Lipid Digestion, Absorption and Assimilation

Human Metabolism Obeys the 1st Law of Thermodynamics:

- $\Delta U = Q - W$
  - $U =$ Kcal of chemical energy stored (mostly as fat).
  - $Q =$ Kcal in food intake.
  - $W =$ Kcal of metabolic and skeletal muscle work.
  - $\Delta U$ represents changes in storage components of the body:
    - TGs of adipose tissue.
    - Glycogen in liver and muscle.
    - Protein from all tissues.
    - $W < Q =$ weight gain.

Properties of Triacylglycerols, Fatty Acids and Cholesterol:

- Triacylglycerol and Fatty Acids
  - Storage:
    - Stored primarily in adipose tissue (limited storage in the muscle as well).
    - Stored dry, and yields about 9 kcal/g.
    - Transported as a component of lipoproteins.
    - TGs can be made de novo in the liver.
  - Regulation of TGs and FAs:
    - Metabolism of TGs and FAs is regulated in such a way that everything that can be stored, will be stored.
    - Stored energy is used during fasting / starvation states.
    - Main objective = to establish energy balance.
    - 98-99% reabsorption of triacylglycerol absorbed in the intestines.

- Cholesterol
  - Storage:
    - Stored as cholesterol esters -- formed by esterification with fatty acids.
    - Cholesterol esters are more lipophilic than free cholesterol (free cholesterol has hydroxyl groups).
  - Sources of Cholesterol:
    - De novo synthesis = $\sim$700mg/day **accounts for majority.
      - 70 mg in the liver.
      - 70 mg in the intestine.
      - 560 in other tissues (used in situ for membranes and other functions).
    - Diet = $\sim$400mg/day
      - Cholesterol in diet is variable, and depends on amount of animal food ingested.
      - Transported to the liver and extrahepatic tissues in the blood.
      - An increase in dietary cholesterol should inhibit de novo synthesis via feedback regulation of HMG-CoA reductase.
  - Regulation of Cholesterol:
    - Cholesterol is not significant as an energy sources, therefore, unlike TGs, the "objective" of regulation of cholesterol metabolism is different. **Want to maintain homeostasis.
    - Cholesterol is used as:
      - Important component of plasma membranes.
Precursor for bile acids (BAs = major player in quantitative turnover of total body cholesterol).
- Precursor for hormones and vitamins (not significant in cholesterol turnover).
  - Biliary cholesterol (cholesterol as a component of bile):
    - About 2g of biliary cholesterol is secreted daily, while the average diet includes about 0.4g of cholesterol per day.
    - Half of this total body cholesterol (1.2g) is reabsorbed in the ileum of the intestines, while the other half is excreted in the feces.
    - **Bile salts are reabsorbed much more efficiently.**

**Bile Salts**

- General Properties:
  - Synthesized in the liver, stored in the gallbladder.
  - Cholecystokinin (released in response to the presence of lipids in the duodenum), stimulates contraction of the gallbladder, forcing bile into the duodenum.
  - Bile acids are amphipathic, and serve to emulsify diacyl- and triacylglycerols, and cholesterol esters along with pancreatic lipase and colipase.
  - Form mixed micelles (microscopic, and soluble) with products of fat hydrolysis.
    - Micelles are smaller than emulsified bodies of lipids, and are actually considered to be in solution (soluble).

- Synthesis: see pg. 75
  - Stimulated by substrate (cholesterol) and inhibited by product (bile salts).
  - Cholesterol \( \rightarrow 7\alpha\text{-Hydroxylcholesterol} \) via \( 7\alpha\text{-Hydroxylase} \)
  - \( 7\alpha\text{-Hydroxylcholesterol} \) is activated by Propionyl-CoA to form Cholyl-CoA or Chenodeoxycholyl-CoA.
  - Both products react with either Glycine or Taurine to form Glycocholic / Glycochenodeoxycholic Acid and Taurocholic / Taurochenodeoxycholic Acid (**Four primary bile salts**).
  - The primary bile salts are excreted into the gut and acted on by bacterial enzymes to form secondary bile acids:
    - Glycocholic and Taurocholic acid are converted to Deoxycholic Acid (A secondary bile salt).
    - Glycochenodeoxycholic and Taurochenodeoxycholic acid are converted to Lithocholic Acid (A secondary bile salt).

**Sites of Lipid Digestion & Absorption**

- Stomach -- Fat digestion begins (gastric lipase).
  - Gastric Lipase-- secreted by glands in the stomach.
  - Acid pH is optimum (~pH 2).
  - Reation: Triacyl-glycerol \( \rightarrow \) Fatty Acid + 1,2-Diacylglycerol
  - **10-30% of triacylglycerol hydrolysis occurs in the stomach.**

- Duodenum -- *Site of most lipid digestion.*
  - Pancreatic Lipase -- secreted by pancreas into the intestines.
  - Reaction:
    - Step 1: Triacylglycerol \( \rightarrow \) Fatty Acid + 1,2-Diacylglycerol
    - Step 2: Diacylglycerol \( \rightarrow \) Fatty Acid + Monoacylglycerol
**~70% of hydrolyzed triglycerides enter enterocytes as 2-Monoglycerol + Fatty Acid, but there are other ways they can enter mucosal cells: (optional reactions)**

- **Step 3:** 2-monoacylglycerol ----(isomerase)----> 1-monoacylglycerol
- **Step 4:** 1-monoacylglycerol ----(pancreatic lipase)----> fatty Acid + glycerol

- **Jejunum -- *Site of most triglyceride absorption.**
  - **Villi** in the intestines increase total surface area, and facilitate absorption.
- **Ileum -- *Site of bile and cholesterol absorption.**
  - **Cholesterol Esterase** -- converts cholesterol esters to free cholesterol and free fatty acid.

**Intestinal Uptake of TGs**

- Fatty acids and monoacylglycerols are transported into intestinal epithelial cells via **Fatty Acid Transport Protein (FATP).**
- Fatty acids are activated to Fatty Acyl-CoAs via ATP and CoA and reincorporated into monoacylglycerols or incorporated into available glycerol-3-phosphate backbones.
- **Inhibition of TG Uptake via the drug Alli (Orlistat):**
  - Inhibits **pancreatic lipase.**
  - About 1/3 of TGs remain intact and unabsorbed.
  - Causes intestinal problems (nausea) and **steatorrhea** (high-fat fecal matter) with high-fat diet.
  - Patients become averse to fat in diet, and revert to high-protein / high-carbohydrate diet (therefore not a very effective treatment).

**Intestinal Uptake of Cholesterol**

- Cholesterol is transported into intestinal epithelial cells via **NPC1L1 Receptors** (Nieman-Picke C1-Like Protein 1).
- Cholesterol is re-esterified via **Acyl-CoA:Cholesterol acyltransferase (ACAT)** and has one of three fates:
  - Incorporated into **chylomicrons** for transport to the lymph system and then to the blood.
  - In situ utilization in membranes or as a metabolic precursor.
  - Excreted back into the intestine for via **ATP-Binding Cassette Protein (ABC Protein)** and the hydrolysis of ATP.
- **Inhibition of cholesterol uptake:**
  - **Benecol and Promise Take Control:**
    - Margarines that contain plant **stanol esters** or **plant sterols.**
    - Serve to **inhibit uptake of cholesterol into micelles** and **inhibit luminal cholesterol esterase** in the intestine.
  - **Zetia (generic name = Ezetimibe)**
    - Inhibits enterocyte cholesterol transporter **NPC1L1.**
  - **Cholestyramine and Colestipol:**
    - Non-absorbable resins that bind bile acids and reduce recycling of bile acids to the liver.
    - Result: hepatic cholesterol is redirected to synthesis of bile acids (de novo synthesis of cholesterol in the liver still compensates).
    - **Soluble fiber** also increase bile acid excretion by inhibiting their reabsorption.

**Overview of Lipid Digestion:**
- Triglycerides and Cholesterol esters are hydrolyzed by lipases and esterases respectively.
- Monoacylglycerols, fatty acids and cholesterol are incorporated into **micelles** (glycerol is not***).
- Monoacylglycerols, fatty acids, cholesterol and glycerol are all transported or diffuse into intestinal epithelial cells (enterocytes).
- Monoacylglycerols and fatty acids are re-esterified, and cholesterol are reformed into cholesterol esters.
- Triglycerides and cholesterol esters are packaged into **chylomicrons**, and secreted into the lymph.