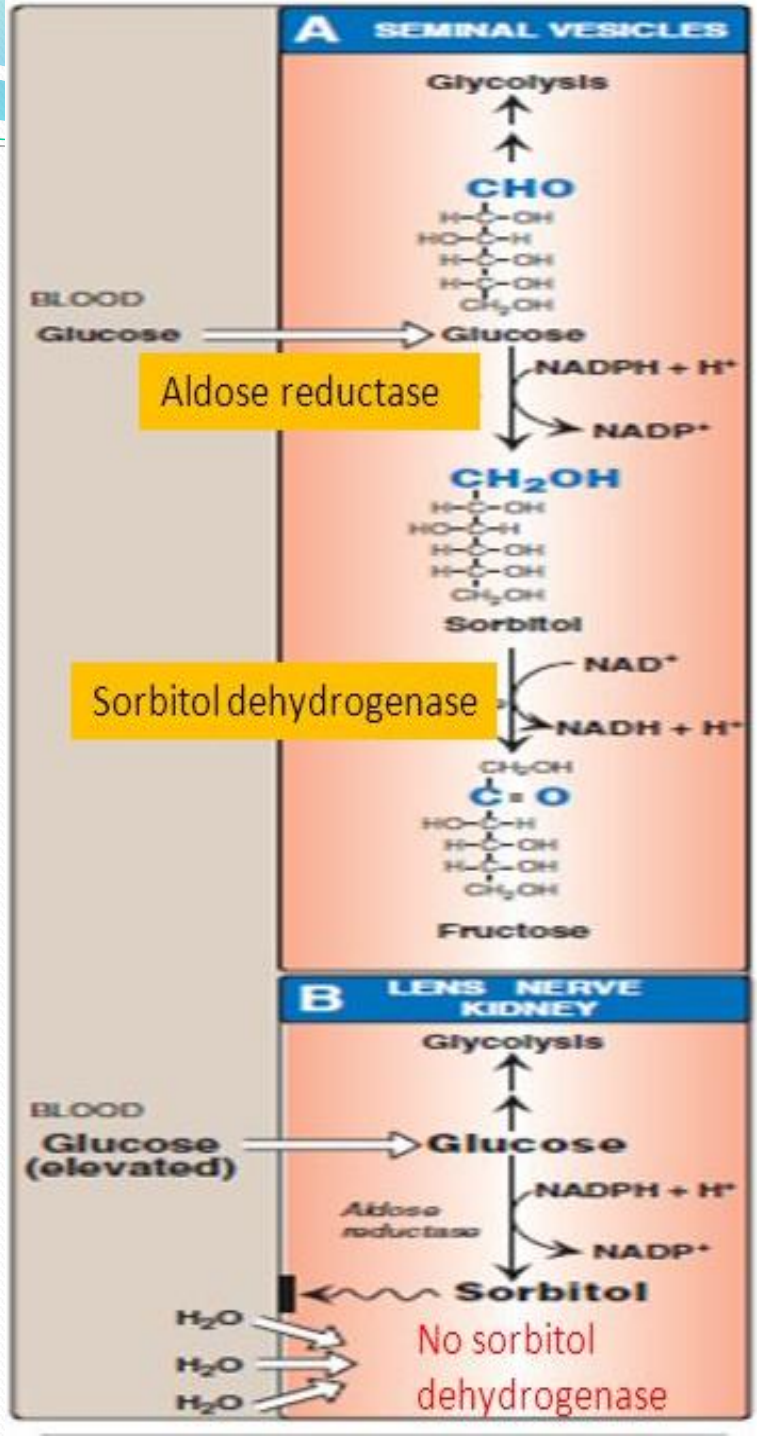

ATP
ADP
Hexokinase
GLUCOSE
Glucose 6-P
GLYCOGEN
Glucose 6-phosphatase
P_i
Phosphogluco-isomerase
GLUCONEO-GENESIS
SUCROSE
FRUCTOSE
Sucrase
Fructose 6-P
ESSENTIAL FRUCTOSURIA
• Deficiency of *fructokinase*
• Autosomal recessive (1:130,000 births)
• Benign condition
• Fructose accumulates in urine.
ATP
Fructose 1,6-bisphosphatase
Fructokinase
ADP
P_i
Fructose 1,6-bis-P
Fructose 1-P
Aldolase A, B, C
HEREDITARY FRUCTOSE INTOLERANCE
• Autosomal recessive (1:20,000 births)
• Deficiency of *aldolase B* leads to intracellular trapping of fructose 1-phosphate.
• This causes severe hypoglycemia, vomiting, jaundice, hemorrhage, hepatomegaly, renal dysfunction, hyperuricemia, and lactic acidemia.
• Fructose, sucrose, and sorbitol can cause hepatic failure and death.
• Treatment is removal of fructose and sucrose from the diet.
Aldolase B
Dihydroxyacetone P
Glyceraldehyde
ATP
$NADH + H^+$
Triose P isomerase
Triose kinase
Alcohol dehydrogenase
NAD^+
Glyceraldehyde 3-P
Glycerol
ADP
Triose P isomerase
ATP
Dihydroxyacetone P
$NADH + H^+$
GLYCOLYSIS
Glycerol kinase
Glycerol 3-P dehydrogenase
ADP
PHOSPHOGLYCERIDES
Glycerol 3-P
NAD^+
PYRUVATE
TRIACYLGLYCEROLS

CONVERSION OF GLUCOSE TO FRUCTOSE VIA SORBITOL:

- SITES OF SYNTHESIS OF SORBITOL:
- Lens, retina, schwann cells of peripheral nerves, liver, kidney, placenta, red blood cells and cells of the ovaries and seminal vesicals.

EFFECT OF HYPERGLYCEMIA ON SORBITOL METABOLISM:

Elevated intracellular glucose concentration and adequate supply of NADPH cause aldose reductase to produce significant increase in the amount of sorbitol,which cannot pass efficiently through the cell membranes and in turn remain trapped in the cell.



EFFECT OF HYPERGLYCEMIA ON SORBITOL METABOLISM:

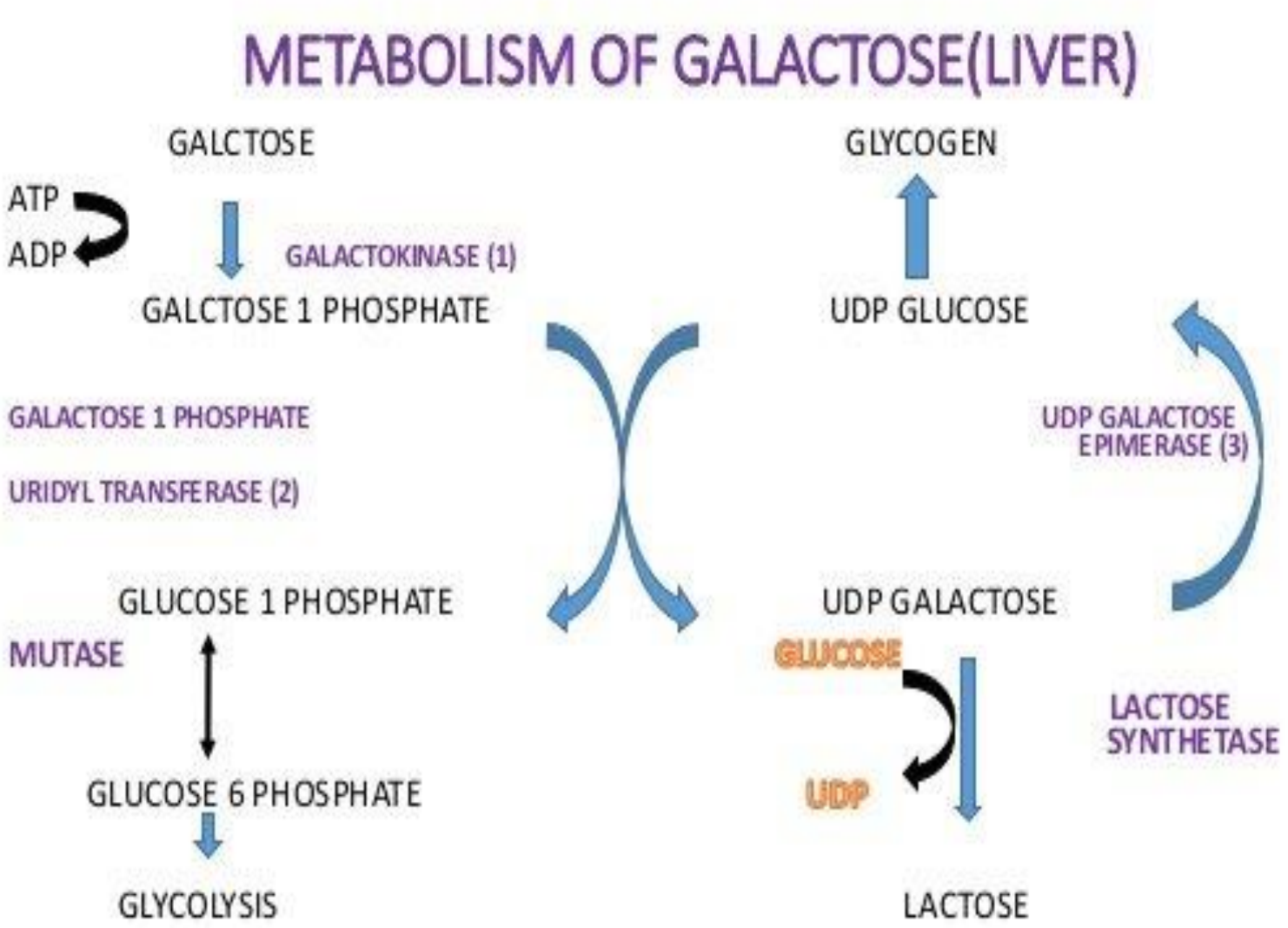
- This is exacerbated when sorbitol dehydrogenase is low or absent(in lens , retina , kidney, nerve cells).
- As a result sorbitol accumulates in these cells causing strong osmotic effects and therefore cell swelling as a result of water retention.

PATHALOGICAL ALTERATIONS ASSOCIATED WITH DIABETES:

1. Cataract formation.
2. Peripheral neuropathy.
3. Diabetic nephropathy.
4. Diabetic retinopathy.

GALACTOSE METABOLISM

- Major dietary source of galactose is LACTOSE
- Obtained from milk and milk products
- Galactose can also be obtained from lysosomal degradation of complex CHO like glycoproteins and glycolipids
- Entry into cells is not insulin dependent

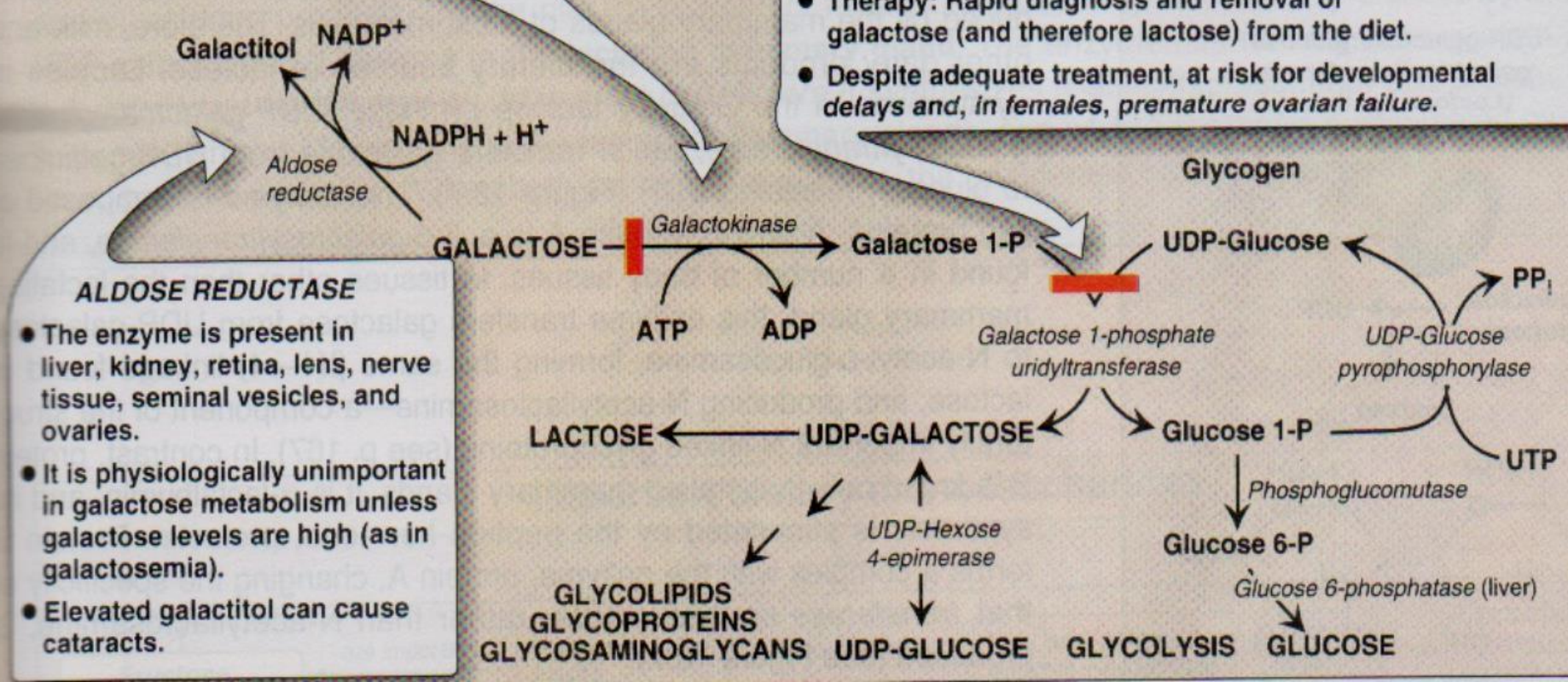

METABOLISM OF GALACTOSE(LIVER)
GALCTOSE
ATP
ADP
GALACTOKINASE (1)
GALCTOSE 1 PHOSPHATE
GALACTOSE 1 PHOSPHATE
URIDYL TRANSFERASE (2)
GLUCOSE 1 PHOSPHATE
MUTASE
GLUCOSE 6 PHOSPHATE
GLYCOLYSIS
GLYCOGEN
UDP GLUCOSE
UDP GALACTOSE EPIMERASE (3)
UDP GALACTOSE
GLUCOSE
UDP
LACTOSE SYNTHETASE
LACTOSE

GALACTOKINASE DEFICIENCY

- Rare autosomal recessive disorder
- Causes elevation of galactose in blood (galactosemia) and urine (galactosuria)
- Causes galactitol accumulation if galactose is present in the diet.
- Elevated galactitol can cause cataracts.
- Treatment is dietary restriction.

CLASSIC GALACTOSEMIA

- *Galactose 1-phosphate uridyltransferase* (*GALT*) deficiency.
- Autosomal recessive disorder (1:30,000 births).
- Causes galactosemia and galactosuria, vomiting, diarrhea, and jaundice.
- Accumulation of galactose 1-phosphate and galactitol in nerve, lens, liver, and kidney tissue causes liver damage, severe mental retardation, and cataracts.
- Prenatal diagnosis is possible by chorionic villus sampling. Newborn screening is available.
- Therapy: Rapid diagnosis and removal of galactose (and therefore lactose) from the diet.
- Despite adequate treatment, at risk for developmental *delays and, in females, premature ovarian failure.*



ALDOSE REDUCTASE

- The enzyme is present in liver, kidney, retina, lens, nerve tissue, seminal vesicles, and ovaries.
- It is physiologically unimportant in galactose metabolism unless galactose levels are high (as in galactosemia).
- Elevated galactitol can cause cataracts.


Thank
You