**Lipid Metabolism**

**17.1: Lipid Transport**

* Summarize the roles of lipoproteins in lipid metabolism.
  + Explain why lipoproteins are needed to transport lipids.
  + Relate a lipoprotein’s density to its lipid content.
  + Describe the functions of LDL and HDL in cholesterol transport.

**Lipoproteins**

* Lipids travel as lipoproteins with varying densities (HDL, LDL, IDL, VLDL, chylomicrons)
* Chylomicrons: intestine to other tissues (TAGs to adipose and cholesterol to liver)
* VLDL: release TAGs to tissues, become cholesterol-dense LDLs; 50-65% TAG
* LDL: circulating lipoprotein; taken up by tissues; 45-50% cholesterol
* HDL: transport excess cholesterol from tissues back to liver

**Atherosclerosis**

* Lipid accumulation in vessel walls leads to inflammation and recruitment of WBCs (macrophages)
* Macrophages consume accumulated lipids and recruit additional macrophages, increasing inflammation
* Plaque forms: cholesterol, cholesteryl esters, dead macrophages, proliferating SMCs; possible calcification

**Cholesterol Delivery**

* Receptor mediated endocytosis
* Lipoprotein degraded, cholesterol released to cytosol, receptor recycled
* **Familial hypercholesterolemia:** genetic defect in LDL receptor
* Causes rise in serum levels, atherosclerosis, early death
* **Non-familial hypercholesterolemia:** Tx with PCSK9 inhibitor leads to increased recycling of LDL receptor to cell surface (PCSK9 causes degradation of LDL receptor)

**Cholesterol Uptake**

* HDLs remove excess cholesterol from cells
* ABC transporter (flippase) moves cytosolic cholesterol to outer leaflet of PM; followed by diffusion into nearby HDL
* Tangier disease: defects in transporter gene cause accumulation in tissues

**17.2: Fatty Acid Oxidation**

* Describe the chemical reactions required to oxidize fatty acids.
  + Explain how fatty acids are activated by ATP.
  + Describe how fatty acyl groups are imported into mitochondria.
  + List the substrates and products of each cycle of β oxidation.
  + Compare the pathways for oxidizing saturated, unsaturated, and odd-chain fatty acids.
  + Summarize the role of peroxisomes in fatty acid oxidation.

**Sources and functions of lipids**

* Consumed or synthesized from small precursors
* Free energy, structural, signaling molecules
* Immediate catabolism or long-term storage
* Oxidation of f.a.s is a source of free energy
* Dietary TAGs are primary source of free f.a.s

**Triacylglycerols**

* TAGs hydrolyzed extracellularly by lipoprotein lipases (extracellular peripheral enzyme)
* Mobilization of stored TAGs occurs via intracellular hormone-sensitive lipase
* Released TAGs travel via albumin carrier
* Free f.a. concentration remains low to avoid membrane disruption
* Deployed to liver and muscle cells (cardiac muscle prefers to burn f.a.s)

**Fatty Acid Activation**

* Two step reaction, catalyzed by acyl-CoA synthetase (cytosolic)
* 1: f.a. displaces diphosphate of ATP forming acyladenylate
* 2: HSCoA displaces AMP from acyladenylate forming acyl-CoA
* Overall, but subsequent hydrolysis of PP*i* makes reaction thermodynamically spontaneous
* Specific synthetases for various length f.a.s

**Carnitine Shuttle**

* Acyl groups must enter mitochondria via shuttle system (no transport for CoA adducts)
* 1: cytosolic carnitine acyltransferase transfers acyl group to carnitine
* 2: carnitine transporter allows entry to matrix
* 3: mitochondrial carnitine acyltransferase acyl group to HSCoA
* 4: Carnitine returns to cytosol via transporter; acyl group remains in matrix for oxidation

**Beta Oxidation**

* Spiral pathway: two less carbons each round, leading to successive round
* Acyl-CoA >>> acetyl-CoA for further oxidation
* Seven rounds for C16 f.a. to 8 acetyl-CoAs
* Can surpass glycolysis in terms of acetyl-CoA supplied
* Feeds electrons into ETC >>> ATP
* Four steps per round, yields on acetyl-CoA and acyl-CoA less two carbons
* C16 f.a.: 7 rounds, 8 acetyl-CoA
* Oxidation occurs at C3 (two carbons from carbonyl carbon)
* Acetyl units lost from activated CoA end (not methyl end)
* Source of free energy when CH2O unavailable
* 1 round produces 1 QH2 (1.5 ATP), 1 NADH (2.5 ATP), and 1 acetyl-CoA (10 ATP)
* Regulation depends on availability of free CoA as well as NAD+/NADH, Q/QH2 ratios

**Beta Oxidation of *cis* Fatty Acids**

* Oleate/Linoleate: round 4 presents a problem due to 3,4 double bond
* Enoyl-CoA isomerase converts *cis* 3,4 to *trans* 2,3 double bond
* Linoleate round 5: reductase uses NADPH to reduce *trans* 2,3 and *cis* 4,5 double bonds to *trans* 3,4 double bond; isomerase rearranges *trans* 3,4 to *trans* 2,3 double bond
* Reactions required to bypass double bonds reduce the total free energy released from catabolism of unsaturated fatty acids (QH2 bypass = 1.5 ATP and NADPH reduction = 2.5 ATP = 4 ATP lost)

**Beta Oxidation of Odd-Chain Fatty Acids**

* C3 fragment resulting from oxidation is propionyl-CoA.
* In order to utilize the energy conserved in the thioester bond, propionyl-CoA must be fully converted to pyruvate to enter the CAC as acetyl-CoA.
* Propionyl-CoA >>> Succinyl-CoA >>> CAC
* Prosthetic group of methylmalonyl-CoA mutase derived from cobalamin
* Vitamin B12 is obtained from dietary animal products
* Malabsorption or dietary deficiency causes disease
* Succinyl-CoA >>> CAC >>> Pyruvate >>> Acetyl-CoA >>> CAC

**Peroxisomal Fatty Acid Oxidation**

* Electrons are transferred to O2, producing H2O2
* Catalase breaks down H2O2; subsequent reactions are the same as mitochondrial oxidation
* Peroxisome = chain shortening system; partially degraded acyl-CoAs continue to mitochondria for further oxidation
* Branched-chain f.a.s are not recognized by mitochondrial enzymes; peroxisomes compensate for lack of recognition due to (branched) methyl groups
* Deficiencies in peroxisomal enzymes or peroxisomes results in fatality

**17.3: Fatty Acid Synthesis**

* Describe the chemical reactions required to synthesize fatty acids and ketone bodies.
  + Explain the purpose of the acetyl-CoA carboxylase reaction.
  + List the substrates and products for the seven steps of fatty acid synthesis.
  + Compare fatty acid synthesis and fatty acid oxidation.
  + Summarize the ways that palmitate can be modified.
  + Explain how fatty acid synthesis is regulated.
  + Describe the steps of ketone body synthesis and degradation.

**Citrate Transport System**

* ATP-citrate lyase undoes exergonic citrate synthase reaction
* Provides Acetyl-CoA for fatty acid synthesis (cytosolic)
* Pyruvate regenerated by cytosolic malic enzyme
* Citrate and pyruvate can cross the mitochondrial membrane via specific transport proteins.
* Provides acetyl-CoA for lipid synthesis = “acetyl-CoA shuttle”
* Pyruvate is regenerated

**Acetyl-CoA Carboxylase**

* Main regulatory step
* Similar to propionyl-CoA carboxylase and pyruvate carboxylase
* CO2 (as HCO3-) is activated by biotinylation (consumes ATP)
* Carboxylate group transferred to acetyl-CoA (enzyme regenerated)
* Malonyl-CoA donates 2-carbon acetyl unit to build f.a.

**Fatty Acid Synthase (mammalian)**

* Multifunctional enzyme (540 kD)
* Seven catalytic reactions
* Swinging pantothenate arm in ACP

**Reactions 1 and 2: Transacylations**

Transacylations prime enzyme with reactants for subsequent condensation reaction.

**Reaction 3: Condensation**

Condensation reaction decarboxylates malonyl-ACP, which attacks acetyl thioester to form acetoacetyl-ACP

3-ketoacyl-ACP synthase

**Reactions 4-7: Reduction, Dehydration, Reduction (NADPH), Transfer/Reloading**

CO2 released

2 NADPH consumed (steps 4 and 6); supplied by PPP

Malonyl-CoA (per round) costs 1 ATP per molecule

7 rounds = 42 ATP (35 ATP from 14 NADH + 7 ATP)

**Chain Lengthening**

CO2 released

2 NADPH consumed (steps 4 and 6); supplied by PPP

Malonyl-CoA (per round) costs 1 ATP per molecule

7 rounds = 42 ATP (35 ATP from 14 NADH + 7 ATP)

Pantothenate shuttles intermediates between active sites of enzyme complex

Multienzyme complex increases efficiency

**Elongases and Desaturases**

* Elongation occurs in either ER or mitochondria
* Desaturation occurs in ER via membrane-bound enzymes
* Palmitoleate (C16) and oleate (C18) are common (*cis* double bonds at 9,10)
* *Trans* fatty acids are rare in plants and animals (consumed in food)
* Mammals cannot synthesize fatty acids with double bonds beyond C9
* Arachidonate (C20) requires these and other lipids, thus, they must be consumed.
* Fish and plants are abundant sources (omega-3s)
* Deficiencies can delay growth and wound healing

**Control of Fatty Acid Metabolism**

* Abundance: carbohydrates and amino acids incorporated into f.a.s and stored as TAGs
* Acetyl-CoA carboxylase = main regulatory step
* Inhibited by palmitoyl-CoA and activated by citrate
* Allosterically regulated by phosphorylation
* Malonyl-CoA provides acetyl groups for synthesis, thus, inhibits carnitine acyltransferase to block transport and degradation

**Ketogenesis**

* Fasting: tissues depend on f.a.s from TAG; brain uses ketone bodies synthesized from acetyl-CoA via ketogenesis, sparing amino acids from degradation
* Ketone bodies are transported via bloodstream to CNS
* Excess acetoacetate >>> acetone
* Ketones = acids = pH drop (ketoacidosis)
* Ketones can be converted back to to acetyl-CoA by tissues after release from the liver
* Liver lacks 3-ketoacyl-CoA transferase

**17.4: Synthesis of Other Lipids**

* Summarize the synthesis of triacylglycerols, phospholipids, and cholesterol.
  + Explain how acyl groups are activated for transfer.
  + Describe the roles of CTP in glycerophospholipid synthesis.
  + Identify the regulated step of cholesterol synthesis.
  + Describe the metabolic fates of cholesterol.

**Glycerol-3-Phosphate Dehydrogenase**

* Glycolytic intermediates provide the scaffold for TAG synthesis
* NADH required for reduction (via dehydrogenase reaction)
* Fatty acyl groups are activated to CoA thioesters by acyl-CoA synthetase; consumes ATP

**Triacylglycerol Synthesis**

* Palmitate at C1; oleate at C2
* Provides precursors for glycerophospholipids
* Head groups or lipid portion activated by CTP

**Phospholipid Synthesis**

* Ethanolamine and choline are activated with CTP before being added to DAG
* Phopsphatidylserine synthesized by head group exchange
* Phosphatidylinositol synthesis: DAG activated (vs. head group)

**Cholesterol Synthesis**

* Synthesized in cytosol
* HMG-CoA production is last common step to ketogenesis
* HMG-CoA cleavage releases mevalonate
* Mevalonate + 2 P*i* – CO2 = isopentenyl pyrophosphate = isoprene derivative (C5)
* Statins lower cholesterol levels by inhibiting mevalonate synthesis
* Six isoprene units form C30 squalene
* Cyclization >>> folded squalene >>> cholesterol
* Rate determining step = HMG-CoA reductase (HMG-CoA >>> mevalonate); controlled by rates of synthesis and degradation as well as phosphorylation at Ser residue
* Statins inhibit HMG-CoA reductase with nanomolar K*I* (vs. substrate K*M* of ~4 µM)

**Fates of Cholesterol**

* Incorporation into cell membranes
* Acylated to form ester for storage or packaging as VLDL
* Steroid hormone precursor
* Bile acid precursor (disposal route)
* Cholesterol synthesis regulated by product inhibition of enzymes
* Cholesterol import regulated by repression of transcription of LDL receptor