"Cholesterol, Lipoprotein, and Steroid Metabolism"

I. Overview

Cholesterol – General Characteristics

- Cholesterol is the major steroid alcohol in animals.
- It performs a number of essential functions in the body.

Structural and Functional Roles of Cholesterol

- Structural Component:
    - Present in all cell membranes.
    - Modulates membrane fluidity.
- Precursor Molecule (in specialized tissues):
    - Bile acids
    - Steroid hormones
    - Vitamin D

Importance of Cholesterol Supply

- It is critically important that cells of the body receive an appropriate supply of cholesterol.

Hepatic Role in Cholesterol Homeostasis

Central Role of the Liver

- The liver plays a central role in regulating the body's cholesterol homeostasis.

Sources of Hepatic Cholesterol Pool

- Cholesterol enters the hepatic cholesterol pool from:
  - Dietary cholesterol
  - Cholesterol synthesized de novo by:
    - Extrahepatic tissues
    - The liver itself

Cholesterol Elimination Pathways

Routes of Cholesterol Elimination from Liver

- Cholesterol is eliminated from the liver via:
  - Unmodified cholesterol in the bile
  - Conversion to bile salts, which are secreted into the intestinal lumen
  - Incorporation into plasma lipoproteins, which:
    - Carry lipids to peripheral tissues

Imbalance and Atherosclerosis

Influx-Efflux Imbalance

- In humans, the balance between cholesterol influx and efflux is not precise.

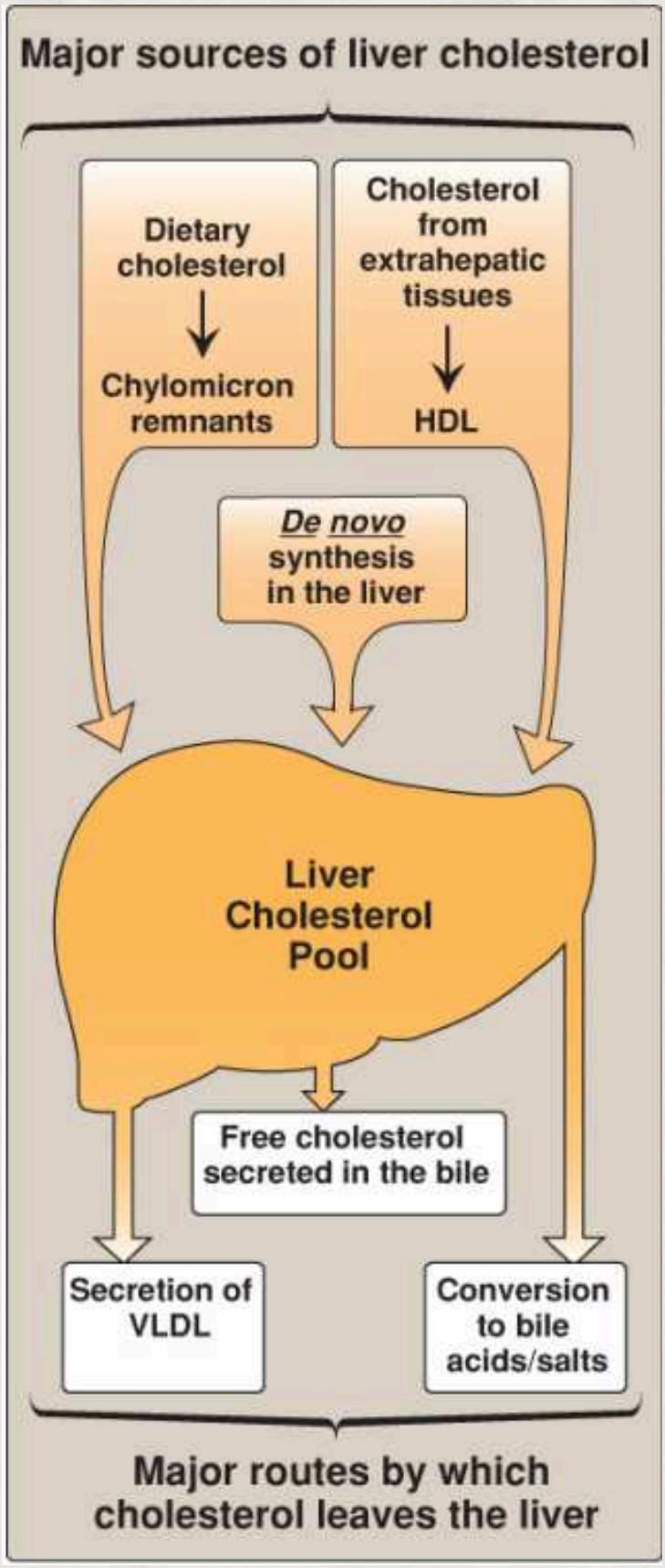
Consequences of Imbalance

- Gradual deposition of cholesterol in tissues occurs.
- This is especially significant in endothelial linings of blood vessels.

Atherosclerosis

- Lipid deposition leads to plaque formation.
- Plaque formation causes:
    - Narrowing of blood vessels (atherosclerosis)
    - Increased risk of:
        - Cardiovascular disease
        - Cerebrovascular disease
        - Peripheral vascular disease

Sources of Liver Cholesterol (Influx) and Routes by which Cholesterol Leaves the Liver (Efflux)



II. Cholesterol Structure

General Properties

- Cholesterol is a very hydrophobic compound.

Core Structure

- Composed of four fused hydrocarbon rings (A-D), collectively called the steroid nucleus.
- Contains an eight-carbon, branched hydrocarbon chain attached to carbon 17 of the D ring.

Ring Modifications

- Ring A: has a hydroxyl group at carbon 3.
- Ring B: has a double bond between carbon 5 and carbon 6.

A. Sterols

Definition of Sterols

- Steroids with:
    - 8 to 10 carbon atoms in the side chain at carbon 17
    - A hydroxyl group at carbon 3
- Classified as sterols.

Cholesterol as a Sterol

- Cholesterol is the major sterol in animal tissues.

Sources of Cholesterol

- Arises from:
    - De novo synthesis
    - Absorption of dietary cholesterol

Intestinal Uptake of Cholesterol

- Mediated by the Niemann-Pick C1-like 1 (NPC1L1) protein.

- NPC1L1 is the target of the drug ezetimibe, which:
    - Reduces absorption of dietary cholesterol.

Note: Plant Sterols (Phytosterols)

Feature	Plant Sterols (e.g., β-sitosterol)	Cholesterol
Absorption in Humans	Poorly absorbed (≈5%)	≈40% absorbed
Fate in Enterocytes	Actively transported back into the intestinal lumen	Some transported back as well

Defects in the efflux transporter (ABCG5/8) cause:

- Sitosterolemia: plant sterols accumulate in blood and tissues.
- Consequences:
    - Reduced blood flow

- Increased risk of:
  - Heart attack
  - Stroke
  - Sudden death

Dietary Use of Plant Sterols

- Some cholesterol is transported back, so plant sterols:
  - Reduce absorption of dietary cholesterol
- Daily ingestion of plant sterol esters (e.g., in spreads):
  - Is a dietary strategy to reduce plasma cholesterol levels

B. Cholesteryl Esters

Structure

- Most plasma cholesterol is in esterified form:
  - Fatty acid (FA) is attached at carbon 3

Properties

- More hydrophobic than free (nonesterified) cholesterol.

Location

- Not found in membranes
- Normally present at low levels in most cells

Transport Requirements

- Due to hydrophobicity, cholesterol and esters must be:
    - Transported in association with protein
        - As part of a lipoprotein particle, or
    - Solubilized by:
        - Phospholipids
        - Bile salts in the bile

III. Cholesterol Synthesis

Tissues Involved

- Cholesterol is synthesized by virtually all tissues in humans.
- Tissues contributing most significantly to the cholesterol pool:
    - Liver
    - Intestine
    - Adrenal cortex
    - Reproductive tissues, including:
        - Ovaries
        - Testes
        - Placenta

Substrates and Energy Sources

- Carbon atoms in cholesterol are provided by:
    - Acetyl coenzyme A (CoA)

- Reducing equivalents are provided by:
    - Nicotinamide adenine dinucleotide phosphate (NADPH)

Energy Considerations

- The pathway is endergonic.
- Driven by:
    - Hydrolysis of high-energy thioester bond of acetyl CoA
    - Hydrolysis of terminal phosphate bond of ATP

Enzyme Locations

- Synthesis requires enzymes located in:
    - Cytosol
    - Smooth endoplasmic reticulum (SER) membrane
    - Peroxisome

Regulation and Homeostasis

- The pathway is responsive to changes in cholesterol concentration.

- Regulatory mechanisms balance:
    - Rate of cholesterol synthesis
    - Rate of cholesterol excretion

Clinical Relevance

- Imbalance in regulation may lead to:
    - Elevated circulating plasma cholesterol
    - Potential for vascular disease

A. 3-Hydroxy-3-Methylglutary Coenzyme A (HMG CoA) Synthesis

Step Similarity

- The first two reactions are similar to ketone body synthesis pathway.

Sequence of Reactions

Step	Enzyme/Process	Product
1	Condensation of two acetyl CoA molecules	Acetoacetyl CoA
2	Addition of a third acetyl CoA by HMG CoA synthase	3-Hydroxy-3-methylglutaryl CoA (HMG CoA) -> a six-carbon compound

Isoenzymes of HMG CoA Synthase

- Liver parenchymal cells contain two isoenzymes:
    - Cytosolic enzyme:
        - Participates in cholesterol synthesis
    - Mitochondrial enzyme:
        - Functions in ketone body synthesis

B. Mevalonate Synthesis

Catalyzed Reaction

- HMG CoA is reduced to mevalonate by:
    - HMG CoA reductase

Key Characteristics

- This step is:
    - Rate-limiting
    - Key regulated step in cholesterol synthesis
- Occurs in the:
    - Cytosol
- Requires:
    - Two NADPH molecules as reducing agents
- Releases:
    - CoA

- The reaction is:
    - Irreversible

Enzyme Details: HMG CoA Reductase

- Integral membrane protein of the SER
- Catalytic domain projects into the cytosol

C. Cholesterol Synthesis From Mevalonate

[1] Formation of 5-Pyrophosphomevalonate

- Mevalonate is converted to 5-pyrophosphomevalonate in two steps.
- Each step involves the transfer of a phosphate group from ATP.

[2] Formation of Isopentenyl Pyrophosphate (IPP)

- 5-pyrophosphomevalonate is decarboxylated to form:
    - Isopentenyl pyrophosphate (IPP) — a five-carbon isoprene unit.
- The reaction requires ATP.

Note:

- IPP is the precursor of the isoprenoids family:
    - Cholesterol is a sterol isoprenoid.
    - Nonsterol isoprenoids include:
        - Dolichol
        - Ubiquinone (coenzyme Q)

[3] Isomerization to Dimethylallyl Pyrophosphate

- IPP is isomerized to:
    - 3,3-dimethylallyl pyrophosphate (DPP)

[4] Formation of Geranyl Pyrophosphate (GPP)

- IPP and DPP condense to form:
    - 10-carbon geranyl pyrophosphate (GPP)

[5] Formation of Farnesyl Pyrophosphate (FPP)

- A second IPP molecule condenses with GPP to form:
    - 15-carbon farnesyl pyrophosphate (FPP)

Note:

- Prenylation = covalent attachment of farnesyl to proteins (e.g., ras)
    - Function: Anchors proteins to inner face of plasma membranes

[6] Formation of Squalene

- Two molecules of FPP combine and are:
    - Reduced
    - Release pyrophosphate
- Product: 30-carbon squalene

Note:

- Squalene is made from six isoprenoid units
- ATP Requirement:
    - 3 ATP per mevalonate → IPP
    - Therefore, 18 ATP required to form polyisoprenoid squalene

[7] Formation of Lanosterol

- Squalene is converted to lanosterol in two reactions
- Enzymes are:
    - SER-associated
- Co-factors used:
    - Molecular oxygen (O_2)
    - NADPH

Mechanism:

- Hydroxylation of linear squalene triggers cyclization to lanosterol

[8] Conversion of Lanosterol to Cholesterol

- A multistep process involving:
    - Shortening of side chain
    - Oxidative removal of methyl groups
    - Reduction of double bonds
    - Migration of a double bond

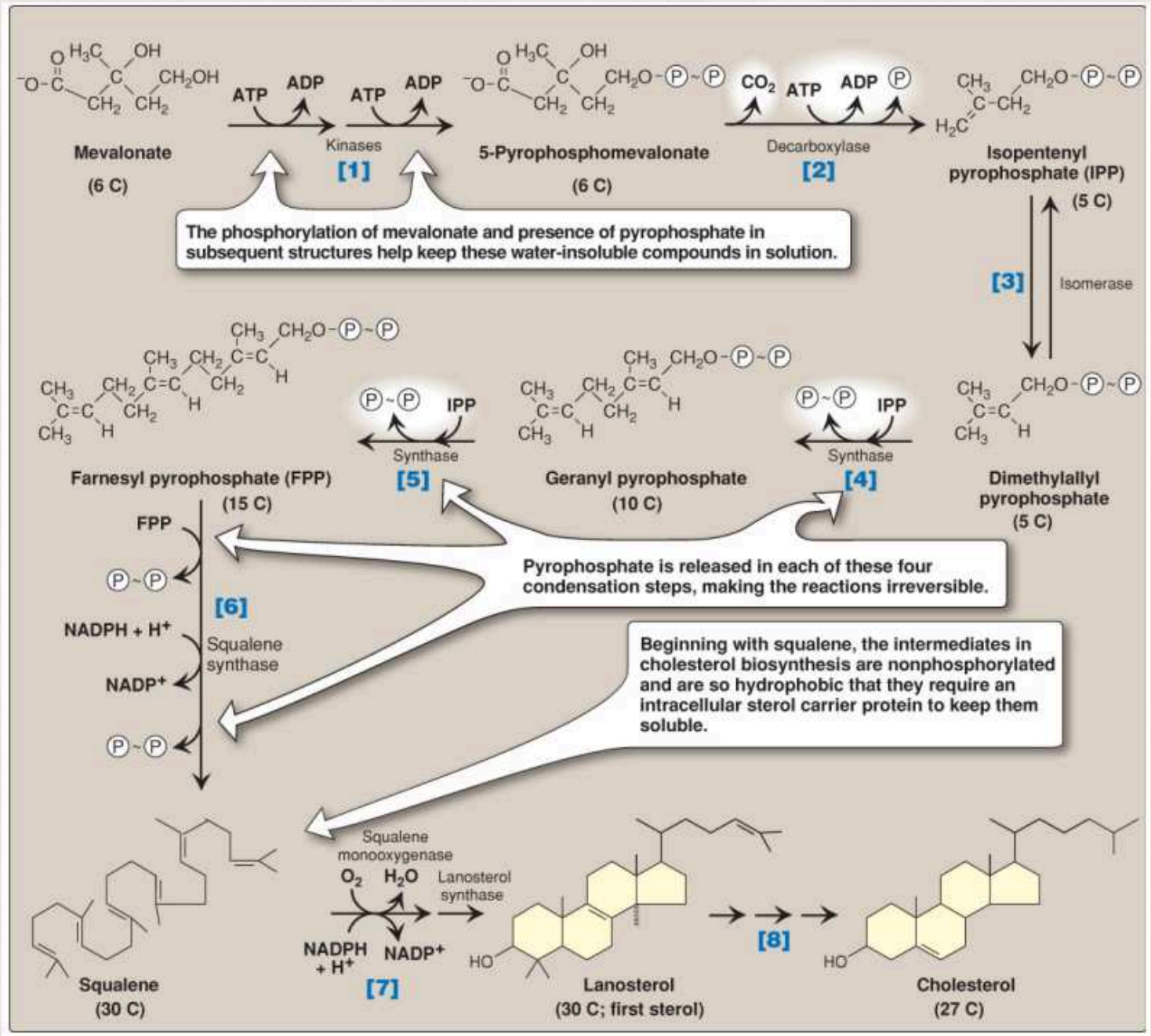
Clinical Correlation: Smith-Lemli-Opitz Syndrome (SLOS)

- Cause: Partial deficiency of:
    - 7-dehydrocholesterol-7-reductase
        - Enzyme that reduces the double bond in 7-dehydrocholesterol (7-DHC) to form cholesterol
- Inheritance: Autosomal-recessive
- Pathophysiology: Impaired cholesterol biosynthesis
- SLOS is one of several:
    - Multisystem embryonic malformation syndromes linked to defective cholesterol synthesis

Note:

- 7-DHC is also the precursor of vitamin D_3 in the skin

Synthesis of Cholesterol from Mevalonate



D. Branch-Point Reactions in the Biosynthesis of Cholesterol

Diversion of Intermediates

- Cholesterol synthesis intermediates are shunted for modification of other molecules.

First Branch Point

- Begins at Step 2 of the cholesterol synthesis pathway:
  - Formation of isopentenyl pyrophosphate (IPP) – 5C

Subsequent Isoprenoid Products

- Sequential addition of 5-carbon isoprene units forms:
  - Geranyl pyrophosphate (GPP) – 10C
  - Farnesyl pyrophosphate (FPP) – 15C
  - Geranylgeranyl pyrophosphate (GGPP) – 20C

Functional Roles of Farnesyl & Geranylgeranyl Groups

Modification	Product	Function
Farnesylation	Heme → Heme A	Specialized heme in cytochrome a of the electron transport chain
Farnesylation / Geranylgeranylation	Proteins (e.g., ras oncogene)	Anchors proteins to membranes; activates cell signaling for proliferation
Geranylgeranylation	Dolichol	Required for sugar transfer in glycoprotein synthesis
Geranylgeranylation	Ubiquinone	Lipid-soluble electron carrier in oxidative phosphorylation

Pharmacological Relevance: Bisphosphonates

- Bisphosphonates are used to:
    - Inhibit bone resorption in:
        - Osteoporosis
        - Paget disease

- New-generation bisphosphonates can:
    - Kill cancer cells
    - Mechanism: Inhibit synthesis of:
        - Farnesyl-PP
        - Geranylgeranyl-PP

E. Cholesterol Synthesis Regulation

Key Regulatory Enzyme

- HMG CoA reductase is the major control point for cholesterol biosynthesis.

- It is subject to multiple types of metabolic control.

1. Sterol-Dependent Regulation of Gene Expression

a. Transcriptional Control

- Gene expression of HMG CoA reductase is regulated by:
    - Sterol regulatory element-binding protein 2 (SREBP-2)

b. Mechanism of Activation

- SREBP-2 binds DNA at:
    - Sterol regulatory element (SRE) (a cis-acting site upstream of the gene)
- Inactive SREBP-2 is an:
    - Integral protein of the SER membrane
    - Associates with SREBP cleavage-activating protein (SCAP)

c. Low Sterol Conditions

- SREBP-2-SCAP complex translocates from:
    - Endoplasmic reticulum (ER) → Golgi apparatus
- In Golgi membrane:
    - Two proteases sequentially cleave SREBP-2
    - Generate a soluble fragment that:
        - Enters the nucleus
        - Binds the SRE
        - Activates transcription

Result:

→ Increased HMG CoA reductase synthesis

→ Increased cholesterol synthesis

d. High Sterol Conditions

- Sterols bind to SCAP at its sterol-sensing domain
- SCAP then binds to:
    - Insulin-induced gene proteins (INSIGs) in the ER membrane
- Effect:
    - SCAP-SREBP complex is retained in the SER
    - Prevents activation of SREBP-2
    - Leads to downregulation of cholesterol synthesis

Note on SREBP-1c

- SREBP-1c:
    - Upregulates expression of enzymes involved in:
        - Fatty acid synthesis

- Responds to insulin

2. Sterol-Accelerated Enzyme Degradation

- HMG CoA reductase is a sterol-sensing integral protein of the SER membrane.

- When sterol levels are high in the SER:

  - Reductase binds to INSIG proteins
  - (See Fig. 18.7)
  - Binding leads to:
    - Transfer to the cytosol
    - Ubiquitination
    - Proteasomal degradation of the enzyme

3. Sterol-Independent Phosphorylation / Dephosphorylation

Enzyme	Action	Result
AMP-activated protein kinase (AMPK)	Phosphorylates HMG CoA reductase	Inactivates the enzyme
Phosphoprotein phosphatase	Dephosphorylates HMG CoA reductase	Activates the enzyme

- Regulation is covalent.

Note:

- AMPK is activated by AMP
- Therefore, when ATP levels are low, AMP levels rise → cholesterol synthesis decreases
- Mechanism is similar to fatty acid synthesis regulation

4. Hormonal Regulation

- HMG CoA reductase activity is influenced by hormones:

Hormone	Effect
Insulin ↑	Favors dephosphorylation → Activates HMG CoA reductase
Glucagon ↑ and Epinephrine ↑	Opposite effect → Inhibits the reductase
Cholesterol levels ↑	Also contribute to inhibition

5. Drug Inhibition (Statins)

Statins as Enzyme Inhibitors

- Statin drugs (e.g.):
    - Atorvastatin
    - Fluvastatin
    - Lovastatin
    - Pravastatin
    - Rosuvastatin
    - Simvastatin
- These are:
    - Structural analogs of HMG CoA
    - (Or are metabolized to such)
    - Act as reversible, competitive inhibitors of HMG CoA reductase

Clinical Use

- Used to decrease plasma cholesterol levels in patients with hypercholesterolemia

Recognized Adverse Effects

- Muscle pain
- Fatigue
- Weakness
- Rhabdomyolysis

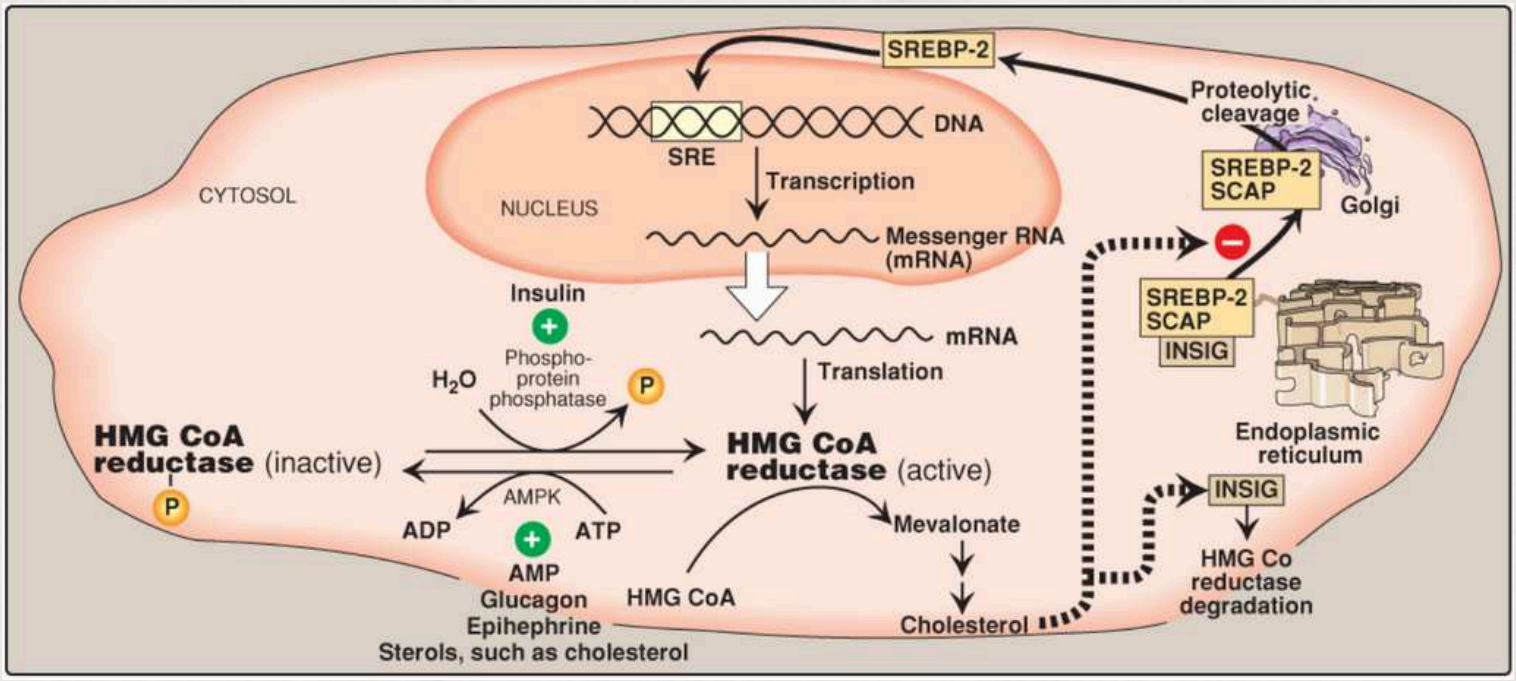
Possible Mechanism:

- Inhibition of:
    - Heme A synthesis
    - Ubiquinone synthesis
- Both are essential for oxidative phosphorylation and energy production

Genetic Polymorphisms & Statin Response

Protein	Genetic Marker	Effect
Organic anion transporting polypeptide (OATP1B1 / SLCO1B1)	Polymorphism at nucleotide 521 T>C	Biomarker for simvastatin myopathy

Regulation of Hydroxymethylglutaryl Coenzyme A (HMG CoA) Reductase



IV. Cholesterol Degradation

Human Inability to Fully Degrade Cholesterol

- Humans cannot metabolize the cholesterol ring structure to carbon dioxide (CO_2) and water.

Routes of Elimination

- The intact steroid nucleus is eliminated via:
    - Conversion to bile acids and bile salts
        - A small percentage is excreted in feces
    - Direct secretion of cholesterol into bile
        - Bile transports cholesterol to the intestine for elimination

Bacterial Modification in the Intestine

- Some cholesterol in the intestine is modified by bacteria before excretion.
- Primary bacterial products:
    - Coprostanol
    - Cholestanol
        - Both are reduced derivatives of cholesterol
- These compounds, together with cholesterol, form the:
    - Bulk of neutral fecal sterols

V. Bile Acids and Bile Salts

General Composition of Bile

- Bile is a watery mixture of organic and inorganic compounds
- Most important organic components:
    - Phosphatidylcholine (PC) (also called lecithin; see Chapter 17)
    - Conjugated bile salts

Bile Transport

- Bile can:
    a. Pass directly from the liver (site of synthesis) into the duodenum via the common bile duct
    b. Be stored in the gallbladder when not immediately needed for digestion

A. Structure

Core Features of Bile Acids

- Contain 24 carbon atoms

- Have:
    - Two or three hydroxyl groups
    - A side chain terminating in a carboxyl group

Acid–Base Properties

- Carboxyl group has a pKa ≈ 6
- In the duodenum (pH ≈ 6):
    - About half the molecules are:
        - Protonated → Bile acids
        - Deprotonated → Bile salts

Terminology Note

- "Bile acid" and "bile salt" are often used interchangeably

Stereochemistry

- Hydroxyl groups: oriented α (lie below the plane of rings)
- Methyl groups: oriented β (lie above the plane of rings)

Functional Role: Amphipathic Emulsifiers

- Molecules have:
    - Both a polar surface and a nonpolar surface
- Therefore, they act as:
    - Emulsifying agents in the intestine

Function:

→ Aid in preparation of dietary fat (triacylglycerol [TAG])

→ Enable degradation by pancreatic digestive enzymes

B. Synthesis

Site & General Description

- Bile acids are synthesized in the liver
- The pathway is:
    - Multistep
    - Multi-organelle

- Key transformations of the cholesterol molecule:
    - Hydroxyl groups are inserted at specific positions on the steroid structure
    - Double bond of the B ring of cholesterol is reduced
    - Hydrocarbon chain is shortened by 3 carbons
        - A carboxyl group is introduced at the end of the chain

Primary Bile Acids

- Most common products:
    - Cholic acid (a triol)
    - Chenodeoxycholic acid (a diol)

- These are termed primary bile acids

Rate-Limiting Step

Step	Enzyme	Location	Type
Hydroxylation at C-7 of steroid nucleus	7-α-hydroxylase	SER-associated	Cytochrome P450 (CYP) monooxygenase

- Enzyme is found only in the liver

Regulation of 7-α-Hydroxylase Expression

Negative Feedback (Downregulation)

- Bile acids and cholesterol:
    - Downregulate expression of 7-α-hydroxylase

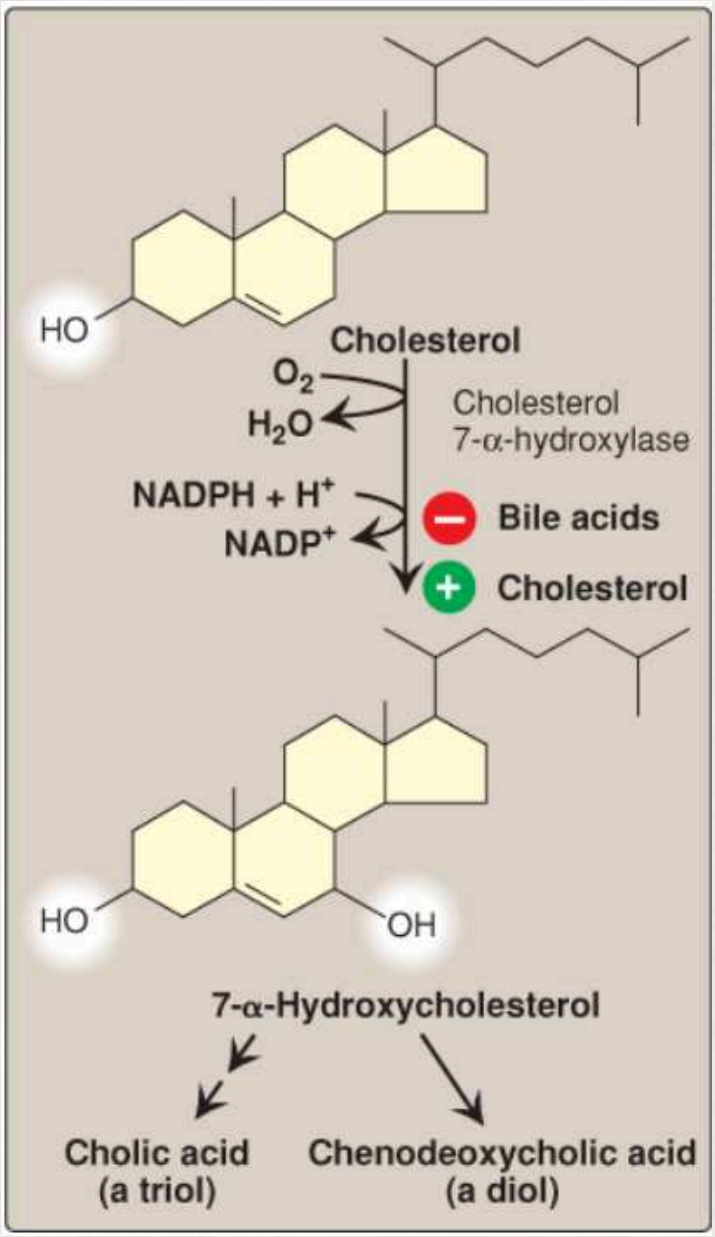
Transcriptional Regulation

Stimulus	Nuclear Receptor	Effect on 7-α-Hydroxylas
↑ Cholesterol in liver	Liver X receptor (LXR)	Upregulates transcription
↑ Bile acids	Bile acid receptor (BAR) a.k.a. Farnesoid X receptor (FXR)	Downregulates transcription

Summary:

- Cholesterol ↑ → LXR activation → ↑ 7-α-hydroxylase expression → ↑ bile acid synthesis
- Bile acids ↑ → FXR/BAR activation → ↓ 7-α-hydroxylase expression → ↓ bile acid synthesis

Synthesis and Regulation of the Bile Acids, Cholic Acid and Chenodeoxycholic Acid from Cholesterol



C. Conjugation

Process Overview

- Before leaving the liver, bile acids are conjugated with:
    - Glycine
    - Taurine (an end product of cysteine metabolism)

Type of Bond

- Amide bond formation occurs between:
    - Carboxyl group of the bile acid
    - Amino group of glycine or taurine

Resulting Conjugated Structures

Conjugating Molecule	Resulting Bile Acids
Glycine	Glycocholic acid, Glycochenodeoxycholic acid
Taurine	Taurocholic acid, Taurochenodeoxycholic acid

- Ratio of glycine:taurine forms in bile ≈ 3:1

Ionization Properties & Detergent Function

Conjugate	Functional Group Added	Ionization at Alkaline pH
Glycine	Carboxyl group (lower pKa)	Fully ionized (–)
Taurine	Sulfonate group	Fully ionized (–)

- At the alkaline pH of bile and duodenum, both modifications result in fully ionized (negatively charged) bile salts

Functional Advantage

- Conjugated, ionized bile salts:
    - Are more effective detergents than unconjugated bile acids
    - Have enhanced amphipathic nature
    - Therefore, only conjugated forms are found in bile

Clinical Note

- Individuals with genetic deficiency in cholesterol → bile acid conversion:
    - Treated with exogenous chenodeoxycholic acid

Excretory Function

- Bile salts serve as the only significant route for cholesterol excretion:
    - As a metabolic product of cholesterol
    - As a solubilizer of cholesterol in bile

D. Enterohepatic Circulation

Definition

- The continuous cycle of:

1. Bile salt secretion into bile
2. Passage through duodenum (some undergo deconjugation & dehydroxylation → secondary bile salts)
3. Reabsorption in ileum
4. Return to liver as primary + secondary bile salts

→ This entire process is termed enterohepatic circulation

Efficient Reabsorption

- >95% of bile salts secreted into the intestine are efficiently reabsorbed and reused

Liver Transport

- Liver secretes bile salts into bile via:
    - Bile salt export pump

Intestinal Reabsorption

- In the terminal ileum, bile salts are:
    - Reabsorbed via:
        - Apical sodium (Na^+)–bile salt cotransporter
    - Returned to blood via a separate transport system

Note:

- Lithocholic acid is poorly absorbed

Hepatic Reuptake

- Hepatocytes efficiently reabsorb bile salts from the blood
    - Via an isoform of the bile salt cotransporter

Note:

- Albumin binds bile salts in blood (similar to FA transport)

Quantitative Summary

Parameter	Value
Bile salts secreted daily	15–30 g
Bile salts lost in feces	~0.5 g/day (<3%)
Bile salts synthesized in liver from cholesterol (to replace fecal loss)	~0.5 g/day

Clinical Application: Bile Acid Sequestrants

- Cholestyramine:
    - Binds bile salts in the gut → prevents reabsorption → promotes fecal excretion
    - Used to treat hypercholesterolemia

Mechanism:

- Removal of bile salts → relieves feedback inhibition on bile acid synthesis

- → More cholesterol diverted into bile acid synthesis

Note:

- Dietary fiber also binds bile salts and increases excretion

E. Bacterial Action on Bile Salts

Site of Action

- A small portion of bile salts reaches the colon
- Here, they are modified by intestinal microbiota

Types of Bacterial Modifications

Modification Type	Description
Deconjugation	Removal of glycine and taurine from bile salts
Dehydroxylation	Removal of hydroxyl group at C-7

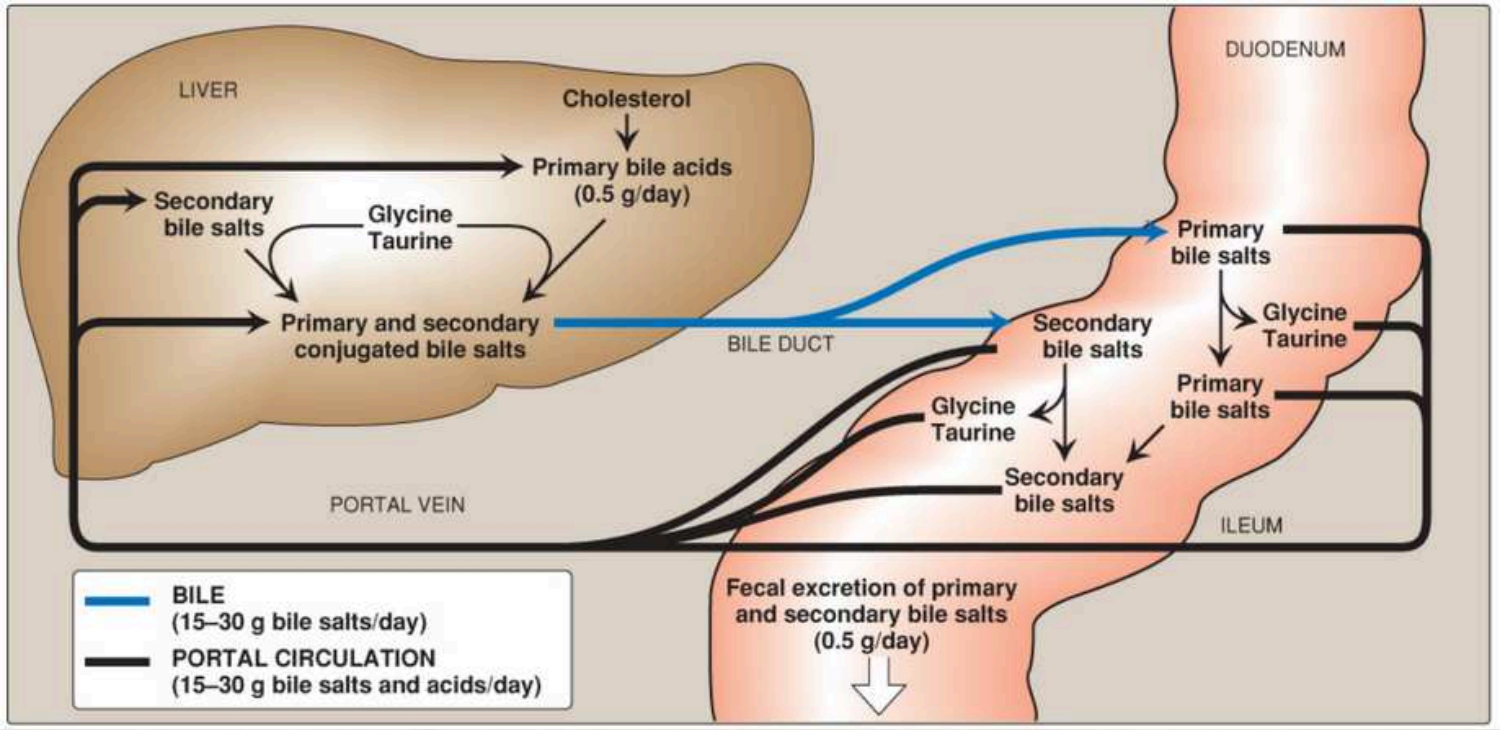
Examples of Secondary Bile Acids:

Precursor (Primary Bile Acid)	Secondary Bile Acid
Cholic acid	Deoxycholic acid
Chenodeoxycholic acid	Lithocholic acid

Fate of Secondary Bile Acids

- Small proportion:
    - Absorbed by colonic epithelium
    - May be reconjugated and hydroxylated by liver enzymes → secondary bile salts
- Majority:
    - Eliminated in feces

Enterohepatic Circulation of Bile Salts.
(Note: Ionized bile acids are called bile salts.)



F. Bile Salt Deficiency: Cholelithiasis

Cholesterol Solubilization Requirement

- Movement of cholesterol from liver into bile must be accompanied by:
    - Simultaneous secretion of phospholipid (phosphatidylcholine [PC])
    - Secretion of bile salts

Pathogenesis of Gallstones

- If this dual process is disrupted, and more cholesterol is present than can be solubilized by:
    - Bile salts and PC →
    - Cholesterol may precipitate in the gallbladder

→ Leads to cholesterol gallstone disease or cholelithiasis

Major Causes

1. Decrease in bile acids in the bile

1. Increased cholesterol secretion into bile
    - Seen with fibrates (e.g., gemfibrozil) used to lower blood cholesterol & TAG

Treatment Options

Treatment	Description
Laparoscopic cholecystectomy	Surgical removal of the gallbladder via small incision → treatment of choice
Oral chenodeoxycholic acid	Given to patients unable to undergo surgery → supplements bile acid pool → causes gradual gallstone dissolution (takes months to years)

Gallstone Types (Epidemiology)

- Cholesterol stones: >85% of cases
- Bilirubin and mixed stones: Account for the remainder

VI. Plasma Lipoproteins

Structure

- Plasma lipoproteins are:
    - Spherical macromolecular complexes of:
        - Lipids
        - Proteins (apolipoproteins)

Major Classes of Lipoprotein Particles

Type	Description
Chylomicrons	Largest, TAG-rich particles
Chylomicron remnants	Leftover after TAG delivery
Very-low-density lipoproteins (VLDLs)	TAG carriers from liver
VLDL remnants (IDLs)	Intermediate-density lipoproteins
Low-density lipoproteins (LDLs)	Cholesterol-rich, atherogenic
High-density lipoproteins (HDLs)	Involved in reverse cholesterol transport
Lipoprotein (a) [Lp(a)]	LDL-like particle with apolipoprotein(a)

Differentiating Factors Among Lipoproteins

- Lipid and protein composition
- Size
- Density
- Site of origin

Note on Composition

- Lipoprotein particles constantly interchange:
    - Lipids
    - Apolipoproteins

→ Therefore, actual composition is variable

Functions

- Solubilize component lipids for plasma transport
- Provide efficient transport mechanism of lipids:
    - To and from tissues

Clinical Relevance

- In humans, there is a gradual deposition of lipid, especially cholesterol, in tissues

A. Composition

General Structure of Lipoproteins

- Core:
    - Neutral lipids:
        - Triacylglycerol (TAG)
        - Cholesteryl esters
- Surface shell:
    - Amphipathic apolipoproteins
    - Phospholipids
    - Nonesterified (free) cholesterol

Amphipathic Orientation

- Surface molecules are oriented with:
    - Polar portions exposed on the outer surface
    - → This renders the particle soluble in aqueous solutions

Lipid Sources

- TAG and cholesterol in lipoproteins are derived from:
    - Dietary (exogenous) sources
    - De novo (endogenous) synthesis

Clinical Measurement of Cholesterol

- Cholesterol content of plasma lipoproteins is measured in fasting blood
- Friedewald equation (to calculate LDL-C):

$$\text{LDL C} = \text{Total C} - \text{HDL C} - (\text{TAG}/5)$$

- Assumes TAG:cholesterol ratio in VLDL = 5:1
- Goal value for total cholesterol: <200 mg/dL

1. Size and Density of Lipoproteins

Lipoprotein	Density	Size	Lipid %	Protein %
Chylomicrons	Lowest density	Largest	Highest (mainly TAG)	Lowest
VLDLs	Lower than LDL	Large	High TAG	Moderate
LDLs	Denser than VLDL	Smaller	High cholesterol	Higher protein ratio
HDLs	Highest density	Smallest	Lower lipid	Highest protein %

Separation methods:

- Electrophoresis
- Ultracentrifugation by density

2. Apolipoproteins

Functions:

- Provide recognition sites for cell-surface receptors
- Act as activators or coenzymes for enzymes in lipoprotein metabolism

Structural Roles:

- Some apolipoproteins are essential structural components:
    - Cannot be removed
    - Particles cannot form without them
- Other apolipoproteins:
    - Can be freely transferred between lipoproteins

Classification:

- Apolipoproteins are grouped by:
  - Structure and function
  - Denoted by letters
  - Each class has subclasses:
    - e.g., apo C-I, apo C-II, apo C-III

Note:

- Functions of all apolipoproteins are not yet fully known

B. Chylomicron Metabolism

Overview

- Chylomicrons are:
  - Assembled in intestinal mucosal cells
  - Transport dietary (exogenous) lipids:
    - TAG
    - Cholesterol
    - Fat-soluble vitamins
    - Cholesteryl esters

- TAGs account for ~90% of total chylomicron lipid content

1. Apolipoprotein Synthesis: Apo B-48

Feature	Detail
Unique to	Chylomicrons
Site of synthesis	Rough Endoplasmic Reticulum (RER)
Post-translational modification	Glycosylated in RER → Golgi
Genetic origin	Encoded by apo B gene, same as apo B-100
Difference from apo B-100	Apo B-48 = N-terminal 48% of apo B protein
Mechanism	Posttranscriptional cytosine → uracil editing in mRNA → nonsense stop codon → translation of only 48%

(Note: Apo B-100 is synthesized by the liver and found in VLDL and LDL)

2. Chylomicron Assembly

Component	Detail
Enzymes involved	Located in Smooth ER (SER)
Key protein	Microsomal Triglyceride Transfer Protein (MTP)
Function of MTP	Loads apo B-48 with lipid before ER-to-Golgi transition
Packaging	In Golgi → secretory vesicles
Exocytosis	Vesicles fuse with plasma membrane → lipoproteins released
Entry into circulation	Enters lymphatic system → via thoracic duct → empties into left subclavian vein

3. Nascent Chylomicron Modification

Stage	Detail
Nascent chylomicron	Released from intestinal mucosal cell
Functionally incomplete	Requires further modification in plasma

→ Modified by HDL, which transfers:

- Apolipoprotein E (apo E)
    - Recognized by hepatic receptors
- Apolipoprotein C (apo C)
    - Includes apo C-II → activator of lipoprotein lipase (LPL)

(Note: Apo C-III, found on TAG-rich lipoproteins, inhibits LPL)

4. Triacylglycerol (TAG) Degradation by Lipoprotein Lipase (LPL)

Enzyme Properties

- Lipoprotein lipase (LPL) is an extracellular enzyme.
- Anchored to capillary walls of most tissues, especially:
    - Adipose tissue
    - Cardiac muscle
    - Skeletal muscle

- Not expressed by adult liver

Note:

- Hepatic lipase (found on surface of liver endothelial cells) plays a role in TAG degradation in chylomicrons, VLDL, and HDL metabolism.

Mechanism of TAG Hydrolysis

- Activated by apo C-II (from circulating chylomicrons)
- Function: Hydrolyzes TAG →
    - Free fatty acids (FA)
    - Glycerol

Product	Fate
FA	Stored (in adipose) OR used for energy (in muscle)
Glycerol	Taken up by liver → converted to dihydroxyacetone phosphate (DHAP) → enters glycolysis, gluconeogenesis, or lipid synthesis

Clinical Note: LPL or Apo C-II Deficiency

- Condition: Type I hyperlipoproteinemia / familial chylomicronemia
- Biochemical Finding:
    - Severe chylomicron-TAG accumulation ⩾1,000 mg/dL even in the fasted state
- Manifestation: Hypertriacylglycerolemia
- Risk: Increased chance of acute pancreatitis
- Treatment: Dietary fat reduction

S. Lipoprotein Lipase (LPL) Expression

Tissue	Regulation
Adipose tissue	↑ LPL synthesis in fed state (↑ insulin)
Muscle tissue	↑ LPL synthesis in fasted state (↓ insulin)

- Tissue-specific isozymes of LPL are regulated by:
    - Nutritional state
    - Hormonal levels

Note:

Highest LPL concentration is in cardiac muscle, reflecting high FA use for cardiac energy needs

6. Chylomicron Remnant Formation and Hepatic Uptake

Transformation of Chylomicrons

- As chylomicrons circulate:
    - >90% of core TAG is degraded by LPL
    - → Particle decreases in size
    - → Increases in density

- C apolipoproteins (e.g., C-II, C-III) are returned to HDL

- Apo B-48 and apo E remain on remnant

Remnant Uptake by Liver

- Remaining particle = chylomicron remnant
- Rapidly removed by the liver
- Hepatic cell membranes contain lipoprotein receptors that recognize apo E

Endocytosis Process

1. Chylomicron remnant binds receptor

2. Endocytosed into hepatocyte

3. Vesicle fuses with lysosome

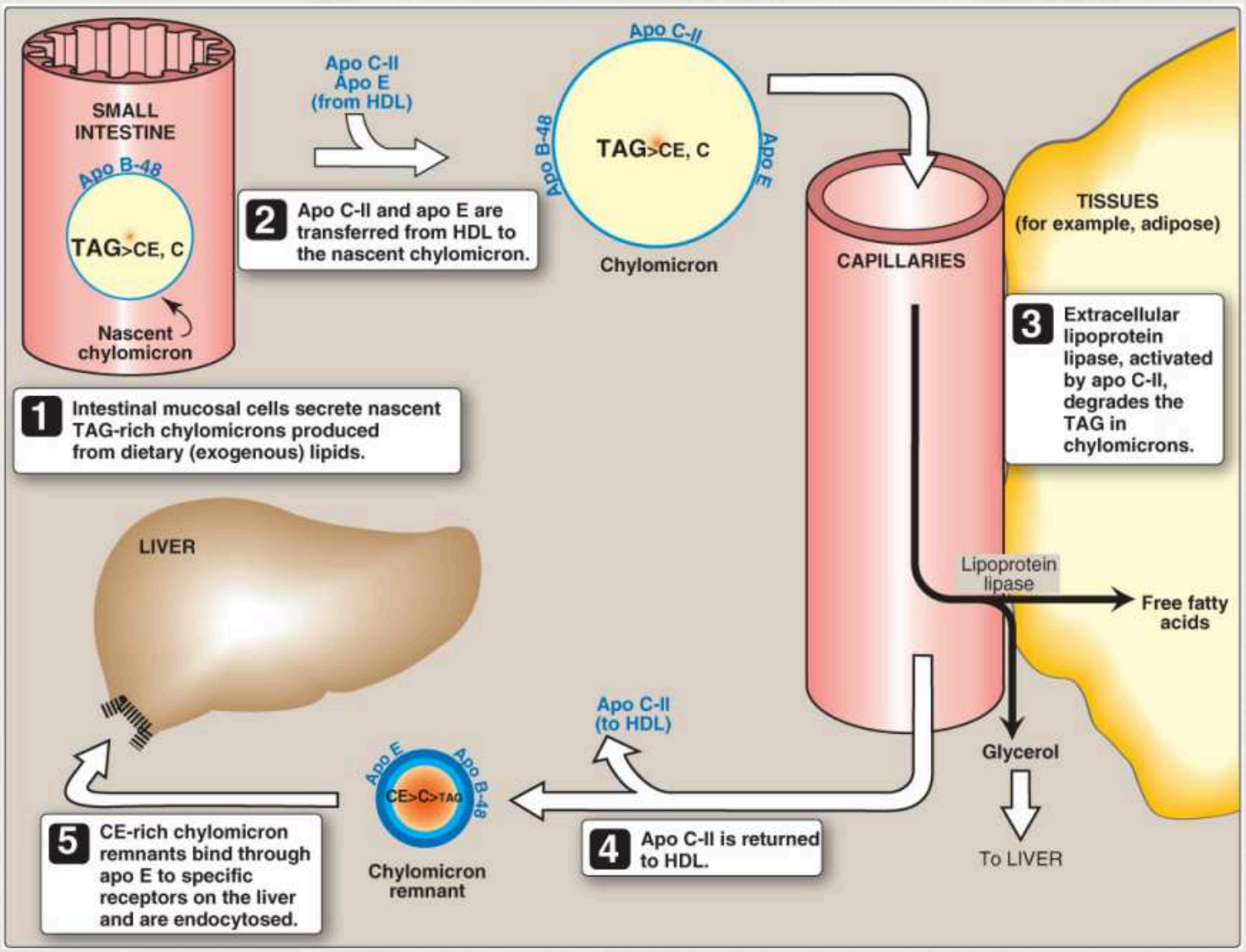
4. Hydrolytic degradation of:
    - Apolipoproteins
    - Cholesteryl esters
    - Other remnant components

5. Release of:

- Amino acids
- Free cholesterol
- Fatty acids

6. Receptor is recycled

Metabolism of Chylomicrons.



C. Very-Low-Density Lipoprotein (VLDL) Metabolism

Overview

- VLDLs are produced in the liver.
- Composed predominantly of endogenous triacylglycerol (TAG) (~60%).
- Function: Transport endogenous TAG from liver (site of synthesis) to peripheral tissues, where:
    - TAG is degraded by lipoprotein lipase (LPL) (as occurs with chylomicrons).

Note:

- Nonalcoholic fatty liver (hepatic steatosis) occurs when there's an imbalance between hepatic TAG synthesis and VLDL secretion.
- Common in obesity and type 2 diabetes mellitus.

1. Release from the Liver

- VLDLs are secreted into the blood by the liver as nascent particles containing:
    - Apolipoprotein B-100 (apo B-100)
- VLDLs acquire:
    - Apo C-II and apo E from circulating HDL
    - Apo C-II is essential for activation of LPL

Abetalipoproteinemia:

- A rare hypolipoproteinemia caused by microsomal triglyceride transfer protein (MTP) defect.
- Results in failure to load apo B with lipid, so:
    - Few VLDLs or chylomicrons are formed.
    - TAG accumulates in liver and intestine.
    - Fat-soluble vitamin absorption ↓.
    - LDLs are low.

2. Modification in the Circulation

- As VLDLs circulate:
    - TAG is degraded by LPL
    - → VLDL decreases in size and increases in density.
- Surface components (including apo C and apo E):
    - Are returned to HDL
    - VLDL retains apo B-100.
- Exchange of lipids with HDL:
    - Some TAG is transferred from VLDL → HDL
    - Cholesteryl esters (CE) are transferred from HDL → VLDL
    - Mediated by:
        - Cholesteryl ester transfer protein (CETP)

3. Conversion to Low-Density Lipoproteins (LDL)

Formation of IDL and LDL

- With continued modification:
    - VLDL is converted in plasma to LDL
    - IDLs (intermediate-density lipoproteins) of varying sizes are formed during this transition.

Fate of IDL

- IDL can be:
    - Taken up by liver via receptor-mediated endocytosis using apo E as the ligand.

Apolipoprotein E (apo E) Isoforms and Clinical Implications

Isoform	Prevalence	Characteristics
E-2	Least common	Binds poorly to receptors
E-3	Most common	Normal receptor binding
E-4	Variable prevalence	↑ Risk of late-onset Alzheimer disease (dose-dependent; homozygotes = highest risk)

E-2 Homozygotes:

- Impaired clearance of IDL and chylomicron remnants.
- → Familial type III hyperlipoproteinemia (aka familial dysbetalipoproteinemia / broad beta disease).
- Clinical features:
    - Hypercholesterolemia
    - Premature atherosclerosis

D. Low-Density Lipoprotein (LDL) Metabolism

Composition and Function

- LDL particles:
    - Contain less triacylglycerol (TAG) than VLDLs.
    - Contain a high concentration of cholesterol and cholesteryl esters.
    - Carry ~70% of plasma cholesterol.
- Primary role: Deliver cholesterol to peripheral tissues or return it to the liver.

1. Receptor-Mediated Endocytosis

a. Receptor Specificity

- LDL binds to LDL receptors on the plasma membrane.
    - These receptors recognize apo B-100 (not apo B-48).
    - Also bind apo E → Called apo B-100/apo E receptors.

Note:

The same mechanism is used for chylomicron remnants and IDL uptake by the liver.

b. Mechanism of Uptake

[1] LDL receptors:

- Negatively charged glycoproteins, clustered in clathrin-coated pits on the cell membrane.
- Clathrin (cytosolic side): stabilizes the pit.

[2] LDL-receptor complex is endocytosed:

- Forms a vesicle that enters the cytoplasm.

Clinical note:

- Deficiency of functional LDL receptors → Type IIa hyperlipidemia (Familial Hypercholesterolemia – FH):
- ↑ Plasma LDL-C
- ↑ Risk of premature atherosclerosis
- Inheritance: Autosomal dominant

- Other causes:
    - Mutated apo B-100 → ↓ receptor binding
    - ↑ Activity of PCSK9 (proprotein convertase subtilisin/kexin type 9) → ↑ degradation of LDL receptors
    - PCSK9 inhibitors are now used to treat hypercholesterolemia

[3] Vesicle fusion:

- Clathrin coat is removed.
- Vesicles fuse into larger compartments → endosomes.

[4] Acidification of endosome:

- Endosomal ATPase pumps H^+ → ↓ pH.
- LDL dissociates from its receptor.
- Receptors migrate to one side of the endosome.
- LDL particles remain free in the lumen.

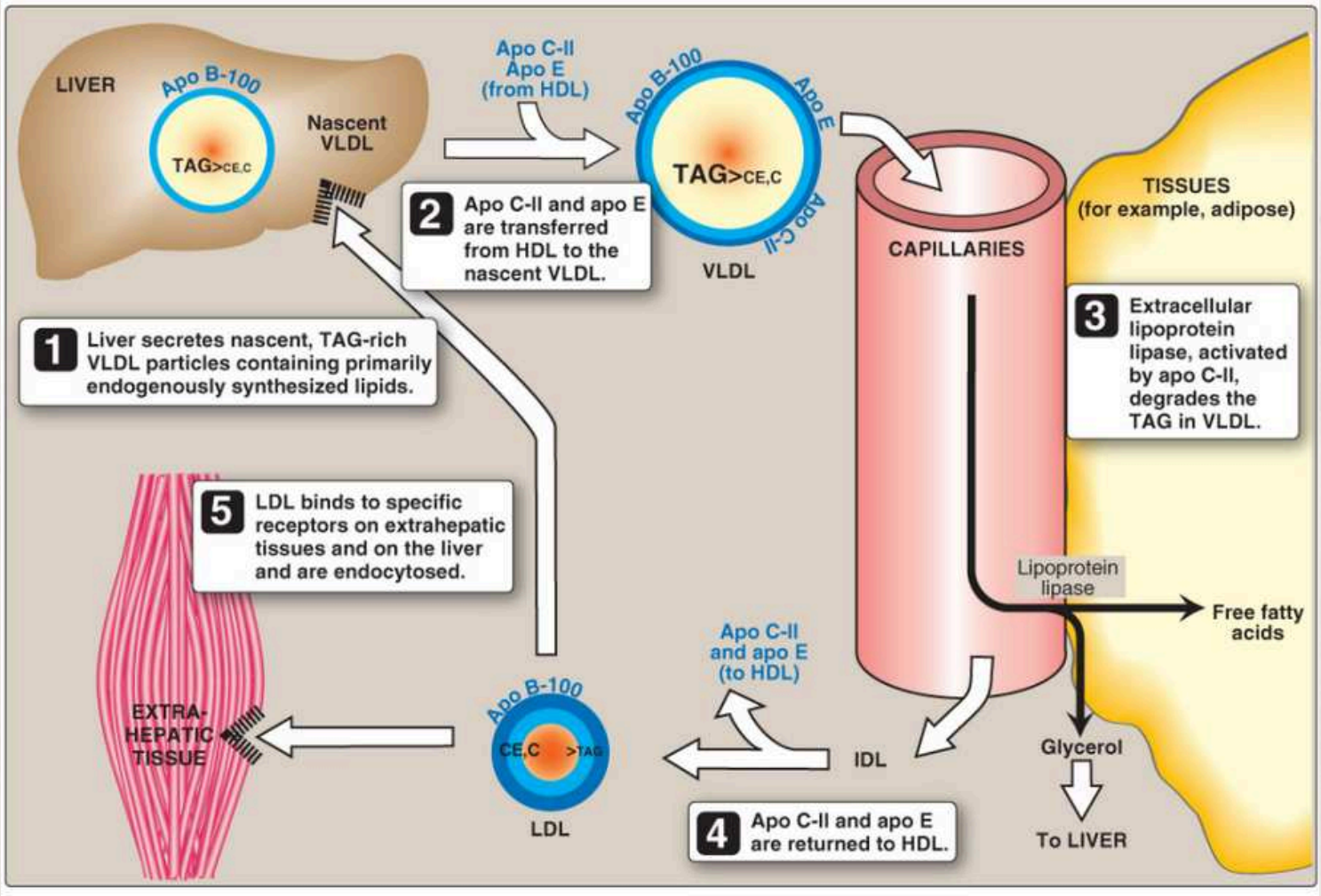
[5] Receptor recycling and LDL degradation:

- Receptors → recycled back to the plasma membrane.
- LDL particles → sent to lysosomes, where:
  - Degraded by lysosomal acid hydrolases → release:
    - Free cholesterol
    - Amino acids
    - Free fatty acids
    - Phospholipids

Note on Lysosomal Storage Disorders:

- Wolman disease: Deficiency in lysosomal acid lipase → impaired hydrolysis of cholesteryl esters.
- Niemann-Pick disease type C: Defective transport of free cholesterol out of lysosomes.
- Both are autosomal recessive disorders.

Metabolism of Very-Low-Density Lipoprotein (VLDL) and Low-Density Lipoprotein (LDL) Particles



2. Endocytosed Cholesterol and Cholesterol Homeostasis

Overview

Cholesterol derived from chylomicron remnants, IDL, and LDL influences cellular cholesterol homeostasis through three major mechanisms

Inhibition of Cholesterol Synthesis

- High intracellular cholesterol inhibits HMG CoA reductase gene expression:
    - ↓ De novo cholesterol synthesis.
    - ↑ Degradation of HMG CoA reductase enzyme.
- Mechanism:
    - Regulation occurs via the SRE (sterol regulatory element) and SREBP-2 (sterol regulatory element-binding protein 2).
    - High cholesterol inhibits the activation of SREBP-2, preventing it from entering the nucleus and promoting transcription of HMG CoA reductase.

Downregulation of LDL Receptor Synthesis

- High intracellular cholesterol also ↓ synthesis of new LDL receptor proteins:
    - ↓ LDL-C uptake into the cell.

- Mechanism:
    - Similar to reductase regulation, this also involves SRE-SREBP-2 interaction.
    - Coordinated regulation ensures that if cholesterol is abundant, both:
        - Synthesis (HMG CoA reductase) and
        - Uptake (LDL receptor)
        - are downregulated.

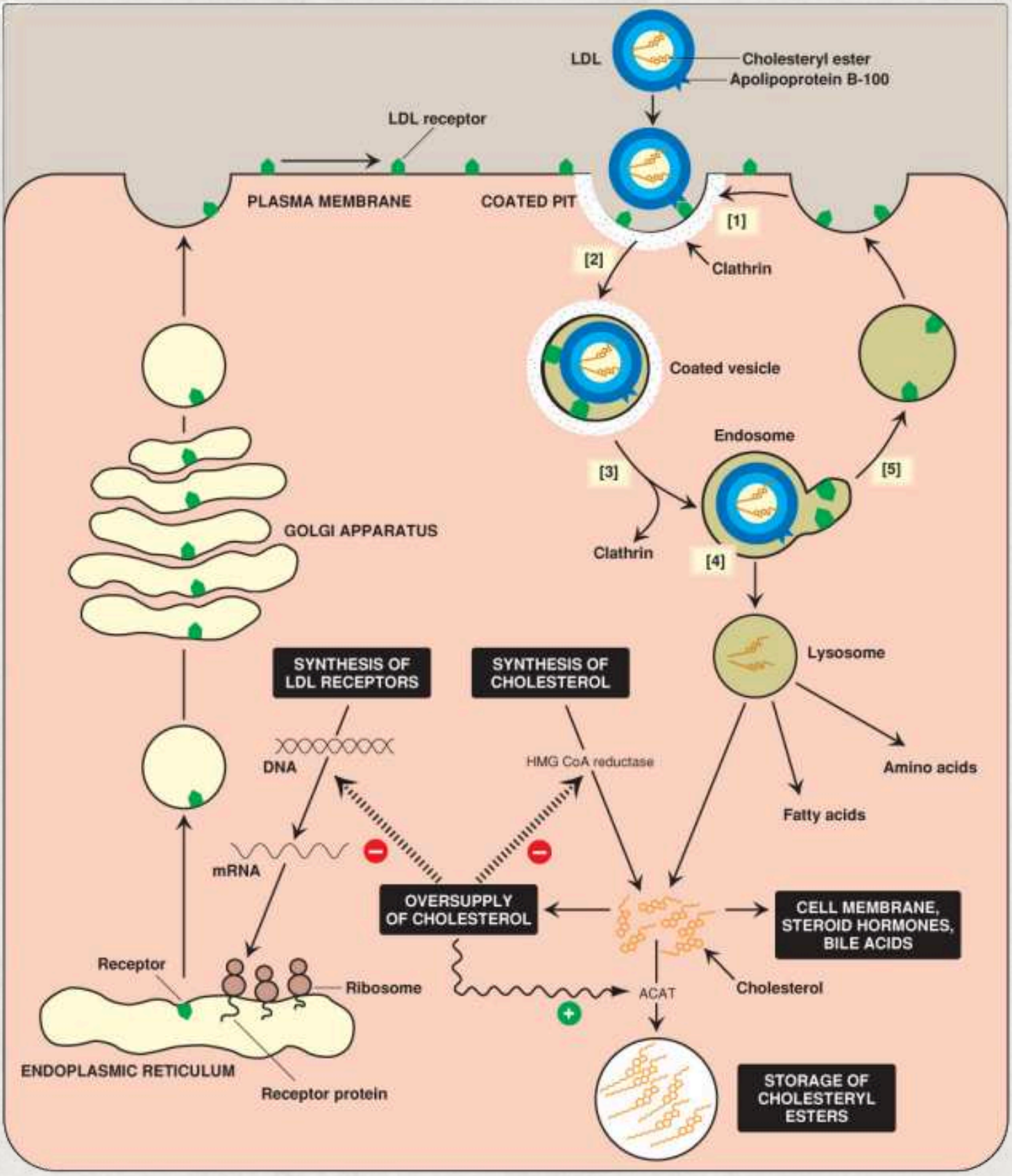
Storage via Cholesteryl Ester Formation

- If the cholesterol is not needed immediately, it is esterified:
    - Enzyme: Acyl CoA:cholesterol acyltransferase (ACAT)
    - Reaction:
        - Fatty acyl CoA + free cholesterol → cholesteryl ester
        - Esterified cholesterol can be stored in lipid droplets.
- ACAT activity increases when intracellular cholesterol is high.

Summary Table

Regulation Point	Trigger	Outcome
HMG CoA Reductase	↑ Intracellular cholesterol	↓ Gene expression, ↑ Enzyme degradation
LDL Receptor	↑ Intracellular cholesterol	↓ Gene expression, ↓ LDL-C uptake
ACAT	↑ Intracellular cholesterol	↑ Cholesteryl ester formation (storage)

Cellular Uptake and Degradation of Low-Density Lipoprotein (LDL) Particles



3. Uptake by Macrophage Scavenger Receptors

Macrophage Uptake via Scavenger Receptors (SRs)

- Macrophages express scavenger receptor class A (SR-A):
    - These receptors bind a broad range of ligands, especially chemically modified LDL

Modified LDL Recognition

- SR-A binds LDL in which:
    - Lipid or apo B component has been oxidized (oxidized LDL).
    - These modified LDLs are not recognized efficiently by normal LDL receptors.

Key Differences from LDL Receptor Pathway

- Scavenger receptors are not downregulated by increased intracellular cholesterol:
    - Unlike LDL receptors, which are tightly regulated by cholesterol levels.

    - Macrophages can continue to take up cholesterol uncontrollably.

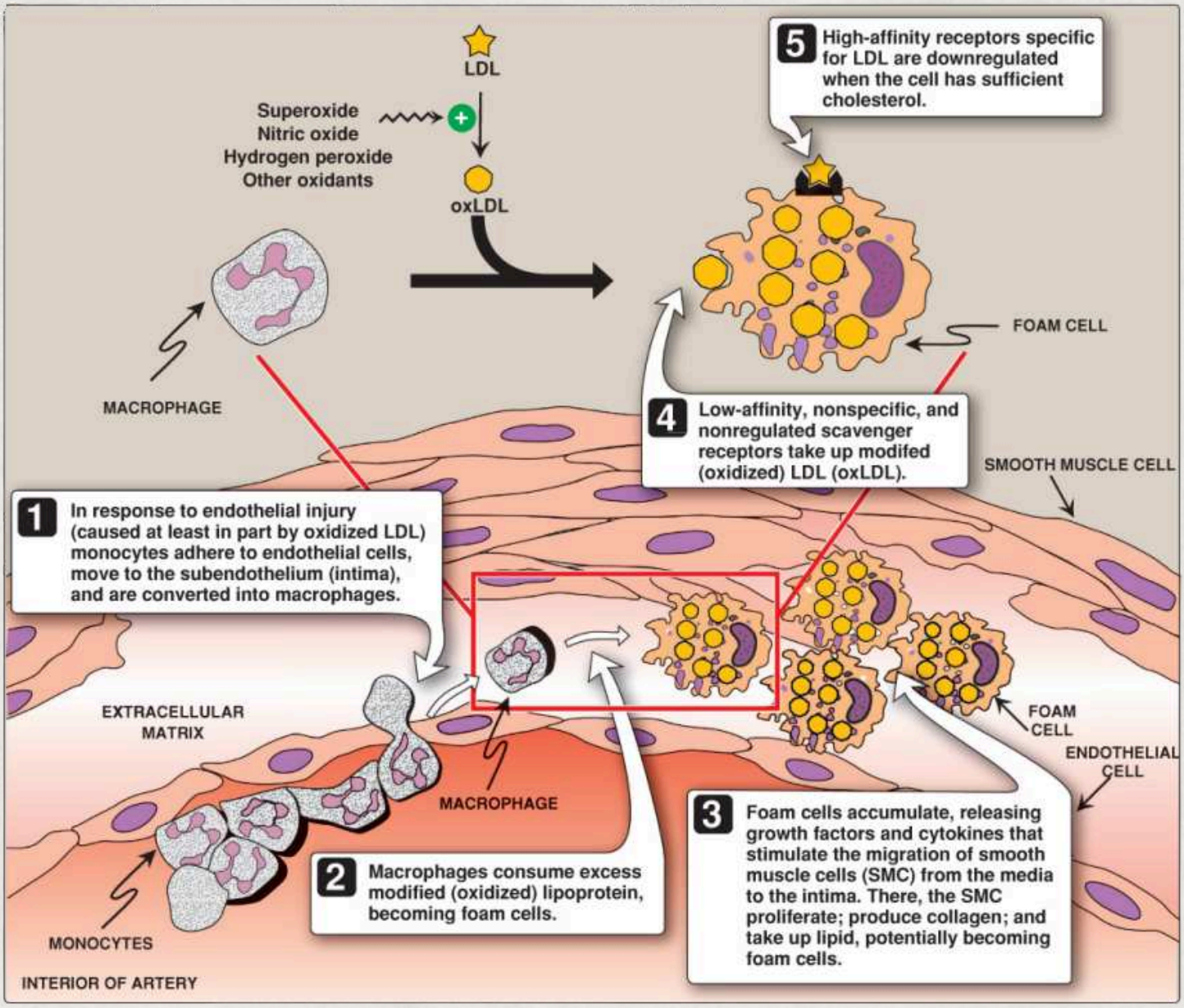
Foam Cell Formation

- Excess cholesteryl esters accumulate inside macrophages:
    - Transforms macrophages into "foam cells".
- Foam cells are a hallmark of early atherosclerotic plaques:
    - They accumulate within the intima of blood vessels.
    - Trigger chronic inflammation, fibrous cap formation, and eventual plaque rupture.

Clinical Note

- LDL-C is the primary contributor to atherosclerosis:
    - Particularly when oxidized and taken up by SR-A on macrophages.
    - Preventing LDL oxidation or lowering LDL-C levels reduces atherosclerotic risk.

Role of Oxidized Low-Density Lipoprotein (LDL) Particles in Plaque Formation in an Arterial Wall



E. High-Density Lipoprotein (HDL) Metabolism

HDL Overview

- HDLs are a heterogeneous family of lipoproteins with complex, partially understood metabolism.

- Formed in the blood by addition of lipids to apo A-I:

    - Apo A-I is made and secreted by the liver and intestine.
    - Apo A-I comprises ~70% of HDL apolipoproteins.

I. Apolipoprotein Supply Function

- HDL serves as a circulating reservoir of apolipoproteins:

    - Apo C-II: Activates lipoprotein lipase (LPL); transferred to VLDL and chylomicrons.
    - Apo E: Required for receptor-mediated endocytosis of IDLs and chylomicron remnants.

2. Uptake of Nonesterified Cholesterol

- Nascent HDL particles:
    - Initially disc-shaped, rich in phospholipids (mostly PC), and apo A, C, E.
- Function: Take up free cholesterol from peripheral (non-hepatic) tissues.
- Return cholesterol to liver as cholesteryl esters.
- High phospholipid content of HDL enhances its ability to solubilize and accept cholesterol.

3. Cholesterol Esterification by LCAT

- LCAT (lecithin:cholesterol acyltransferase):
    - Synthesized and secreted by the liver.
    - Activated by apo A-I on HDL
- Mechanism:
    - Transfers FA from carbon 2 of PC (lecithin) to cholesterol.

    - Forms:
        - Cholesteryl ester: Hydrophobic; moves to HDL core.
        - Lysophosphatidylcholine: Binds albumin in plasma.

- Maintains a cholesterol gradient to allow continued uptake by HDL

HDL Maturation

- As HDL collects cholesteryl esters:
    - Converts from nascent HDL → HDL_3 (cholesteryl ester-poor) → HDL_2 (cholesteryl ester-rich).
- Hepatic lipase:
    - Found on liver endothelium.
    - Degrades TAG and phospholipids.
    - Converts HDL_2 back to HDL_3.

Role of CETP (Cholesteryl Ester Transfer Protein)

- Facilitates cholesteryl ester exchange:
    - Transfers cholesteryl esters from HDL to VLDL, in exchange for TAG.
- Results:
    - Prevents product inhibition of LCAT.
    - Since VLDL becomes LDL, transferred cholesteryl esters eventually go to liver via LDL uptake.

4. Reverse Cholesterol Transport (RCT)

Role and Importance

- Reverse cholesterol transport (RCT) is the process by which cholesterol is moved from peripheral tissues to the liver for:
    - Bile acid synthesis or
    - Direct excretion via bile.
- Key mechanism in maintaining cholesterol homeostasis.

- Basis for why HDL is termed "good cholesterol":
    - Higher HDL levels = Lower atherosclerosis risk.
    - Exercise and estrogen both raise HDL levels.

Process of RCT

1. Cholesterol efflux from peripheral cells:
    - Mediated by ABCA1 (ATP-binding cassette transporter A1).
    - Transfers cholesterol to lipid-poor nascent HDL particles.
    - (Note: Tangier disease is caused by ABCA1 deficiency → nearly absent HDL levels due to apo A-I degradation.)

2. Cholesterol esterification:
    - Carried out by LCAT once cholesterol enters HDL
    - Converts cholesterol to cholesteryl esters → stored in the HDL core.
    - Converts HDL_3 → HDL_2.

3. Selective uptake by liver or steroidogenic tissues:

    - HDL_2 binds liver receptors (or to steroidogenic cells).
    - Scavenger receptor class B type 1 (SR-BI):
        - Mediates uptake of cholesteryl esters.
        - HDL particle itself is not internalized—only the ester is taken in.
    - Lipid-depleted HDL is returned to circulation as HDL_3.

ABCA1 Transporter and Related Disorders

- ABCA1:

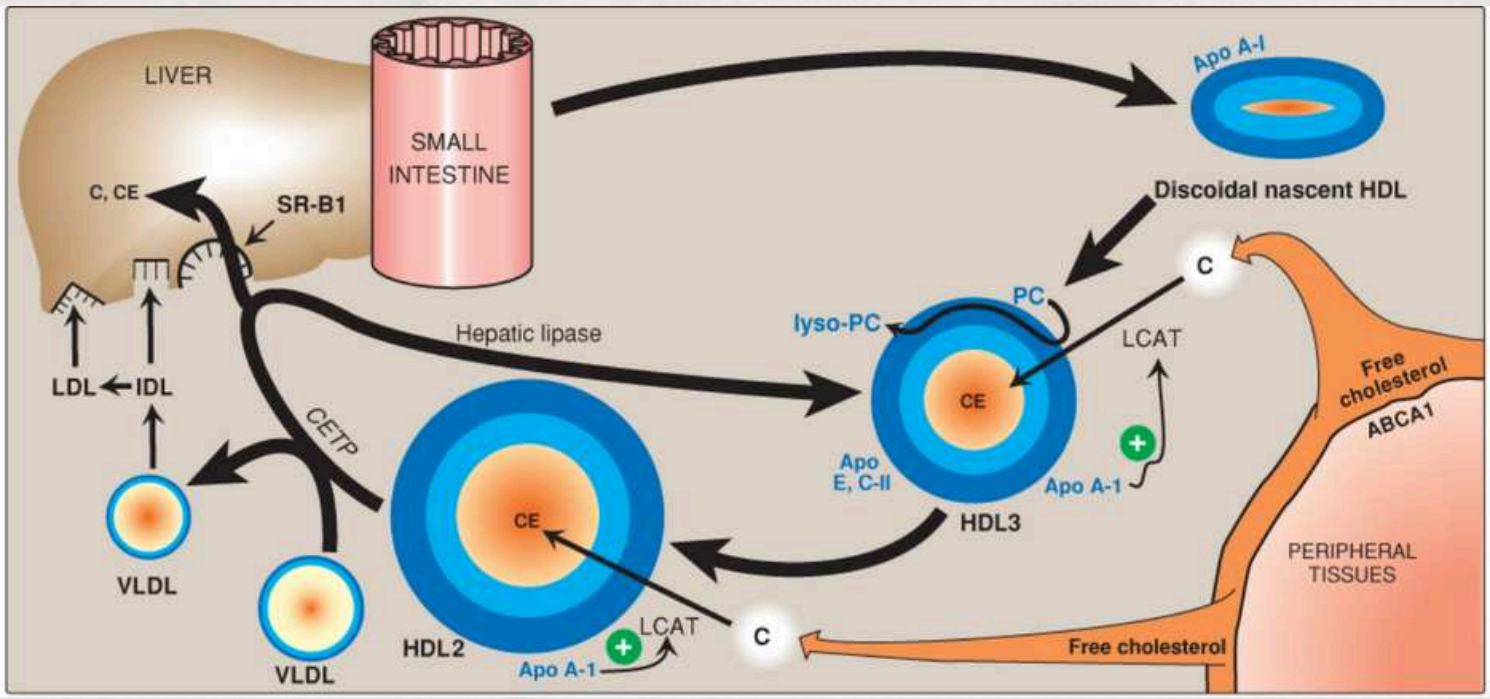
    - Belongs to ATP-binding cassette (ABC) family of transporters.
    - Uses ATP hydrolysis to transport lipids and other materials across membranes.

- Related disorders caused by ABC transporter mutations:

    - Tangier disease: ABCA1 deficiency → almost no HDL
    - Sitosterolemia: Defective transport of plant sterols.

- Cystic fibrosis: CFTR gene (a chloride channel ABC protein).
- X-linked adrenoleukodystrophy: Impaired peroxisomal FA transport.
- Neonatal respiratory distress syndrome: Due to reduced surfactant secretion.
- Cholestatic liver disease: Due to decreased bile salt secretion.

Metabolism of High-Density Lipoprotein (HDL) Particles



F. Lipoprotein (a) [Lp(a)] and Heart Disease

Structure

- Lp(a) is structurally almost identical to LDL
- Key difference: Contains an additional apolipoprotein(a) [apo(a)].
    - Apo(a) is covalently linked to apo B-100 at a single site.
    - Apo(a) is structurally similar to plasminogen:
        - Plasminogen is the inactive precursor of plasmin, a protease that breaks down fibrin.
        - Fibrin is the main protein component of blood clots.

Clinical Significance

- Lp(a) is an independent risk factor for coronary heart disease (CHD).
- Its atherogenic potential may be due to:
    - Interference with fibrinolysis (due to apo(a)'s structural similarity to plasminogen).
    - Promotion of atherosclerosis.

Regulation and Impact of Lifestyle

- Circulating Lp(a) levels are mostly genetically determined.

- Diet and medications can influence Lp(a) to a limited extent:

    - Trans fatty acids: Increase Lp(a) levels.
    - Niacin (vitamin B3):
        - Decreases Lp(a), LDL-C, and TAG.
        - Increases HDL-C.

VII. Steroid Hormones

Overview

- Cholesterol is the precursor for all steroid hormones, including:

    - Glucocorticoids (e.g., cortisol)
    - Mineralocorticoids (e.g., aldosterone)
    - Sex hormones:
        - Androgens (e.g., testosterone)
        - Estrogens
        - Progestins

- Glucocorticoids + mineralocorticoids = Corticosteroids

- Sites of synthesis:

    - Adrenal cortex: cortisol, aldosterone, androgens
    - Ovaries & placenta: estrogens, progestins
    - Testes: testosterone

Transport in Blood

- Steroid hormones are hydrophobic → require carrier proteins:

    - Albumin: nonspecific carrier (e.g., carries aldosterone)
    - Specific plasma proteins: tighter binding
        - Example: Corticosteroid-binding globulin (CBG) aka transcortin → transports cortisol

Genetic Disorders

- Enzyme deficiencies in steroid hormone biosynthesis cause various diseases:

    - Result in deficiency of downstream hormones
    - Accumulation of precursor hormones/metabolites

- Collectively termed Congenital Adrenal Hyperplasia (CAH):
    - Leads to adrenal hyperplasia (enlarged adrenal glands)
- Example: Addison disease = adrenocortical insufficiency due to autoimmune destruction of adrenal cortex

A. Synthesis of Steroid Hormones

Initial Reaction

- First & rate-limiting step:
- Cholesterol → Pregnenolone (21C)
- Enzyme: Cholesterol side-chain cleavage enzyme
    - Also called P450scc, desmolase
    - Type: Cytochrome P450 (CYP), located in inner mitochondrial membrane
    - Requires NADPH and O_2

Cholesterol Sources

- Newly synthesized cholesterol

- Uptake from lipoproteins
- Hydrolysis of cytosolic cholesteryl esters by esterases

Transport Control

- Cholesterol → outer mitochondrial membrane → transferred to inner membrane
- Mediated by Steroidogenic Acute Regulatory (StAR) protein
    - Major regulatory step in steroidogenesis

Further Steps

- Pregnenolone → Progesterone:
    - Via oxidation + isomerization
- Progesterone → Other steroid hormones:
    - Through CYP-catalyzed hydroxylation reactions in SER and mitochondria

B. Adrenal Cortical Steroid Hormones

Hormonal Control

- Steroid hormones of the adrenal cortex are synthesized and secreted in response to hormonal signals (not stored).

- Types of adrenal cortical steroids include:

    - Glucocorticoids (e.g., cortisol)
    - Mineralocorticoids (e.g., aldosterone)
    - Androgens

Site of Production

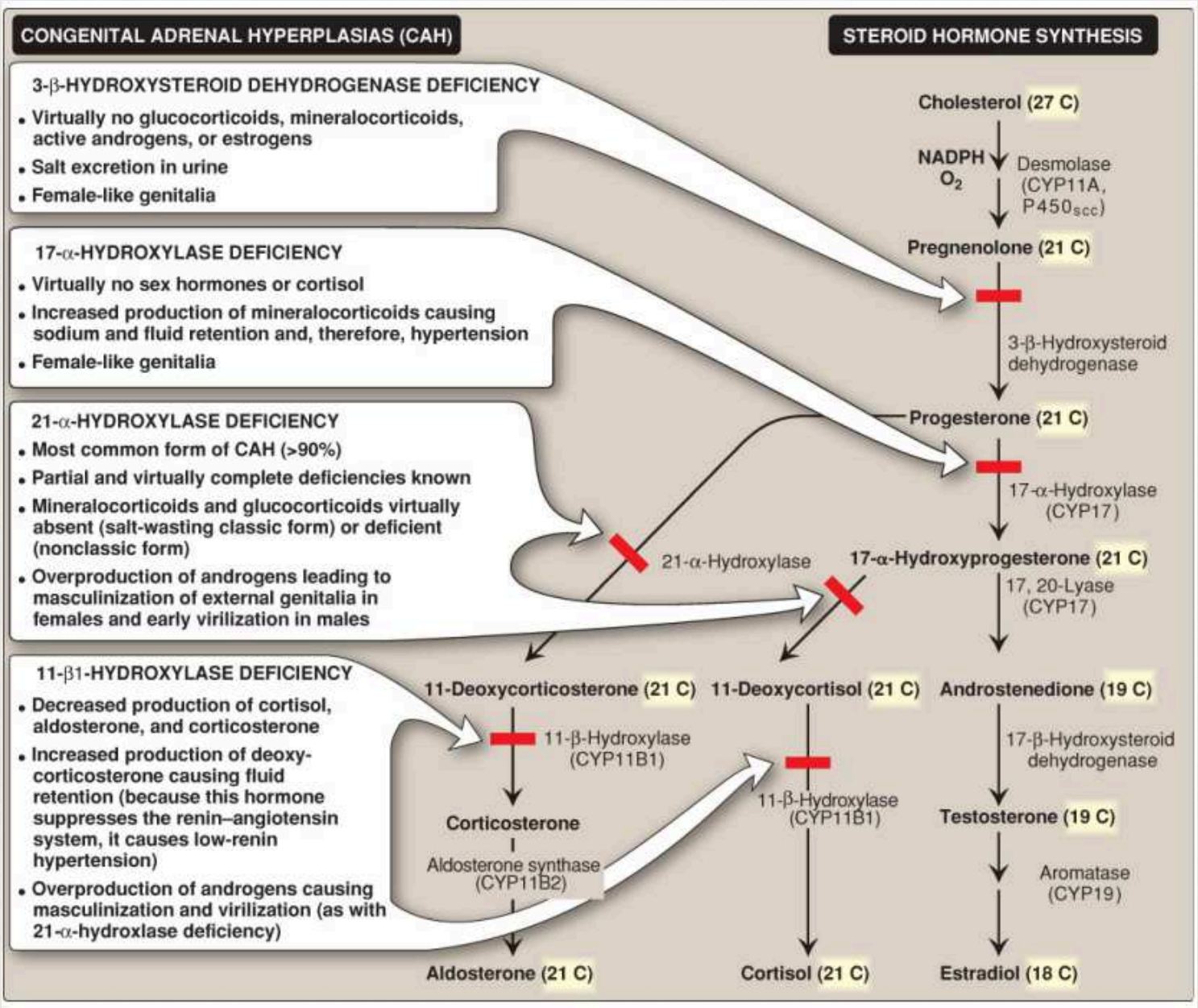
- Different hormones are produced in distinct zones of the adrenal cortex:

    - Each zone responds to specific regulatory signals from the body

Adrenal Medulla (Contrast)

- The adrenal medulla, distinct from the cortex, synthesizes and secretes catecholamines (e.g., epinephrine and norepinephrine)

Steroid Hormone Synthesis and Associated Diseases



1. Cortisol

Site of Production

- Produced in the zona fasciculata (middle layer) of the adrenal cortex.

Regulation

- Controlled by the hypothalamic-pituitary-adrenal (HPA) axis:
    - Stress (e.g., infection) → hypothalamus secretes corticotropin-releasing hormone (CRH).
    - CRH travels via hypothalamic capillaries to the anterior pituitary.
    - Anterior pituitary secretes adrenocorticotropic hormone (ACTH).
    - ACTH stimulates the adrenal cortex to produce cortisol.

Mechanism

- ACTH binds to a G protein-coupled receptor (GPCR) on adrenal cells:
    - Activates adenylyl cyclase → ↑ cAMP → activates protein kinase A (PKA).
    - PKA phosphorylates:
        - Cholesteryl ester hydrolase (esterase) → releases free cholesterol.
        - StAR protein → transports cholesterol into mitochondria

Functions of Cortisol

- Stress hormone – helps body adapt to stress.
- Increases gluconeogenesis (energy production during fasting/stress).
- Suppresses immune and inflammatory responses.

Feedback Regulation

- Rising cortisol levels inhibit both CRH and ACTH (negative feedback).

- CAH (Congenital Adrenal Hyperplasia):
    - ↓ Cortisol → ↑ ACTH → adrenal hyperplasia.

2. Aldosterone

Site of Production

- Produced in the zona glomerulosa (outer layer) of the adrenal cortex.

Regulation

- Stimulated by:
    - ↓ Plasma Na^+ / ↑ K^+ ratio.
    - Angiotensin II (Ang-II).

Renin-Angiotensin-Aldosterone System (RAAS)

- Angiotensinogen (from liver) → Angiotensin I (Ang-I) via renin (from kidney).

- Ang-I → Ang-II via angiotensin-converting enzyme (ACE) (mainly in lungs).

Mechanism

- Ang-II binds to cell surface receptors.
- Signal transduction via phosphatidylinositol 4,5-bisphosphate (PIP2) pathway (not cAMP).

Function of Aldosterone

- Acts on kidney tubules:
  - ↑ Na^+ and water reabsorption.
  - ↑ K^+ excretion.
- Leads to ↑ blood volume and blood pressure.

Clinical Note

- ACE inhibitors block Ang-II formation → used to treat renin-dependent hypertension.

3. Androgens (Adrenal)

Site of Production

- Produced in zona reticularis and zona fasciculata of the adrenal cortex.

Major Forms

- Dehydroepiandrosterone (DHEA)
- Androstenedione

Conversion

- Weak androgens, but:
    - Converted to testosterone (stronger androgen) in testes via aromatase (CYP19).
    - Converted to estrogens in ovaries (mainly in premenopausal women).

Clinical Note

- In postmenopausal women, estrogen is produced extragonadally (e.g., breast tissue).

- Aromatase inhibitors are used to treat estrogen-responsive breast cancer in postmenopausal women.

C. Gonadal Steroid Hormones

Gonads

- Testes and ovaries synthesize steroid hormones needed for:
    - Sexual differentiation
    - Reproduction

Hormonal Control

- Gonadotropin-Releasing Hormone (GnRH) (from hypothalamus) stimulates:
    - Anterior pituitary to release:
        - Luteinizing hormone (LH)
        - Follicle-stimulating hormone (FSH)

Function of LH

- Testes: Stimulates testosterone production.

- Ovaries: Stimulates production of estrogens and progesterone.

Function of FSH

- Ovaries: Stimulates follicular growth.
- Testes: Stimulates spermatogenesis.

Mechanism

- Both LH and FSH bind GPCRs on target cells → ↑ cAMP → activation of steroidogenesis.

D. Mechanism of Action of Steroid Hormones

Transport and Entry

- Steroid hormones are lipophilic:
    - Diffuse across plasma membrane.
    - Bind to intracellular receptors (cytosolic or nuclear).

Nuclear Activity

- Hormone–receptor complex:
    - Translocates to nucleus.
    - Dimerizes and binds to Hormone Response Elements (HREs) on DNA.
    - Associates with:
        - Coactivators → ↑ transcription
        - Corepressors → ↓ transcription

Structural Notes

- Binding causes conformational change exposing DNA-binding domain.
- Domain contains a zinc finger motif for specific DNA interaction.

Superfamily Members

- Receptors for:
    - Steroid hormones
    - Thyroid hormone
    - Retinoic acid
    - 1,25-dihydroxycholecalciferol (vitamin D)

E. Further Metabolism of Steroid Hormones

Inactivation Site

- Liver

Metabolic Modifications

- Reduction of unsaturated bonds.
- Hydroxylation (addition of –OH groups).

Conjugation

- Made more water-soluble via:
    - Glucuronic acid
    - Sulfate (from PAPS, 3′-phosphoadenosyl-5′-phosphosulfate)

Excretion

- Water-soluble conjugates do not need protein carriers.

- Excreted in:
    - Urine
    - Feces