Lipids 3: Triacylglycerols (Triglycerides)

Key Concepts

- Fatty acids are stored as triacylglycerides.
- Triacylglycerols are the major energy reserve in humans.
- Most triacylglycerides are stored in adipose tissue.
- Insulin stimulates lipogenesis and inhibits beta-oxidation.
- The liver plays a major role in lipid metabolism.
- Ketone bodies are produced in the liver and used in other tissues during fasting.

Energy Reserves

- Triacylglycerols ~100,000 kcal (~16% of body weight in humans) *vast majority.
- Protein (muscle) ~25,000 kcal
- Glycogen ~600 kcal
- **Fats are anhydrous, this is key for energy storage. Glycogen binds water, which "dilutes" energy storage capacity.

Adipocytes -- Storage site for lipids

- Adipocytes can be up to 90% triglyceride (TG) by weight.
  - Triglycerides = glycerol backbone (CH2OH-CHOH-CH2OH) + 3 Fatty Acids attached via ester bonds.
- **Nucleus and cytoplasm are pushed to a narrow rim around the lipid portion of cell.
- Hypertrophy of adipocytes occurs in obesity.

Digestion and Transport of Dietary Triglycerides

- Triacylglycerides are broken down by bile salts and pancreatic lipases in the lumen of the small intestine:
  - Triglycerides ----> Fatty Acids + Monoacylglycerols
  - FAs and MAGs cross the plasma membrane from the small intestine into mucosal cells, where they reform as TGs.
  - In mucosal cells, the TGs associate with other lipids and proteins to form chylomicrons, then they enter the lymph system, followed by the blood.
  - From the blood, chylomicrons are stored in adipose cells.
    - Storage occurs when dietary sources of carbs are sufficient to meet energy demands.
    - TGs (associated with chylomicrons) enter the cell via the action of Lipoprotein Lipase, which is stimulated by insulin.

Triglyceride Mobilization (From adipocytes for use in beta-oxidation) -- Occurs at times of high energy demand.

- The overall process stimulates breakdown of TGs in adipocytes to FFAs and glycerol, which are transported to tissues for oxidation. **FFAs are carried by plasma albumins.
- 7-Transmembrane Proteins on the surface of adipose cells are bound by glucagon, EPI and NE.
- 7TM receptor is G-protein coupled, and it activates adenylate cyclase.
- Adenylate cyclase catalyzes the conversion of ATP--->cAMP, and cAMP activates Protein
Kinase A.
- Protein Kinase A phosphorylates and activates Perilipin which releases Co-Activator (CA), which activates Adipose Triglyceride Lipase (ATGL).
- ATGL-CA catalyzes the cleavage of one FA from a TG molecule, forming a Diacylglyceride.
- At the same time that it activates Perilipin, Protein Kinase A also activates Hormone-Sensitive Lipase (HS Lipase), which converts diacylglycerides to monoacylglycerides.
- Finally, MAG Lipase forms glycerol and fatty acids from monoacylglyceride.
- ***See pg. 198 for details, and the regulation of FA Synthesis / TG Breakdown.

Fate of Glycerol Remaining After Lipolysis
- Glycerol leftover from lipolysis is absorbed by the liver.
- In the liver, glycerol is converted to glycerol-3-phosphate, which may serve as a backbone for triglyceride synthesis.
- Glycerol-3-phosphate can also be converted via two steps to Glyceraldehyde-3-Phosphate, which can then enter the glycolysis or gluconeogenesis pathway **(in a starvation state, gluconeogenesis will be favored in the liver).

Triacylglycerol Biosynthesis
- Glycerol-3-Phosphate serves as backbone, and Fatty Acyl-CoA groups are added sequentially.
  - Fatty acids are converted to Fatty Acyl-CoA via Acyl-CoA Synthetase.
- **The acyl-CoA is frequently saturated.
- Reaction 1: Glycerol-3-P Acyltransferase
  - Glycerol-3-P + Fatty Acyl-CoA ----> Monoacyl-glycerol-3-P (Lysophosphatidate).
- Reaction 2: 1-Acyl-Glycerol-3-P Acyltransferase
  - Monoacylglycerol-3-P + Acyl-CoA ----> Diacylglycerol-3-P (Phosphatidate).
- The acyl-CoA is frequently unsaturated.
- Reaction 3: Phosphatidate Phosphatase Reaction (non-enzymatic dephosphorylation).
  - Phosphatidate + H2O ----> Diacylglycerol
- Reaction 4: Diacylglyceride Acyltransferase
  - Diacylglycerol + Acyl-CoA ----> Triacylglycerol
  - Acyl-CoA can be either saturated or unsaturated.

Fate of Fatty Acids in Fasting, Starved or Diabetic State -- Ketone Metabolism
- In a starvation state, fatty acids are broken down by beta-oxidation in various tissues, forming acetyl-CoA that can enter the TCA cycle.
- However, in the liver, during a starvation state (also in diabetes, when glucose uptake is deficient) gluconeogenesis is the favored pathway, so oxaloacetate needed for the TCA cycle to function is depleted.
- Instead, the liver uses acetyl-CoA formed from oxidation of FAs to synthesize ketone bodies:
  - The three major ketone bodies are Acetoacetate, β-Hydroxybutyrate, and Acetone.

Ketogenic Pathway Reactions:
- Reaction 1: Acetoacetyl-CoA Thiolase *reversible, only goes forward if there is excess Acetyl-CoA
  - 2 Acetyl-CoA <---- Acetoacetyl-CoA (4C)
- Reaction 2: **HMG-CoA Synthase Reaction**
  - Acetoacetyl-CoA + Acetyl-CoA ----> 3-Hydroxy-3-methyl-glutaryl-CoA
- Reaction 3: **HMG-CoA Lyase Reaction** ***Remember for exam, key rate-limiting enzyme in ketone formation.***
  - HMG-CoA ----> **Acetoacetate** (*1st ketone body) + Acetyl-CoA
- Reaction 4: **β-Hydroxybutyrate (D-3-Hydroxybutyrate) Dehydrogenase** *reversible*
  - Acetoacetate + NADH + H+ <----> β-Hydroxybutyrate (2nd ketone body) + NAD+
- Formation of Acetone: Nonenzymatic, spontaneous
  - Acetoacetate ----> Acetone + CO2

**Acetoacetate as an Energy Source in Some Tissues**

- Acetoacetate is converted to Acetoacetyl-CoA by **Succinyl-CoA Transferase** (Succinyl-CoA --> Succinate)
  - **the liver lacks Succinyl-CoA transferase, and therefore cannot utilize ketones for energy**.
- Acetoacetyl-CoA is converted to 2 Acetyl-CoA via Acetoacetyl-CoA Thiolase *(reverse of rxn 1 in ketogenesis).
- Acetyl-CoA can then enter the TCA cycle.
- **Acetoacetate can be used efficiently in muscle and heart muscle tissue.**
- The brain relies most heavily on glucose, but can use ketones if needed.
- The liver lacks succinyl-CoA transferase, and therefore cannot use ketones for energy.

**The Ketogenic Pathway and Diabetes**

- When glucose utilization is impaired, as it is in diabetes, the limited amount of oxaloacetate made in the liver is consumed for gluconeogenesis.
- As a result, acetyl-CoA generated from FA oxidation is converted to ketone bodies in the liver.
- Ketone body accumulation beyond what tissues can utilize can be toxic in diabetes patients--**ketoacidosis.**