"Glycogen Metabolism"

I. Overview

Importance of Blood Glucose

- A constant source of blood glucose is an absolute requirement for human life.
- Glucose is the greatly preferred energy source for the brain.
- Glucose is the required energy source for cells with few or no mitochondria, such as mature red blood cells.
- Glucose is essential as an energy source for exercising muscle.
    - It serves as the substrate for anaerobic glycolysis in muscle.

Sources of Blood Glucose

- Blood glucose can be obtained from three primary sources:
    - The diet
    - Glycogen degradation

- Gluconeogenesis

Dietary Glucose

- Dietary intake of glucose and glucose precursors is sporadic.

- Glucose precursors include:

  - Starch (a polysaccharide)
  - Disaccharides
  - Monosaccharides

- Depending on the diet, dietary intake is not always a reliable source of blood glucose.

Gluconeogenesis

- Gluconeogenesis can provide sustained synthesis of glucose.

- It is somewhat slow in responding to a falling blood glucose level.

Glycogen: Rapidly Mobilized Glucose Reserve

- The body has developed mechanisms for storing a supply of glucose in a rapidly mobilized form: glycogen.
- In the absence of a dietary source of glucose:
    - Glucose is rapidly released into the blood from liver glycogen.
- Similarly:
    - Muscle glycogen is extensively degraded in exercising muscle.
    - This degradation provides muscle tissue with an important energy source.

Glucose Synthesis When Glycogen Stores Are Depleted

- When glycogen stores are depleted, specific tissues synthesize glucose de novo.
- Carbon sources for gluconeogenesis include:
    - Glycerol
    - Lactate
    - Pyruvate

    - Amino acids

II. Structure and Function

Major Glycogen Stores

- The main stores of glycogen are found in:
    - Skeletal muscle
    - Liver
- Most other cells store small amounts of glycogen for their own use.

Functional Role of Glycogen

- Muscle glycogen:
    - Serves as a fuel reserve for the synthesis of ATP during muscle contraction.
- Liver glycogen:
    - Maintains the blood glucose concentration, particularly during the early stages of a fast.

- (Note: Liver glycogen can maintain blood glucose for <24 hours.)

A. Amounts in Liver and Muscle

- Muscle:
  - Approximately 400 g of glycogen.
  - Makes up 1% to 2% of the fresh weight of resting muscle.
- Liver:
  - Approximately 100 g of glycogen.
  - Makes up to 10% of the fresh weight of a well-fed adult liver.
- What limits the production of glycogen at these levels is not clear.
- In glycogen storage diseases (GSDs):
  - The amount of glycogen in the liver and/or muscle can be significantly higher.

- (Note: In the body, muscle mass is greater than liver mass. Consequently, most of the body's glycogen is found in skeletal muscle.)

B. Structure

- Glycogen is a branched-chain polysaccharide made exclusively from α-D-glucose.
- Primary glycosidic bond:
    - α(1→4) linkage
- Branching occurs:
    - After an average of 8 to 14 glucosyl residues
    - Each branch contains an α(1→6) linkage
- A single glycogen molecule can contain up to 55,000 glucosyl residues.
- Glycogen polymers exist as:
    - Large, spherical cytoplasmic granules (particles)

- These granules also contain:
    - Most of the enzymes necessary for glycogen synthesis and degradation

C. Glycogen Store Fluctuation

- Liver glycogen:
    - Increases during the well-fed state.
    - Is depleted during a fast.
- Muscle glycogen:
    - Is not affected by short periods of fasting (a few days).
    - Is only moderately decreased in prolonged fasting (weeks).
- Muscle glycogen is synthesized to replenish muscle stores after they have been depleted following strenuous exercise.
- (Note: Glycogen synthesis and degradation go on continuously. The difference between the rates of these two processes determines the levels of stored glycogen during specific physiologic states.)

III. Synthesis (Glycogenesis)

- Glycogen is synthesized from molecules of α-D-glucose.
- The process occurs in the cytosol.
- It requires energy supplied by:
    - ATP (for the phosphorylation of glucose)
    - Uridine triphosphate (UTP)

A. Uridine Diphosphate Glucose Synthesis

- α-D-glucose attached to uridine diphosphate (UDP) is the source of all the glucosyl residues that are added to the growing glycogen molecule.
- UDP-glucose is synthesized from:
    - Glucose 1-phosphate
    - UTP
    - Enzyme: UDP-glucose pyrophosphorylase

- Pyrophosphate (PPi) is the second product of the reaction.
    - It is hydrolyzed to two inorganic phosphates (Pi) by pyrophosphatase.
    - The hydrolysis is exergonic, which ensures that the UDP-glucose pyrophosphorylase reaction proceeds in the direction of UDP-glucose production.
- (Note: Glucose 1-phosphate is generated from glucose 6-phosphate by phosphoglucomutase. Glucose 1,6-bisphosphate is an obligatory intermediate in this reversible reaction.

.B. Primer Requirement and Synthesis

- Glycogen synthase:
    - Catalyzes the formation of α(1→4) linkages in glycogen.
    - Cannot initiate chain synthesis using free glucose as an acceptor from UDP-glucose.
    - Only elongates existing chains of glucose.
    - Therefore, requires a primer.

- A fragment of glycogen can serve as a primer.
- In the absence of a fragment, the homodimeric protein glycogenin serves as the acceptor of glucose from UDP-glucose.
- The side-chain hydroxyl group of tyrosine-194 in glycogenin is the site where the initial glucosyl unit is attached.
- The reaction is catalyzed by glycogenin itself via autoglucosylation, making glycogenin an enzyme.
- Glycogenin then catalyzes the transfer of at least four molecules of glucose from UDP-glucose.
    - This produces a short, α(1→4)-linked glucosyl chain.
- This short chain serves as a primer for elongation by glycogen synthase, which is recruited by glycogenin.
- (Note: Glycogenin stays associated with and forms the core of a glycogen granule.)

C. Elongation by Glycogen Synthase

- Elongation of a glycogen chain involves:
    - The transfer of glucose from UDP-glucose to the nonreducing end of the growing chain.
    - Formation of a new glycosidic bond between:
        - The anomeric hydroxyl group of carbon 1 of the activated glucose
        - And carbon 4 of the accepting glucosyl residue

- (Note: The nonreducing end of a carbohydrate chain is one in which the anomeric carbon of the terminal sugar is linked by a glycosidic bond to another molecule, making the terminal sugar nonreducing.)

- The enzyme responsible for making α(1→4) linkages in glycogen is glycogen synthase.

- (Note: The UDP released when the new α[1→4] glycosidic bond is made can be phosphorylated to UTP by nucleoside diphosphate kinase [UDP + ATP ⇄ UTP + ADP].)

D. Branch Formation

- If no other synthetic enzyme acted on the glycogen chain:
    - The resulting structure would be a linear (unbranched) chain of glucosyl residues.
    - These would be attached by α(1→4) linkages.
    - Such a compound is found in plant tissues and is called amylose.
- In contrast, glycogen:
    - Has branches located, on average, eight glucosyl residues apart.
    - Forms a highly branched, tree-like structure.
- This structure is:
    - Far more soluble than unbranched amylose.
    - Has more nonreducing ends, allowing:
        - Faster addition of new glucosyl residues.
        - Faster removal of glucosyl residues.
    - This greatly accelerates glycogen synthesis rate and dramatically increases glycogen size.

1. Branch Synthesis

- Branches are made by the action of:
    - Branching enzyme: amylo-α(1→4)→α(1→6)-transglycosylase
- This enzyme:
    - Removes a set of 6 to 8 glucosyl residues from the nonreducing end of the glycogen chain.
    - Breaks an α(1→4) bond.
    - Attaches the removed segment to a nonterminal glucosyl residue by an α(1→6) linkage.
    - Thus functions as a 4:6 transferase.
- The resulting ends can now be further elongated by glycogen synthase:
    - New nonreducing end
    - Old nonreducing end (from which residues were removed)

2. Additional Branch Synthesis

- After elongation of the two ends:
    - Their terminal 6 to 8 glucosyl residues can be removed.
    - These can be used to make additional branches.

IV. Degradation (Glycogenolysis)

- The degradative pathway that mobilizes stored glycogen in liver and skeletal muscle:
    - Is not a reversal of the synthetic reactions.
    - Requires a separate set of cytosolic enzymes.

- When glycogen is degraded:
    - The primary product is glucose 1-phosphate, obtained by breaking α(1→4) glycosidic bonds.
    - Free glucose is also released from each α(1→6)-linked glucosyl residue (branch point).

A. Chain Shortening

- Glycogen phosphorylase:
    - Sequentially cleaves α(1→4) glycosidic bonds between glucosyl residues.
    - Acts at the nonreducing ends of glycogen chains.
    - Uses simple phosphorolysis (not hydrolysis), producing glucose 1-phosphate.
    - Continues until four glucosyl units remain on each chain at a branch point.

- The resulting structure is called a limit dextrin.
    - Phosphorylase cannot degrade it any further.

- (Note: Phosphorylase requires pyridoxal phosphate, a derivative of vitamin B6, as a coenzyme.)

B. Branch Removal

- Branches are removed by the two enzymic activities of a single bifunctional protein, the debranching enzyme.

1. oligo-α(1→4)→α(1→4)-glucantransferase activity:

    - Removes the outer three of the four glucosyl residues remaining at a branch.
    - Transfers them to the nonreducing end of another chain, thereby lengthening it.
    - Breaks an α(1→4) bond and makes an α(1→4) bond.
    - Functions as a 4:4 transferase.

2. amylo-α(1→6)-glucosidase activity:

    - Removes the remaining glucose residue attached via an α(1→6) linkage.
    - Does so hydrolytically, releasing free (nonphosphorylated) glucose.

- After branch removal:

    - The glucosyl chain is again available for degradation by glycogen phosphorylase.
    - Degradation continues until four glucosyl units in the next branch are reached.

C. Glucose 1-Phosphate Isomerization to Glucose 6-Phosphate

- Glucose 1-phosphate, produced by glycogen phosphorylase, is:
  - Isomerized in the cytosol to glucose 6-phosphate by phosphoglucomutase.

- In the liver:

  - Glucose 6-phosphate is transported into the endoplasmic reticulum (ER) by glucose 6-phosphate translocase.
  - In the ER:
    - It is dephosphorylated to glucose by glucose 6-phosphatase.
      - Same enzyme used in the last step of gluconeogenesis
  - The resulting glucose is transported from the ER to the cytosol.
  - Hepatocytes release glycogen-derived glucose into the blood to help maintain blood glucose levels until gluconeogenesis becomes active.

- (Note: Muscle lacks glucose 6-phosphatase. Consequently:
    - Glucose 6-phosphate cannot be dephosphorylated or released into the blood.
    - Instead, it enters glycolysis, providing energy needed for muscle contraction.)

D. Lysosomal Degradation

- A small amount (1% to 3%) of glycogen is degraded by the lysosomal enzyme acid α(1→4)-glucosidase (acid maltase).

- The purpose of this autophagic pathway is unknown.

- Deficiency of acid maltase causes:
    - Accumulation of glycogen in lysosomal vacuoles.
    - Leads to GSD type II: Pompe disease.

- (Note: Pompe disease, caused by acid maltase deficiency, is the only GSD that is a lysosomal storage disease.)

- Lysosomal storage diseases:
    - Are genetic disorders characterized by accumulation of abnormal amounts of carbohydrates or lipids.
    - Caused primarily by:
        - Decreased lysosomal degradation due to:
            - Absence, or
            - Decreased activity or amount of a specific lysosomal acid hydrolase responsible for degradation.

Glycogen Storage Diseases

Type[a]	Deficient Enzyme	Main Signs/Symptoms
I – Von Gierke disease	Glucose-6-phosphatase	Lactic acidosis, hypoglycemia, hyperuricemia, Impaired growth, bone thinning
II – Pompe disease[a]	Acid α-glucosidase (acid maltase)	Excess glycogen in lysosomes. Normal blood sugar. Enlarged liver and heart; muscle weakness and heart problems in severe forms
III – Cori disease[a]	Glycogen debranching enzyme (4:4 transferase)	Enlarged liver, growth delay, fasting hypoglycemia, abnormal glycogen structure, elevated fat in blood, possible muscle weakness
IV – Andersen disease	Glycogen branching enzyme (4:6 transferase)	Growth delay, enlarged liver, myopathy; death by age 5 usually
V – McArdle disease[a]	Muscle glycogen phosphorylase (myophosphorylase)	Muscle weakness and cramping after exercise; usually a relatively benign, chronic condition
VI – Hers disease	Liver glycogen phosphorylase	Liver enlargement; hypoglycemia; developmental delay
VII – Tarui disease	Muscle phosphofructokinase	Exercise-induced muscle cramps, developmental delay, hemolytic anemia in some

V. Regulation of Glycogenesis And Glycogenolysis

- Glycogen metabolism is tightly regulated to maintain blood glucose homeostasis.

- In the liver:

    - Glycogenesis is accelerated in the well-fed state.
    - Glycogenolysis is accelerated during fasting.

- In skeletal muscle:

    - Glycogenolysis occurs during active exercise.
    - Glycogenesis begins when the muscle is at rest.

- Regulation occurs at two levels:

    a. Hormonal (covalent) regulation: via phosphorylation/dephosphorylation of enzymes to meet whole-body needs.
    b. Allosteric regulation: by effector molecules to meet specific tissue needs.

A. Covalent Activation of Glycogenolysis

- Hormones involved: Glucagon (liver) and Epinephrine (liver + muscle)

- Hormone binding occurs at G protein-coupled receptors (GPCRs) on the plasma membrane, triggering a cascade.

1. Protein Kinase A (PKA) Activation

- Hormone (glucagon/epinephrine) binds to GPCR → activates G protein → activates adenylyl cyclase.
- Adenylyl cyclase converts ATP to cyclic AMP (cAMP).
- cAMP activates PKA by:
    - Binding to PKA's regulatory subunits.
    - Releasing the catalytic subunits (active).
- Active PKA phosphorylates several enzymes involved in glycogen metabolism.
- (Note: When cAMP is degraded, inactive tetrameric PKA reforms.)

2. Phosphorylase Kinase Activation

- Exists in:
    - Inactive "b" form
    - Active "a" form
- PKA phosphorylates phosphorylase kinase b → a (active form).

3. Glycogen Phosphorylase Activation

- Exists in:
    - Inactive dephosphorylated "b" form
    - Active phosphorylated "a" form
- Phosphorylase kinase a phosphorylates glycogen phosphorylase b → a, initiating glycogenolysis.

4. Signal Amplification

- Each hormone → multiple PKA molecules
- Each PKA → multiple phosphorylase kinases

- Each phosphorylase kinase → many glycogen phosphorylase a

- Result: Amplified glycogen breakdown

5. Maintenance of Phosphorylated State

- Protein phosphatase-1 (PP1):

    - Normally removes phosphate groups.
    - Is inhibited by inhibitor proteins, which are activated by cAMP.
    - Result: Prolonged activation of glycogenolysis enzymes.

- Insulin:

    - Activates phosphodiesterase, which degrades cAMP.
    - Opposes effects of glucagon and epinephrine.

B. Covalent Inhibition of Glycogenesis

- Glycogen synthase exists in two forms:

    - Active "a" form = dephosphorylated
    - Inactive "b" form = phosphorylated

- Phosphorylation = Inactivation
    - Occurs at multiple sites on glycogen synthase.
    - The more phosphorylated, the less active the enzyme becomes.
    - Catalyzed by several protein kinases, including:
        - PKA (protein kinase A)
        - Phosphorylase kinase

- Dephosphorylation by PP1 (Protein Phosphatase-1):
    - Converts inactive glycogen synthase b → active "a" form
    - Promotes glycogenesis

C. Allosteric Regulation of Glycogenesis and Glycogenolysis

- Allosteric regulation allows enzymes to rapidly respond to metabolite levels and energy status of the cell.

- Can override hormonal (covalent) regulation.

- Enzymes exist in equilibrium between:
    - R (relaxed) state = more active
    - T (tense) state = less active
    - Effectors shift R/T balance, altering activity without changing phosphorylation.

1. Regulation in the Well-Fed State

- Glycogen synthase b:
    - Allosterically activated by glucose 6-phosphate in liver and muscle (↑ in fed state)

- Glycogen phosphorylase a:
    - Allosterically inhibited by:
        - Glucose 6-phosphate
        - ATP (high-energy signal)
        - In liver only: Free glucose also inhibits

2. Glycogenolysis Activation by AMP

- In muscle, glycogen phosphorylase b (myophosphorylase) is:
    - Activated by AMP without phosphorylation
    - AMP binds allosterically and shifts enzyme to active R state
- AMP levels ↑ during:
    - Anoxia
    - ATP depletion
    - Extreme exercise conditions
- AMP also activates PFK-1 in glycolysis → glucose from glycogen is oxidized for energy

3. Glycogenolysis Activation by Calcium (Ca^{2+})

- Ca^{2+} release occurs in:
    - Muscle → in response to neural stimulation
    - Liver → in response to epinephrine binding α_1-adrenergic receptors

- Ca^{2+} binds to calmodulin (CaM):
    - CaM is a ubiquitous Ca^{2+}-binding protein
    - Binds 4 Ca^{2+} ions → changes conformation
    - Ca^{2+}-CaM complex activates enzymes by binding as an essential subunit

Role in Phosphorylase Kinase Activation

- Phosphorylase kinase is a tetramer, and its δ-subunit is calmodulin
- Binding of Ca^{2+} to CaM activates phosphorylase kinase b
    - This occurs without needing phosphorylation by PKA
    - Allows cAMP-independent activation of glycogenolysis

Note: Epinephrine acting on β-adrenergic receptors → activates cAMP pathway (not Ca^{2+})

a. Muscle Phosphorylase Kinase Activation

- Trigger: Muscle contraction → ↑ ATP demand

- Process:
    - Nerve impulses → depolarization
    - Ca^{2+} released from sarcoplasmic reticulum into sarcoplasm
    - Ca^{2+} binds CaM (δ-subunit) → activates phosphorylase kinase b
    - Phosphorylase kinase b → activates glycogen phosphorylase → glycogen → glucose 6-phosphate → glycolysis

b. Liver Phosphorylase Kinase Activation

- Trigger: Epinephrine → physiological stress → ↑ blood glucose demand

- Process:
    - Epinephrine binds α_1-adrenergic GPCRs in hepatocytes
    - Activates phospholipid-dependent cascade
    - Ca^{2+} released from ER into cytoplasm
    - Ca^{2+}-CaM complex → activates hepatic phosphorylase kinase b
    - Initiates glycogenolysis

Additional Role: Released Ca^{2+} also helps activate protein kinase C, which can:

- Phosphorylate & inactivate glycogen synthase a

VI. Glycogen Storage Diseases (GSDs)

Definition:

- A group of genetic disorders caused by deficiencies in enzymes involved in glycogen degradation or (less commonly) glycogen synthesis.

Common Clinical Features

- Hypoglycemia (↓ blood glucose)
- Hepatomegaly (enlarged liver)
- Delayed growth
- Muscle weakness or exercise-induced cramps

Underlying Mechanisms

- Two main outcomes:

    a. Abnormal glycogen structure formation
    b. Excess accumulation of normal glycogen due to impaired degradation

Tissue Specificity

- Liver-specific enzyme defect → leads to hypoglycemia
- Muscle-specific enzyme defect → leads to muscle weakness
- Generalized defects → affect multiple tissues (e.g., heart, kidneys)

Disease Severity Spectrum

- Mild forms: Not life-threatening
- Severe forms: Can be fatal in early childhood

Epidemiology

- 15 recognized types of GSD
- Some types are extremely rare