GLYCOGENESIS AND GLYCOGENOLYSIS
Glycogen

- Storage form of glucose in animals.
- Stored in the liver (6-8%) & muscle (1-2%).
- Quantity more in the muscle (~250g) than liver (75g) due to higher muscle mass.
- Stored as granules in the cytosol.
Glycogen vs. Fat as source of energy:

- Fat cannot be rapidly metabolised like glycogen.
- Fat cannot generate energy in the absence of oxygen.
- Brain requires a continuous supply of glucose, which come from glycogen.
- Fat cannot produce glucose.
Glycogenesis

- The glycogen synthesis occurs by a pathway distinctly different from the reversal of glycogen breakdown.
- It is the intracellular synthesis of glycogen from glucose.

**Site and steps:**

- The main site is the cytosol of liver and muscle cells. In the liver it forms 8-10% of its wet weight and in muscle it forms 1-2% of its wet weight. Most other cells may store minute amounts.
Glycogenesis :- Synthesis of glycogen from glucose.
Site :- Cytosol

Activated Glucose – UDP Glucose

Uridine Triphosphate (UTP)
Structure of Glycogen
Glycogenesis steps

Glucose → Glucose 6 Phosphate
- Hexokinase/glucokinase

Glucose 6 Phosphate → Glucose 1 phosphate
- Phosphoglucomutase

Glucose 1 phosphate → Uridine diphosphate Glucose
- UDPGlc pyrophosphorylase

Glycogenin → Glycogen primer

Uridine diphosphate Glucose → 1→4 glucosyl residues
- Glycogen Synthase

1→4 glucosyl residues → Glycogen (1→4and 1→6 glucosyl units)
- Branching Enzyme
Glycogen primer or Glycogenin required to initiate Glycogen synthesis.
Glycogen Synthase transfers Glucose from UDP-Glucose to the non-reducing end of the Glycogen to form α-1,4 linkages.

Branching enzyme :- Amylo α-1,4 → 1,6 transglucosidase (Glucosyl α-4-6 transferase)
Overall Reaction of Glycogenesis :-

\[(\text{Glucose})_n + \text{Glucose} + 2 \text{ ATP} \rightarrow (\text{Glucose})_{n+1} + 2 \text{ ADP} + \text{ Pi}\]
Glycogen Degradation (Glycogenolysis)

- Definition: It is the degradation of glycogen to glucose 6-phosphate & glucose in muscle & liver respectively.
- Substrate: Glycogen
- Site: Liver, Skeletal Muscles
- Subcellular site: Cytosol.
- Steps:
  1. Action of GLYCOGEN PHOSPHORYLASE
  2. Action of Debranching Enzyme
  3. Formation of Glucose.
Enzymes of Glycogenolysis :-

1. Glycogen Phosphorylase.
2. Debranching enzyme :
   \(\alpha-1:4\) Transferase, \(\alpha-1,6\) and \(\alpha-1,4\) glucosidase
3. Glucose - 6- phosphatase
glycogen phosphorylase

\[ \rightarrow \]

Pi

glucose-1-phosphate

\[ \rightarrow \]

debranching enzyme

glucotransferase

\[ \rightarrow \]

H_{2}O

glucose

\[ \rightarrow \]

debranching enzyme

glucosidase

\[ \rightarrow \]

glycogen phosphorylase
- GLUCOSE-6-PHOSPHATASE ABSENT IN MUSCLES

- LYSOSOMAL DEGRADATION
  - Alpha 1,4 glucosidase.
    (acid maltase)
Regulation of glycogenesis & Glycogenolysis

Key enzyme of Glycogenesis- Glycogen Synthase

Key enzyme of Glycogenolysis- Glycogen Phosphorylase

Three Regulatory Mechanisms

1. Allosteric Regulation.
2. Hormonal Regulation.
3. Influence of Calcium.
Allosteric Regulation of Glycogen Metabolism

- When substrate availability & energy level is high, Glycogen synthesis is increased.
- When glucose concentration is low & energy level low, Glycogen breakdown is enhanced.
- In well-fed state, Glucose-6-P allosterically activates Glycogen Synthase. At the same time, allosterically inhibits Glycogen Phosphorylase.
- Free Glucose in the liver is also a allosteric inhibitor of Glycogen Phosphorylase.
Glycogen phosphorylase

Glucose-6-phosphate
ATP

Glucose (liver)

Ca$^{2+}$

Glycogen synthase

Glucose-1-phosphate

Glycogen

Glucose-6-phosphate
Hormonal Regulation of Glycogen Metabolism

- Hormones control Glycogen synthesis & degradation by covalent modification i.e., phosphorylation & Dephosphorylation.

- cAMP acts as second messenger.

- cAMP activates Protein Kinase.

- Protein Kinase causes phosphorylation of enzymes, either activating or deactivating them.
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Glycogen phosphorylase

Glycogen synthase

Glucose

Glucose-6-phosphate

ATP

Ca\textsuperscript{2+}, AMP

Glucose-1-phosphate

Glucose-6-phosphate
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ATP → cAMP → cAMP dependent Protein Kinase → Phosphorylation

Glucagon, Epinephrine + Adenylate cyclase → cAMP → Phosphodiesterase → 5’AMP

Insulin + Phosphodiesterase → 5’AMP

- Inactive Glycogen synthase
- Active Glycogen Phosphorylase
Effect of Calcium:

- Muscle contracts

- $\text{Ca}^{2+}$ ions released from sarcoplasmic reticulum of muscle

- $\text{Ca}^{2+}$ ions bind to calmodulin (calcium binding protein)

- Calcium calmodulin complex directly activates Protein Kinase without the involvement of cAMP.
Glycogen Storage Diseases

**Type I: VON GIERKE’S DISEASE (G-6-phosphatase)**

**Commonest**
- Fasting Hypoglycemia.
- Adrenaline has no effect.
- Lactic Acidosis.
- Hyperuricemia.
- Liver Enlargement – Cirrhosis.
- TYPE II (POMPE’S): Lysosomal Maltase (α-1,4 glucosidase).
- TYPE III (CORI’S / LIMIT DEXTRINOSIS): Debranching Enzyme
- TYPE V (McARDLE’S): Muscle Phosphorylase
- TYPE VI (HER’S): Liver Phosphorylase
- TYPE VII (TARUI’S): Phosphofructokinase
- TYPE VIII (PHOSPHORYLASE KINASE)
- TYPE IX (GLYCOGEN SYNTHASE)
QUESTIONS ???

1) What is Glycogen?
2) Monosaccharide B) Disaccharide C) Homopolysaccharide D) Heteropolysaccharide
2) It is a Storage form of
A) Carbohydrate  B) Protein  C) Lipid  D) All of above
3) Key enzyme of Glycogenesis-
A) Hexokinase  B) Glucose - 6- phosphatase  C) Glycogen Phosphorylase  D) Glycogen Synthase
4) Key enzyme of Glycogenolysis
A) Glucose - 6- phosphatase  B) Glycogen Phosphorylase  C) Glycogen Synthase  D) None of Above
5) Site of Glycogenesis
A) Mitochondria  B) Cytosol  C) Lysosome  D) Nucleus
ANSWERS

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