Carbohydrate Storage and Synthesis in Liver and Muscle: Glycogen
Glucose Fuel Storage and mobilization for oxidation

- **Introduction**
- **Structure of Glycogen** – highly branched α(1,4)-glucose polymer
- **Glycogenesis** – Glc incorporated into glycogen (liver & muscle, kidney)
- **Glycogenolysis** – Glucose mobilized from glycogen in liver and muscle
- **Hormonal regulation of hepatic glycogenesis vs. glycogenolysis** – insulin vs. glucagon
- **Mechanisms of glucagon action** – Signals phosphorylations, pathways flip
- **Glycogenolysis in liver** – plasma glycemia maintenance: acute vs. postabsorbutive
- **Glycogenolysis in muscle** – Mobilizing glucose for ATP contraction activity
- **Regulation of glycogenesis** – replenish glycogen stores vs. immediate needs
- **Gluconeogenesis** – de novo (new) glucose from non-carbohydrate carbon skeletons
- **Regulation of gluconeogenesis** – De novo glucose synthesis fueled by fat oxidation
- **Interconversions of fructose/galactose/mannose/glucose** – glycoproteins, etc., ...
- **Inborn errors of metabolism** – glycogen storage diseases
- Red cells and the brain – Have an absolute requirement for blood glucose for their energy metabolism.

- These cells consume about 80% of the glucose (200 g, 1.1 mol, ca. 1500 kcal) consumed per day by a 70 kg human, in good health.

- Blood and extracellular fluid volume contains about 10 g glucose – must be replenished constantly.

- Assumes a blood volume = 7 L, hematocrit = 45%, and no other distribution system operates.

- Normally, blood [glucose] range is between 4 – 6.5 mM = glycemia (about 80 – 120 mg/dL)
Prandial (meal): preprandial, postprandial, ... postabsorptive

Before meal
- **hypoglycemia** (4–2.5 mM, 45 mg/dL);
- extreme hypoglycemia, <2.5 mM, life-threatening hypoglycemia rapidly compromises brain function, leading to confusion and disorientation.

After meal
- **glycemia** rapidly exceeded by absorbed glucose from digestible meal carbohydrate), rapidly becomes ...
- **hyperglycemia** (>6.5 mM) lasts 2-3 hrs, ... glycemia

Post meal
- **homeostasis** glycemia maintained: ~ 4-5 mM (80-100 mg %), resting [glucose].
- **Such control due to**: in part, **glycogen synthesis** (all tissues). Up to max of 1—2 % of muscle tissue wt (work) and 4—6 % liver wt for later release of glucose from liver to supply glucose to body.
Glycogenesis vs. glycogenolysis
Liver maintains blood [glucose]

Glucose stored as glycogen: highly branched dendrite-like polymer, a polysaccharide.

- **Glycogenesis** – glycogen synthesized during and after a meal.
- **Glycogenolysis** releases glucose into blood (Like a controlled time-release)

Total heptic glycogen stores barely able to maintain blood [glucose] beyond 12 hour (fasting).

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Fig. 12.1 Sources of Blood Glucose....
- **Gluconeogenesis** makes new glucose during post absorptive state, before meals, and during sleep. Glycogenolysis declines to near depletion of glycogen after 12-24 hrs – Liver uses gluconeogenesis to maintain blood [glucose].
**Glycogen Storage**
Various Tissues

**Carbohydrate Metabolism**
Structure

- Blood glucose = 10 g, tissues needs easily deplete.
- Glycogen degraded to glucose-1P $\rightarrow$ G6P $\rightarrow$ for oxidative metabolism in tissues to synthesize ATP.
- Liver: G6P $\rightarrow$ G + P, by G6P phosphatase.
- Muscle lacks G6P phosphatase.

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**Fig. 12.2** Tissue distribution of carbohydrate energy reserves (70 kg adult).

- Highly branched dendritic polymer

**Fig. 12.3** Close-up of glycogen structure.
Structure of Glycogen Properties

KEY FEATURES

- **Non-reducing end**
  - $\alpha$-1,6 acetal linkage

- **Reducing end**
  - $\alpha$-1,4 acetal linkage

- **Benedict's solution**
  - Alcohol
  - Hemiacetal
  - Acetal
Glycogen metabolism
Anabolism vs. Catabolism

**Glycogenesis**
- Glucose $\rightarrow$ glycogen
- 5 steps
  1. Glucokinase
  2. Phosphogluco-mutase
  3. UDP-Glc PPase
  4. Glycogen synthase
  5. Branching

**Glycogenolysis**
- Glycogen $\rightarrow$ glucose
- 4 steps
  1. Glycogen phosphorylase
  2. transglycosylase
  3. transglycosylase
  4. G6Pase

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**Fig. 12.4**

Glycogenesis (L)
Glycogenolysis (R)

Regulatory enzyme
Rate-limiting enzyme
Glycogenesis Carbohydrate Metabolism vs. glycolysis, PMP

In: Liver, Muscle, Adipose tissues

Priority: favor synthesis of glycogen first: save first!

- **Portal blood**: delivers glucose-rich blood to liver during/shortly after a meal.
- **Liver rich in GLUT-2**: high capacity, low affinity ($k_m > 10$ mM), **high glucose flux**.
  - **Glucokinase (GK)**: gene induced by continuous glc-rich diet.
  - **GK $k_m \approx 5-7$ mM**: activity ↑ when portal blood [Glc] ↑ above 5 mM.
  - **GK not G6P inhibited**: thus G6P pushed into all pathways — glycolysis, PMP, and glycogenesis (muscle uses lipid oxidative metabolism for ATP).

**Fate of excess glucose**

- In Liver: goes to
  - **glycogenesis reserve**: for maintaining post absorptive blood [glc].
  - **glycolysis**: after glycogen reserve is full.
  - **energy/ATP synthesis and triglycerides**: **FAS and TGs** exported to adipose tissue for storage.
- In muscle: glucose ➔ stored in glycogen; glycolytic pyruvate formed.
- In adipose: glucose ➔ DHAP ➔ glycerol ➔ TGs
- In RBC: glucose ➔ pyruvate ➔ lactate; ➔ NADPH (protect from ROS)
Fate of diet fuels
Glucose is central metabolite

Carbohydrate Metabolism
Overview of Topics

DIET → carbohydrate, protein, fat

Digestion and Absorption

Intestines → Glucose, amino acids, TGs

Transport via portal vein

GLUCOSE

Gluconeogenesis ↔ amino acids

Glycogenolysis ↔ amino acids

Liver

Muscles

Movement

GLYCOGEN

Glycogenesis ↔ Glycogenolysis

Organs

Brain

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Glucagon, Epinephrine, Cortisol, Insulin

- **Glycogenolysis:** response to low blood [glc] from:
  - Post absorptive utilization.
  - Response to stress.
- **3 hormones — activation mode:**
  - **Glucagon**—3.5 kd peptide, from α-cells of endocrine pancreas; main function: activate hepatic glycogenolysis to maintain normoglycemia.
  - **Epinephrine**—tyrosine derivative, a catecholamine from adrenal medulla activates glycogenolysis in response to acute stress.
  - **Cortisol**—adrenocortical steroid varies diurnally in plasma, but may be chronically elevated under continuously stressful conditions.

![Hormonal control of glycogenolysis](image)

Fig. 12.5 Hormones involved in control of glycogenolysis.
Glucagon, epinephrine (adrenalin), cortisol, insulin

- Glucagon t/2 ~ 5 minutes. (removal from blood by receptor binding, renal filtration, proteolytic inactivation in liver.)
- Elevated blood [glucagon]: between meals; chronically elevated during fasting or low-carbohydrate diet.
- Decreased blood [glucagon]: decreases during and soon after a meal ([glucose] is very high).
Glycogenolysis is activated in response to stress

- Physiologic -- in response to increased blood glucose utilization during prolonged exercise.
- Pathologic -- as a result of blood loss.
- Psychological -- in response to acute or chronic threats.
- Acute stress (regardless of source): activates glycogenolysis through the action of catecholamine hormone, epinephrine (released by the adrenal medula).
- During prolonged exercise: both glucagon and epinephrine contribute to stimulation of glycogenolysis.
Insulin secretion by pancreas β-cells when blood [glucose] is high.
Synthesized as single peptide chain zymogen: proinsulin.
In secretory granules, selective proteolysis releases an internal peptide and a 2-chained (via 2 -S–S- ) insulin hormone.
Insulin elicits uptake and intracellular use or storage of glucose, an anabolic hormone.
Hyperglycemia results in elevated blood [insulin] associated with fed state.
Hyperinsulinism associated with “insulin resistance” and if chronic can lead to diabetes type-2 and related pathologies.

2. G-protein-GDP in resting state: releases GDP, α-subunit binds GTP.


4. α-GTP binds to adenylate cyclase (AC).

5. AC converts ATP → cAMP (+PP; → 2 P).

6. cAMP binds regulatory subunit of protein kinase A: active catalytic subunit released = PKA.

7. PKA phosphorylates 3-enzymes: uses ATP
   - Inhibitor 1 → inhibitor-1 (+P) ACT.
   - phosphorylase kinase b → PKa (+P) ACT.
   - glycogen synthase a → b (+P) INACT.

Fig 12.6 Mobilization of liver glycogen by glucagon.
PKA phosphorylates 3-enzymes: uses ATP

- Inhibitor 1 → inhibitor-1 (+P) ACT.
- Phosphorylase Kinase b → PK a (+P) ACT.
- Glycogen Synthase a → GS b (+P) INACT.

Phosphorylase kinase a: uses ATP

Glycogen Phosphorylase b → GP a (+P)

7. Glycogen Phosphorylase a: glycogenolysis releases G1P

8. Inhibitor 1-P keeps phospho-protein phosphatase (PPP) inactive: glycogen degradation continues.

Fig 12.6 Mobilization of liver glycogen by glucagon.
Glycogen Carbohydrate Metabolism
Reciprocal Synthesis and Degradation
Regulation Mechanism

Phosphorylation-Dephosphorylation

Phosphorylase $b$

Phosphorylase $a$

Glycogen synthase $D$

Glycogen synthase $I$

PPP = Protein Phosphatase

ATP → ADP

ADP → ATP

PPP = Protein Phosphatase
Glycogenolysis floods system with G1P, G6P, and glucose

- Prandial glucose used up, glycemia falls into hypoglycemia.
- Glucagon’s enzyme cascade amplification turns on liver glycogenolysis – balanced inhibition of glycogenesis. Also produces inhibition of ...
  - Protein synthesis – uses considerable ATP and GTP
  - Cholesterol synthesis – uses ATP
  - Fatty acid (FA) synthesis – uses ATP to activate acetyl CoA (malonyl CoA)
  - Triglyceride (TGs) synthesis from glycolytic DHAP derived from glucose
  - Glucose synthesis (gluconeogenesis) – uses GTP
  - Glucose utilization (glycolysis) – uses ATP
- Key enzymes phosphorylated in opposing pathways, avoids futile cycles.
- Glucagon shifts liver metabolism to keep blood [glc] glycemic to maintain vital body functions (see Ch 20).
Termination of glucagon response  
Carbohydrate Metabolism  
Hepatic mechanisms

Must be rapid

- **Rapid, redundant shutdown mechanisms:** accompany blood [glucagon] ↓. Enzyme cascade for amplifying glycogenolysis activation is via dephosphorylation.

1. Gα-GTP → Gα-GDP: by phosphodiesterase
2. *Phosphodiesterase*: cAMP → AMP
3. [cAMP]↓, R-cAMP dissociates
4. 2R + 2C → R₂C₂: *adenylate cyclase* inactive again.
5. *PhosphoProtein Phosphatase (PPP)*: removes-P;
   - all enz-P → enz + P; glycogenolysis stops.
   - *Inhibitor 1*, increases PPP activity.

- **Glycogenolysis stops.**
Six rare genetic diseases affect glycogen synthesis at different enzyme deficiency steps in the pathway.

Fig. 12.8 Major classes of glycogen-storage diseases.
Glucagon, Epinephrine, Cortisol, Insulin

- **Epinephrine** (Adrenaline) and precursor (norepinephrine also hormonally active), derived from tyrosine. Adrenal gland cells release when neural signals trigger the fight-or-flight response; many diverse physiological effects follow.

- **Epinephrine** stimulates release of G1P from glycogen; produces elevated intracellular [G6P]. Glycolysis increases in muscle; liver releases glucose into the bloodstream.
Epinephrine binds to α- and β-adrenergic receptors.

Two pathways stimulated.

β-receptor: similar to glucagon mechanism. G-proteins, cAMP.

- Epinephrine response: augments glucagon’s during severe hypoglycemia: rapid heartbeat, sweating, tremors and anxiety.

α-receptor: G-proteins, active membrane isozyme of phospholipase C (PLC): specific for cleavage of membrane phospholipid (PL), and PIP₂.

- PIP₂ → DAG + IP₃, 2nd messengers.
- DAG activates PKC (like PKA).
- IP₃ promotes Ca²⁺ into cytosol.
- Ca²⁺ binds calmodulin: activates phosphorylase kinase, leads to activation of glycojen phosphorylase: glucose released to blood.

Fig. 12.9 Glycogenolysis via α-adrenergic receptor
Muscle lacks glucagon receptor and \textit{G6Phosphatase} enzyme.

- Muscle reacts to epinephrine not glucagon.
- \(\beta\)-adrenergic receptor (cAMP) activates glycogenolysis for:
  - Fight or flight
  - Prolonged exercise
- 2 hormone independent modes:
  - Influx of Ca\(^{2+}\) activates \textit{phosphorylase kinase} via Ca\(^{2+}\)–calmodulin complex.
  - AMP activates phosphorylase directly
- 2 ADP \(\leftrightarrow\) ATP + AMP; \([\text{AMP}]\uparrow\)
- AMP activates \textit{phosphorylase}.

Fig 12.10 Regulation of PKA in muscle.
- **Insulin’s 2 main functions:**
  - Lowers blood glucose by reversing the effect of glucagon’s phosphorylation of enzymes and proteins.
  - Stimulates gene expression of carbohydrate metabolism enzymes.

Fig 12.11 Regulatory effects of insulin on hepatic and muscle carbo metab.
Gluconeogenesis (GNG) Glucose from non carbohydrates

Carbohydrate Metabolism

Cytosol-Mitochondrion

3-Sources: Lactate, amino acids, glycerol

- **Gluconeogenesis**: essential during fasting and starvation, when hepatic glycogen depleted, to maintain blood glucose.
- **Energy and carbon source required**: oxidation of FA released from adipose tissue provides ATP; carbons from 3-sources.
- **Lactate from RBC and active muscle.**
- **Large muscle mass**: major source of glucogenic amino acids; transamination.
- **Glycerol from TGs**: DHAP via glycerol-3P.
- **3 glycolytic irreversible reactions**: PK, PFK-1, GK bypassed by phosphatases: FBPase, and G6Pase after PEPCKase
- **1,3BPG \(\rightleftharpoons\) 3PG is reversible, \(\Delta G\) similar.
- **Lactate cycle**: Cori cycle (ch 20). Muscle lactate and pyr \(\rightarrow\) liver-GNG \(\rightarrow\) glc, to muscle-glycolysis \(\rightarrow\) lactate
- **Glucose-alanine cycle**: [muscle: glc \(\rightarrow\) pyr \(\rightarrow\) ala] \(\rightarrow\) [liver: \(\rightarrow\) GNG \(\rightarrow\) glc] \(\rightarrow\)[muscle: glc \(\rightarrow\) pyr \(\rightarrow\) ala]...

Fig 12.12 Pathways of gluconeogenesis.
Regulating gluconeogenesis

Control: liver PFK1 and F1,6BPase

- **Gluconeogenesis vs. glycolysis**: avoid a futile cycle; active GNG—inhibit glycolysis Enz-P or inactive GNG—active glycolysis. Enz

- **F26BP**: allosteric (+) regulator of F16BP. Made by:
  - PFK2: F6P → F26BP; enhances glycolysis.
  - F26BPase: F6P ← F26BP; enhances GNG.
  - PFK2/F26BPase: a bifunctional, with ‘P’ switch:
    - PFK2/F26BPase ⇌ PFK2/F26BPase-P
  - PFK1: F6P → F16BP; F26BP ↑Rx rate!
  - F16BPase: F6P ← F16BP; F26BP inhibits GNG!
  - [acetyl CoA↑]: slows TCA; act. PC [OAA↑] → Glc

- **Glucagon**: promotes phosphorylation (PK, inact.)
- **Insulin**: promotes de-phosphorylation (PK act.)

- During fasting: glucagon↑, PK-P inact, GNG↑, EM↓
- Eat Carbo meal: insulin↑, PK act, GNG↓, EM↑
Fructose and galactose Carbohydrate Metabolism Sugar Interconversions

ketose

Exclusively in liver

(\(\alpha\)-D-Fructose)

\(\text{glycolysis}\)

\(\text{PEPCK}\)

\(\text{glycolysis}\)

\(\text{pyruvate}\)

\(\text{PEP}\)

\(\text{pyruvate}\)

\(\text{PDH}\)

\(\text{PC}\)

\(\text{OAA}\)

\(\text{Acetyl CoA}\)

\(\text{glycolysis}\)

\(\text{PEPCK}\)

\(\text{epimers}\)

\(\alpha\)-D-Glucopyranose

\(\beta\)

\(\alpha\)-D-Galactopyranose

\(\text{OAA}\)

\(\text{Acetyl CoA}\)

\(\text{PEP}\)

\(\text{pyruvate}\)

\(\text{PDH}\)

\(\text{PC}\)

\(\text{OAA}\)

\(\text{Acetyl CoA}\)

Exclusively in liver

\(\alpha\)-D-Glucose

\(\beta\)

\(\alpha\)-D-Galactose

\(\text{pyruvate}\)

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Fig. 12.14 Features of hormone action. Multihormonal regulation of gluconeogenesis illustrates fundamental principles of hormone action.
- Red cells and the brain – Have an absolute requirement for blood glucose for their energy metabolism.

- These cells consume about 80% of the glucose (200 g, 1.1 mol, ca. 1500 kcal) consumed per day by a 70 kg human, in good health.

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- Assumes a blood volume = 7 L, hematocrit = 45%, and no other distribution system operates.

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Gluconeogenesis
backup system – makes new glucose

- Liver can synthesize glucose from *non carbohydrate* precursors.
- Amino acids supply carbon skeletons, as does glycerol.
- During starvation*, liver uses degraded muscle protein as the primary precursor of glucose; also lactate (from glycolysis) and glycerol (from fat).
- Fatty acids from triacylglycerides (TAGs) mobilized (from adipose tissue**) provide the energy for gluconeogenesis.

* Metabolically may begin about 12 hours after the last meal.
** During well-fed states, excess glucose is converted to triacylglycerides (TGs) in adipose cells.
GLUT-2 transporter – getting **GLUCOSE** in and out of cell

- A high capacity GLUT-2 transporter (low-affinity, $km > 10 \text{ mM}$) allows glucose free entry into and exit from liver cells across the plasma membrane.

- Liver cells have a large number of GLUT-2, so high [glucose] coming from the portal blood can easily enter the cytoplasm.
Keeping glucose in the cell – investing for metabolism

- **Glucokinase (GK)** specifically phosphorylates glucose to glucose-6-phosphate (G6P) trapping glucose inside cell. Liver has copious amounts of GK.

- GK gene is inducible (more GK made) when a high carbohydrate diet is continued.

- $K_{\text{m}}^{\text{GK}} \sim 5-7 \text{ mM}$, GK becomes more active when portal blood [glucose] exceeds 5 mM (100 mg%).

- **G6P is not a product inhibitor of GK!** (G6P inhibits hexokinase)
Pathway options for G6P

Carbohydrate Metabolism
Pathways in the cytosol

What fates await G6P?

After a carbohydrate meal, G6P floods the cell via GK. G6P forced into several major pathways:

- **Glycogenesis** – yields highly branched, dense glucose polymer. After glycogen is replenished, then ...

- **Glycolysis** – oxidizes excess G6P to pyruvate (and lactate) for energy production and triglyceride (TAG) synthesis for export to adipose cells...and

- **Pentose phosphate pathway** – yields NADPH (and ribose and other sugars) for fatty acid synthesis (there goes the waistline!)
UDP-Glucose adds glucose to glycogen via **Glycogen Synthase**

**Three-step Pathway**

1. *Phosphoglucomutase*

2. *UDP-glucose pyrophosphorylase*

3. **Glycogen Synthase**
Glycogenin Carbohydrate Metabolism

Glycogenesis

{Octamer of Glucose—glycogenin protein} primer

- Glycogen Synthase – requires glycogen primer eight $\alpha$-1,4-linked glucose residues (at least).
- Primer = Glucose$_8$–Tyr$_{C1}$–Glycogenin ($Mr$ 37,000 protein).
- Glycosyltransferase adds C$_1$ of Glu$_1$-ppU to a tyrosyl residue of Glycogenin; 7 UDP-Glu yield 8-mer Glucose$_8$-Glycogenin protein primer.
- Glycogen Synthase adds glu of UDP-glu to non reducing C$_4$-OH of Glucose-Glycogenin synthesizing a glycogen 50,000 polymer.
- amylo-(1,4 to 1,6)-transglycolase creates the branches; transfers 6-mer to the C$_6$-OH so 4-residues separate branches formed by $\alpha$-1,6-acetal linkage.
- All the enzymes required are associated with the glycogen for rapid synthesis of glycogen
Branching Glycogen  
α-1,6 acetal linkage

Carbohydrate Metabolism  
Glycogenesis pathway

1. Glucosyl-transferase

2. Amylo-1,4–1,6-transglycosylase

3. Glycogen Synthase

4. Amylo-1,4–1,6-transglycosylase

5. Glucosyl-transferase

6. Glycogen Synthase

7. Amylo-1,4–1,6-transglycosylase

UDP-glucose

Glycogenin
Glycogen synthase

A principle?

Regulate a pathway after a branch branch*

- **Step 3, Glycogen synthase is regulated, not 1 or 2**

```
  ▶️ Glucose-1P
     |   Regulate here?
     v
  UDP-glucose
     |   Regulate here.
     v
  Glycogen

  Glycoproteins
  Glycolipids
  Other sugars
```

* Recall: Does the regulated, committed step of glycolysis (F1,6BP) follow this principle?
Using phosphate to cleave C—O bonds: phosphorolysis

* Glucose stored as glycogen or starch
  animals plants

Muscle
Liver
ribosome

Non-reducing end
Branch point
4-residues from branch
Glycogen Phosphorylase
Liver vs. Muscle

Carbohydrate Metabolism
Glycogenolysis Pathway

Fate of glycogen → glucose

**Muscle**

Glycogen

↓

Glucose 1P

↓

Glucose 6P

↓

Glucose

Liver

↓

Glucose 1P

↓

Glucose 6P

↓

Glucose

P Glc mutase

Enzyme

Glucose 1P

↔

Glucose 6P

Hex Kinase

G6Pase

Brain
RBC
Fat cells
Peripheral tissues

Glucose

↓

CO₂ + H₂O

TCA

2 ATP

3 ATP

[ATP]

[AMP]