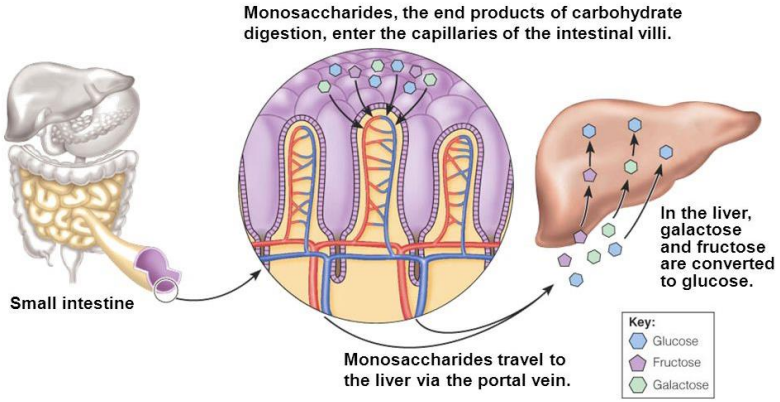
Fructose Metabolism

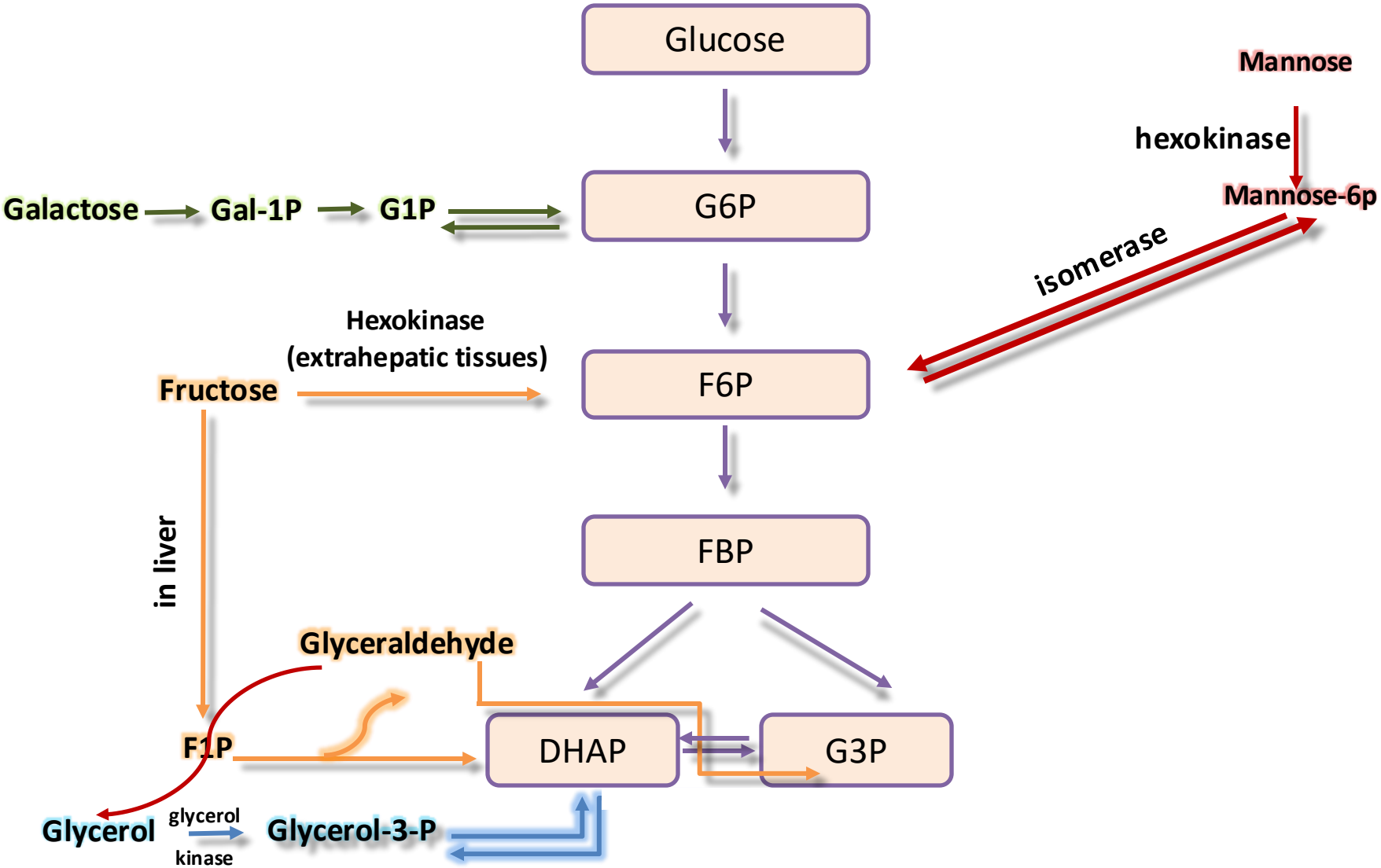


Dr. Nesrin Mwafi

Biochemistry & Molecular Biology Department

Faculty of Medicine, Mutah University

Other substrates enter Glycolysis

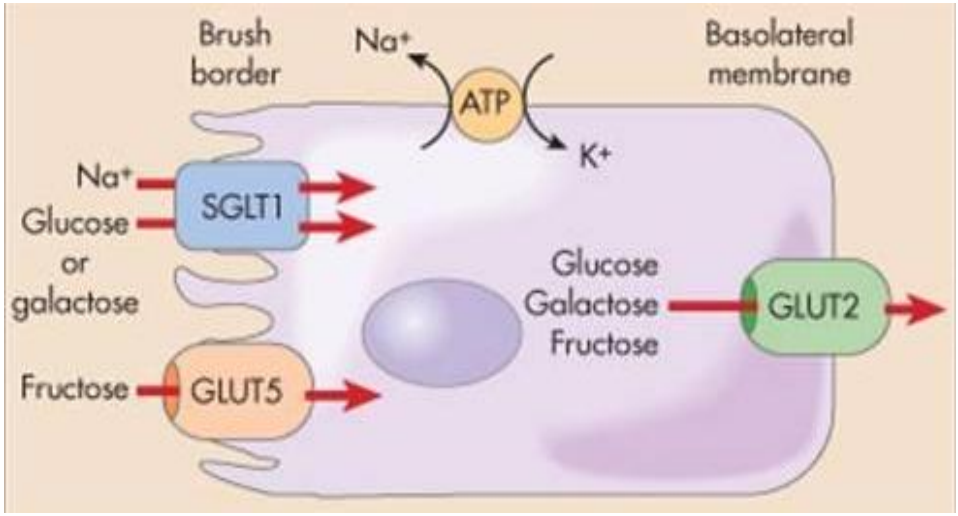


Fructose Sources

- **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

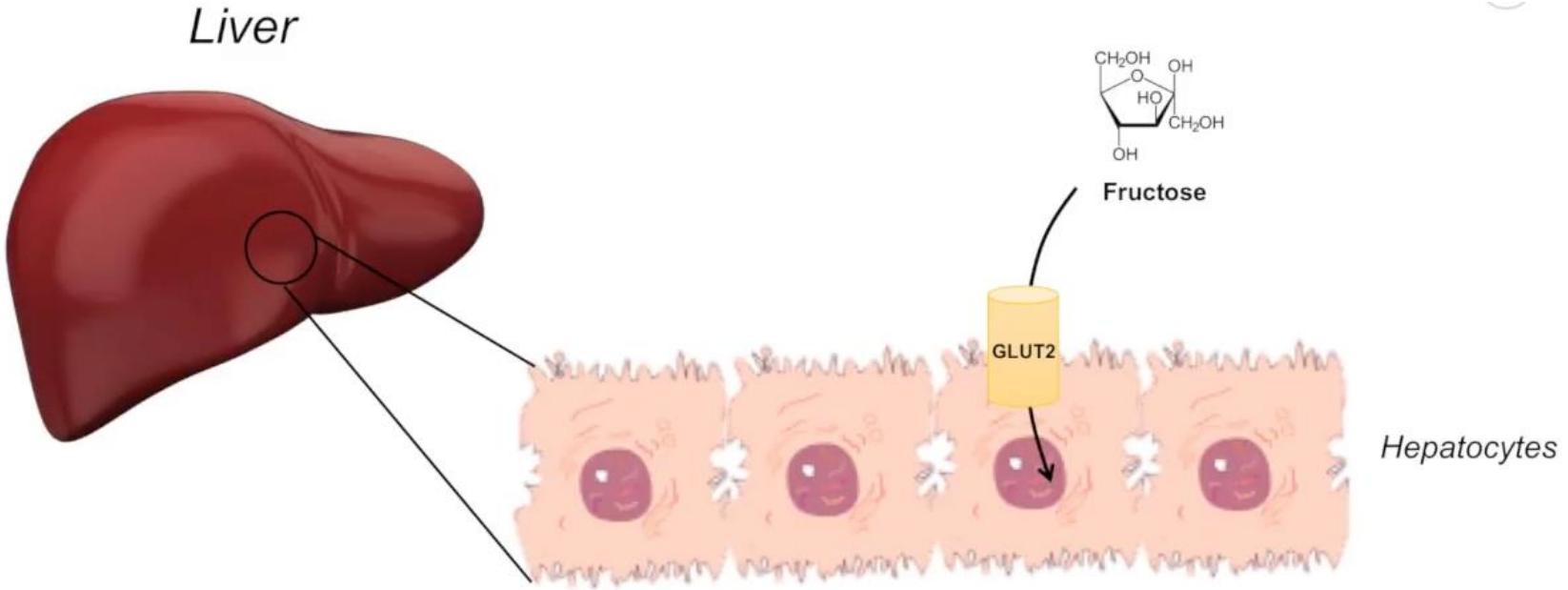
- Free fructose is absorbed from intestinal lumen through GLUT5 found at the apical membrane of the intestinal absorptive cells (enterocytes)
- Fructose then crosses to blood capillaries through GLUT2 at the basolateral membrane
- Fructose absorption and entrance into cells is insulin independent
- Glucose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



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.** This pathway is uncontrolled as it bypasses the regulatory step 1 and 3 in glycolysis



Fructose Metabolic Pathways

2. Minor Pathway in other tissues **(Extrahepatic cells like testis as fructose is considered as major source for energy required for sperm motility)**

- Fructose is phosphorylated by hexokinase and the generated fructose-6-phosphate directly joins the glycolysis in a highly controlled and regulated way

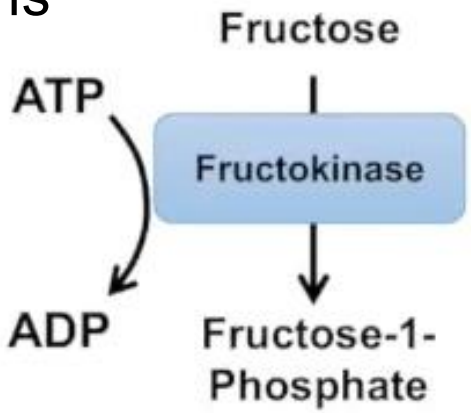
Fructose Metabolism in Liver

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

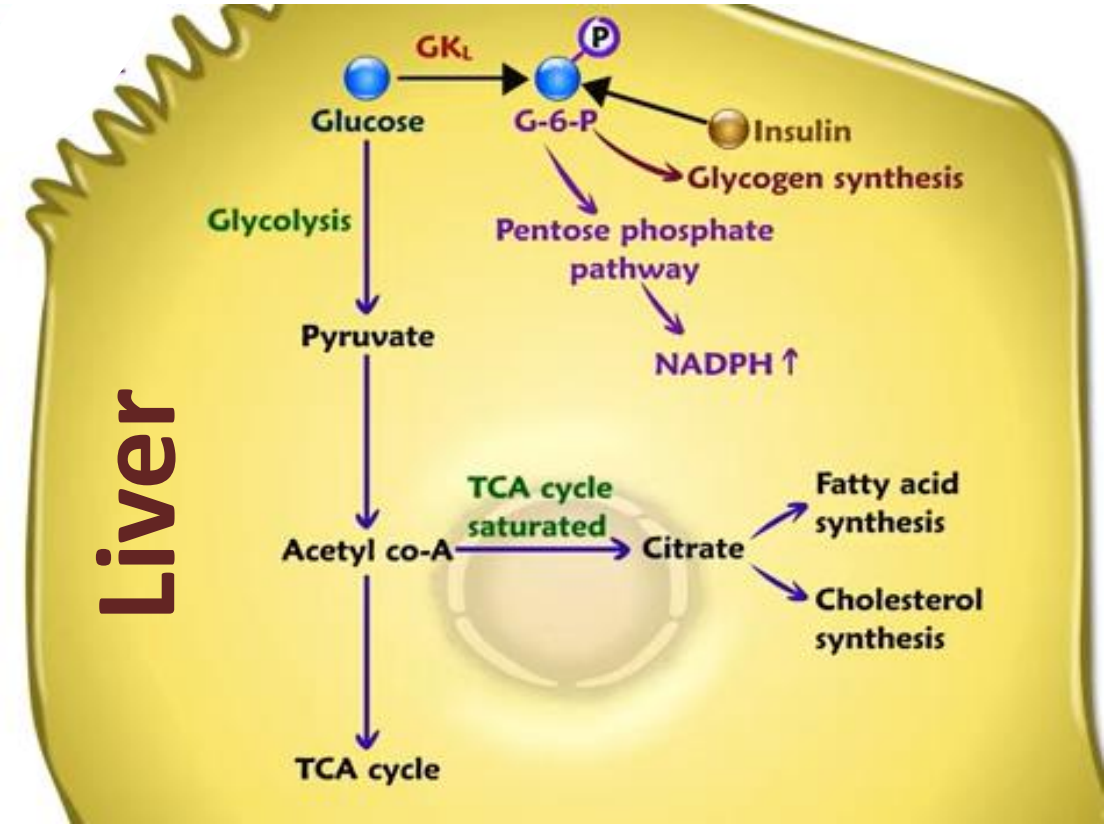
1. Phosphorylation of fructose by the hepatic enzyme **fructokinase** (irreversible) to generate fructose-1-phosphate.

- 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

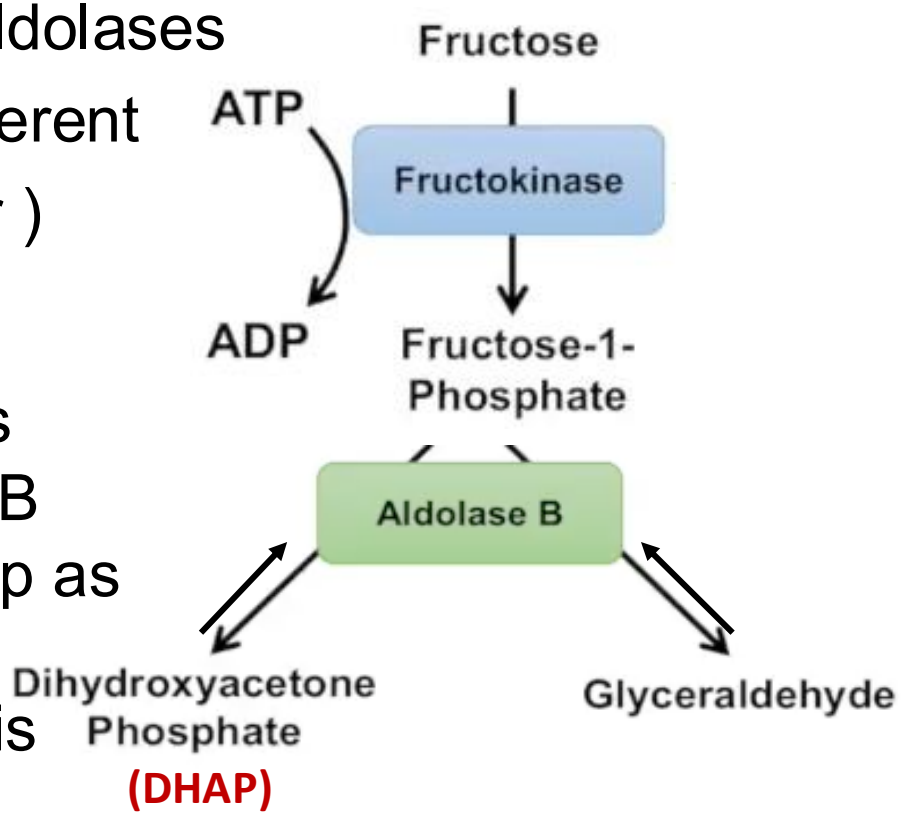


- Glycolysis is insulin-dependent and highly regulated. On the other hand, fructolysis is insulin independent and unregulated pathway

Fructose Metabolism in Liver

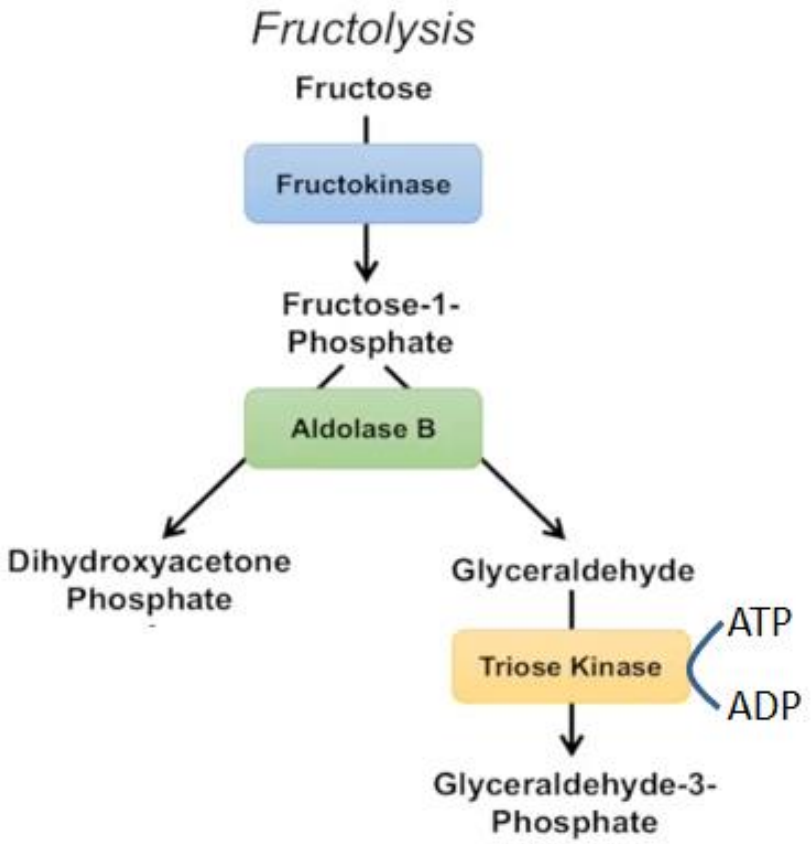
2. The reversible cleavage of F-1-P by aldolase B to produce dihydroxyacetone phosphate **(DHAP)** and glyceraldehyde

- Three different isoforms of aldolases (A, B & C) expressed in different tissues (aldolase B: in liver)
- All isoforms utilizes fructose 1,6 bisphosphate as substrate. But only aldolase B can also work on fructose-1-p as a substrate so it mediates both glycolysis and fructolysis

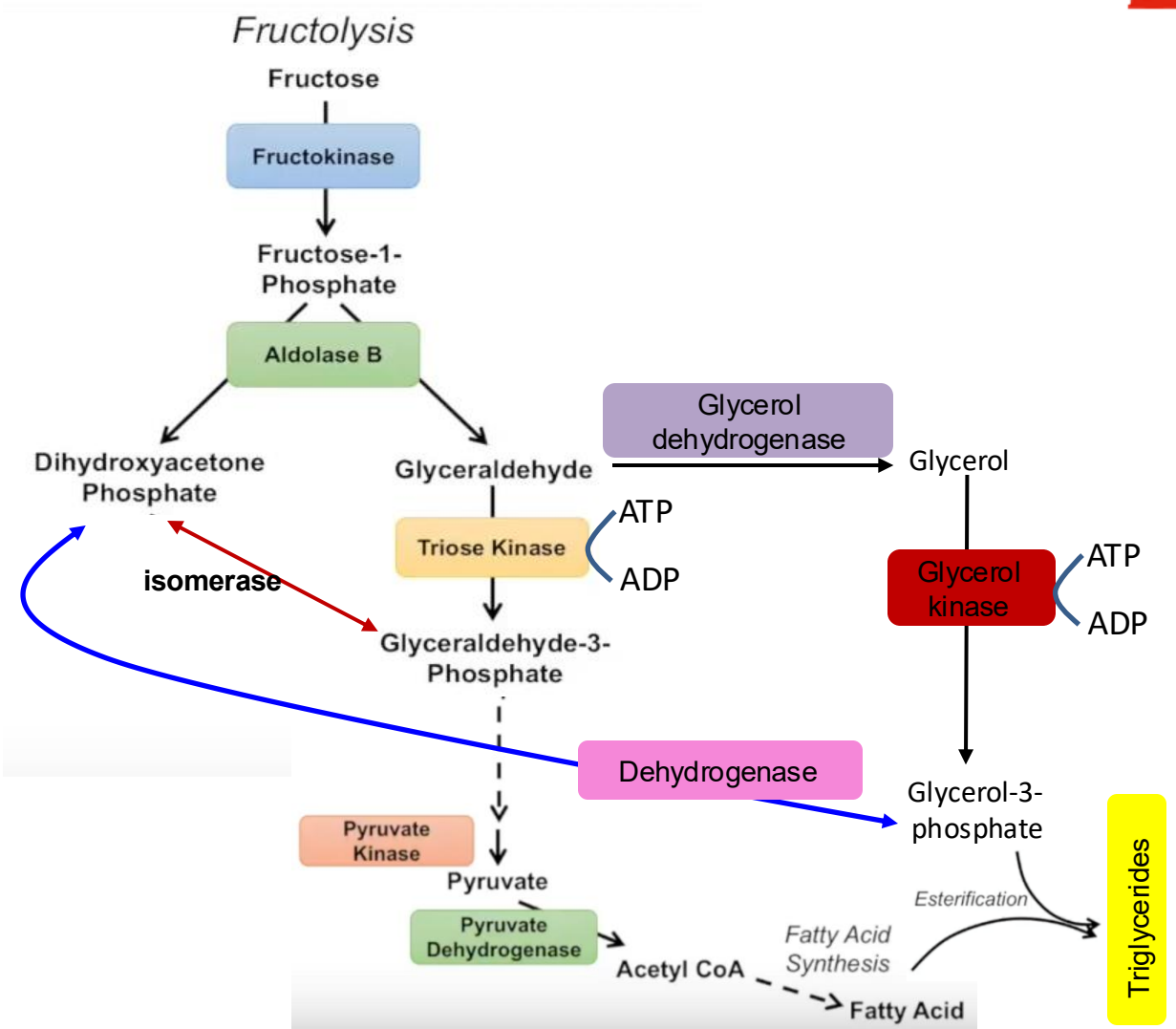


Fructose Metabolism in Liver

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



Fructose Metabolism in Liver



Fructose Metabolism in Liver

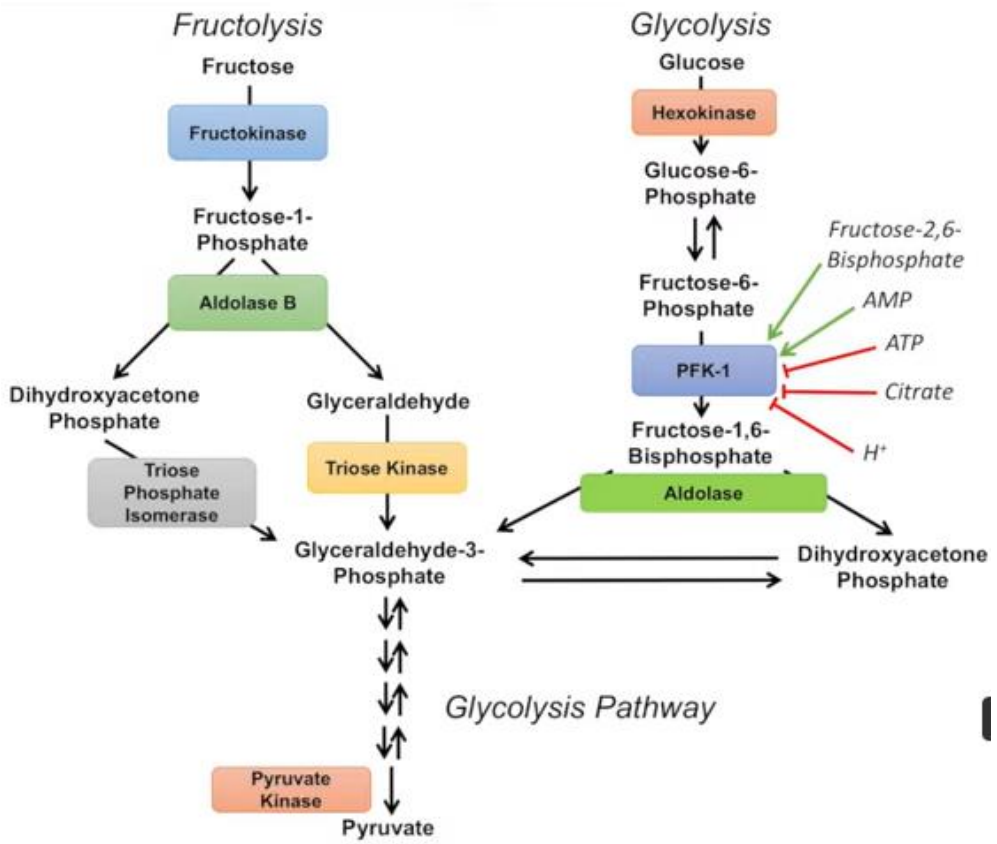
- Alternatively, glyceraldehyde is reduced to glycerol by glycerol dehydrogenase then phosphorylated by glycerol kinase to produce glycerol-3-phosphate
- Glycerol-3-phosphate is also reversibly converted to DHAP
- DHAP is reversibly converted by isomerase to GAP so can join the glycolysis at this point

- **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

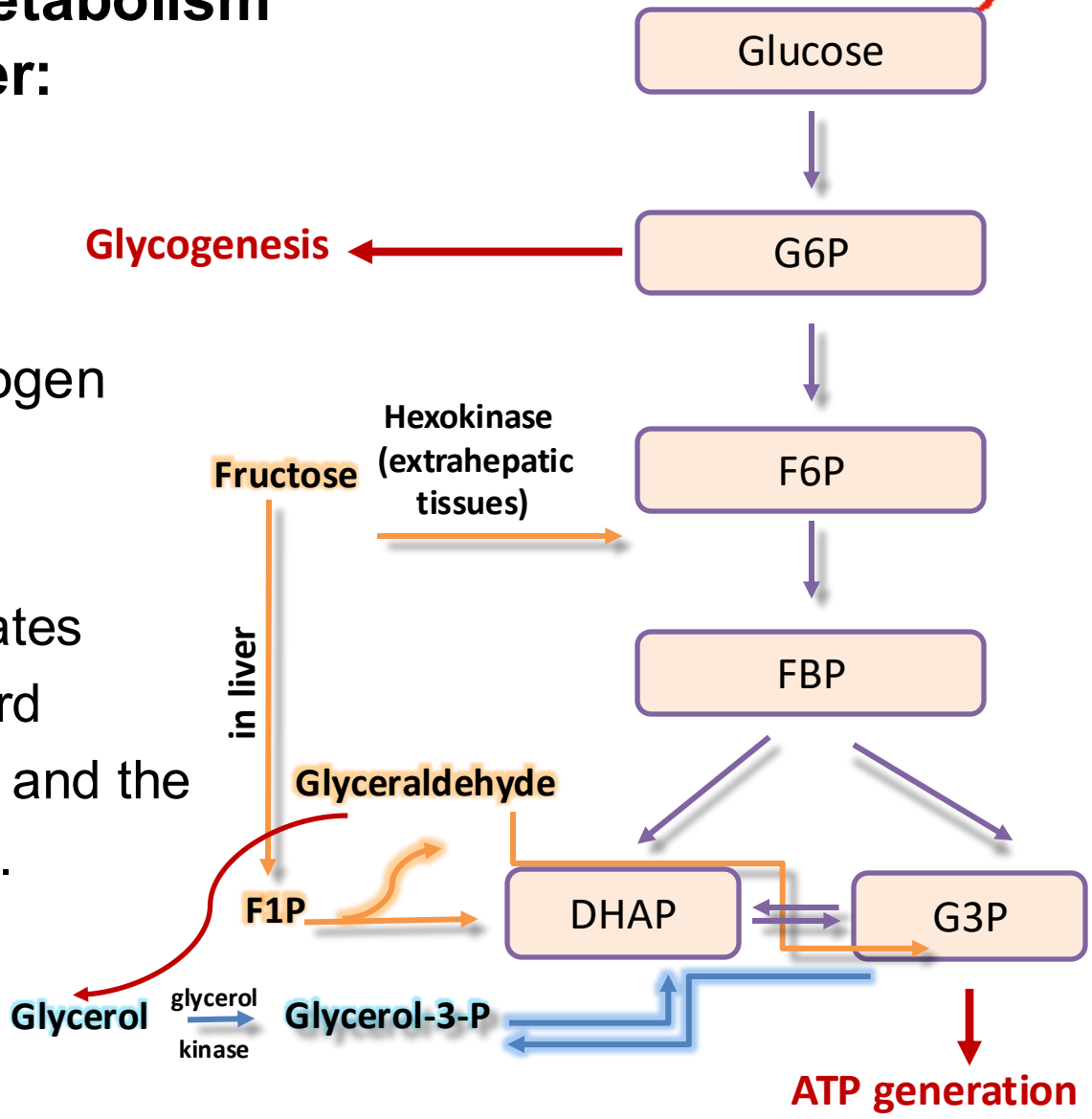
- Prolonged unregulated T.G production can lead to non-alcoholic fatty liver diseases, onset of obesity, CVD, high blood pressure and onset of diabetes.



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:**

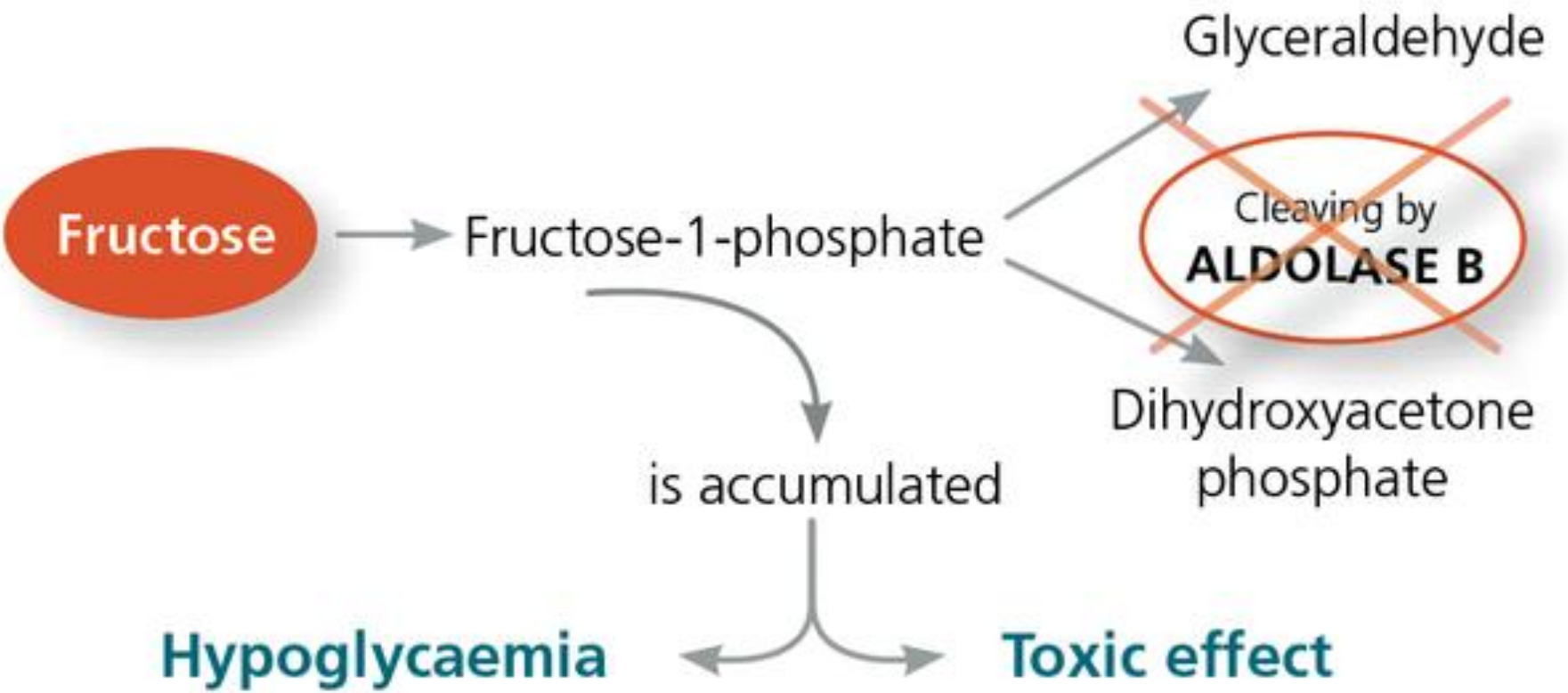
1. Essential fructosuria: deficiency of the hepatic fructokinase enzyme which results in the incomplete metabolism of fructose in the liver and consequently its excretion in the urine unchanged. It does not require a treatment as it is asymptomatic (benign condition). It is autosomal recessive

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 (healthy people):**

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)



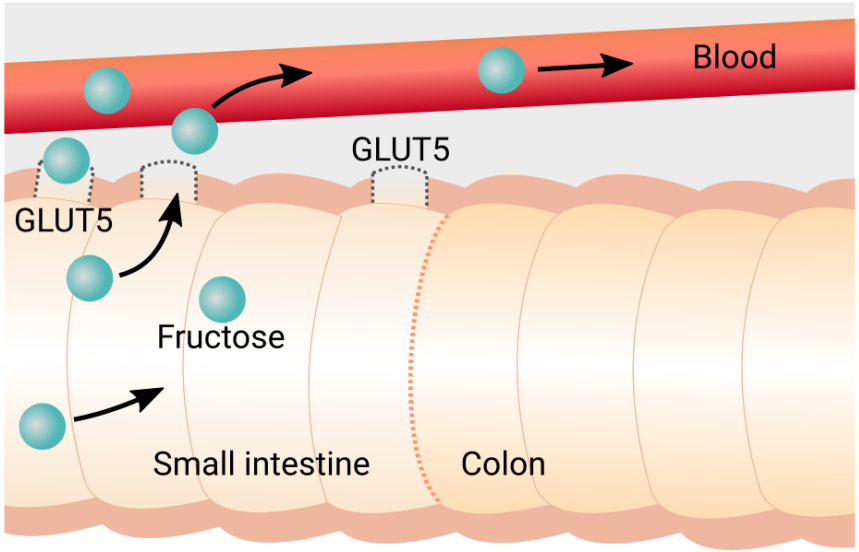
Inhibition of gluconeogenesis and glycogenolysis due to depletion of inorganic phosphate (P_i) stores in liver

Cirrhosis, liver damage and kidney failure (reduction in ETC efficiency due to depletion of P_i stores). Hepatomegaly and the associated nausea and abdominal pain due to accumulation of glycogen

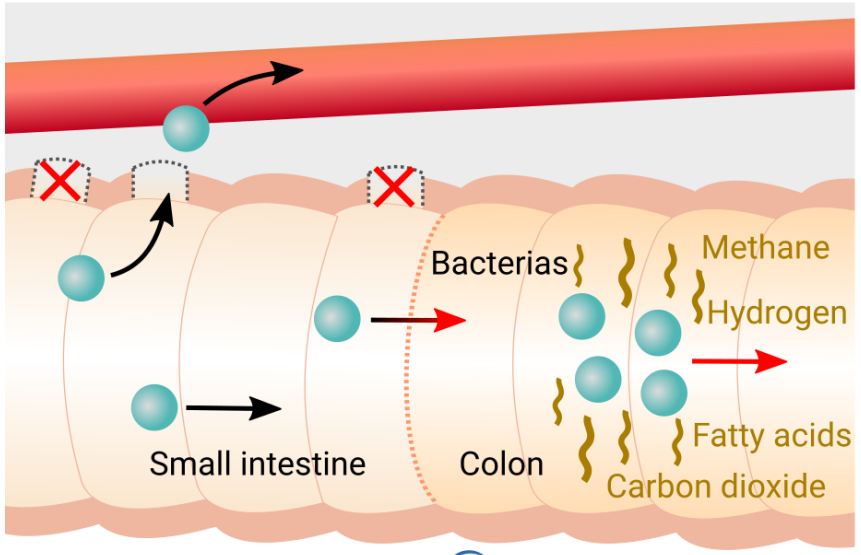
Dietary Fructose Intolerance (DFI)

- 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

Normal fructose absorption



Fructose malabsorption



by www.fructohelp.com