

Metabolism

Introduction

Metabolism is the sum of all enzyme-catalyzed chemical reactions within a living cell, responsible for maintaining life. These reactions are grouped into highly regulated and integrated pathways. The overall process is divided into Catabolism (energy-releasing breakdown) and Anabolism (energy-requiring synthesis).

- Metabolic pathways are interconnected by key intermediates, notably **Acetyl-CoA**, which links the breakdown and synthesis of carbohydrates, lipids, and some amino acids.
- **Insulin** and **Glucagon** are the primary hormones regulating metabolism, controlling the switch between the fed (anabolic) and fasted (catabolic) states.
- Pathways are spatially segregated: **Catabolism** is often mitochondrial (e.g., TCA cycle, β -Oxidation), while **Anabolism** is often cytosolic (e.g., Fatty Acid Synthesis).

Learning Objectives

By the end of this module, you will be able to:

- Identify the rate-limiting enzymes and major end products of carbohydrate, lipid, and nitrogen metabolic pathways.
- Explain the principles of **reciprocal regulation** governing opposing pathways (e.g., Glycolysis vs. Gluconeogenesis).
- Describe the role of key coenzymes like **NADPH** (Pentose Phosphate Pathway) in reductive biosynthesis.
- Detail the interconnectedness of Pyruvate and Acetyl-CoA as metabolic hubs under different physiological conditions.
- Summarize the mechanism for safely detoxifying and excreting nitrogen waste via the **Urea Cycle**.

Key Concepts and Definitions

Term	Definition
Reciprocal Regulation	The mechanism where the same regulatory molecule or signal has opposite effects on two opposing pathways (e.g., Fructose-2,6-bisphosphate activates glycolysis and inhibits gluconeogenesis).
Anaplerotic Reaction	A reaction that replenishes intermediates of the TCA cycle (e.g., Pyruvate Carboxylase synthesizing OAA).
Allosteric Regulation	Control of an enzyme's activity by the binding of a small molecule (effector) at a site other than the active site..
Glucogenic Amino Acid	An amino acid whose carbon skeleton can be converted into glucose (via Pyruvate or TCA intermediates).
Ketogenic Amino Acid	An amino acid whose carbon skeleton can be converted into Acetyl-CoA or acetoacetate (ketone bodies).
Urea Cycle	The primary pathway in mammals for removing excess, toxic ammonia by converting it into nontoxic urea for excretion.

Detailed Discussion

Carbohydrate Metabolism

Pathway	Key Reactions/Goals	Important Enzymes & Location	Regulation & Examples
a. Glycolysis (Catabolic)	Glucose → 2 Pyruvate ($C_6 \rightarrow 2 \times C_3$). Generates 2 ATP and 2 NADH.	Hexokinase (HK, irreversible, inhibited by G6P), Phosphofructokinase-1 (PFK-1, major control, cytosol), Pyruvate Kinase (PK, irreversible).	Fed State: Insulin activates PFK-1 (via Fructose-2,6-bisphosphate). ATP and Citrate (high energy) inhibit PFK-1. Example: Red blood cells rely solely on glycolysis for ATP.

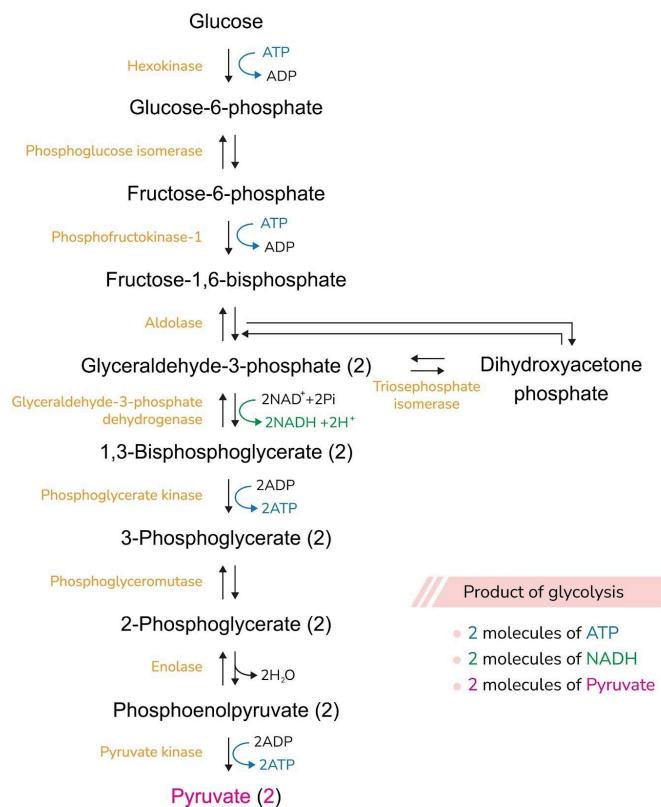
b. Tricarboxylic Acid (TCA) Cycle (Amphibolic)	Complete oxidation of Acetyl-CoA to 2 CO ₂ . Generates 3 NADH, 1 FADH ₂ , 1 GTP (or ATP) per Acetyl-CoA.	Pyruvate Dehydrogenase Complex (PDC), Citrate Synthase, Isocitrate Dehydrogenase, α-Ketoglutarate Dehydrogenase. (Mitochondrial Matrix).	High Energy Inhibition: NADH and ATP inhibit PDC and Isocitrate Dehydrogenase. Ca ²⁺ (muscle contraction) activates PDC and Isocitrate Dehydrogenase.
c. Pentose Phosphate Pathway (PPP) (Anabolic/Catabolic)	1. Oxidative Phase: G6P → Ribulose-5-P (Produces 2 NADPH). 2. Non-Oxidative Phase: Interconverts sugars for glycolysis/nucleotide synthesis.	Glucose-6-Phosphate Dehydrogenase (G6PD, rate-limiting, cytosol).	G6PD is strongly inhibited by high levels of NADPH (product). NADPH is essential for fatty acid synthesis and neutralizing reactive oxygen species.
d. Glycogenolysis (Catabolic)	Breakdown of stored glycogen to Glucose-1-Phosphate (G1P). G1P → G6P. Liver uses G6Pase to release free glucose into blood.	Glycogen Phosphorylase (rate-limiting), Debranching Enzyme (Liver & Muscle Cytosol).	Fasted/Stress State: Glucagon (liver) and Epinephrine (muscle) activate Glycogen Phosphorylase via phosphorylation.
e. Glycogenesis (Anabolic)	Synthesis of glycogen from UDP-Glucose. G6P → G1P → UDP-Glucose → Glycogen.	Glycogen Synthase (rate-limiting), Branching Enzyme (Cytosol).	Fed State: Insulin activates Glycogen Synthase via dephosphorylation. G6P is an allosteric activator.
f. Gluconeogenesis (Anabolic)	Synthesis of Glucose from non-carb precursors (Lactate, Amino Acids, Glycerol). Bypasses 3 irreversible steps of glycolysis.	Pyruvate Carboxylase (Mito), PEP Carboxykinase (PEPCK, Cytosol), Fructose-1,6-bisphosphatase, Glucose-6-phosphatase.	Fasted State: Glucagon and Cortisol induce enzyme synthesis. Fructose-1,6-bisphosphatase is Inhibited by Fructose-2,6-bisphosphate (reciprocal control with

			glycolysis).
g. Photosynthesis (Anabolic - in plants/algae)	Light energy → Chemical energy (ATP, NADPH) → Glucose from CO ₂ .	Rubisco (Carbon fixation, rate-limiting, Chloroplast Stroma).	Rubisco activity is regulated by light (via thioredoxin), CO ₂ , and Mg ²⁺ .

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Glycolysis pathway

Glycolysis is the process of converting glucose into energy.
 The final products are two molecules of pyruvate, water, ATP, and NADH.
 The process activity takes place in a cell's cytoplasm and does not need oxygen.



Example of Reciprocal Regulation (Glycolysis vs. Gluconeogenesis): In the liver, high ATP (high energy state) inhibits PFK-1 (stopping glycolysis) and activates Fructose-1,6-bisphosphatase (starting gluconeogenesis), ensuring energy is stored, not

wasted. Conversely, low ATP/high AMP activates PFK-1 and inhibits Fructose-1,6-bisphosphatase.

Lipid Metabolism

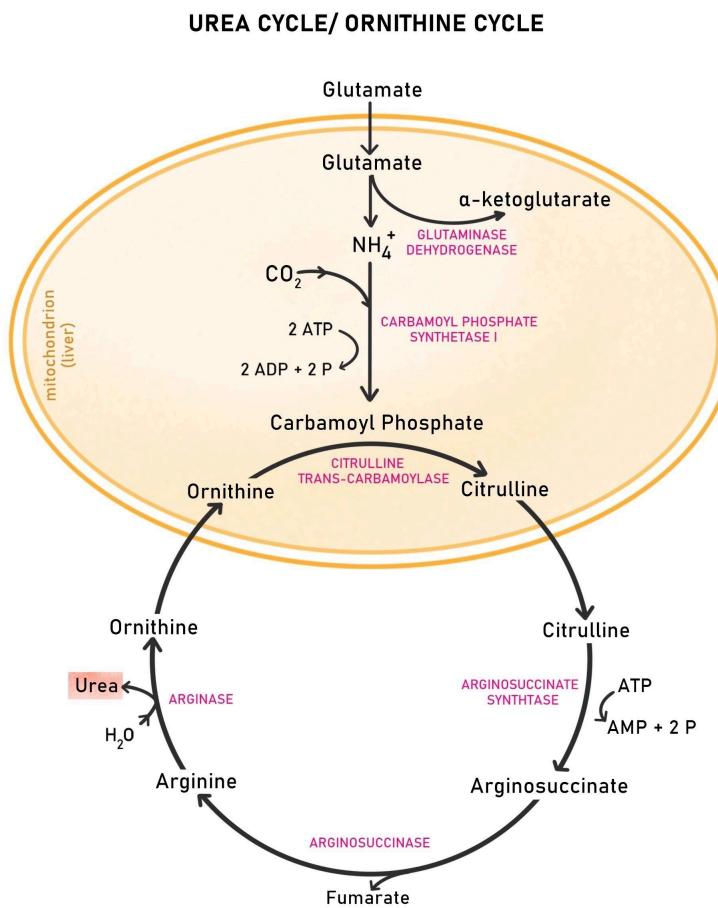
Pathway	Key Reactions/Goals	Important Enzymes & Location	Regulation & Examples
a. Lipolysis (Catabolism of Triglycerides)	Hydrolysis of Triacylglycerol (TAG) into 3 Fatty Acids and 1 Glycerol.	Hormone-Sensitive Lipase (HSL), Adipose Triglyceride Lipase (ATGL) (Adipose Tissue Cytosol).	Fasted/Stress State: HSL is Activated by Epinephrine/Glucagon (via phosphorylation). Inhibited by Insulin .
b. β-Oxidation of Fatty Acids (Catabolic)	Fatty Acyl-CoA is repeatedly oxidized, cleaving C_2 units to produce Acetyl-CoA, NADH, and $FADH_2$.	Carnitine Palmitoyl Transferase I (CPT I, rate-limiting for mitochondrial entry), Acyl-CoA Dehydrogenase (Mitochondrial Matrix).	CPT I is strongly Inhibited by Malonyl-CoA (the first committed intermediate of fatty acid synthesis). This prevents simultaneous synthesis and breakdown.
c. Formation of Ketone Bodies (Ketogenesis) (Catabolic)	Synthesis of Acetoacetate and β -Hydroxybutyrate from excess Acetyl-CoA.	Mitochondrial HMG-CoA Synthase (Liver Mitochondria).	Occurs during prolonged fasting or unmanaged diabetes when OAA is diverted to gluconeogenesis, causing Acetyl-CoA to accumulate. Ketone bodies can fuel the brain, sparing glucose.
d. Biosynthesis of Fatty Acids (Anabolic)	Synthesis of Palmitate (C16) from Acetyl-CoA. Requires ATP and NADPH (from PPP).	Acetyl-CoA Carboxylase (ACC, rate-limiting, cytosol), Fatty Acid Synthase .	Fed State: ACC is Activated by Insulin (dephosphorylation) and Citrate. Inhibited by Palmitoyl-CoA and

			Glucagon.
e. Biosynthesis of Triglycerides (Anabolic)	Esterification of Fatty Acyl-CoA to a Glycerol-3-Phosphate backbone.	Glycerol-3-phosphate acyltransferase (Liver/Adipose ER and Cytosol).	Fed State: High activity when precursors (Fatty Acyl-CoA, G3P derived from glucose) are abundant (stimulated by Insulin).
f. Biosynthesis of Cholesterol (Anabolic)	Synthesis of cholesterol from multiple Acetyl-CoA units.	HMG-CoA Reductase (Rate-limiting, ER membrane).	Feedback Inhibition: High intracellular cholesterol inhibits the enzyme. Hormonal: Insulin activates; Glucagon inhibits. It is the target of statin drugs.

Nitrogen Metabolism

Pathway	Key Reactions/Goals	Important Enzymes & Location	Regulation & Examples
a. Nitrogen Fixation (Anabolic - Microorganisms)	N_2 (atmospheric nitrogen) $\rightarrow \text{NH}_3$ (ammonia). Highly energy-intensive.	Nitrogenase Complex (requires ATP, protected from O_2).	Occurs in symbiotic bacteria (Rhizobium) in legume root nodules. Essential for converting atmospheric N_2 into a biologically usable form for all life.
b. Metabolism of Amino Acids (Catabolic/Anabolic)	Catabolism: Amino group is removed (transamination) and sent to the Urea Cycle. The carbon skeleton is	Aminotransferases (Transaminases, e.g., ALT/AST), Glutamate Dehydrogenase (Liver Mitochondria).	Fasted State/High Protein: Amino acid catabolism increases. Carbon skeletons of glucogenic amino

	used for energy or biosynthesis.		acids (Alanine) are converted to Pyruvate or TCA intermediates for gluconeogenesis.
c. Urea Cycle (Catabolic/Detoxification)	Convert toxic NH_4^+ (ammonia) into non-toxic Urea for excretion. Occurs across the mitochondrial and cytosolic compartments of liver cells.	Carbamoyl Phosphate Synthetase I (CPS I, rate-limiting, mitochondrial), Arginase .	Activation: CPS I is allosterically activated by N-acetylglutamate (NAG). NAG levels rise when amino acid catabolism is high, providing the signal to dispose of nitrogen waste.



References

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2. Berg, J. M., Tymoczko, J. L., Gatto, G. J., & Stryer, L. (2015). *Biochemistry* (8th ed.). W. H. Freeman.
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