# LIPIDS METABOLISM

## FATTY ACID SYNTHESIS

* needed when Glucose level falls
* De Novo Synthesis : cytoplasm of liver, lactating glands, adipose tissues
* Enzymes :
  1- Acetyl CoA Carboxylase (2 domains)
  2- Fatty acid synthase (multi-dimential enzyme 7 domains)
* Coenzymes
  1- Biotin
  2- NADPH
  3- ATP
  4- $CO_2$ (from $HCO_3^-$)
* STEPS :
  Condensation
  Reduction
  Dehydration
  Reduction
* Acetyl CoA and Malonyl CoA used as precursors

* Acetyl CoA used through ~~Citrate~~ malate-citrate shuttle

* Acetyl CoA (2-C) — ⊖ ~~Insulin~~ Epinephrine, Glucagon; ⊕ Insulin

Biotin →
ATP →
$CO_2$ →

Acetyl Co-A carboxylase
⊖ AMPK

Components
1. Biotin Carboxylase
2. Trans Carboxylase

Melonyl CoA (3-C)

FAS → Addition of two carbon from malonyl CoA to carboxyl end of a series of acyl acceptors

~~FAS~~

* Fatty Acid Synthase (7 domains)

1- Acyl carrier Protein
2- Condensing Domain
β-keto acyl synthase

} Initial Domains

$C_{16}$-Palmitate → Upto $C_{16}$ single bonds

* NADPH required ~~from~~ for fatty acid synthesis it is obtained from: (1) HMP Shunt

(2) Oxaloacetate → Malate —NADPH→ Pyruvate

# TAG SYNTHESIS / STORAGE

$C_{16} \longrightarrow C_{18} \xrightarrow{\text{Desaturase}}$ Double bond b/w $C_9$ and $C_{10}$

- Donor : Malonyl CoA
- Reductant Source : NADPH

* Desaturase enzyme Requires : $O_2$, NADH, FAD, cytochrome $b_5$

* 3 Fatty Acid + Glycerol → TAG

Fatty Acid 1 = Saturated

F.A 2 = Unsaturated

FA 3 = Saturated / unsaturated

Glycerol obtained from liver and adipose tissue

In Liver :

Glucose

↓

Glucose-6-Phosph

↓

Fructose-6-Phosphate

↙ ↘

G-3-P DHAP

↓

G-3-P

In Adipose :

Glucose

↓

DHAP

↓

Glycerol-3-Phosphate

$F_1$ →

↓

Lysophosphatidic acid

$F_2$ →

↓

Phosphatidic Acid (DAG-P)

→ P

↓

DAG

$F_3$ → ↓

TAG

* TAG stored as lipid droplets in white, and brown adipocytes

In white adipocytes they serve to produce energy (through β-oxidation)

In brown adipocytes they serve to produce heat.

# TAG MOBILIZATION/β-OXIDATION

TAG

Adipose Triglyceride Lipase ~~Lipase~~

DAG

Hormon sensitive lipase

MAG

MAG-Lipase

Adipose ~~lack~~ Glycerol kinase

Glycerol

Liver

Glycerol kinase

Glycerol-3-phosphate

DHAP

Glucose

Fatty Acids

(Thiokinase) Acyl CoA synthetase

F.A bind with serum albumin in plasma and transported to muscle tissue

Cytoplasm

Fatty Acyl Co A

Carnitine

CoA

CPT-1 (Carnitine palmityl Transferase 1)

Acyl Carnitine

when glucose level falls, glucagon and norepinephrine binds to adipocyte receptors and activate cAMP which activate protein kinase A that phosphorylate and activate hormone sensitive lipase which acts on DAG and convert it into MAG

*CPT-I : enzyme of inner mitochondrial membrane
*CPT-II: enzyme of



90% Carnitine present in skeletal muscles

Acyl Carnitine (in cytoplasm)

Mitochondria | Translocase

* LCFA converted in cytosol to its CoA derivated by thiokinase, an enzyme of outer mitochondrial membrane

Acyl Carnitine (in mitochondria)

CoA ↘ | CPT-2

Carnitine ↙

* Inner mitochondrial membrane impermeable to CoA

Acyl CoA

# β-OXIDATION → occurs in ~~mitochondrial matrix~~

Even Chain F.A (16-C)

Oxidation/Dehydrogenation — Fatty Acyl CoA

FAD → $FADH_2$ — Dehydrogenation or Oxidation

Hydration

Oxidation/Dehydrogenation

Cleavage

Trans-2-Enoyl CoA (Double bond added)

$H_2O$ → Hydration

2-C (Acetyl CoA)
↑
4-C
↑
6-C
↑
8-C
↑
10-C
↑
12-C

3-Hydroxyacyl CoA

$NAD^+$ → $NADH$ — Dehydrogenation (Oxidation)

3-Ketoacyl CoA (Another double bond)

Thiolase — Cleavage

Fatty Acyl CoA + Acetyl CoA (2-C)

(14-C)

* In each cycle of β oxidation products formed

1 $FADH_2$, 1 $NADH_2$, 1 Acetyl CoA (2 formed in last cycle)

* How many cycles for fatty acid calculation =

$$\frac{\text{No. of Carbons}}{2} - 1$$

e.g $\frac{16}{2} - 1 = 7$ cycles

For 7 cycles = 7 $FADH_2$, 7 $NADH_2$, 8 Acetyl CoA

Energy Yield = $(7 \times 2)_{ATP}$ $(7 \times 3)ATP$ $(8 \times 12)ATP$

~~14 + 21 + 96~~

+

* Short Chain Fatty acids donot need carnitine shuttle. They easily diffuse through mitochondria and are used for β-oxidation.

MCAD (Medium Chain Fatty Acyl Dehydrogenase) used for medium chain fatty acids.

MCAD deficiency lead to hypoglycemia, hypoketonemia

* In odd chain fatty acid compound, 3-C chain is left in last reaction of β-oxidati which remains as propionyl CoA.

Propionyl CoA

↓

Dimethyl melonyl CoA

↓

L-methyl melonyl CoA

↓ vitamin B12

Succinyl CoA

↓ ~~vitamin B12~~

enter TCA cycle

* β-oxidation of Unsaturated F.A (having Double Bond)

After 3 rounds (upto double bond), the molecule has cis configuration which is converted to trans by an isomerase enzyme, and further cleaved

* β-Oxidation of Very long Chain F.As ≥ 22 carbons

→ Peroxisomal β-oxidation

→ First step differ

Long Chain FA [This $FADA_2$ is not energy produced]

Acyl CoA oxidase ↓ FAD → $FADH_2$ ..... $H_2 + O_2 \rightarrow H_2O_2$

$H_2O_2 \xrightarrow{\text{catalase}} H_2O + O_2$

* Melonyl CoA - inhibits CPT-I

*

# KETOGENESIS / Ketolysis

Acetyl CoA ⟶ Ketone bodies (Ketogenesis)

* Acetyl CoA usually goes through TCA cycle but in excessive breakdown it is converted to ketone bodies

* In excessive fat breakdown, β-oxidation inhibits pyruvate dehydrogenase of TCA cycle. while activates pyruvate carboxylase due to which conversion of pyruvate to Acetyl CoA is blocked and pyruvate is converted into oxaloacetate and eventually into glucose.

* Due to β-oxidation, NAD/NADH ratio decrease which inhibit OAA binding with Acetyl CoA and oxaloacetate (OAA) is converted to glucose

* Ketone Bodies:

1- Acetone

2- Acetoacetate

3- β-hydroxybutarate / 3-hydroxybutyrate

2 Acetyl CoA (from β-oxidation)

combine → CoA

Acetoacetyl CoA

HMG CoA synthase → Acetyl CoA, CoA

HMG CoA (6-C)

→ CoA

Acetoacetate

~~Acetoacetone~~ (or)

Acetone

3-Hydroxybutarate

* These ketone bodies broken down again into acetyl CoA in the tissues to be used in TCA cycle

* Diabetes melitis → ~~Ketonuria~~ Ketonemia and Ketouria

* HMG CoA synthase is rate-limiting step and present only in liver

# CHOLESTEROL DEGRADATION

* Cholesterol Fates

1- Part of cell membrane

2- Converted to cholesteryl ester in presence of ACAT (Acyl Cholesterol Acyl Transferase)

Cholesteryl ester + B-100 ⟶ VLDL

3- Bile salts

4- Steroid hormones

5- Vitamin D

* Formation of Bile Salt from Sterol:

→ 27-C to 24-C

→ hydroxylation (OH) → 3OH groups

Hydroxylation at position 7 in presence of 7-α-hydroxylase is rate limiting reaction

→ carboxylation (COOH): This carboxyl group is protonated in initial portion of duodenum while deprotonated in terminal portion of duodenum

- 3 OH groups on sterol : Cholic acid
- 2 OH groups on sterol : Chenodeoxycholic acid
- 1 OH group on sterol: 7-α-hydroxycholesterol

Primary bile salts

*Conjugation : Addition of glycine or taurine to bile salts

Cholic acid → (Glycine/taurine) → Glycocholic / Taurocholic

Chenodeoxycholic acid → (Glycine/Taurine) → Glycochenodeoxycholic / Taurodeoxycholic

Glycocholic / Taurocholic + Glycochenodeoxycholic / Taurodeoxycholic → Bile salts along with bile

Bile salts along with bile → Intestine (Duodenum)

Intestine (Duodenum) → Deconjugation, Dehydroxylation → Secondary Bile Salts (15-30g)

- Deoxycholic acid
- Lithocholic acid

Secondary Bile Salts → Excrete (0.5g)

Secondary Bile Salts → Ileum Reabsorption (95%) → Portal Blood → Liver (Recirculated)

•Phosphatidylcholine (PC), or lecithin and conjugated bile salts are quantitatively the most important organic components of bile.

HMG → 3 Hydroxy- 3 [illegible]



* Cholelithiasis → Cholesterol Gallstone Disease

* Cholesterol is soluble in bile salts to presence of phosphatidyl choline in bile.
→ Due to decrease of phosphatidyl choline in bile, cholesterol accumulates in gallbladder and produce gallstones leading to cholelithiasis.

* Cholesterol Synthesis ~~Triglycerol~~

2 Acetyl CoA
↓ →CoA
Acetoacetyl CoA
HMG CoA sythase: Acetyl CoA →CoA
HMG CoA
HMG CoA Reductase (Rate-limiting): 2NADPH →2NADP →CoA
Mevalonate
↓
Cholesterol

- Precursor of Cholesterol = Acetyl CoA
- Rate limiting Step = HMG CoA Reductase
- Regulation: (1) HMG CoA Reductase (2) Insulin dephosphorylates/ activates reductase enzyme. Glucagon and epinephrine inhibits reductase.

# LIPOPROTEIN

→ Spherical macromolecule containing lipid (inside) and protein (outside)
↳ Proteins called Apolipoprotein

* Classification of Lipoprotein:

1- Chylomicrons

2- VLDL

3- LDL

4- HDL

* Functions of Lipoprotein:

1- Transport lipids in plasma

* Composition:

1- Innev Core → Lipid : TAG, cholesteryl ester, cholesterol

2- Outer Core → Protein : Phospholipid
↳ Free cholesterol in outer layer

* Exogenous (from diet) Phospholipids load into chylomicrons

Endogenous (made in body) Phosphilipids load into VLDL

: Total Cholesterol = VLDL + LDL + HDL

* Density :

HDL > LDL > VLDL > Chylomicrons

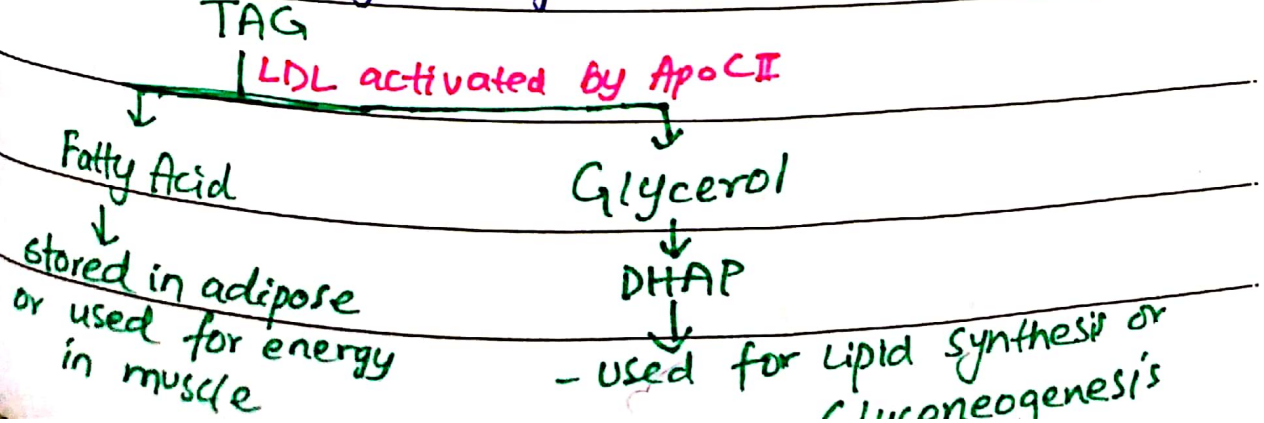
* Size :

Chylomicrons > VLDL > LDL > HDL

* Chylomicrons have high TAG content while less cholesteryl ester content

# CHYLOMICRON METABOLISM

* Lipid Core : TAG (exogenous TAG)
* Apoprotein : Apo-B48 → (48% protein)
  * Synthesized in intestine
* Microsomal Transport Protein (MTP) loads Apo-B48 with lipid core and assemble chylomicron
* Nascent Chylomicron synthesized in intestine.
* In plasma : Tempory attachment of APO-CII and APO-E (derived from HDL) and move to blood capillaries where:
  - APO-CII → Activate Lipoprotein Lipase that break down TAG into Glycerol and free F.A due to which chylomicron is converted into chylomicron remnant as major TAG is removed
  - APO-E → Recognize liver receptors and endocytose chylomicrons remnants into liver to be completely degraded



# LDL METABOLISM

* Lipid Core : Cholesteryl ester and TAG (endogenous)
* Protein : Apo B-100
* Synthesized in Liver
* Moved to plasma and Apo-E and Apo-CII loaded (from HDL)
* Capillary : TAG → Glycerol + F.A
* Moved outside of capillary and known as Intermediate Density Lipoprotein having cholesteryl ester and Apoprotein
* Move to liver by endocytosis through Apo-E OR IDL may condense to LDL and endocytose in extrahepatic tissues and broken down by acid hydrolases of lysosome

Endocytosis : LDL + Clathrin → endocytosis → Endosome → Clathrin Recycled

Endosome → LDL released

↓

Lysosomal breakdown

↓

- Amino Acids
- Cholesterol

* If cholesterol in excess:

Cholesterol —ACAT→ Cholesteryl ester

* Lysosomal Storage Diseases:

1. Wolman Disease → inability to hydrolyze lysosomal cholesteryl esters

2. Niemann-Pick Disease → inability to transport free cholesterol out of lysosome

*ACAT - Acyl CoA: cholesterol Acyl Transferase

* In excess cholesterol, cholesteryl esters accumulate in macrophages and cause their transformation into "foam cells" which participitate in formation of atherosclerotic plaque.

LCAT : Lecithin Cholesterol Acyl Transferase
↓ synthesized and secreted by Liver



# HDL METABOLISM

* HDL provide Apo CII, Apo-E
* Reverse cholesterol Reaction : converts cholesterol into cholesteryl ester
* Apolipoprotein : ~~Apo-A1~~ Apo-A1

HDL + Cholesterol $\xrightarrow{LCAT}$ Cholesteryl ester

[HDL converted into $HDL_3$]

* Cholesterol rich HDL → $HDL_2$ → carried to Liver
* $HDL_2 \xrightarrow{\text{Hepatic Lipase}} HDL_3$

VLDL $\xrightarrow{TAG}$ HDL

HDL $\xrightarrow{\text{Cholesteryl ester}}$ VLDL

: Rest of cholesteryl ester moved to liver

* HDL is a "good" cholesterol carrier. Exercise and estrogen raise HDL levels.
* Nascent HDL are disc shaped particles containing primarily phospholipid (largely phosphatidylcholine) and apoA, C and E. They take up cholesterol from peripheral tissues and return it to liver as cholesteryl esters.

Triacyl Glycerol (TAG)

↓ Pancreatic lipase (remove FA at carbon 1 and 3)

2-monoacyl-glycerol (2-MAG) + FFA

Cholesteryl Ester

↓ Cholesteryl ester hydrolase

Cholesterol + FFA

Phospholipid

↓ Phospholipas $A_2$ (removes one FA from carbon no. 2)

Lysophospholipid

↓ Lysophospholipase (removes FA from carbon no. 2)

Glycerophosphoryl base

* Steatorrhea → increased lipid in feces due to lipid malabsorption
* Familial chylomicronemia (Type I hyperlipoproteinemia) is a rare, autosomal-recessive disorder caused by deficiency of LPL or its coenzyme apo C-II. The result is fasting chylomicronemia and severe hypertriacylglycerolemia, which can cause pancreatitis
* Essential Fatty Acids → cannot be synthesized in body ⊖: Linoleic acid, α-Linolenic acid
* Adenosine-Monophosphate-activated protein kinase (AMPK) phosphorylates and inactivates Acetyl CoA Carboxylase (ACC)
Metformin lowers blood glucose by increasing AMPK-mediated glucose uptake by muscle.

* CPT-I Deficiency : Inability to use LCFA for fuel during fast → leads to severe hypoglycemia, coma and death

* Disorders of fatty acid oxidation present with hypoketosis (due to decrease availability of acetyl CoA) and hypoglycemia (bcz of increased reliance on glucose for energy)

* Normal Level of ketone bodies in blood = < 3mg/dL

* Diabetes Mellitis : Type 1

→ Ketonemia (due to insufficient insulin)

→ Ketouria

→ Ketoacidosis

* Patients with deficiency of LPL or APO-C II (Type I hyperlipoproteinemia or familial chilomicronemia) show a dramatic accumulation of Chylomicron-TAG in plasma even in the fasted state. They are at increased risk of acute

* In well fed state LPL (Lipoprotein Lipase) synthesis is increased in adipose (for stage) but decreased in muscle tissue
In fasting state, LPL synthesis is increased in muscle (for energy production)
* In a chylomicron, about 90% is TAG
* About 70% of plasma Cholesterol is in LDL
* Phospholipids are important solubilizers of cholesterol
* RCT (Reverse Cholesterol Reaction) by HDL involves:
1- Efflux of cholesterol from peripheral cells to HDL
2- Esterification of cholesterol by LCAT
3- Binding of Cholesteryl-ester rich HDL ($HDL_2$) to Liver
4- Selective transfer of cholesteryl ester to liver cells

5. Release of Lipid depleted HDL ($HDL_3$)

# ★STEROID HORMONE SYNTHESIS

Cholesterol (27 C)

(Refer to Pg 238 LippincoH)

Desmolase and Cytochrome P450 (on inner mitochondrial membrane)

Rate-Limiting Reaction

← NADPH
← $O_2$

Pregnenolone is the parent compound for all steroid hormones

Pregnenolone (21 C)

Progesterone (21 C)

21-α-Hydroxylase

17-α- Hydroxylase (CYP17)

11-Deoxycorticosterone (21C)

17-α-Hydroxyprogesterone (21C)

Corticosterone

11-Deoxycortisol (21C)

Androstenedione (19C)

Aldosterone (21C)

Testosterone (19C)

Aromatase

Cortisol (21C)

Estradiol (18C)