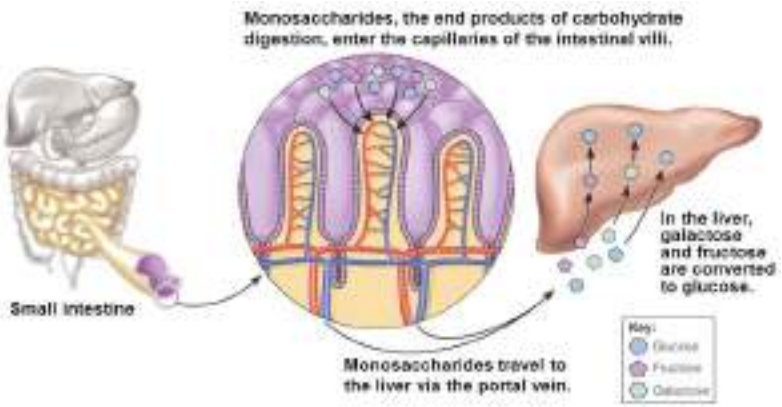
Fructose & Galactose Metabolism



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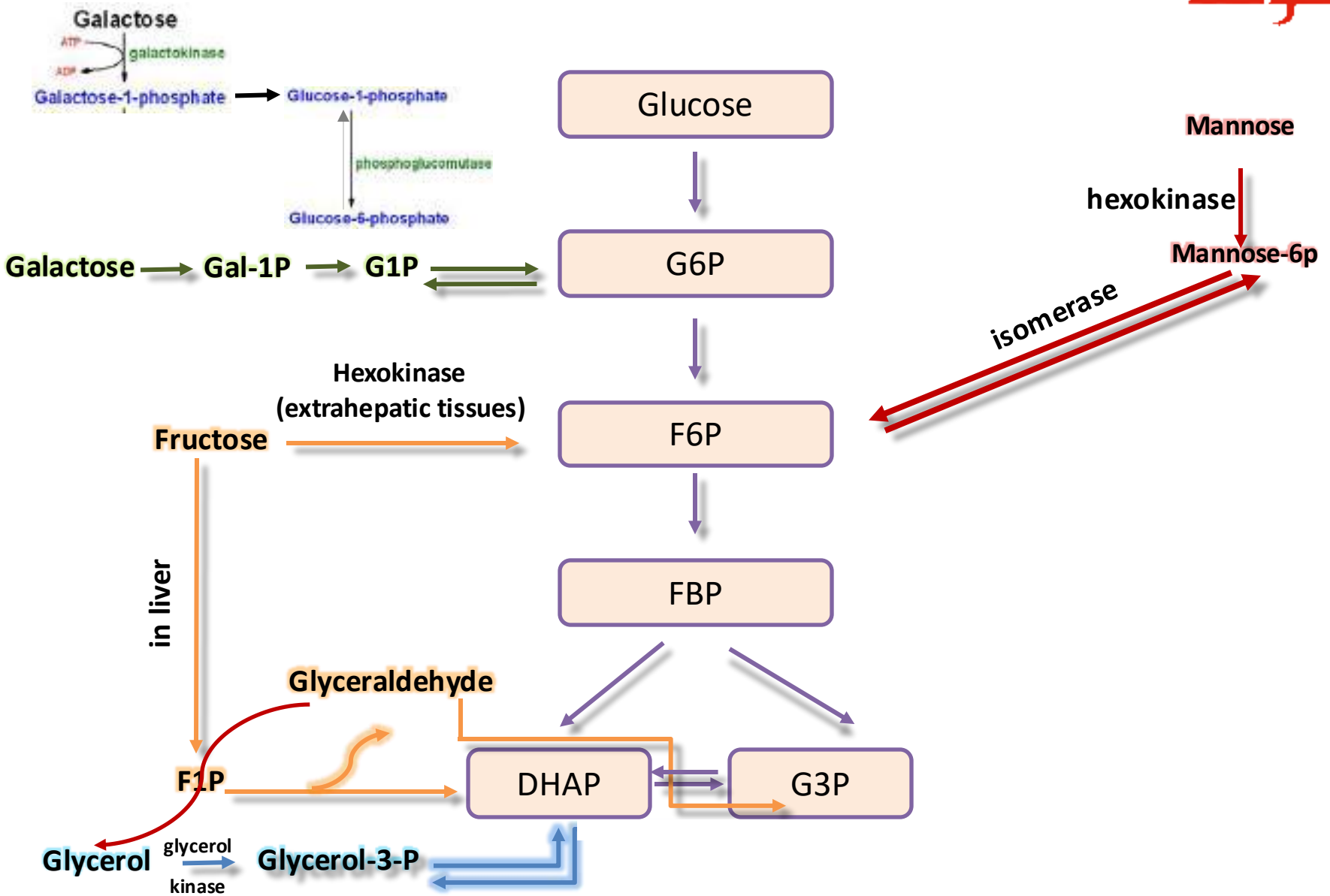
Other substrates enter Glycolysis



Fructose Sources

- **Dietary Sources of Fructose:**

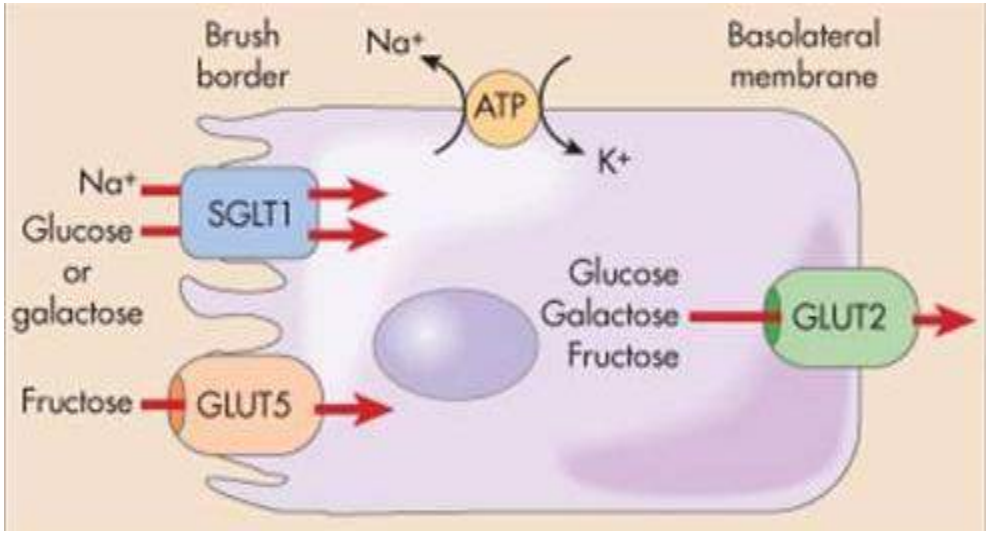
1. Sucrose (table sugar) consists of glucose and **fructose**

2. Free fructose: fruits **(fruit sugar)** honey, vegetables

3. Sweetener: High Fructose Corn Syrup **(HFCS)**

Fructose Absorption

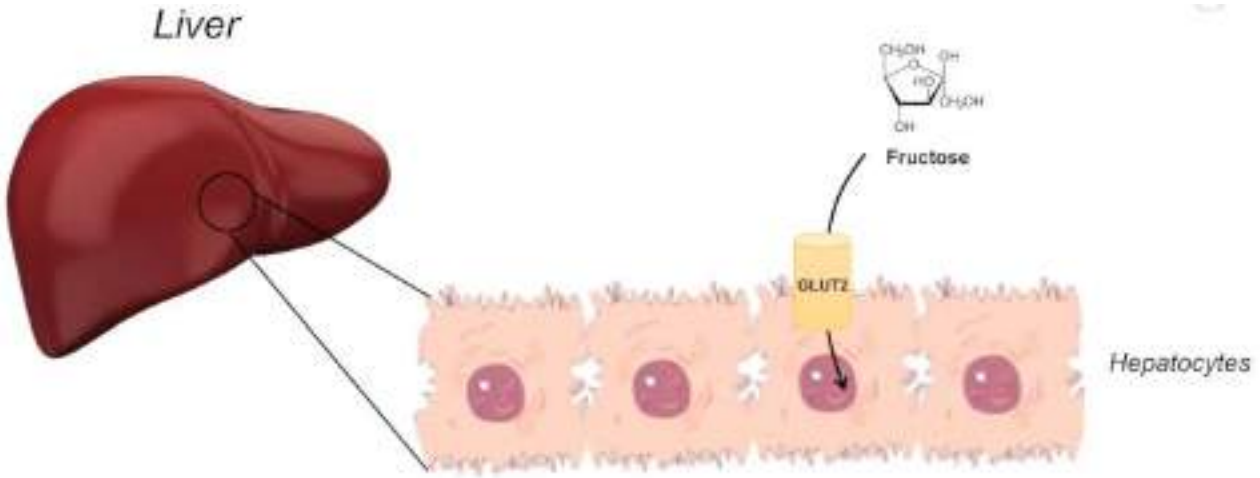
- Free fructose is absorbed from intestinal lumen through GLUT5 found at the apical membrane of the intestinal absorptive cells (enterocytes)
- Fructose then crosses to blood capillaries through GLUT2 at the basolateral membrane
- Fructose absorption and entrance into cells is insulin independent
- Glucose and Galactose are absorbed via SGLT1 at the apical end and then through GLUT2 at the basolateral membrane.



Fructose Metabolic Pathways

- Fructose can be converted into glycolytic intermediates by one of two metabolic pathways according to the cell type:

1. Major Pathway (called Fructose-1-phosphate OR fructolysis) in **Liver**



2. Minor Pathway in other tissues **(Extrahepatic cells like kidney and testis)**

the fructose is phosphorylated by hexokinase and the generated fructose-6-phosphate directly joins the glycolysis

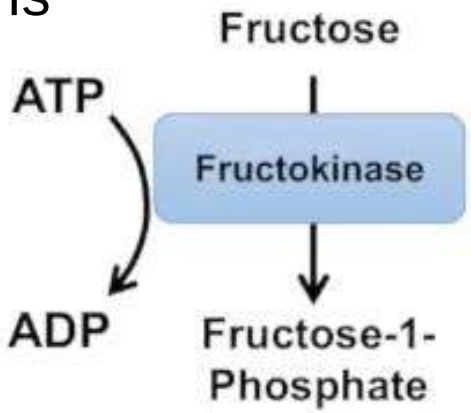
Fructose Metabolism in Liver

- Fructose-1-phosphate (F-1-P) pathway **(Fructolysis)** consists of 3 steps:

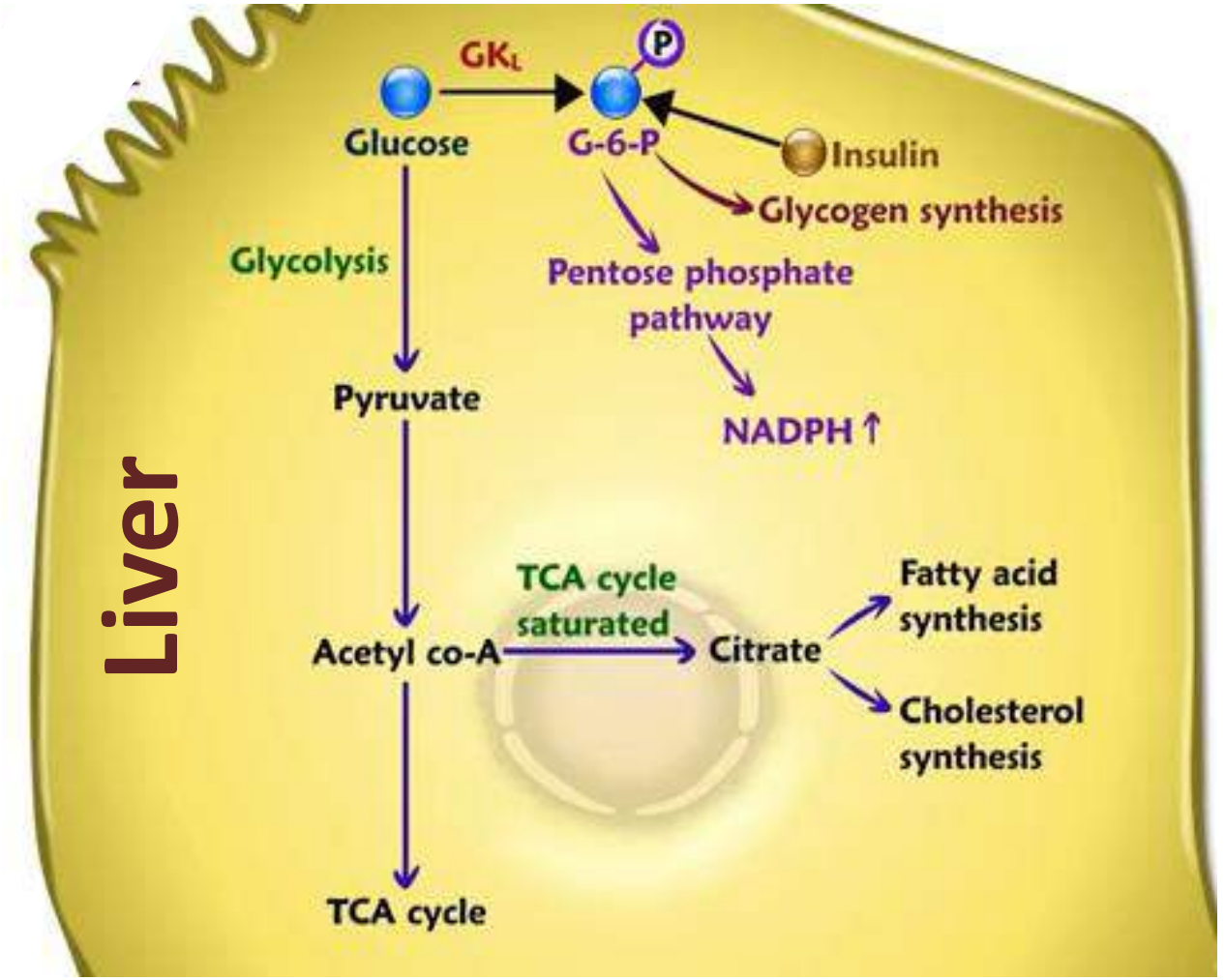
1. Phosphorylation of fructose by the hepatic enzyme **fructokinase** (irreversible) to generate fructose-1-phosphate.

- This step is important to trap fructose and maintain continuous flow inside hepatocytes and to destabilize fructose (an activation step)

- Fructose is removed from blood of diabetic patient at normal rate since the activity of fructokinase is not affected by insulin or sugar concentration like glucokinase



Glucose Metabolism in Liver

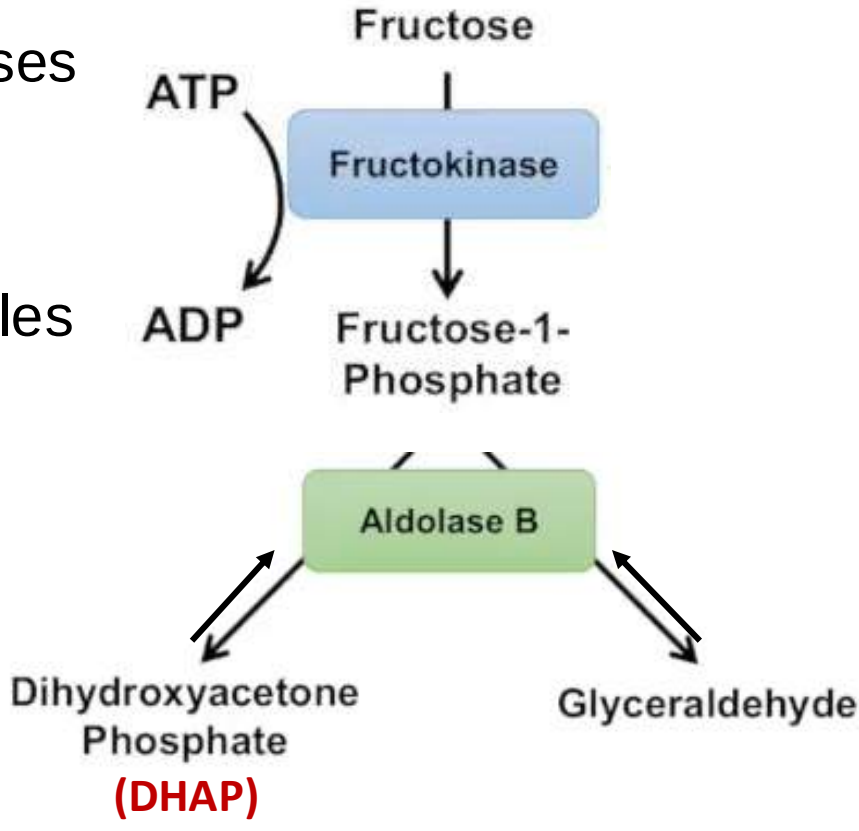


Fructose Metabolism in Liver

2. The reversible cleavage of F-1-P by aldolase b (also known as F-1-P Aldolase) to produce dihydroxyacetone phosphate **(DHAP)** and glyceraldehyde

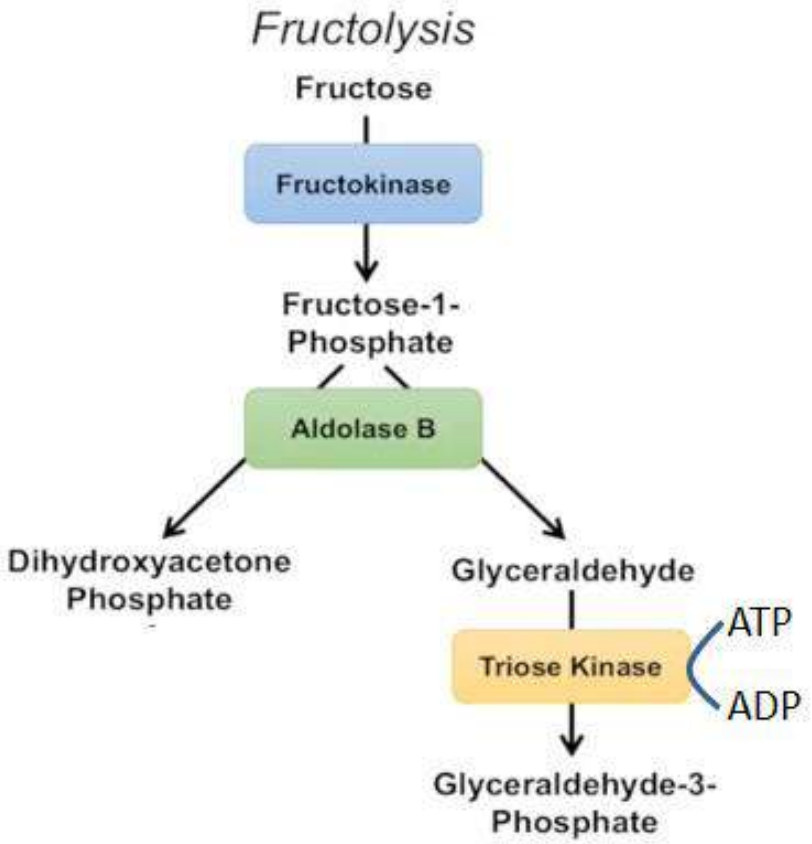
- Three different isoforms of aldolases (A, B & C) expressed in different tissues
  - Aldolase A: in most cells like muscles
  - Aldolase B: in liver and kidney
  - Aldolase C: in brain

- Only aldolase B can work on fructose-1-p as a substrate

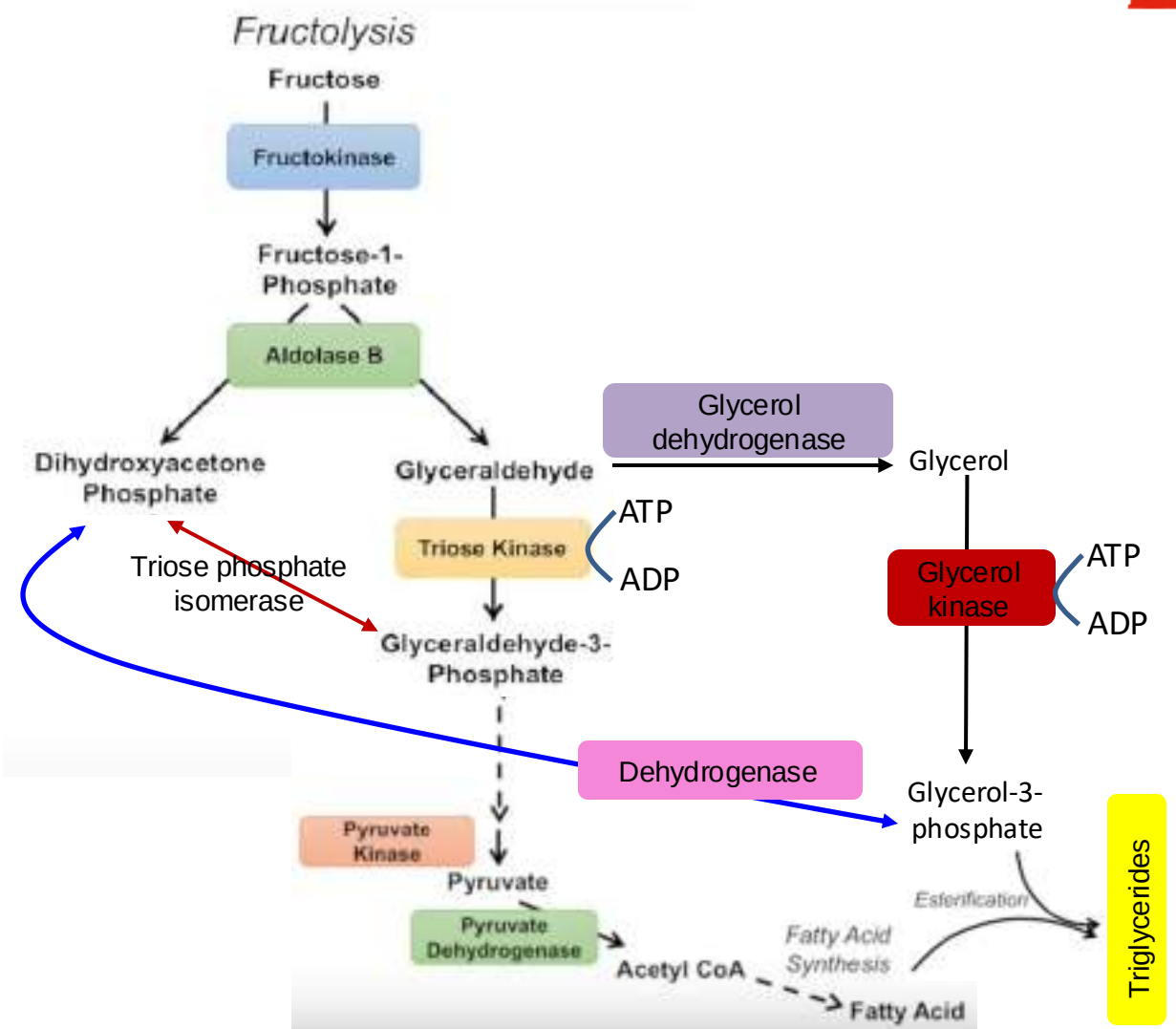


Fructose Metabolism in Liver

3. Phosphorylation of glyceraldehyde to form glyceraldehyde-3-phosphate (GAP) by triose kinase.



Fructose Metabolism in Liver



Fructose Metabolism in Liver

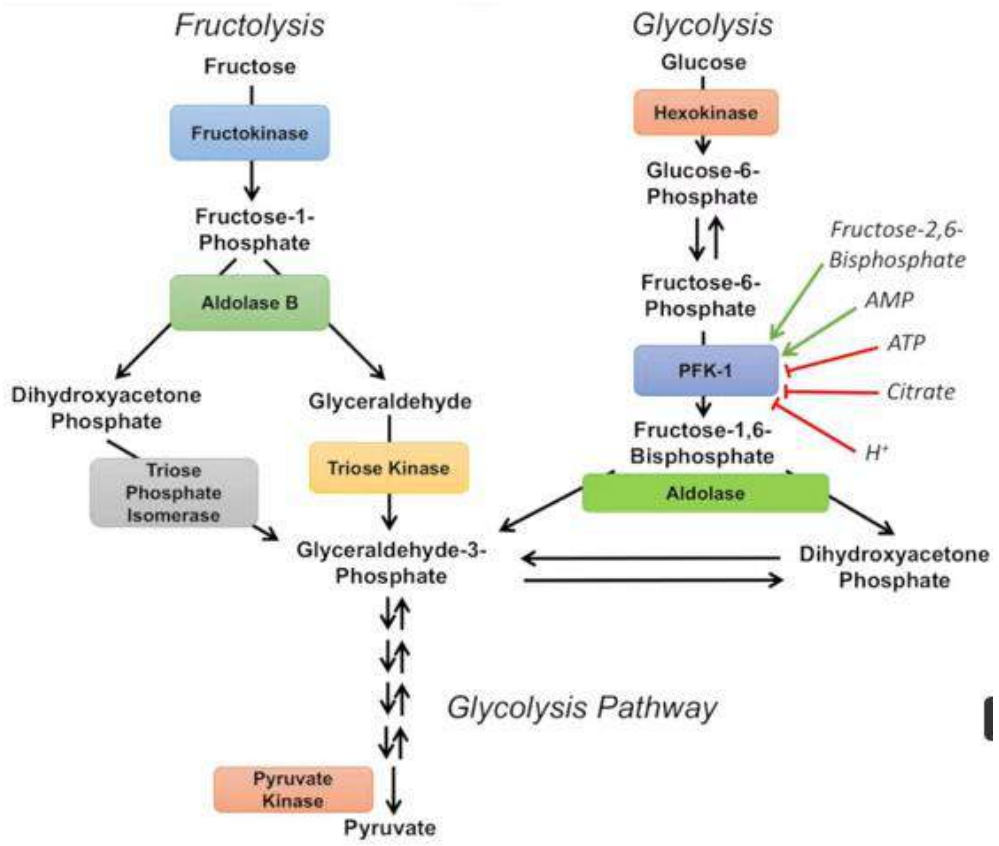
- Alternatively, glyceraldehyde is reduced to glycerol by glycerol dehydrogenase then phosphorylated by glycerol kinase to produce glycerol-3-phosphate
- Glycerol-3-phosphate is also reversibly converted to DHAP
- DHAP is reversibly converted by isomerase to GAP so can join the glycolysis at this point

- **Conclusion:** DHAP and glyceraldehyde are very important intermediates which connect carbohydrates with lipid metabolism
- The fat produced from fructose either stored in liver leading to non-alcoholic fatty liver disease or packaged inside VLDL and released into bloodstream to be processed by other tissues like adipose tissue

Fructose Metabolism in Liver is unregulated

- Unlike glycolysis in hepatocytes, fructolysis is uncontrolled because it bypasses the regulatory rate-limiting step catalyzed by PFK-1 found in glycolysis

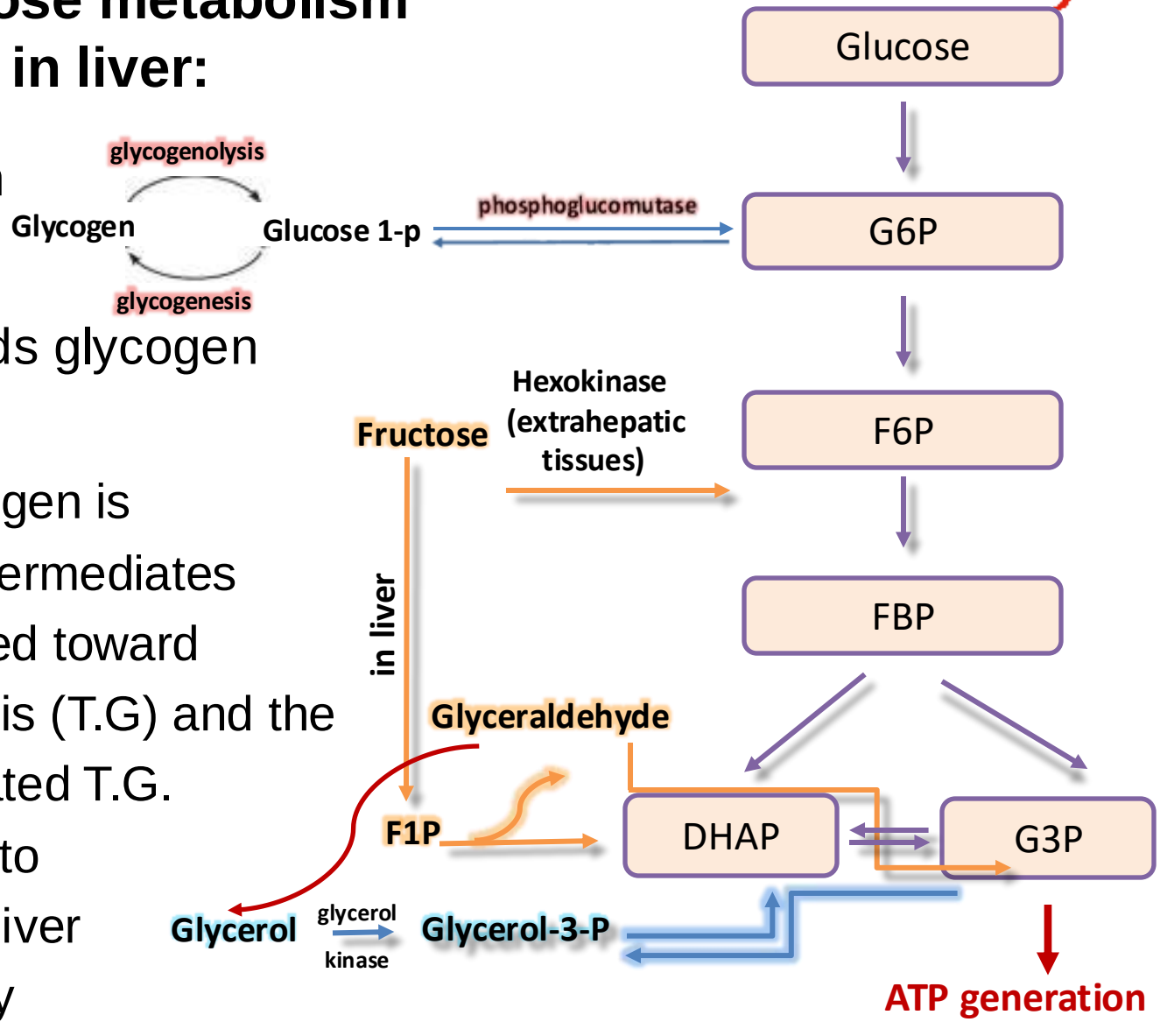
- Prolonged unregulated T.G production can lead to non-alcoholic fatty liver diseases, onset of obesity, CVD, high blood pressure and onset of diabetes.



Fates of Fructolysis intermediates

- **Fates of fructose metabolism intermediates in liver:**

1. ATP generation
2. Directed towards glycogen replenishment
3. Once liver glycogen is replenished, the intermediates are primarily directed toward triglyceride synthesis (T.G) and the prolonged unregulated T.G. formation can lead to non-alcoholic fatty liver disease and obesity



Does fructose a good energy source in diabetic patient ????!!!!!

- Diabetic patients tolerate fructose better than other sugars:

- its entrance to the cell and the activity of its metabolic enzymes are insulin-independent compared to glucose

- it skips the first two regulatory steps of glycolysis

Abnormalities in Fructose Metabolism

- **Inborn errors in fructose metabolism:**

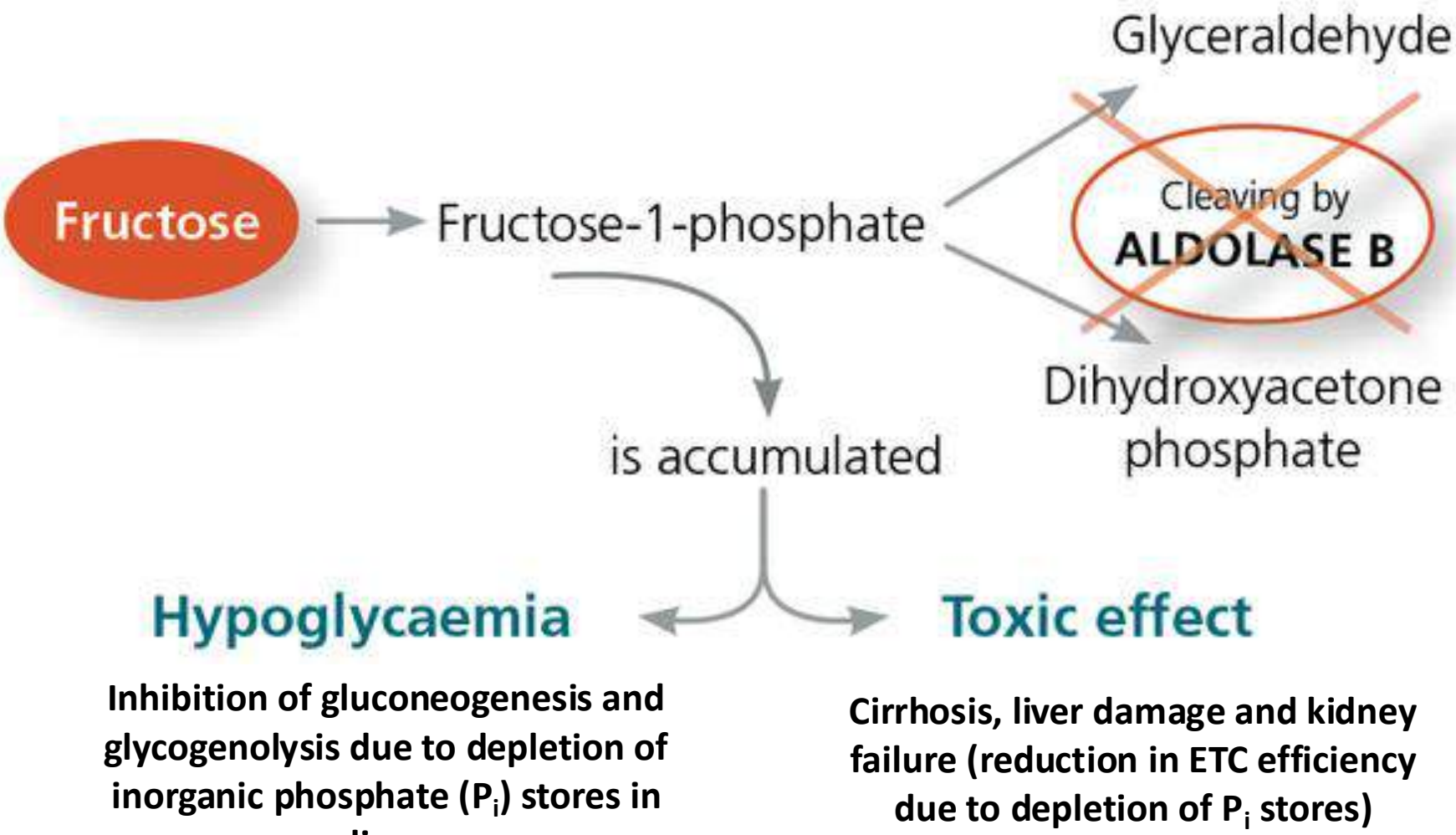
1. Essential fructosuria: deficiency of the hepatic fructokinase enzyme which results in the incomplete metabolism of fructose in the liver and consequently its excretion in the urine unchanged. It does not require a treatment as it is asymptomatic (benign condition). It is autosomal recessive

2. Hereditary fructose intolerance (HFI): deficiency of the aldolase B enzyme which results in the accumulation of fructose-1-phosphate (severe condition). Symptoms: vomiting, abdominal pain, **hypoglycemia**, **Jaundice**, hemorrhage, **hepatomegaly** and renal failure. It can be treated by limiting fructose intake (fructose, sucrose and sorbitol). It is autosomal recessive

- **Reduced phosphorylation potential:**

Intravenous (I.V.) infusion of fructose can lower the phosphorylation potential of liver cells by trapping P_i due to phosphorylation of fructose by fructokinase. Additionally, fructose in high amounts is lipogenic so fructose is contraindicated for total parenteral nutrition (TPN) solutions

Hereditary Fructose Intolerance (HFI)

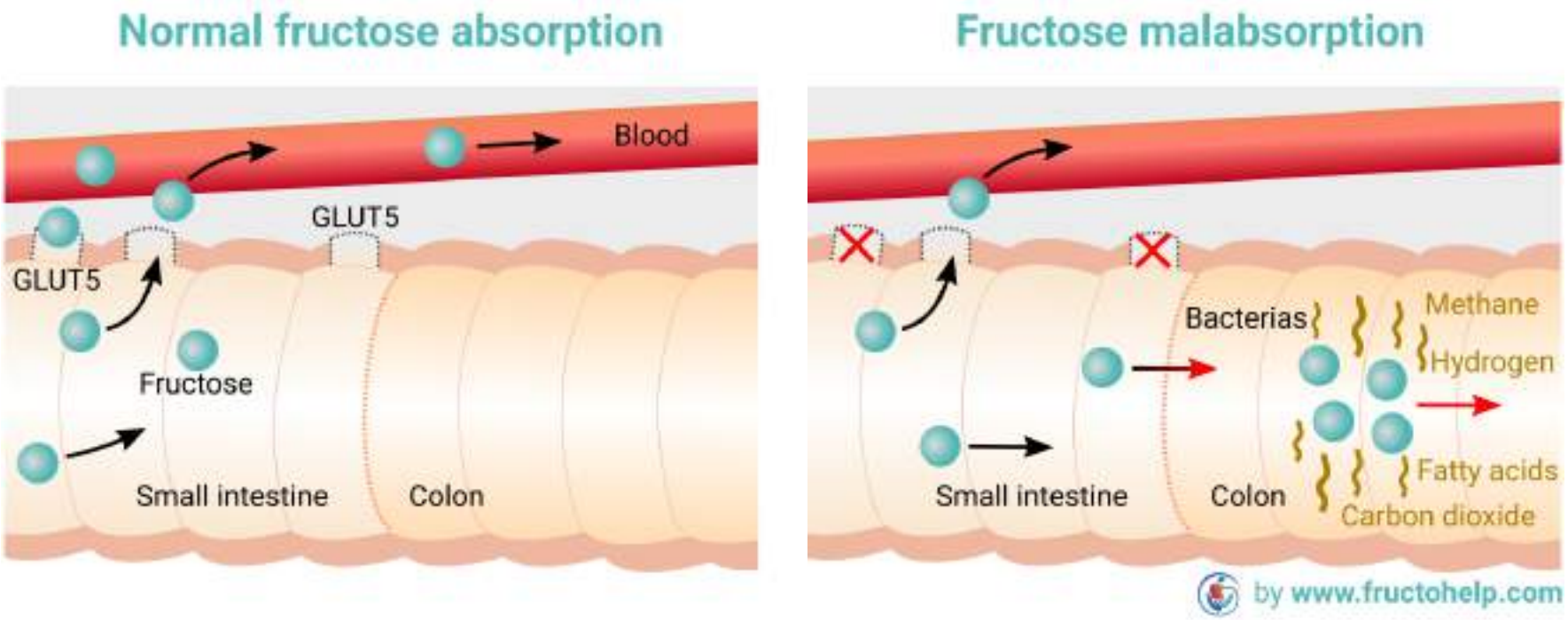


Inhibition of gluconeogenesis and glycogenolysis due to depletion of inorganic phosphate (P_i) stores in liver

Cirrhosis, liver damage and kidney failure (reduction in ETC efficiency due to depletion of P_i stores)

Dietary Fructose Intolerance (DFI)

- Dietary Fructose Intolerance **(DFI):** is also known as **fructose malabsorption** due to impaired absorption of fructose from small intestine as result of deficiency in fructose carriers (GLUT5)
- Symptoms: abdominal pain & cramps, diarrhea, bloating and flatulence, nausea



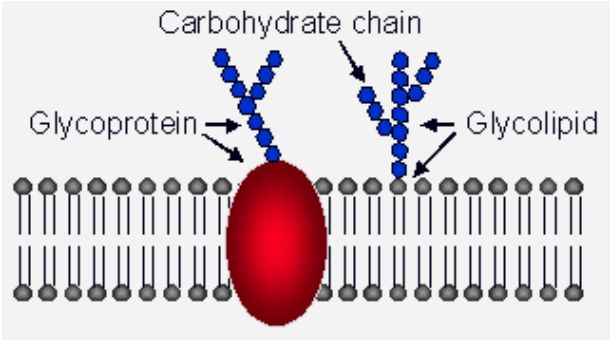
Galactose Sources

- **Dietary Sources of Galactose:**

1. Lactose (milk sugar) consists of glucose and **galactose**

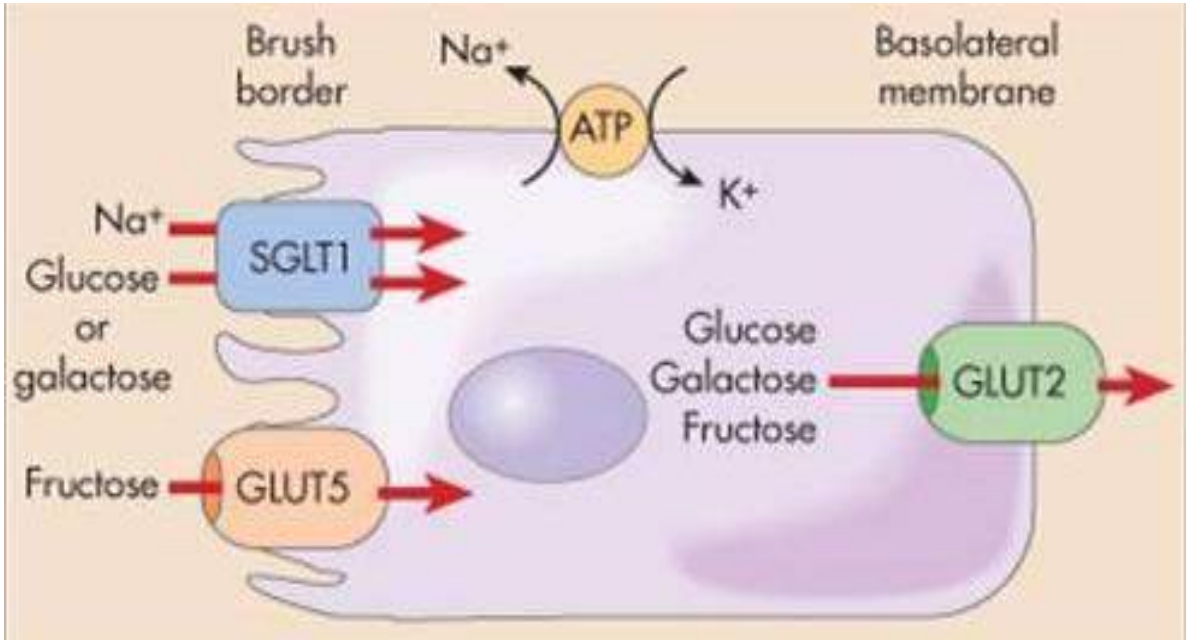
2. Free galactose: fruits & vegetables such as **avocadoes**, papaya, bananas, apples

3. Obtained also from lysosomal degradation of complex CHO (e.g. glycoproteins and glycolipids which are important membrane components)



Galactose Absorption

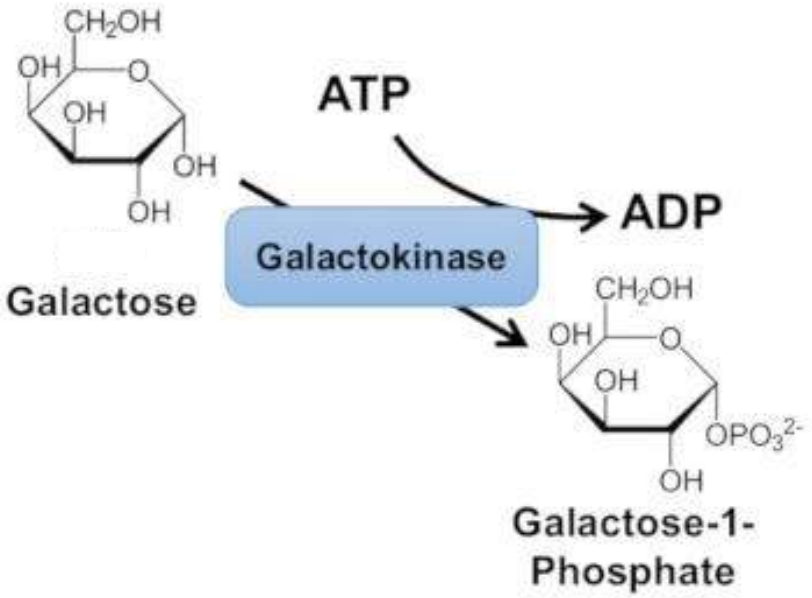
- Free galactose is absorbed from intestinal lumen through SGLT1 (sodium dependent) found at the apical membrane of the intestinal absorptive cells (enterocytes)
- Galactose then crosses to blood capillaries through GLUT2 at the basolateral membrane
- Galactose absorption and entrance into cells is **insulin independent**



Galactose Metabolism

- Unlike glucose, galactose as well as fructose do not have their own catabolic pathways and should be metabolized into molecules which are part of the glycolysis
- Galactose is metabolized to glucose-6-phosphate in 3 steps:

1. Phosphorylation of galactose to galactose-1-phosphate (Gal-1-p) by galactokinase (trapping, continuous influx of galactose and destabilization or activation)

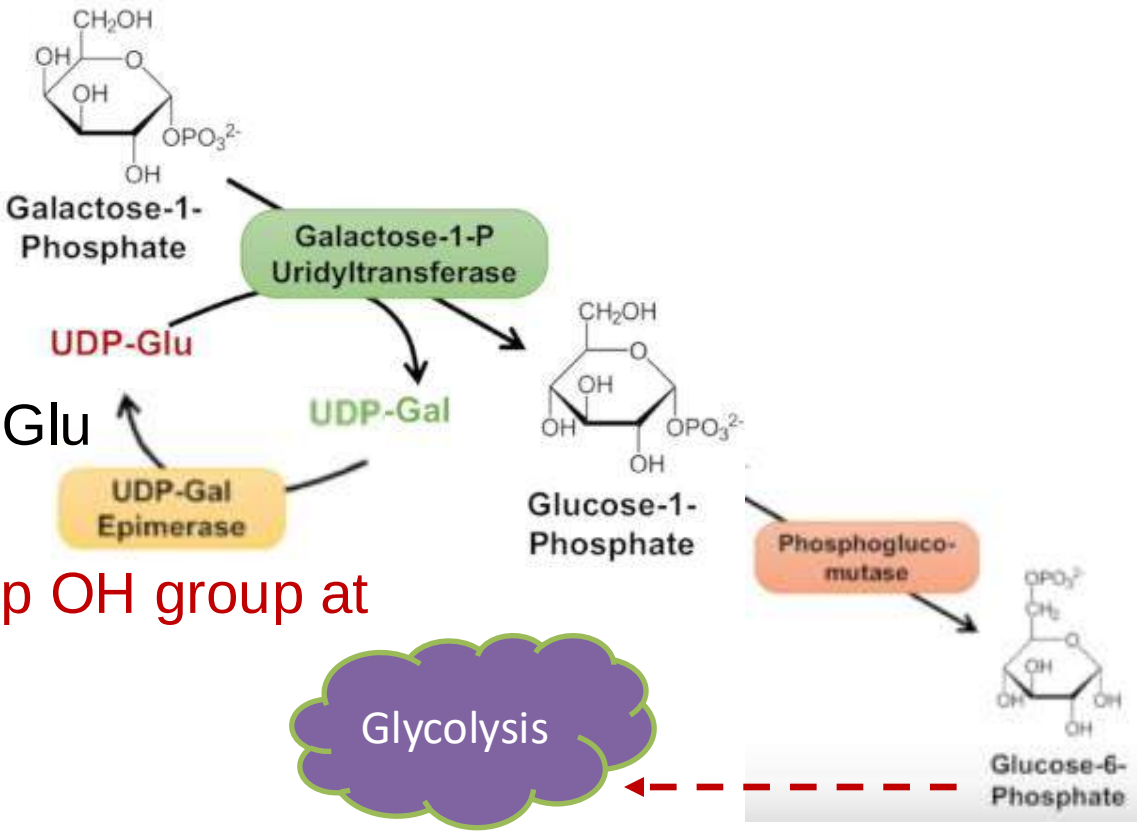


Galactose Metabolism

2. Gal-1-p Uridyltransferase enzyme transfers uridine monophosphate (UMP) group to Gal-1-p forming UDP galactose and glucose-1-phospate

3. Glu1-p is converted to glu6-p by the enzyme phosphoglucomutase (reversible)

4. Regeneration of UDP-Glu from UDP-Gal using epimerase enzyme (flip OH group at C4 from up to down)



Galactosemia

- Galactosemia: is a rare genetic disorder characterized by the inability to metabolize galactose due to deficiency in one of the three enzymes involved in galactose metabolism: