Lipids

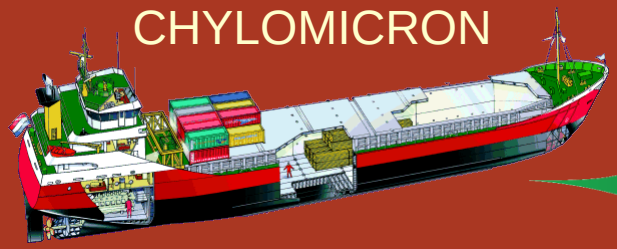
Everything you wanted to know and more!

Lipids

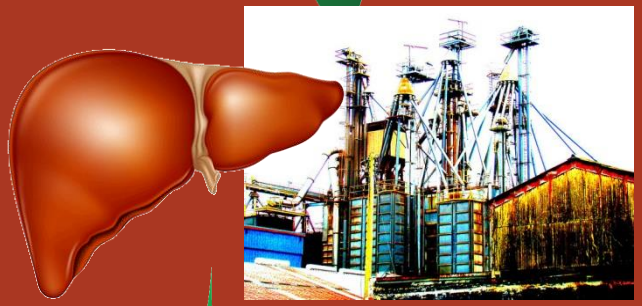
- Physical properties
  - Soluble in organic solvents
  - Insoluble in water
- Biological Functions
  1. Hormone & hormone precursor
  2. Aid in digestion
  3. Energy storage & metabolic fuel
  4. Functional and Structural membrane component
  5. Insulation-for nerves and against heat loss

Lipids

CHYLOMICRON



LIVER



VLDL

LDL

HDL

Lipids-Chemistry

- Composition of C-H bonds makes energy rich
- Transport through triglycerides, cholesterol cholesteryl esters, phospholipids

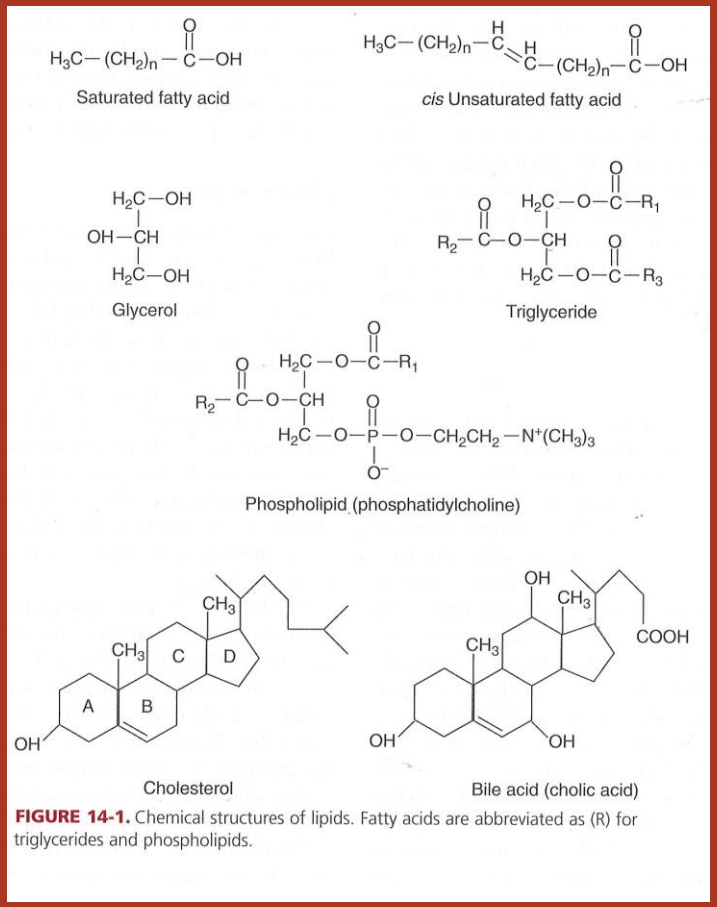


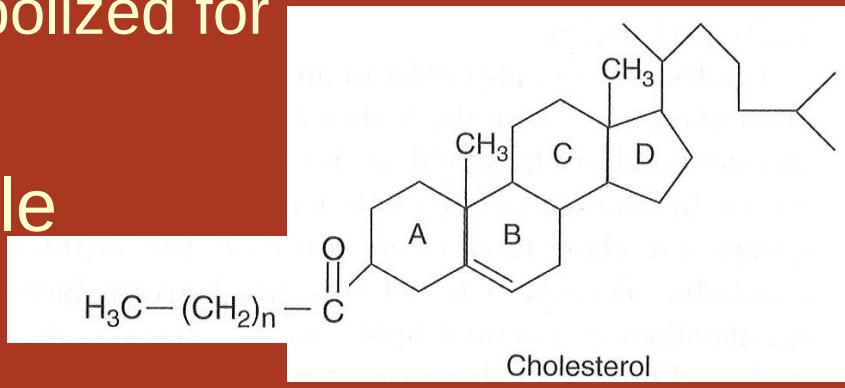
FIGURE 14-1. Chemical structures of lipids. Fatty acids are abbreviated as (R) for triglycerides and phospholipids.

Lipids-Chemistry

- Fatty Acids
  - R-COOH only a small amount of plasma portion
  - Saturation C=C or C-C
  - Usually part of trigly or phospholipids
- Glycerol Esters
  - Triglycerides for energy
  - Phospholipids hydrophilic heads

Lipids-Chemistry

- Cholesterol
  - 4 rings, only 1 hydrophilic group, amphipathic (free chol.)
  - Esterified cholesterol has NO polar groups
  - *Almost* exclusively Animalia
    - Unable to be catabolized for energy
  - Converted to usable products

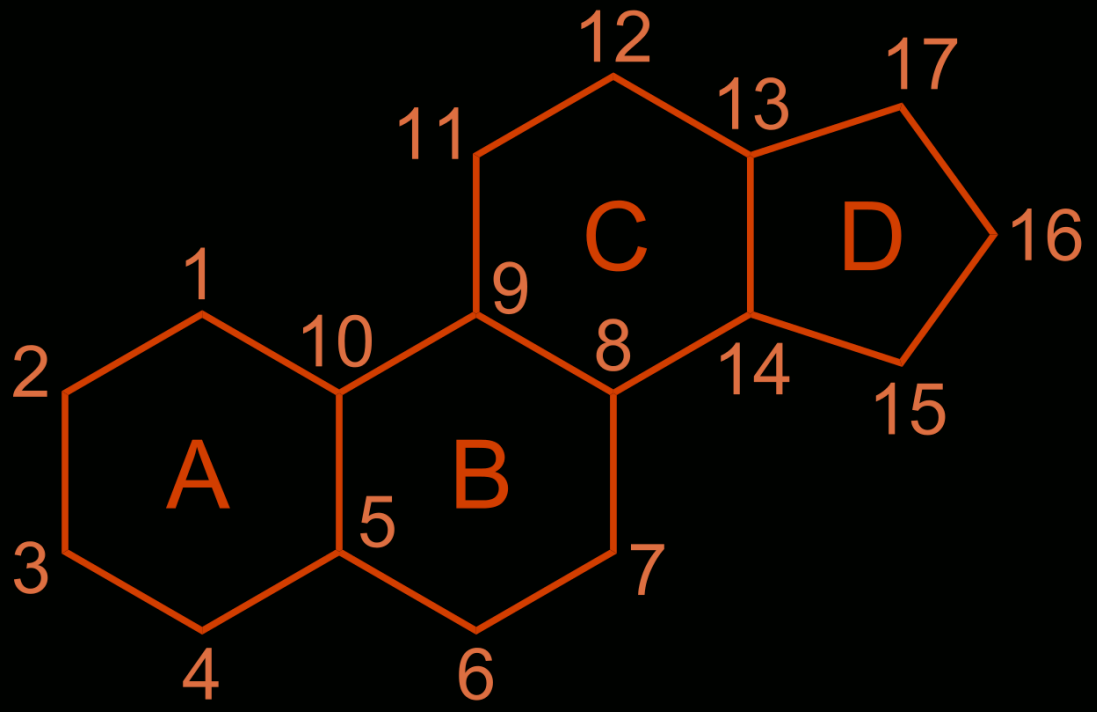


Cholesterol

FUN WORD ALERT!!!

FUN WORD ALERT!!!

perhydrocylcopentanophenanthrene



Lipids-Lipoproteins

- Spherical 10-1200 nm wide
  - Proteins are apolipoproteins on surface
- Size ∝ lipid content
- Ultracentrifuge into fractions
  - Chylomicron, VLDL, LDL, HDL

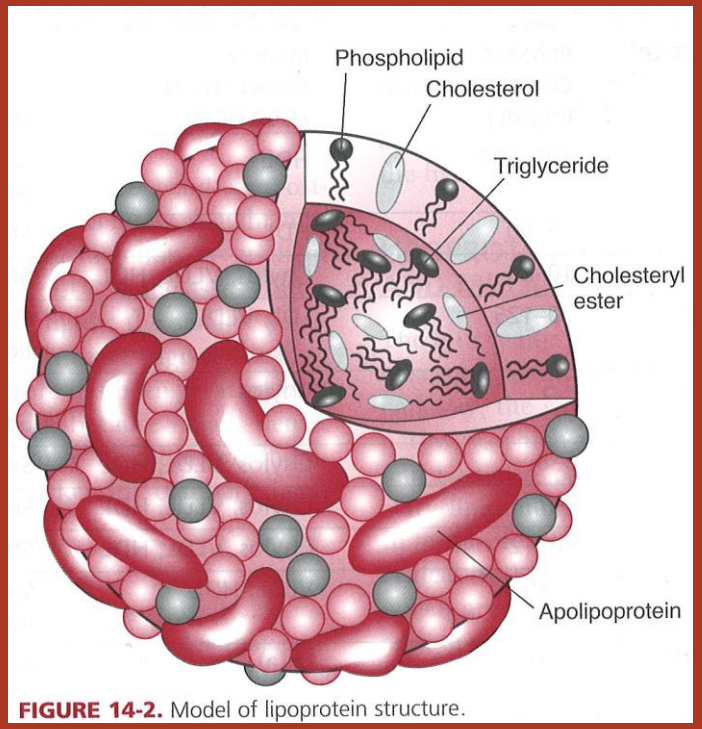


FIGURE 14-2. Model of lipoprotein structure.

Lipids-Lipoproteins

TABLE 14-1 CHARACTERISTICS OF THE MAJOR HUMAN LIPOPROTEINS

CHARACTERISTICS	CHYLOS	VLDL	LDL	HDL
Density (g/mL)	<0.93	0.93–1.006	1.019–1.063	1.063–1.21
Molecular weight (kD)	$(0.4–30) \cdot 10^9$	$(10–80) \cdot 10^6$	$2.75 \cdot 10^6$	$(1.75–3.6) \cdot 10^5$
Diameter (nm)	80–1,200	30–80	18–30	5–12
Total lipid (% by weight)	98	89–96	77	50
Triglyceride (% by weight)	84	44–60	11	3
Total cholesterol (% by weight)	7	16–22	62	19

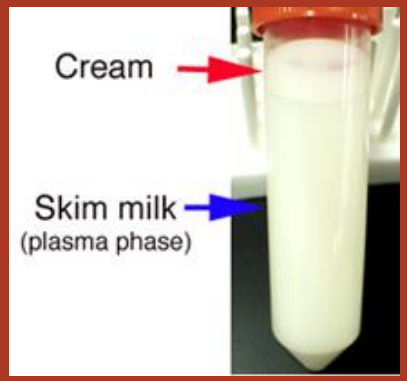
Lipids-Apolipoproteins

TABLE 14-2 CHARACTERISTICS OF THE MAJOR HUMAN APOLIPOPROTEINS

APOLIPOPROTEIN	MOLECULAR WEIGHT (kD)	PLASMA CONCENTRATION (mg/dL)	MAJOR LIPOPROTEIN LOCATION	FUNCTION
Apo A-I	28,000	100–200	HDL	Structural, LCAT activator, ABCA1 lipid acceptor
Apo A-II	17,400	20–50	HDL	Structural
Apo A-IV	44,000	10–20	Chylos, VLDL, HDL	Structural
Apo B-100	5.4×10^5 10^5	70–125	LDL, VLDL	Structural, LDL receptor ligand
Apo B-48	2.6×10^5	<5	Chylos	Structural, remnant receptor ligand
Apo C-I	6,630	5–8	Chylos, VLDL, HDL	Structural
Apo C-II	8,900	3–7	Chylos, VLDL, HDL	Structural, LPL cofactor
Apo C-III	9,400	10–12	Chylos, VLDL, HDL	Structural, LPL inhibitor
Apo E	34,400	3–15	VLDL, HDL	Structural, LDL receptor ligand
Apo(a)	$(3–7) \cdot 10^5$	<30	Lp(a)	Structural, plasminogen inhibitor

Lipids-Lipoproteins

- Chylomicrons
  - Only with apo B-48
  - Largest, turbidity-causing
  - Produced by intestines for absorption
    - Once absorbed lipases hydrolyze the triglycerides and cholesterol esters
    - 2-3 hours after meals they peak in blood
    - Liver takes up the rest
  - Nice creamy layer! YUM!



Lipids-Lipoproteins

- Very Low Density Lipoproteins VLDL
  - Produced by liver
  - Apo B-100, Apo E, Apo Cs
  - Carries endogenous triglycerides to tissues
    - Causes turbidity in fasting specimens, no creamy layer
  - Ingestion of carbs, sat/trans fatty acids ↑ VLDL production

Lipids-Lipoproteins

- Low-Density Lipoproteins LDL
  - Apo B100
  - Formed by lipolysis of VLDL
  - Taken in by peripheral cells and liver
    - Can also infiltrate intracellular spaces
    - Macrophages become foam cells or do they?
    - Atherosclerotic plaques
      - Smaller subtypes are more dangerous

Lipids-Lipoproteins

- High-Density Lipoprotein HDL
  - Smallest and most dense
  - Synthesized by liver and intestines
    - Discoidal → spherical
    - Apo A-I x2
    - HDL_2 HDL_3

Lipids-Lipoproteins

- Lipoprotein(a)
  - Similar to LDL
    - apo (a) and apo B-100
    - Heterogenous # of kringle sequences
    - Remain constant
      - Increases risk of CHD
      - May promote clotting ↑ MI ↑ Stroke

Lipids-Metabolism

- Absorption Pathway
  - Special mechanisms needed to absorb
- Exogenous Pathway
  - Ingested fats distributed & transferred
- Endogenous Pathway
  - Packaging and distribution to cells of the body

Lipids-Metabolism

- Lipid Absorption
  - 60-130g of polar substances/day
  - Pancreatic lipase chops off F.A.s
  - Amphipathic lipids aggregate with bile acids (micelle formed)
  - Intestinal wall reesterifies into triglycerides & chol. esters
  - Packaged with apo B-48 (Chylomicron formed)

Lipids-Metabolism

- Exogenous Pathway
  - Chylomicrons secreted into lymphatics
    - Enter circulation via thoracic duct
  - Lipoprotein Lipase is activated in circulation
    - Triglycerides→FFAs & glycerol (cell food)
      - Excess is reesterified inside cell as Trigly

Lipids-Metabolism

- Exogenous Pathway
  - Chylomicron remnants are recycled
    - Apo E receptor allows for liver uptake
      - » FFAs, free Chol., amino acids
    - Chosterol recycled with bile ½ will be reabsorbed
    - Some apolipoproteins and lipids are transferred to HDL

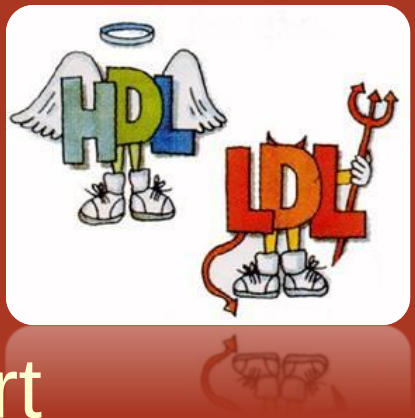
Lipids-Metabolism

- Endogenous Pathway
  - Liver takes triglycerides and makes VLDL (some made de novo from carbs)
  - LPL also digests TG to FFAs & glycerol
  - VLDL shrinks to VLDL remnant
    - Further transformed to LDL through lipolysis
  - LDL delivers cholesterol to peripheral tissues

Lipids-Lipid Metabolism

- Endogenous Pathway
  - LDL receptors on cells take up cholesterol
    - Excess cholesterol is digested by ACAT into esters (LCAT outside of cells)
  - If LDL receptor is faulty blood LDL ↑
    - Premature atherosclerosis

Lipids-Metabolism



- Reverse Cholesterol Transport Pathway
  - For cholesterol to go BACK from periphery HDL to the rescue
  - Free cholesterol esterified by LCAT
    - Captured by HDL
    - ½ transferred to LDL on its way back to liver by CETP

Lipids-In the Lab

- Reference Ranges
  - Total Cholesterol - 140-200 mg/dL
  - LDL ---------- 40-75 mg/dL
  - HDL ---------- 50-130 mg/dL
  - Triglycerides -------- 60-150 mg/dL
- Fasting Lipids
  - 12-14 hours after last eating

Lipids-In the Lab

- Risk markers
  - ↑Cholesterol ↑Heart disease
    - Genetic and lifestyle influences
  - HDL negative risk factor
    - Among homogenous lifestyle ↑HDL ↓Heart disease
  - All adults get lipid panel every 5 years

Lipids-Dyslipidemias

- Hyperlipoproteinemia
  - Hypercholesterolemia
    - Closest link to heart disease
    - FH 1:1,000,000 homozygotes
      - Total Chol. 900-1000 mg/dL MI while teenager
    - FH 1:500 heterozygotes
      - Total Chol. 300-600 mg/dL symptomatic 20-50
    - Primarily increased LDL
      - HMG-CoA reductase inhibitors
      - “LDL pheresis”

Lipids-Dyslipidemias

- Hypertriglyceridemia
  - Borderline high 150-200mg/dL
  - High 200-500 mg/dL
  - Very High >500 mg/dL
  - Deficency in LPL or apo CII (LPL co-factor)
  - “Cream over clear”

Lipids-Dyslipidemias

- Combined hyperlipidemia
  - FCH some have one, the other or both ↑
  - Dysbetalipoproteinemia (type III)
    - ↑VLDL ↑Chylomicrons from defective catabolism
      - » VLDL Chol : total Chol >0.30
    - Apo E2/2 alelle
- Lp(a) Elevation
  - ↑CHD and CVD
  - Drug resistant

Lipids-Dyslipidemias

- Hypolipoproteinemia
  - Hypoalphalipoproteinemia
    - Decrease in circulating HDL
      - < 40 mg/dL
      - Absence of hypertriglyceridemia
      - Almost zero HDL? Tangier Disease
    - Possibly transitory with stresses

Lipids-Analysis

- “Cutpoints” set by NCEP based upon epidemiological studies
- Standardization and comparability of results enacted
- Analytes
  - Cholesterol
  - Triglyceride
  - Lipoproteins

Lipids-Analysis

- Cholesterol Measurement
  - Abell-Kendall
    - Ref Method: hexane extraction after hydrolysis with alcoholic KOH followed by Liebermann-Burchard color reagent
    - Complicated, but agrees with isotope dilution mas-spec “definitive method”
  - Replaced by enzymatic reagents

Lipids-Analysis

2/3 ↘ 1/3 ↘

$$\text{Cholesterol ester} + H_2O \xrightarrow{\text{Cholesteryl esterase}} \text{Cholesterol} + \text{Fatty Acid}$$

$$\text{Cholesterol} + O2 \xrightarrow{\text{Cholesterol oxidase}} \text{Cholestone} + H_2O_2$$

$$H_2O_2 + \text{dye} \xrightarrow{\text{peroxidase}} \text{change in color @500nm}$$

Absorbed
Appears

Lipids-Analysis

$$\text{Triglyceride} + H_2O \xrightarrow{\text{Bacterial Lipase}} \text{Glycerol} + \text{Fatty Acid}$$

$$\text{Glycerol} + \text{ATP} \xrightarrow{\text{Glycerokinase}} \text{Glycerophosphate} + \text{ADP}$$

$$\text{Glycerophosphate} + O_2 \xrightarrow[\text{oxidase}]{\text{Glycerophosphate}} \text{Dihyroxyacetone} + H_2O_2$$

$$\text{H2O2} + \text{Dye} \rightarrow \text{Color Change}$$

Free glycerol in serum can contribute to false high results

How could we fix this?

Lipids-Analysis

- Lipoproteins
  - Electrophoresis
    - Agarose
    - As go to α Bs go to β and chylos go nowhere
  - Ultracentrifugation
  - Chemical precipitation
  - Antibodies
  - Chromatography
    - Detergents and antibodies most common

Lipids-Analysis

- Blockage of non-HDL lipoproteins
  - "When cholesterol esterase and cholesterol oxidase enzymes are modified by PEG, they show selective catalytic activities toward lipoprotein fractions, with the reactivity increasing in the order: LDL < VLDL ≈ chylomicrons < HDL"
    - HDL-Cholesterol plus 3rd generation product insert © 2014, Roche Diagnostics

$$\text{HDL}-\text{cholesterol esters} + \text{H}_2\text{O} \xrightarrow[\text{oxidase}]{\text{PEG}-\text{Cholesterol}} \text{HDL}-\text{Chol} + \text{RCOOH}$$

$$HDL-Cholesterol + O_2 \xrightarrow[Oxidase]{PEG-Cholesterol} \Delta^4-cholestone + H_2O_2$$

$$2\ \text{H}_2\text{O}_2 + 4-\text{amino}-\text{antipyrine} + \ \text{HSDA} \xrightarrow{\text{peroxidase}} \text{purple}-\text{blue pigment} + 5\ \text{H}_2\text{0}$$

Lipids-Analysis

- LDL
  - Friedewald Equation
    - $\text{LDL} = \text{Total Chol} - \text{HDL} - \left(\frac{\text{Triglycerides}}{5}\right)$
    - Works for up to 400 mg/dL of Trigs
  - Direct Measurements
    - Detergents used to selectively solubilize LDL also Mg^{2+} and a sugar inhibit VLDL and Chylo. action

Lipids

- Any Questions?