METABOLISM

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ARKAN ACADEMY

❖ Fructose metabolism

- Fructose represents 10% of the daily calorie intake
  - Sources: sucrose, Fruits, honey, high-fructose corn syrup
  - Its entry into the cells is **insulin independent** (Doesn't promote the secretion of insulin)
- It can be metabolized by 2 pathways:
  - **General pathway:** Where **Hexokinase** phosphorylates fructose into Fructose 6-phosphate which completes the glycolysis
    - ✓ This pathway is less preferred due to the low affinity of hexokinase to Fructose
  - **Specific pathway:** Where **fructokinase** phosphorylates fructose into Fructose 1-phosphate
    - ✓ **Aldolase B** breaks fructose 1-phosphate into dihydroxyacetone phosphate (**DHAP**) and **Glyceraldehyde**
    - ✓ DHAP is then isomerized into G3P by triosephosphate isomerase
    - ✓ Glyceraldehyde is phosphorylated into G3P
    - ✓ The 2 G3P then complete the glycolysis
    - ✓ The specific pathway is more preferred and faster because it **by-passes the rate limiting step** of glycolysis (which is catalyzed by phosphofructokinase 1)

Sucrase break sucrose into fructose and glucose

- Both fructokinase and hexokinase are ATP dependent
- In the general pathway and the glycolysis, fructose 1,6-bisphosphate is broken down by Aldolase A or B
  - In the specific pathway, only Aldolase B is used
  - Aldolase A in most tissues, aldolase B in liver, kidney and small intestines
  - Aldolase A acts on fructose 1,6 bisphosphate only, but Aldolase B can act on both fructose 1-phosphate and fructose 1,6-bisphosphate
  - **Low activity of aldolase B** causes **fructose intolerance**
- Fructose metabolism produces DHAP and G3P (or Glyceraldehyde) which can enter glycolysis or gluconeogenesis according to the conditions in the cell
- Disorders of Fructose Metabolism:
  - **Fructokinase Deficiency:** It is an autosomal recessive hereditary disorder causes accumulation of fructose in the urine (fructosuria)
    - ✓ This disorder is benign (mild) because it can be compensated by hexokinase
  - **Aldolase B Deficiency:** Hereditary fructose intolerance (Fructose Poisoning)
    - ✓ Severe disturbance in liver and kidney metabolism
    - ✓ This deficiency causes the accumulation of fructose 1-phosphate, which decreases inorganic phosphate level preventing phosphorylation of AMP into ATP (**ATP decreases**, **AMP accumulates** and then degraded)
    - ✓ It causes jaundice, hepatomegaly, vomiting, hemorrhage and can cause **hepatic failure** due to reduced hepatic ATP which can cause death
    - ✓ It can cause hypoglycemia, lacticacidemia (lactic acidosis) and hyperuricemia
    - ✓ These patients should avoid fructose, sucrose and sorbitol
- **Aldose reductase:** An enzyme that converts **glucose into sorbitol** (sugar alcohol)
  - During this reaction, NADPH is oxidized into $NADP^+$
  - It is found in the lens, retina, schwan cells, liver, kidney, ovaries, and seminal vesicle
- **Sorbitol dehydrogenase:** An enzyme that converts **sorbitol into fructose**
  - Reduces $NADP^+$ into NADPH
  - It is found in the liver, ovaries and *seminal vesicles*

Fructose is the major source of energy in the **sperm cells**

- Kidneys, lens, retina and peripheral nerves has a GLUT which is **insulin independent**
  - In diabetic patients, glucose level in the blood increases but insulin is deficient or ineffective so glucose can't enter tissues except kidney, lens and nerves
  - Glucose accumulates in these cells and mostly converted into sorbitol
  - Membranes are **impermeable to sorbitol** causes water withdraw toward the cells, water retention and **swelling** which causes diabetic complications including cataract (in the lens), retinopathy (retina), neuropathy and loss sensation of limbs (peripheral nerves)

❖ Galactose metabolism

- Galactose is an epimer of glucose, found in the lactose (in milk, dietary source)
  - It is also produced during the lysosomal degradation of glycolipids and glycoproteins (no dietary)
  - Its entry to cells is insulin independent
- Galactose is usually used in many pathways other than producing energy (catabolism)
- First of all, galactose must be charged by UDP which is done by:
  - Galactose is phosphorylated into galactose 1-phosphate by **galactokinase** using 1 ATP molecule
  - Exchange of UDP and phosphate between galactose 1-phosphate and UDP-glucose by **GALT** (galactose 1-phosphate uridylyl transferase) producing glucose 1-phosphate and UDP-galactose

Glucose 1-phosphate is converted into glucose 6-P by **phosphoglucomutase** and then used in glycolysis or glycogenesis

- UDP-Galactose can be used in:
  - Synthesis of **lactose** (**mammary glands**) or modified lactose (in males and females)
  - Synthesis of **GAGs** (glycosaminoglycans), and sugar components in **glycolipids & glycoproteins**
  - When galactose has a very large concentration, UDP-galactose is isomerized into UDP-glucose by **UDP-hexose 4-epimerase**, where UDP-glucose is used in the **glycogenesis**
- Disorders in the galactose metabolism:
  - **Deficiency of GALT (classic Galactosemia):** causes accumulation of galactose 1-phosphate
    - ✓ Galactose can be converted into galactitol causing its accumulation
    - ✓ Has similar consequences to those of fructose intolerance
    - ✓ It causes **galactosuria**
    - ✓ They must avoid the intake of galactose
  - **Deficiency of Galactokinase:** causes accumulation of galactose (galactosemia) and **galactosuria**
- When galactose is accumulated it is converted into galactitol by **aldose reductase** which can cause cataract (mostly in the galactokinase deficiency and less in the GALT deficiency)

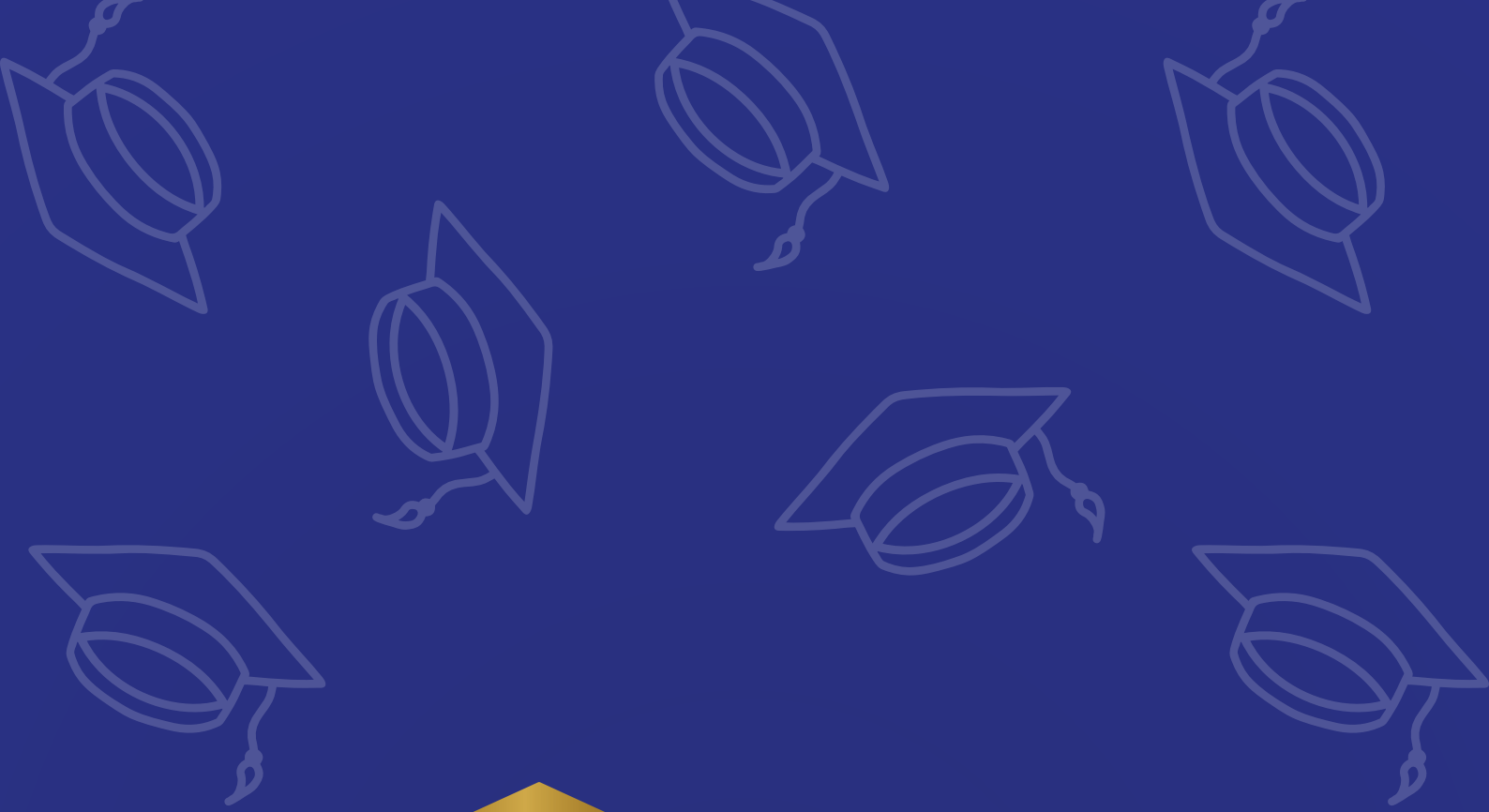
❖ Glucuronic acid metabolism

- It is a quantitatively minor route of glucose metabolism
- It provides biosynthetic precursors and interconverts some less common sugars to ones that can be metabolized
- **UDP-glucose dehydrogenase** oxidizes UDP-glucose into **UDP-glucuronic acid** and converts NAD^+ into NADH
  - It can be used to synthesize **GAGs** and other biosynthetic precursors such as **UDP-xylose**

❖ Lactose Synthesis

- Lactose is Galactosyl β (1→4) glucose
  - Produced by **mammary glands**
  - It is found in GAGs, glycolipids and glycoproteins
  - UDP-Galactose + Glucose → Lactose + UDP
  - It is done by **lactose synthase** (UDP-galactose: glucose galactosyltransferase) which consists of 2 subunits (protein A and protein B)
    - ✓ Protein A = Galactosyl transferase, Protein B = α-lactalbumin
    - ✓ Only in mammary glands, its synthesis is stimulated by **prolactin**

- In glycolipids and N-linked glycoprotein synthesis
  - UDP-Galactose + N-acetyl glucosamine → N-acetyllactosamine
  - It is catalyzed by **protein A**



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