Function of lipids

energy substrate
lipid microenvironment
insulation
membrane component
substrates for further metabolization
modifications of proteins/saccharides
Lipid transport

*postprandial phase* – digestion of lipids from the diet

*fasting state* – delivery of lipids to the tissues in need
Important lipid classes

- **Neutral** = Hydrophobic
- **Polar** = Amphiphilic

- Cholesteryl ester, CE
- Triacylglycerol, TAG (TG)
- Cholesterol, FC
- Phosphatidylcholine, PC
- Sphingomyelin, SPH
- NEFA

Very polar
Structure of lipoprotein

- cca spherical
- micellar
- noncovalent interaction between lipids and proteins
- lipid transporting system
- possible interchange of apoproteins, lipids between lipoproteins
# Plasma lipoproteins

<table>
<thead>
<tr>
<th>Lipoprotein class</th>
<th>Major Lipid class</th>
<th>Apolipoproteins</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>remnant CM</td>
<td>TAG, CE</td>
<td>B-48, E</td>
<td>catabolism of CM</td>
</tr>
<tr>
<td>VLDL (very low density Lp)</td>
<td>TAG</td>
<td>B-100, C-II,-III, E</td>
<td>liver (intestine)</td>
</tr>
<tr>
<td>IDL (intermediate density Lp)</td>
<td>CE</td>
<td>B-100, C-II,-III, E</td>
<td>catabolism of VLDL</td>
</tr>
<tr>
<td>LDL (low density Lp)</td>
<td>CE</td>
<td>B-100</td>
<td>catabolism of IDL</td>
</tr>
<tr>
<td>HDL(_2) (high density Lp) subclass 2</td>
<td>CE, PL</td>
<td>A-I, A-II</td>
<td>liver, intestine catabolism of CM and VLDL</td>
</tr>
<tr>
<td>HDL(_3) (high density Lp) subclass 3</td>
<td>CE</td>
<td>A-I, A-II, minor apolipoproteins</td>
<td>HDL(_2)</td>
</tr>
<tr>
<td>lipoprotein [a]</td>
<td>CE</td>
<td>B-100 &amp; apo [a]</td>
<td>liver</td>
</tr>
</tbody>
</table>
Metabolic lipoprotein pathway
Lipoprotein size

LIPOPROTEIN SUBCLASSES

particle density (g/ml)

particle diameter (nm)

HDL

LDL

IDL

VLDL

chylomicron

HDL2b reverse cholesterol transport

large LDLs

small LDLs

chylomicron remnant

1 nm = 10 angstroms
Plasma apolipoproteins

\textit{apolipoprotein} = \textit{protein part of lipoprotein particle}

many functions (intracellular \neq extracellular)

Non-exchangeable apolipoproteins

structural function: apo B-48, apo B-100

receptor ligands: apo B-48, apo B-100

Exchangeable apolipoproteins

receptor ligands: apo E, apo A-I

structural function: apo A-I

modulation of enzyme activity: apo A-I, apo A-II, apo C-I, apo C-II, apo C-III

enzyme activity: apo K (PON)

acute phase reactant: apo I (SAA)

inhibition of metabolic cascades: apo (a) (thrombolysis?)

apo J (inhibitor of terminal complement complex)
# Important plasma apolipoproteins

<table>
<thead>
<tr>
<th>apolipoprotein</th>
<th>major LP class</th>
<th>concentration (g/l)</th>
<th>function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A-I</strong></td>
<td>HDL_{2,3}</td>
<td>1.20 - 1.40</td>
<td>LCAT activation, HDL-receptor ligand, transport (HDL)</td>
</tr>
<tr>
<td><strong>A-II</strong></td>
<td>HDL_{3}</td>
<td>0.35 - 0.50</td>
<td>Activation of hepatic lipase, transport (HDL)</td>
</tr>
<tr>
<td><strong>A-IV</strong></td>
<td>CM, HDL_{2,3}</td>
<td>&lt; 0.05</td>
<td>RCT, absorption of exogenous TAG</td>
</tr>
<tr>
<td><strong>B-100</strong></td>
<td>VLDL, IDL, LDL</td>
<td>0.60 - 1.20</td>
<td>Transport (VLDL, IDL, LDL), LDL-receptor ligand</td>
</tr>
<tr>
<td><strong>B-48</strong></td>
<td>CM, β-VLDL</td>
<td>&lt; 0.05</td>
<td>Absorption of lipids, apoB-48 receptor ligand, transport (CM, remnant CM)</td>
</tr>
<tr>
<td><strong>C-I</strong></td>
<td>CM, VLDL</td>
<td>0.05 - 0.08</td>
<td>Inhibition of CETP, LCAT activation</td>
</tr>
<tr>
<td><strong>C-II</strong></td>
<td>CM, VLDL</td>
<td>0.03 – 0.07</td>
<td>Activation of LPL</td>
</tr>
<tr>
<td><strong>C-III 0-3</strong></td>
<td>CM, VLDL</td>
<td>0.10 - 0.12</td>
<td>Catabolism of CM_R, inhibition of LPL</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td>HDL_{3}</td>
<td>0.08 - 0.10</td>
<td>Free cholesterol esterification?</td>
</tr>
<tr>
<td><strong>E</strong></td>
<td>CM, VLDL, HDL-E</td>
<td>0.03 - 0.05</td>
<td>LDL-receptor ligand, VLDL-receptor ligand, RCT LRP-receptor ligand, apoER2-receptor ligand</td>
</tr>
</tbody>
</table>

**RCT** - reverse cholesterol transport, **LCAT** - lecithin:cholesterol acyltransferase, **LPL** - lipoprotein lipase, **CE** - cholesterylester, **TAG** - triacylglycerol, **CM_R** - remnant CM, **β-VLDL** – remnant VLDL staying in plasma.
Metabolic lipoprotein pathway

EXOGENOUS PATHWAY

- Exogenous lipids in diet
- Absorption
- Lipids in circulation
- Utilization in liver
- Utilization in extrahepatic tissues

ENDOGENOUS PATHWAY

- Liver
- LDL
- HDL
- Extrahepatic tissues
- Muscles
- Adipose tissue

Diagram showing the metabolic lipoprotein pathway involving liver, adipose tissue, muscles, and extrahepatic tissues, with pathways for exogenous lipids in diet and endogenous lipids in circulation.
Lipid digestion

gastro-salivary phase
Lingual lipase (pH optimum 3.5-6)
secreted by von Ebner’s glands, acts also in stomach
TAG $\rightarrow$ 1,2-DAG, 2,3-DAG + FFA

Gastric lipase (pH optimum 3.5-5.4)
TAG $\rightarrow$ DAG + FFA/glycerol + FFA

significant contribution
to the digestion (10-30 % of TAG)

1. Emulsification of lipids

gastric movements
peristaltic movements
grinding of the antrum

water/lipid interface
Lipid digestion

intestinal phase - pancreatic lipases

Pancreatic lipase (pH optimum 6.5-9)

at the interface of lipid droplets

(facilitated by BA micellarization of products)

\[ \text{TAG} \rightarrow 2\text{-MAG} + \text{FFA} \]

Colipase

exposes the active site of pancreatic lipase

Pancreatic phospholipases PLA\(_1\), PLA\(_2\)

activated by trypsin

\[ \text{PL} \rightarrow 2\text{-lysoPL}, 1\text{-lysoPL} + \text{FFA} \]

Cholesteryl ester hydrolase (BA activated lipase)

\[ \text{CE} \rightarrow \text{FC} + \text{FFA} \]

other substrates: retinyl esters, TAG, PL, Cer

2. lipolysis of lipids
Lipid digestion

intestinal phase - pancreatic lipases
alkaline sphingomyelinase
\[ \text{SPH} \rightarrow \text{Cer} + \text{P-choline} \]
neutral ceramidase
\[ \text{Cer} \rightarrow \text{sphingosine} + \text{FFA} \]
Lipid digestion

intestinal phase - formation of micelles
BA and PL displace lipolysis products from the water-oil interface

mixed micelles

further lipolysis by lipases

3. solubilization of lipids
Lipid absorption – fatty acids
Lipid absorption – sterols
Assembly of chylomicrons
Chylomicrons

SMALL INTESTINE

dietary fat

lymphatics

B-48

TAG FC

nascent chylomicron

A-I
Chylomicrons
Chylomicrons
Chylomicrons
Chylomicrons
Chylomicrons
Metabolic lipoprotein pathway

EXOGENOUS PATHWAY
- Diet
- Intestine
- Chylomicrons (CHM)
  - apo E
  - apo B-48
  - apo C-II
- CHM-remnant (with apo B-48, E)
- LRP receptor
- CHM-remnant (s apo B-48, E)
- VLDL (with apo B, C-II)
- HDL (s apo A-I, A-IV)
- IDL-remnant
- IDL
- HDL3
- HDL2
- IDL
- HDL
- LDL
- apo B-100
- NEFA release
- Adipose tissue
- Endogenous lipids in extrahepatic tissues
- Excess of cholesterol
- Reverse CH transport

ENDOGENOUS PATHWAY
- Liver
- Lipids in circulation
- Utilization in liver
- Utilization in extrahepatic tissues
- Muscles
- Adipose tissue
- Diets >> Intestine
- CHM-remnant
- LRP receptor
- VLDL (with apo B, C-II)
- IDL-remnant
- IDL
- HDL3
- HDL2
- HDL
- LDL
- apo B-100
- NEFA release
- Adipose tissue
- Endogenous lipids in extrahepatic tissues
- Excess of cholesterol
- Reverse CH transport
- Muscles
- Adipose tissue
Assembly of VLDL
Fate of VLDLs
Fate of VLDLs
Fate of VLDLs
Fate of VLDLs
Fate of VLDLs
Fate of VLDLs
Fate of VLDLs
HDL and reverse cholesterol transport
HDL and reverse cholesterol transport
HDL and reverse cholesterol transport
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HDL and reverse cholesterol transport
HDL and reverse cholesterol transport
HDL and reverse cholesterol transport
Reverse cholesterol transport
sterol transport from macrophages
Other roles of HDL

**Exchanges of lipid classes**
- facilitating reverse cholesterol transport (LCAT)
- TAG depletion of VLDL/LDL rich particles (CETP)
- remodelling of HDLs (PLTP)

**Antioxidant properties**
- oxPL (LDL) → oxPL (HDL)
- liberation of oxidized FA from oxPL molecules (PON-1, PAF-AH)

**Particle remodelation**
- part of acute phase response (SAA for PON-1)

**Antiinflammatory/antithrombotic vasodilatory activity**
HDL and oxidative stress

1. Removal of oxidised PL from LDL (oxLDL)
   oxPL (LDL) → oxPL (HDL)
   sdHDL are easy acceptors for oxPL (oxLDL/membranes)

2. Inactivation of oxidised PL
   - via redox active residues in apo A-I (Met)
     PLOOH → PLOH
   - via liberation of oxidized FA from oxPL molecules
     paraoxonase (PON-1)
     hydrolysis of oxPUFA from oxPL/oxCE

platelet-activating factor acetylhydrolase (PAF-AH)
hydrolysis of short chain oxFA from sn-2 position in ox PL
HDL remodelation

functionally defective HDL particles

acute phase response/inflammation

- modification by glycation
- oxidation
- decreased capacity for RCT
- decreased antioxidant capacity of HDL

HDL particles lacking antiatherogenic functions
DISORDERS OF LIPOPROTEIN METABOLISM
DEFINITION AND SIGNIFICANCE OF DISORDERS OF LP METABOLISM

CLASSIFICATION

I. According to changes in lipid/lipoprotein classes:
   a) hyperlipoproteinemia (HLP)
   b) dyslipoproteinemia (DLP)

II. According to the cause:
   a) primary HLP/DLP - independent, genetically determined diseases (60 - 90 %)
   b) secondary HLP/DLP - consequence of disease (state) altering metabolism of LP
Definition of hyperlipoproteinemia, hyperlipidemia and dyslipoproteinemia

**Hyperlipoproteinemia**
= state connected with elevation of one or more LP classes

**Hyperlipidemia**
= state, when concentrations of TC and/or TAG exceed borderline concentration [defined by 90/95th percentiles]

**Dyslipidemia**
- a) = state, characterised by lowered concentration of HDL-C
  HDL-C ≤ 0.9 mmol/l in M (resp. 1.10 mmol/l for F)
- b) more generally, any disorder of LP
Pathogenesis of lipoprotein disorders

I. ↑ synthesis of cholesterol and/or triacylglycerols
   ▶ secretion of LP

II. disturbed metabolism of lipoproteins
   - changes in remodeling of particles
     ▶ abnormal composition:
       LP-X (liver cirrhosis), small dense LDL
   - ↓ catabolism of lipoproteins

III. combination of abovementioned mechanisms

   + interaction of genetically susceptible background and
     non genetic effects (nutritional, metabolic, disease states)
### Classification of phenotypes of hyperlipoproteinemias

#### Primary HLP

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Lipoprotein cholesterol</th>
<th>Primary cause</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CM</td>
<td>VLDL</td>
</tr>
<tr>
<td>I</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>IIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>(CH-R)</td>
<td>b-VLDL</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>V</td>
<td></td>
<td>↑</td>
</tr>
</tbody>
</table>

LPL – lipoprotein lipase, LMF1 – lipase maturation factor 1, HL – hepatic lipase, CH-R – chylomicron remnants, FHC – familial (= monogenic, "receptor") hypercholesterolemia, FCH – familial combined hyperlipoproteinemia, PHC – polygenic hypercholesterolemia, FHTG – familial hypertriacylglycerolemia
### Classification of phenotypes of hyperlipoproteinemias

#### Secondary HLP

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Lipoprotein cholesterol</th>
<th>Secondary cause</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CM</td>
<td>VLDL</td>
</tr>
<tr>
<td>I</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>IIA</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>↑</td>
<td>b-VLDL</td>
</tr>
<tr>
<td>IV</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

**DM – diabetes mellitus**
### Present classification of hyperlipidemias

<table>
<thead>
<tr>
<th>Type of hyperlipidemia</th>
<th>Disorder in lipoprotein class</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia</td>
<td>LDL rarely HDL</td>
<td>Familial (monogenic) hypercholesterolemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polygenic hypercholesterolemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperalfacholesterololemia</td>
</tr>
<tr>
<td>Hypertriacylglycerolemia</td>
<td>VLDL rarely VLDL + CM</td>
<td>Familial endogenous hypertriacylglycerolemia</td>
</tr>
<tr>
<td></td>
<td>rarely CM</td>
<td>Familial mixed hypertriacylglycerolemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Familial hyperchylomicronemia</td>
</tr>
<tr>
<td>Mixed hyperlipidemia</td>
<td>VLDL + LDL rarely IDL</td>
<td>Familial mixed hyperlipidemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Familial dysbetalipoproteinemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Familial hepatic lipase deficiency</td>
</tr>
</tbody>
</table>

LDL – low density lipoproteins, VLDL – very low density lipoproteins, CM - chylomicrons, IDL – intermediary density lipoproteins, HLP - hyperlipoproteinemia
CLASSIFICATION OF DISTURBED LIPID METABOLISM by Sniderman

<table>
<thead>
<tr>
<th>apo B &lt; 1.2 g/l</th>
<th>apo B &gt; 1.2 g/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAG &lt; 1.50 mmol/l</td>
<td>TAG &gt; 1.50 mmol/l</td>
</tr>
<tr>
<td>DLP 1 - normal</td>
<td>DLP2 - TAG↑ apoB~</td>
</tr>
<tr>
<td>DLP3 - TAG~ apoB↑</td>
<td>DLP4 - TAG↑ apoB↑</td>
</tr>
</tbody>
</table>

- DLP 1 - normal (normal individuals)
- DLP2 - TAG↑ apoB~ (secretion of VLDL1 hyperTAG or catabolism of VLDL1 LPL deficiency)
- DLP3 - TAG~ apoB↑ (secretion of VLDL3 polygenic hyperCH or catabolism of VLDL familial hyperCH defect of apoB100)
- DLP4 - TAG↑ apoB↑ (secretion of VLDL2 obesity, DM2, insulin resistance, nephrotic syndrome familial combined hyperlipidemia)

VLDL1, VLDL2, VLDL3 – subpopulations of VLDL particles
## Low concentration of HDL-cholesterol

### Genetic factors
- deficiency/abnormal structure of apo-A-I (e.g. Apo A-I<sub>Milano</sub>)
- Tangier disease (deficiency of ABCA1)
- deficiency of LCAT - ”fish eye disease”
- deficiency and mutations of LPL
- cholesteryl ester storage diseases (lysosomal CEH)
- Niemann-Pick disease (A, B, C variants)

### Non genetic causes
- obesity, hypertriacylglycerolemia
- renal insufficiency
- smoking
- decreased physical activity
- enhanced intake of SFA/diminished supply of PUFA n-3, PUFA n-6
- drugs (thiazides, α-methyl DOPA, spirolactone, phenothiazins)
Endocrinopathies

Hypothyreosis

↓ activity of LDL receptors and LPL (HLP IIA > IIB, III, > IV)
never phenotype HLP I and V, <10% no LP change
with E2/E2 → HLP type III
relatively high frequency
(4, resp. 8 % persons with hypercholesterolemias)

Estrogens (hormonal contraception, gravidity)

↑ VLDL, ↑ LDL and ↑ HDL (FCH) (phenotype IIB, IV)

gravidity

physiological secondary HLP
(estrogens, progesteron, IR, hyperinsulinaemia, human placental lactogen)
Lipid metabolism during fasting

Mobilization of lipid stores

adipose tissue
activation of HSL: TAG $\rightarrow$ glycerol + 3 NEFA

liver

- gluconeogenesis (for brain, muscles)
- depletion of glycogen
- muscle proteins $\rightarrow$ AA
- TCA cycle intermediates (oxaloacetate) are used for gluconeogenesis

albumin

ketone bodies (for brain)

acetylCoA excess
Further reading
Textbooks, monographs

Biochemistry of Lipids, Lipoproteins and Membranes (5th Ed); Vance DE, Vance Je (Eds.), Elsevier, Amsterdam (The Netherlands) 2008

Lehninger Principles of Biochemistry (6th Ed); Nelson DL, Cox MM (Eds.), Susan Winslow, New York (U.S.A.) 2013


High Density Lipoproteins: From Biological Understanding to Clinical Exploitation; Eckardstein A, Kardassis D (Eds.). Springer Open, London (UK) 2015

Lipoproteins in Health and Disease; Betteridge J, Shepherd J, Illingworth R (Eds.). CRC Press, London (UK) 1999

Articles


Web sources
http://themedicalbiochemistrypage.org - the Medical Biochemistry Page