LIPID METABOLISM

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Lipid particles

- VLDL particles are assembled in the liver enter the circulation directly.
- They acquire ApoC_{II} and ApoE from HDL particles in the blood.
- They deliver the newly synthesized particles into muscle and adipose tissue via lipoprotein lipase activity in the capillary beds of those tissues.
- The ApoC_{II} on the VLDL particle activates lipoprotein lipase.
- Fibrates activate peroxisome proliferator activated receptor, PPAR-α, increasing LPL activity.

Lipid particles

- The VLDL remnants (also called IDL particles) may be recycled back to the liver and are internalized via the ApoE receptor.
- The VLDL remnants can acquire additional cholesterol from HDL particles in the circulation and become LDL particles.

Lipid particles

- The LDL particles are internalized by LDL receptors present in peripheral tissue and in the liver.
- The LDL particles digested by lysozomes in these tissues, and the cholesterol is delivered to the tissues.
- Chylomicra are assembled in the intestinal epithelial cells and pass into the lymphatics.
- This allows them to initially bypass the liver.
- They acquire $ApoC_{II}$ and ApoE from HDL particles in the blood.

Lipid particles

- The chylomicron remnants are recycled back to the liver and are internalized via the ApoE receptor.
- The chylomicrons are digested by lysosomes in the liver, and the dietary cholesterol is then present in the liver.

LDL

- LDL dissociates from the receptors inside the acidic endosomes.
- LDL receptors recycle back to the membrane surface.
- Endosomes fuse with lysosomes, which contain hydrolytic proteases, to digest the LDL protein, ApoB-100.
- Lysosomal cholesterol esterase activity cleaves the ester bonds between fatty acids and cholesterol esters.
- Free cholesterol, free fatty acids generated.

LDL receptor

- ATP-driven proton pumps acidify the endosomes that contain the LDL particle/LDL receptor complexes.
- In Tangier disease there is no functioning cholesterol pump and cholesterol accumulates intracellularly.

LDL receptor defects

- I no detectable levels in homozygotes
- II receptors do not migrate to the cell membrane
- III receptors do not leave the endoplasmic reticulum and are degraded
- IV receptors do not migrate to “coated pits” on cell membrane
- V receptors cannot dissociate from the bound LDL particle and cannot be recycled

Familial hypercholesterolemia

- Autosomal dominant.
- 5% of those under age 60 suffering myocardial infarction.
- Atherosclerosis accelerated.
- Xanthomas.
- Defect in LDL receptor gene.
- Homozogytes may present with serum cholesterol >600 mg/dL.
- Death by age 30 if no intervention.
- Heterozygotes may present with serum cholesterol 300-400 mg/dL.

Familial dyslipidemias

- Type I ApoC-2 or LPL deficiency.
- Triglycerides accumulate.
- Type Iia LDL receptor deficiency.
- High levels of LDL.
- Type IIb VLDL overproduction.
- Triglycerides and cholesterol elevated.
- Autosomal dominant.
- Type III ApoE deficiency.
- Triglycerides and cholesterol elevated.

Familial dyslipidemias

- Type IV VLDL overproduction.
- Triglycerides elevated.
- Autosomal dominant.
- Type V VLDL overproduction.
- Triglycerides elevated.

Atherosclerosis

- Intimal injury.
- Endothelial cell dysfunction leads to macrophage entry and accumulation of oxidized LDL particles (foam cell formation).
- Smooth muscle cell migration is stimulated by PDGF and FGF-β.
- Fibrous plaque forms.
- Calcification may be seen in plaque.

Current therapy

- Decrease intake of cholesterol and fats.
- Modest effect, cholesterol synthesized
- Statins block cholesterol synthesis.
- HMG CoA reductase activity targeted.
- LDLR synthesis increased.
- HDL rises.
- Bile-acid binding resins Limits recycling from intestine.
- Liver increases synthesis of LDLR and cholesterol.

Fatty acid metabolism

- Fatty acids are components of phospholipids and glycolipids.
- They are triacylglycerols.
- Fatty acids are produced from triglycerides in chylomicrons and in VLDL through the action of lipoprotein lipase.
- Then they are taken up by cells and enter the cytoplasm by the citrate shuttle system.

Fatty acid metabolism

- Fatty acids are important fuel molecules.
- Oxidation of fatty acids yields ubiquinol and NADH that are used in oxidative phosphorylation
- Also yield Acetyl-CoA used in the TCA cycle.
- The complete oxidation of palmitate yields 106 ATP.
- Odd numbered fatty acids end as propionyl CoA which must be converted to methylmalonyl CoA.

Medium chain fatty acid deficiency

- Medium-chain (4-12 Carbons) acyl-CoA dehydrogenase deficiency leads to diminished production of acetyl-CoA in the mitochondrion.
- HMG-CoA and ketone formation is impaired.
- Most common fatty acid metabolism defect.
- 90% single missense Adenine-Guanine mutation (lysine to glutamate).
- Northern Europeans.
- Episodic hypoglycemia after fasting.

Medium chain fatty acid deficiency

- Excrete dicarboxylic acids (ω-oxidation).
- Hypoketotic.
- Present with vomiting and lethargy after minor illness (upper respiratory, gastroenteritis).

Site of fatty acid activation

- Short chain (2-3 Carbons)
- Cytosol and mitochondrion
- Medium chain (6-10 Carbons)
- Mitochondrial matrix (kidney and liver)
- Long chain (12-20 Carbons)
- Endoplasmic reticulum, outer mitochondrial membrane, peroxisomal membrane
- Very long chain (14-26 Carbons)
- Peroxisomes

Fatty acid metabolism

- β-peroxidation of fatty acids begins in peroxisomes.
- When the chain length has been reduced to 10 Carbon atoms, the process then continues in mitochondria (carnitine shuttle).
- Carnitine is made from lysine.
- Carnitine acyltransferase I is the rate limiting step in fatty acid oxidation (mitochondrion).
- Acetyl CoA is transported away from the liver as aceto-acetic acid.
- Ketone bodies are fuel molecules made from HMG-CoA.
- HMG-CoA synthase is the rate limiting enzyme

Fatty acid metabolism

- Aceto-acetic acid and ketone bodies are metabolized to yield 2 molecules of acetyl CoA and enter the TCA cycle.
- Fatty acid synthesis and degradation are reciprocally regulated.
- Fatty acids are activated to Acyl-CoA in the cytosol and if more than 12 Carbons, are transported across the inner mitochondrial membrane by the carnitine shuttle system and are degraded in mitochondria. (Cytosolic malonyl-CoA inhibits the shuttle).
- <u>This is the rate limiting step.</u>

Fatty acid metabolism

- Carboxylation of acetyl CoA to malonyl CoA is the first step in fatty acid synthesis.
- Biotin, ATP required.
- Insulin, citrate stimulate
- Glucagon, epinephrine inhibit.
- Acetyl-CoA carboxylase is the key enzyme in fatty acid synthesis.

Fatty acid oxidation

- The major process for degradation of long chain fatty acids is β-oxidation.
- Energy is generated.
- The rate of ATP utilization controls the rate of the electron transport chain.
- ω-oxidation is a minor process also utilized when medium chain fatty acids are present in excess.
- Occurs in the endoplasmic reticulum and mitochondria.
- Dicarboxylic acids can also be oxidized when present in excess.

Fatty acid oxidation

- α-oxidation is a minor process that occurs in the endoplasmic reticulum, particularly in neural tissue and in peroxisomes. I
- It is the first step in degradation of branched chain fatty acids.
- Refsum's disease is a result of defeciency of peroxisomal α-hydroxylase.
- Branched fatty acids accumulate, particularly in nervous tissues.
- Retinitis pigmentosa, cerebellar ataxia, and polyneuropathy seen.

Fatty acid oxidation

- Monounsaturated fatty acids undergo isomerization of the double bond (3,4 cis to 2,3 trans) to permit β-oxidation.
- A reductase to shift double bonds is also required for polyunsaturated fatty acids.
- Free fatty acids are carried by albumin (up to 10 are bound) in the blood stream.
- Stimulated by glucagon, but inhibited by insulin.

Regulation of fatty acid oxidation

- When glucose supply is plentiful, glucose is converted to fatty acids.
- Malonyl CoA inhibits carnitine-acyltransferase I (uptake of fatty acids into mitochondria is blocked).
- Glucose spares fat.
- When fatty acid supply is plentiful, fatty acid oxidation controlled by NAD/NADH redox state.
- Fatty acid oxidation produces acetyl CoA and NADH which inhibit pyruvate dehydrogenase (and conversion to citrate).
- Citrate inhibits PFK-1.
- Fat spares glucose.

Ketone body synthesis

- The supply of fatty acids is increased.
- Acetyl CoA carbolxylase is inhibited, malonyl CoA diminishes, permitting carnitine-palmotyl acyltransferase I shifting fatty acids into the mitochondrion for β-oxidation.
- NADH and $FADH_2$ are supplied for oxidative phosphorylation.
- As ATP levels increase, NADH levels fall.
- When NADH levels are elevated, oxaloacetate is converted into malate which then enters the cytoplasm for gluconeogenesis.
- As oxaloacetate falls, acetyl Co A is shifted to ketogenesis.

Ketogenic amino acids

- Tryptophan, phenylalanine, and tyrosine are diverted to the TCA cycle (and gluconeogenesis) as well as lead to the formation of ketone bodies.
- Leucine and lysine are ketogenic.
- They do not form glucose.
- Threonine and isoleucine may be used to form glucose as well.

Ketone body synthesis

- Thiolase condenses two acetyl-CoA units to form aceto-acetyl CoA.
- This enzyme is only present in the liver.
- HMG-CoA synthase condenses acetyl-CoA with aceto-acetyl CoA to form HMG-CoA.
- HMG-CoA lyase converts HMG-CoA to acetoacetate.
- Acetoacetate is converted to β-hydroxybutyrate and enters the bloodstream.
- The ketone bodies acetoacetate and β-hydroxybutyrate are used by muscle and brain where they are metabolized to acetyl-CoA.
- Death generally ensues at 45 days of fasting.

Fatty acid synthesis

- Fatty acids are synthesized in the cytosol by a multifunctional enzyme complex, fatty acid synthetase.
- Beginning with acetyl CoA, malonyl groups are added in seven successive steps until C16, palmitate, is generated.
- Further elongation is not possible in this path.
- Requires pantothenic acid.
- C18, linoleic and linolenic acids, as well as C20, arachidonic acids, are essential and not generated in the cell.

Fats

- Fatty acids with an odd number of Carbon atoms are handled in like fashion.
- They are metabolized to proprionyl CoA rather than acetyl CoA and are converted into succinyl CoA.
- Requires Biotin and Vitamin B12.

Fats

- The ω-numbering system for unsaturated fatty acids describes the position of the last double bond before the end of the chain.
- Fats are finally synthesized from activated fatty acids (acyl CoA) and glycerol 3-phosphate. T
- To supply peripheral tissues, fats are packed by the hepatocytes into lipoprotein complexes of the VLDL type and released into the blood in this form.

Adipose tissue lipolysis

- Adenylate cyclase is stimulated by a decreased insulin/glucagon ratio.
- Generates cAMP that activates protein kinase A.
- Protein kinase A activates hormone sensitive lipase by phosphorylation.
- Hormone sensitive lipase release free fatty acids and glycerol into the blood.
- Free fatty acids are taken up by liver and muscle.
- Glycerol is taken up by the liver and enters into the gluconeogenic pathway.

Complex lipids

- Alcohol plus fatty acid plus additional group.
- Phospholipids:
- Alcohol (glycerol) plus fatty acid plus phosphate group is phosphoglyceride (e.g., phosphatidyl-choline, phosphatidyl-ethanolamine, phosphatidyl-serine).
- Alcohol (sphingosine) plus fatty acid plus phosphate group is phosphosphingoside (ceramide adds choline to the configuration).
- Sphingomyelin is ceramide plus phosphorylcholine
- Galactocerebrosides add galactose to ceramide
- If an oligosaccharide is added, is a ganglioside.

Complex lipids

- Glycolipids:
- Alcohol (sphingosine) plus fatty acid plus sugar. The sugar is added to the ceramide.
- Structurally similar to sphingolipids.

Eicosanoids

- Linoleic acid is he beginning of the arachiodate cascade.
- Phospholipase A_2 releases arachidonic acid from membrane-bound phospholipids.
- Cyclo-oxygenase converts arachidonic acid itno prostaglandin G_2 which then changes to PGH_2 and is converted to thromboxane A_2 (in platelets) , PGI_2, prostacyclin (in endothelial cells), and PGE_2.
- 5-Lipo-oxygenase converts arachidonic acid into 5-HPETE, the precursors of leukotrienes
- LTA_4 is the parent molecule; produced in platelets, white cells, mast cells, vascular tissues.

Tissue specific enzymes

- Peroxidase requires reduced glutathione to generate active 15-OH metabolite.
- PGI synthase makes prostacyclins in vascular smooth muscle.
- TXA synthase is found in platelets.
- Thromboxane has a 6-member ring that contains an Oxygen atom.
- Stimulates aggregation and causes vasoconstriction
- PGD and PGE synthase are found in lymphocytes.

Eicosanoids

- PGE_2, PGD_2 stimulate vasodilation, increase cAMP levels.
- PGI_2
- Inhibit platelet aggregation, leukocyte aggregation, T-cell proliferation.
- $PGF_{2\alpha}$
- Stimulates vasoconstriction, bronchoconstriction, and smooth muscle contraction
- Thromboxanes increase vasoconstriction, platelet aggregation and bronchoconstriction.

Eicosanoids

- LTB_4 increases neutrophil chemotaxis and adhesion.
- Increase IL-1, IL-2, IFN-γ.
- LTA_4 in platelets leads to production of LTC_4 (LTC_4 synthase) as well as lipoxin (12-lipoxygenase).
- LTC_4, LTD_4, LTE_4 increase vascular permeability, vasoconstriction, bronchoconstriction.
- Lipoxins stimulate the production of superoxide ion, necessary for respiratory burst.
- Also are chemotactic.

Eicosanoids

- Lipoxygenase isoforms are issue specific:
- 5-lipoxygenase noted in neutrophils
- 12-lipoxygenase, platelets
- 15-lipoxygenase, eosinophils.

Cholesterol metabolism

- Cholesterol synthesis begins with palmitate.
- HMG-CoA reductate catalysis is the rate limiting step
- HMG-CoA is converted to mevalonate, then to squalene, lanosterol, and , finally, to cholesterol.
- Squalene is the building block of the steroid ring.
- Plasma cholesterol is esterified by lecithin-cholesterol acyltransferase.
- Esterification is activated by apoliproptein A1 which also serves as ligand for the HDL receptor.

Cholesterol metabolism

- Dietary cholesterol is transported in chylomicrons.
- Apolipoprotein E is required for chylomicron uptake by the liver.
- It is also a ligand for the LDL receptor.
- Apolipoproteins A1, B48, CII are also found on its cell membrane.
- Following modification of VLDL by lipoprotein lipase in peripheral tissues, LDL acts as transport of cholesterol from liver to periphery.
- Apolipoprotein B100 on the VLDL acts as ligand for the LDL receptor

Cholesterol metabolism

- HDL is synthesized cholesterol free in the liver
- Is able to take up free cholesterol from tissues
- Mediates cholesterol transport from periphery to liver
- Acts as repository for apoliproteins CII and E, and is able to donate these particles to other lipoproteins.
- Contains apolipoprotein A1 as well.
- Lipoprotein lipase is found on endothelial cell surfaces and requires apoliopoprotein CII as a cofactor for activation.

Cholesterol metabolism

- Lipoprotein (a) resembles plasminogen.
- It is a disulfide bonded apolipoprotein B100 complexed to LDL.
- Free cholesterol (nonesterified) is released to the cytosol.
- Inhibits further cholesterol synthesis by inhibiting HMG-CoA reductase.

Cholesterol metabolism

- Decreases the synthesis of LDL receptor.
- Reduces the internalization of cholesterol-containing LDL particles.
- Stimulates esterification of cholesterol by Acyl-acetyltransferase.
- Cholesterol in the liver is stored as a highly insoluble cholesterol ester.
- Cholesterol may then be incorporated into cell membranes, converted to bile salts, or converted to Vitamin D.

Cholesterol metabolism

- The body cannot degrade the sterol nucleus in bile salts
- Only the 5% loss of bile accounts for the majority of cholesterol excreted per day.