METABOLISM

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ARKAN ACADEMY

Glycogen

- A storage Homo-polysaccharide that stores glucose
- It is highly branched with α 1-4 bonds in the straight strands and α 1-6 bonds on the branching points
  - It has a branch each 10 residues
- Glycogen is stored mainly in the liver and muscles
  - ***Liver*** glycogen is *highly* sensitive to the fasting state even short periods also
  - ***Muscle*** glycogen is *not affected* by short-term fasting

Glycogen Degradation (Glycogenolysis)

- It is done by *glycogen phosphorylase (GP)* from the non-reducing end to reducing end
  - It is responsible for the breakdown of α 1-4 bond
  - It releases glucose in the form of *Glucose 1-Phosphate* then it is converted into *Glucose 6-Phosphate*
    - ✓ Liver, glucose 6-phosphate is converted into *Glucose* by a glucose 6-phosphatase
    - ✓ Muscle, glucose 6-phosphate *remains* in its form
  - Before the branching by about 4 residues (limit dextrin), the degradation stops and a *debranching enzyme* breaks the α 1-6 bond
- ***Lysosomal degradation*** of glycogen is minor pathway important in **muscles**, **heart** and **liver**
  - (1–3) % of glycogen is degraded by *α 1−4 glucosidase (acid maltase)*
  - Type II Pompe disease: A deficiency of this enzyme causes accumulation of glycogen in lysosomes

Glycogen Synthesis (Glycogenesis)

- It is synthesized by *glycogen synthase* which adds activated glucose (***UDP-glucose***) to a primer
  - The primer could be either a ***glycogen fragment*** or ***glycogenin***
    - ✓ Glycogenin is an enzyme with a terminal tyrosine residue
  - UDP-glucose formation requires UTP, in a process of:
    - ✓ *Glucose 6-Phosphate* is converted into *Glucose 1-Phosphate* by *phosphoglycomutase*
    - ✓ *UDP-glucose pyrophosphorylase* converts Glucose 1-Phosphate into *UDP-Glucose*
  - Branches are formed by branching enzyme (4:6 transferase)
  - Approximately **2 ATP** molecules are consumed for every glucose molecule added to glycogen

Glycogen Metabolism Regulation

- In the **fasting** state, ***glucagon*** and ***epinephrine*** are secreted causing more glycogen degradation
  - They cause the production of *cAMP* in the cell which activates *PKA* which phosphorylates:
    - ✓ *Glycogen phosphorylase kinase* (+) which phosphorylates *glycogen phosphorylase* ***b*** into glycogen phosphorylase ***a*** (activated) which activates *degradation*
    - ✓ *Glycogen synthase* (–) which inhibits *synthesis*

- In the **feeding** state, ***insulin*** is secreted causing more glycogen synthesis, by activating:
  - *Phosphodiesterase enzyme* (+) which degrades *cAMP* inhibiting *PKA* and glycogen *degradation*
  - *Protein phosphatase* (+) results in the dephosphorylation of glycogen phosphorylase kinase and glycogen phosphorylase (–) and *glycogen synthase* activating *synthesis*

- In both liver and muscles ***Glucose 6-Phosphate*** and ***ATP***
  - Activate glycogen *synthase*
  - Inhibit glycogen *phosphorylase*

- In the liver ***glucose*** inhibits glycogen *phosphorylase (degradation)*

- In the muscles, Ca^{+2} and ***AMP*** activates *phosphorylase (degradation)* by activating ***PKC*** which also inhibits *synthase*

- ***Calmodulin Dependent protein kinase*** is activated by calcium calmodulin released by IP_3
  - This kinase inhibits glycogen *synthase*

Glycogen Storage Diseases

- Genetic disorders cause the *accumulation* of glycogen in the cells, which can be caused by:
  - Impairment in synthesis causing accumulation of abnormal glycogen
  - Impairment in degradation causing accumulation of normal glycogen

- They range from mild disorders into fatal (in infancy)

- *Type 1a: von Gierke disease:* Glucose-6-phosphatase deficiency
- *Type 1b: von Gierke disease:* Glucose-6-phosphate translocase deficiency
  - Affect ***liver***, ***kidney*** and ***intestine***
  - Cause Severe fasting *hypoglycemia*, *Hepatomegaly*, *fatty liver*, progressive *renal disease*, *Hyper-lactic acidemia*, *hyperuricemia*, *Growth retardation* and *delayed puberty*
  - Normal glycogen structure but increased glycogen stored
  - Treated by gastric infusion of glucose or regular administration of uncooked cornstarch which avoids the production of glycogen

- *McArdle syndrome:* Muscle glycogen phosphorylase deficiency
  - Affects only ***skeletal muscles***
  - *Weakness* and cramping of muscle after exercise
  - No increase of lactate during exercise

- *Type II POMPE Disease:* Lysosomes α (1-4) glucosidase deficiency
  - Massive *cardiomegaly* which can cause early death from heart failure
  - Normal blood sugar, normal glycogen structure
  - PIP_2 is cleaved by phospholipase C into IP_3 and DAG

Past Papers

1. Direct product of glycogen metabolism (degradation):
   A. Glucose-6-phosphate
   B. Glucose
   C. Glucose 1-phosphate
   D. UDP-Glucose

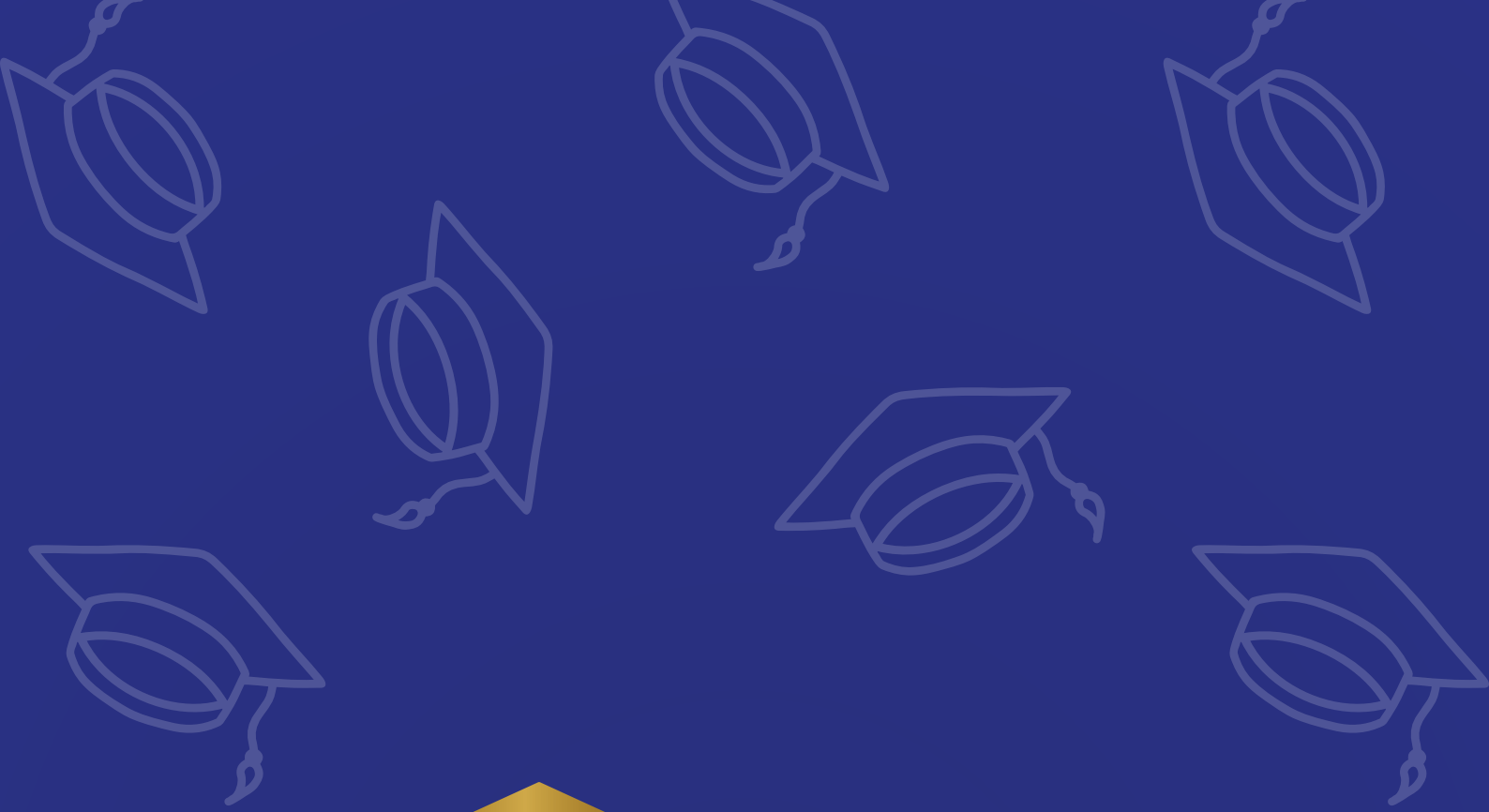
2. What is the function of 4:6 transferase enzyme?
   A. Remove branching points
   B. Replacement of alpha 1-6 bond into alpha 1-4 bond
   C. Introducing branches during the synthesis of glycogen
   D. Production of glycogenin

3. When epinephrine binds to GPCRs, all of the following occur, except:
   A. cAMP activation
   B. Increase GTP binding to G protein
   C. Increase binding of Fructose-2,6-Bisphophate to Phosphofructokinase-1
   D. Activation of Protein kinase A

4. Glycogen synthase add glucose on the following form:
   A. Glucose-1-P
   B. Glucose-6-P
   C. UTP-glucose
   D. UDP-glucose
   E. Galactose them isomerize it to glucose

5. A newborn with organomegaly in several organs due to glycogen storage in lysosomes was diagnosed with pompe's disease. The biochemical deficiency in this patient is:

   A. Glycogenin primer deficiency
   B. Lysosomal α-1,6 glycosidase deficiency
   C. Glucose-6-phosphate deficiency
   D. Glycogen phosphorylase deficiency
   E. Lysosomal α-1,4 glucosidase deficiency



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