30

carbohydratesisomersketone starchlipidproteinamine

Bio chemistry

Doctor 2017 | Medicine | JU

Sheet Slides

DONE BY

Leen Osama

CONTRIBUTED IN THE SCIENTIFIC CORRECTION

Ali Alabbadi

CONTRIBUTED IN THE GRAMMATICAL CORRECTION

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DOCTOR

Faisal

Note: please study pictures thoroughly as they help a lot in understanding the concepts.

Last time we talked about cholesterol synthesis regulation; most of it occurs at the level of HMG reductase, the enzyme that catalyzes the rate limiting step (conversion of HMG CoA to mevalonate. the regulation occurs by more than one mechanisms: 1) feedback inhibition. 2) regulation of gene expression *(1,2 were discussed in the previous sheet)* 3) hormonal regulation and 4) proteolytic regulation.

3. Hormonal regulation:

Glucagon which reflects low blood glucose, **inhibits synthesis** of cholesterol. **Insulin** on the other hand **enhances dephosphorylated** form through the **activation of phosphatase**.

4. Proteolytic regulation:

As with all enzymes, HMG CoA reductase continuously undergoes turnover (there is continuous synthesis and degradation of it). The amount of enzyme can be regulated by changing the rate of synthesis and degradation. High level of cholesterol will enhance proteolysis and the level of the enzyme will be reduced as a result. (if the cell is receiving a good amount of cholesterol, there's no need to synthesize more)

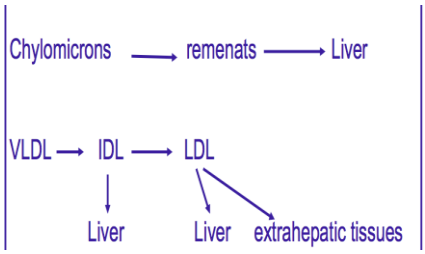
- The 4 mechanisms reflect the importance of regulating cholesterol synthesis.

……

Transport of cholesterol in blood [by LDL and HDL]

Overview

Chylomicrons are synthesized in the small intestine, carried to the blood through the lymph, degraded gradually in the blood, and end up in the liver via endocytosis.



Cholesterol is transported within chylomicrons from the small intestine to the liver. Then, chylomicrons become chylomicron remnants which are taken up by endocytosis in the liver. Similarly, VLDL, which is synthesized in the liver is released and gradually converted to LDL and IDL. 50% of the IDL will be metabolized by the liver, the rest will continue in the bloodstream and is converted to LDL. LDL is very rich in cholesterol and therefore is taken by the liver by endocytosis.

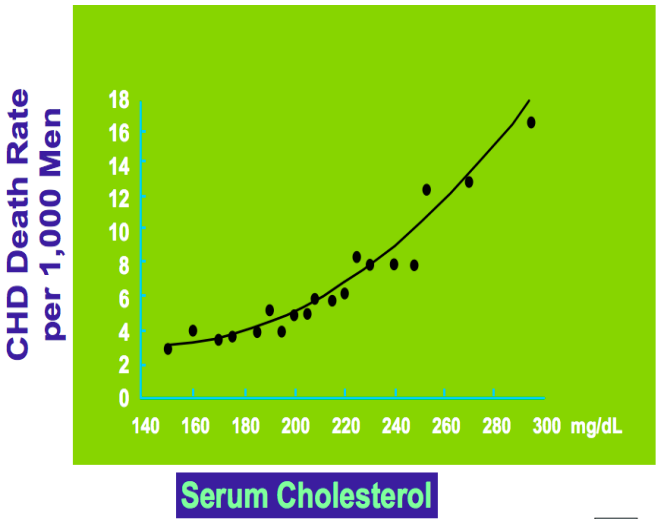
So, cholesterol that is coming from the liver ends up in the liver or in extrahepatic tissues.

- The small intestine is where TAG is obtained from food, and where cholesterol is incorporated in the chylomicrons to be released into the blood. Lipoprotein lipase of the capillaries acts on TAG to produce free FAs and glycerol and consequently the level of TAG is reduced. This results in a relative increase in cholesterol (C) and cholesterol esters (CE) with respect to TAG. The chylomicron remnants composed of TAG< C&CE are taken by the liver in the process of endocytosis along with their contents of C&CE.

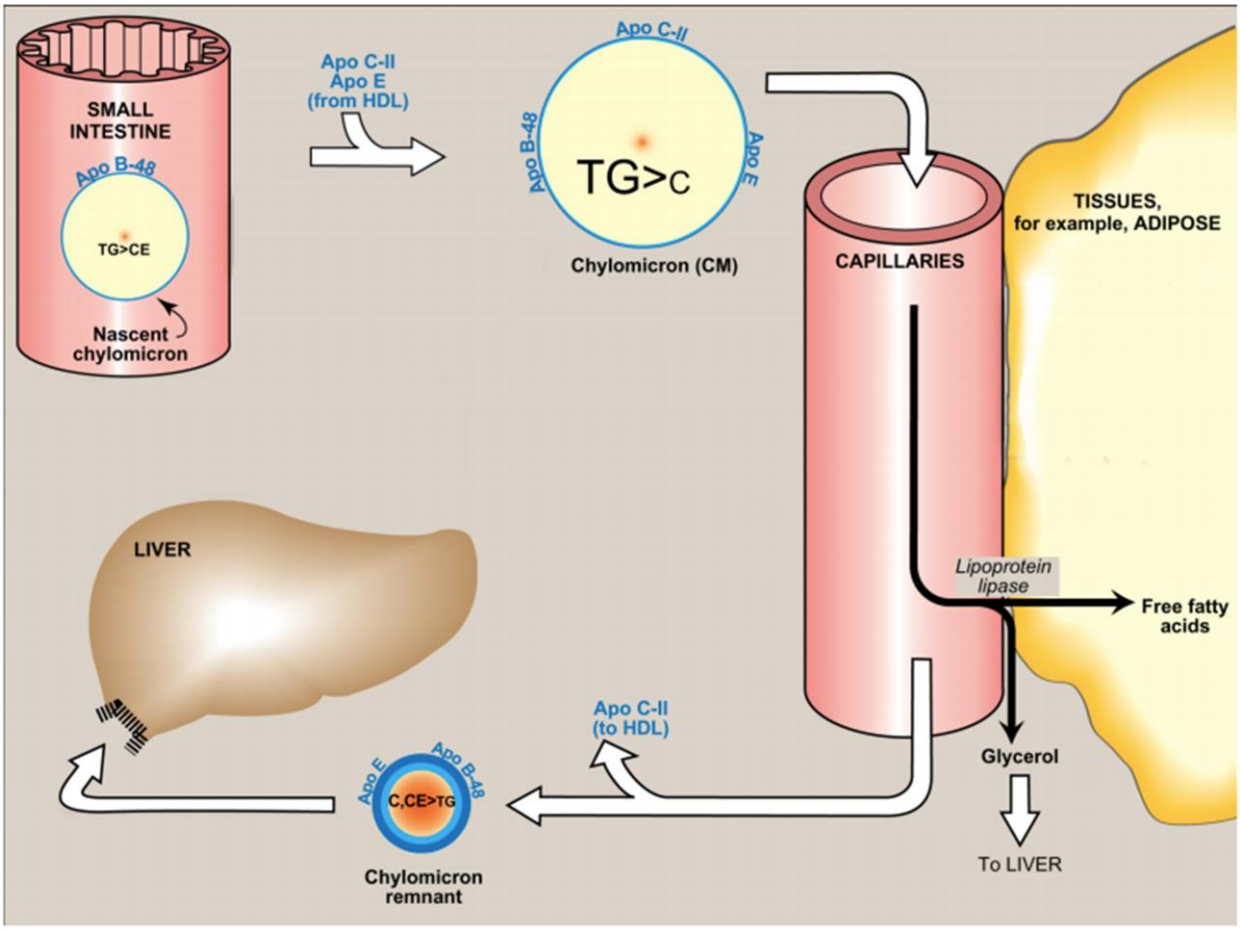
Risk factors for coronary artery disease:

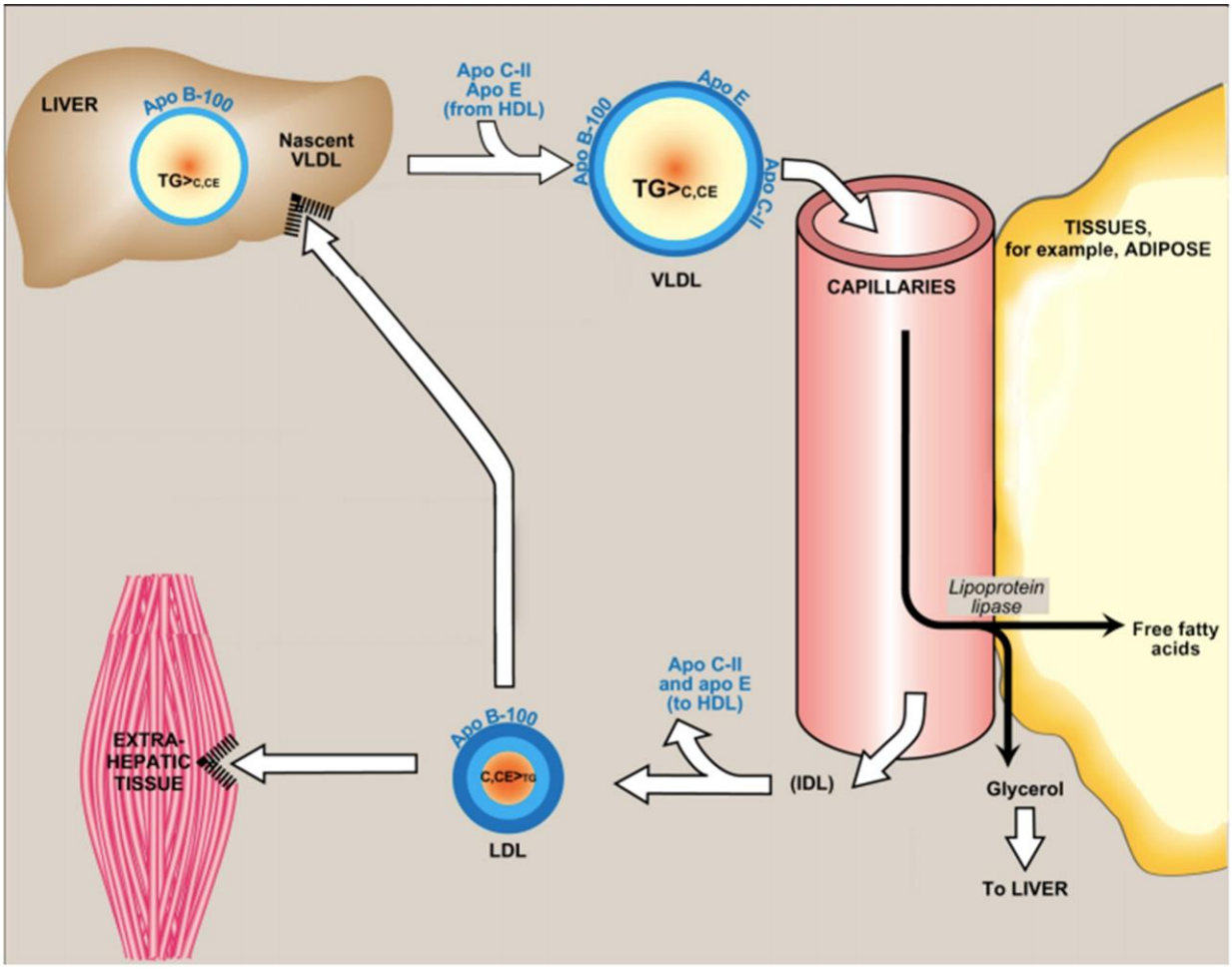
Modifiable (under our control)	Non- modifiable
Cigarette smoking	Males > 45 years
Obesity	Females > 55 years
Hypertension (blood pressure >= 140 / 90 mmHg), controlled by anti-hypertensive drugs.	Males
Physical inactivity	Family history of coronary heart disease
Kidney disease	
Stress	
Diabetes mellitus	
Alcohol consumption	
Elevated LDL: high level of cholesterol in the LDL particles is a risk factor for CAD.	
Reduced HDL: high level of HDL cholesterol is considered a negative factor (protects against CAD).	

Serum cholesterol and CHD:



This graph emphasizes the importance of cholesterol. The death rate per 1000 men admitted to the hospital for myocardial infarction (MI). The rate increases with the level of cholesterol; the higher the level, the more the risk of MI or even death. This encouraged scientists to study cholesterol extensively and see how its level can be reduced.


SMALL INTESTINE
Apo B-48
TG>CE
Nascent chylomicron
Apo C-II
Apo E
(from HDL)
Apo C-II
Apo B-48
TG>C
Apo E
Chylomicron (CM)
CAPILLARIES
TISSUES, for example, ADIPOSE
LIVER
Lipoprotein lipase
Free fatty acids
Apo C-II
(to HDL)
Glycerol
To LIVER
Apo E
Apo B-48
C,CE>TG
Chylomicron remnant


LIVER
Apo B-100
TG>C,CE
Nascent VLDL
Apo C-II
Apo E
(from HDL)
Apo B-100
Apo E
TG>C,CE
Apo C-II
VLDL
CAPILLARIES
TISSUES, for example, ADIPOSE
Lipoprotein lipase
Free fatty acids
Apo C-II
and apo E
(to HDL)
(IDL)
Glycerol
To LIVER
EXTRA-HEPATIC TISSUE
Apo B-100
C,CE>TG
LDL

Measuring cholesterol Level in blood

- Transport of cholesterol to the liver lasts 10-12 hrs. after food intake. Therefore, if we want to measure cholesterol level in the blood we can't rely on measurement after food intake. That is because part of cholesterol is still in the chylomicron remnants. To measure the cholesterol that is not affected by food intake, patient should fast for 12-14 hrs. so that no chylomicrons or chylomicron remnants will be in the circulation.

VLDL synthesis

11:20

- VLDL is synthesized in the liver with high level of TAG, TAG is gradually reduced and VLDL becomes IDL and LDL. IDL can be reabsorbed by endocytosis, while LDL goes to the liver and extrahepatic tissues, and in this manner cholesterol is transported from the liver to different tissues. *(see pictures in the previous page)*
- Within the circulation, exchange of substances occurs between VLDL, HDL, etc.
- LDL that is produced from the action of lipoprotein lipase, TAG, and VLDL will give LDL. so now LDL is smaller with high level of C&CE, then they will be reabsorbed by endocytosis.

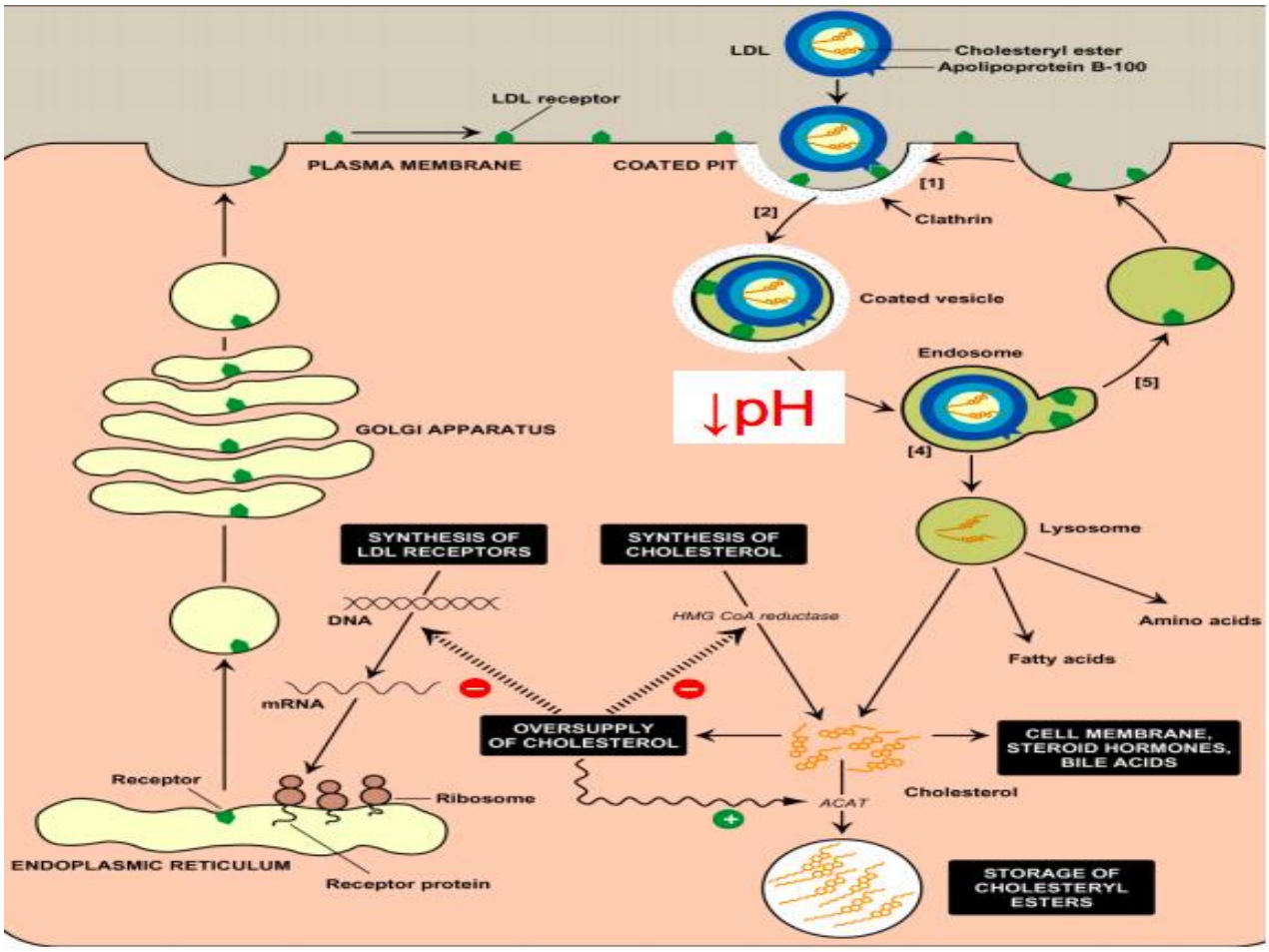
Transport of cholesterol into cells

LDL receptors[endocytosis]

In the plasma membrane, especially in the coated pits, there are receptor proteins called LDL receptors. Coated pits are regions coated with the protein clathrin and have a high amount of LDL receptors.

1- These receptors bind to Apolipoprotein B-100 *(the only lipoprotein in LDL)* and this stimulates endocytosis.
2- Coated pits form vesicles that contain extracellular LDL particles. Then, protons are pumped inside the endosome which increases acidity, and causes detachment of LDL from the receptor.
3- LDL receptor is recycled and taken back to the plasma membrane so that it can work again.

4- The endosome then fuses with the lysosome. In the lysosome, the protein is degraded to give amino acids, fatty acids, as well as cholesterol.



Effect of cholesterol in LDL particles

Cholesterol may be **incorporated into the cell membrane**, **converted to steroid hormones** if the cell produces them, or **converted to bile acids** in the liver. The rest of the different functions of cholesterol also use free cholesterol in LDL as a source.

Storage of cholesterol

Storage requires esterification of cholesterol to cholesterol ester by the action of the enzyme ACAT *(discussed in sheet 29).*

Over supply of cholesterol leads to:

1- **inhibition of HMG CoA reductase**
2- **increased synthesis rate of ACAT** → increase esterification
3- **inhibition of LDL receptors** → reduce number of receptors on the membrane which in turn limits amount of cholesterol taken from LDL **[downregulation].**

Macrophage Scavenger receptors

- They are **nonspecific** receptors; can bind to LDL particle whether it's intact, modified, or damaged.

  The damage may be due to oxidation or destruction. Normal LDL receptors can't bind to the damaged or modified LDL particles, however, scavenger receptors can.

- They **don't undergo downregulation** which means that they keep taking LDL again and again limitlessly. Therefore, the macrophage takes a very large amount of LDL and is called a foam cell.

- When LDL levels are normal AND the level of LDL receptors is good enough, LDL binds to LDLRs. When LDL is damaged or stays for a long time, the macrophage scavenger receptors will clean it from the circulation.

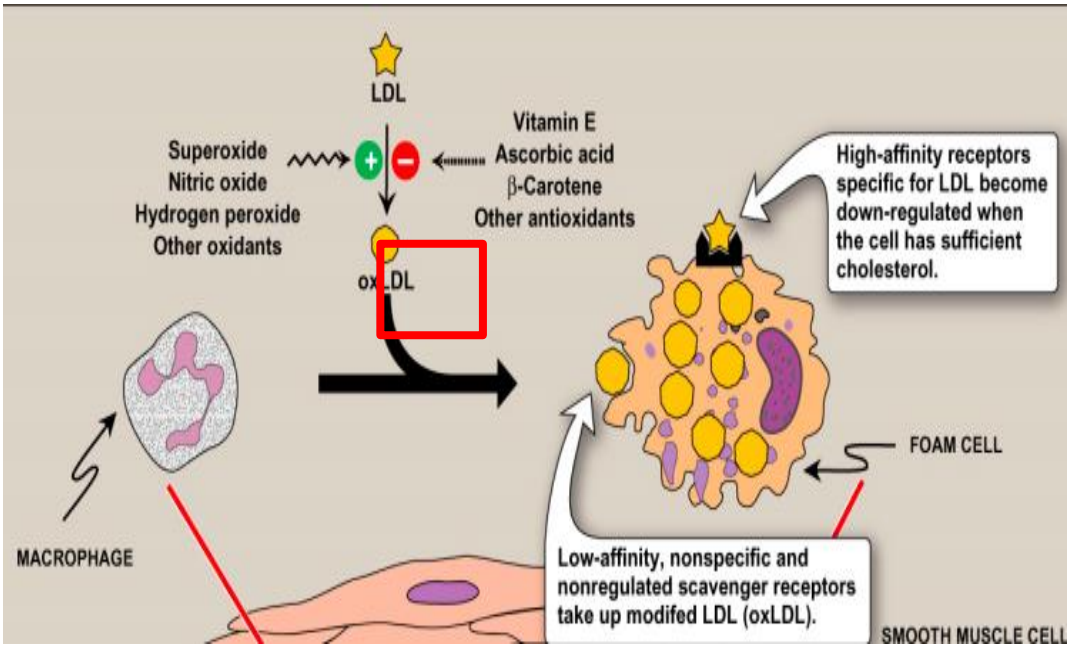
Foam cells accumulate in the sub-endothelial space in the arteries, and this is considered an early **evidence of atherosclerotic plaque**.
Macrophages gradually go to sub-endothelial space and result in the accumulation of cholesterol, which leads to the development of atherosclerosis.

➢ HOW does LDL become oxidized?

By the action of **oxidants** e.g.: superoxide, H2O2, and methyl oxide. So, oxidants enhance foam cell formation.
Smoking as well causes oxidation and damage of LDL particles, thus preventing their binding to LDL receptors.

➢ HOW to prevent oxidation of LDL?

Antioxidants help in maintaining LDL in order to be taken by LDL receptors.



The doctor said that we are not required to know all the details, (pathology not biochemistry)

Clinical correlation: Familial Hypercholesterolemia

(Familial → genetic (مرتبط بالعائلات) hypercholesterolemia → high cholesterol in blood)

normal level of cholesterol: 200 mg/dl

Homozygotes 680 mg/dl → if the patients inherited both genes he would have 3 times higher than normal cholesterol level.

Heterozygotes 300 mg/dl → not that very high

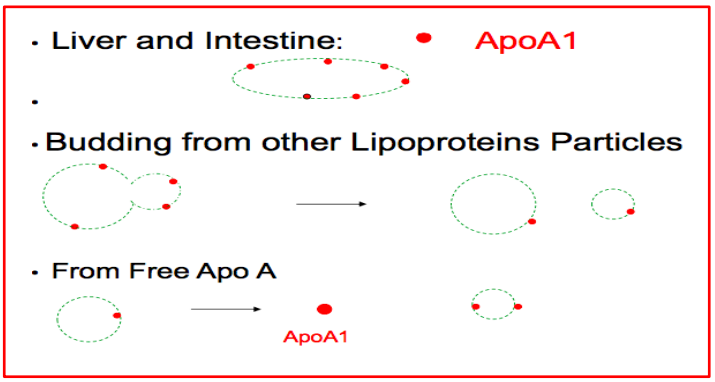
Cause: Absence of LDL receptor <u>OR</u> Abnormal Receptor (can't accept endocytosed LDL). Homozygotes: No Receptors

Heterozygotes: at least ½ of Normal Number

- Accumulation of IDL, more IDL→→more LDL → Cholesterol deposition in tissues. <u>HOW??</u> LDL remains in the circulation for longer periods of time so it will be taken by scavenger receptors of tissues which accumulate under the endothelium. This leads to **atherosclerosis in an early age**, death in childhood, or for example death at less than 20 years due to MI (it's abnormal to die by MI at an early age).

Good cholesterol (cholesterol carried by HDL)

HDL is a carrier of cholesterol, it originates from the liver and the small intestine as a protein called apolipoprotein A-1, which is released into the blood and requires phospholipids. How the particle is formed is not very clear. What is clear is that 1po A1 is produced in the liver and released in the plasma and then HDL will be formed in the blood.



Function of HDL: <u>Reverse transport of cholesterol</u>

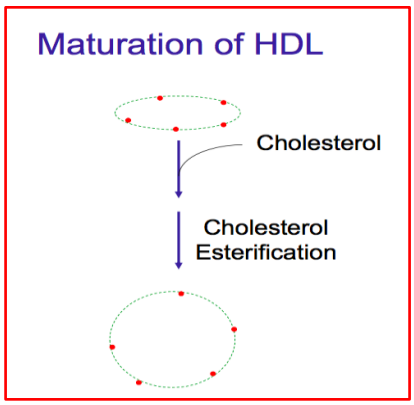
HDL takes cholesterol from foam cells **in the vascular tissues** <u>or</u> **in other tissues** and transports it to liver. Remember that LDL transports cholesterol from the liver to different tissues, where it is taken by foam cells **<u>if</u>** it got modified or damaged.

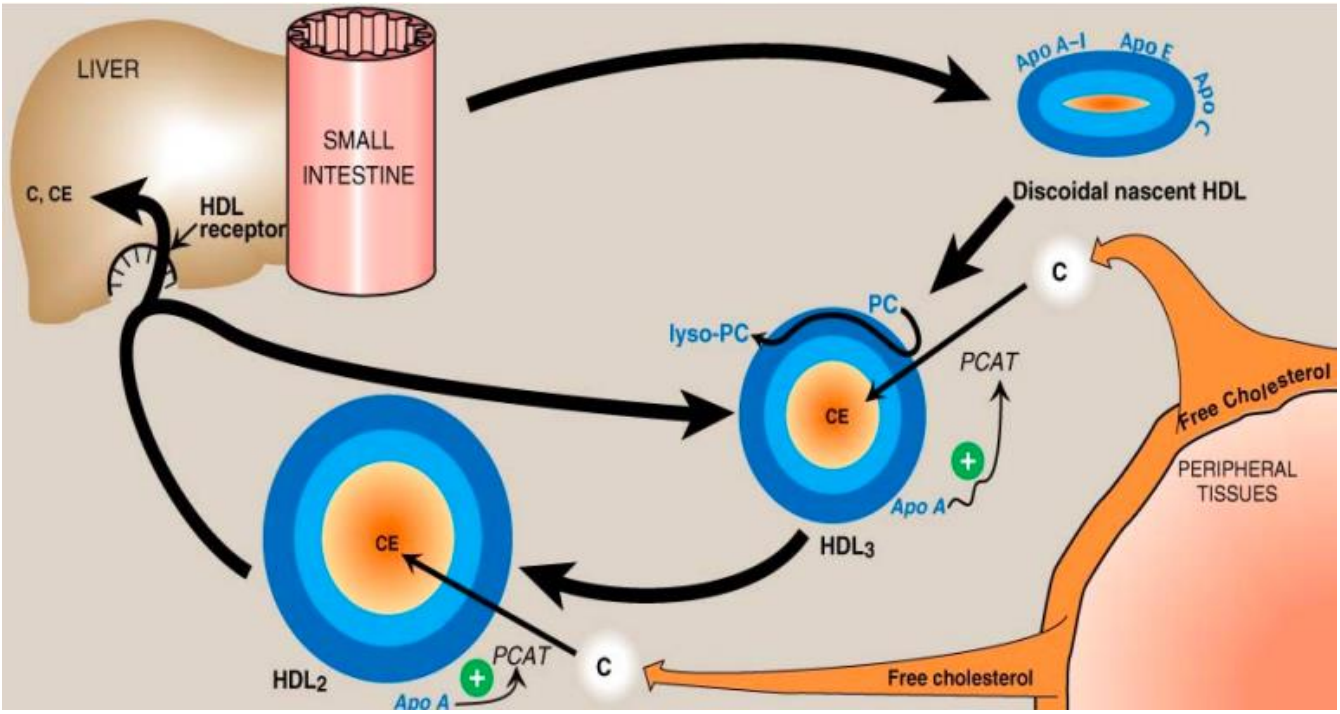
- **Direction of movement:** cholesterol is found on the membrane, and in order to be taken in, it has to move from the inner leaflet to the outer leaflet → this is the role of **ABC 1 protein [ATP Binding Cassette]**.
- ABC proteins are responsible for transport of substrates across membrane.

- **Esterification of cholesterol:** as cholesterol gets esterified, it no longer exists on the HDLs surface, instead it is trapped inside the core of HDL.

  Cholesterol + lecithin $\xrightarrow{\text{LCAT}}$ cholesterol-FA [CE]

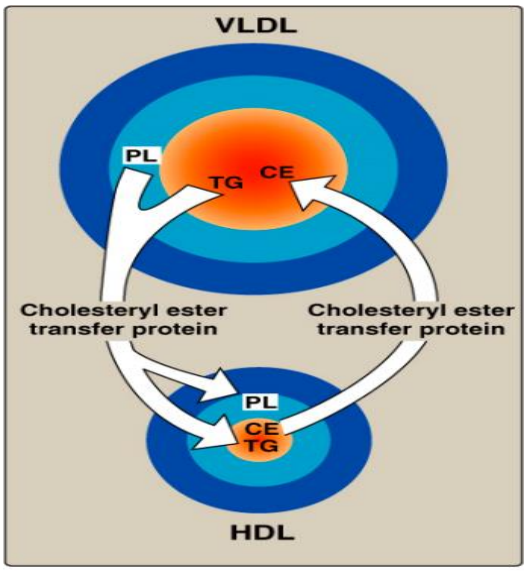
  The shape of the particle **becomes spherical** instead of discoid because CE is in its core.





- Newly synthesized HDL that came from the liver and small intestine containing cholesterol is called **discoid nascent HDL**.
- Free cholesterol is taken from peripheral tissues by HDL.
- The enzyme <u>LCAT in HDL particles that require apoA as an activator,</u> catalyzes the conversion of C into CE [phosphatidyl choline will give lisophosphatidylcholine]. **ABC proteins** transport CE To the core.
- very little cholesterol was in the core, and now it is replaced by cholesterol ester, large **HDL3 particles (full of CE)**.
- HDL3 is converted to a larger particle called **HDL2. HDL2 exchanges contents with VLDL** and ends up being **HDL3 again** *(discussed below)***.**
- The rest of the HDL2 molecules can bind to **Scavenger Receptors Class B1** that are found in the liver, HDL2 delivers cholesterol inside cell <u>without getting inside</u> the cell cholesterol is taken into different tissues through foam cells.
  That is why high level of cholesterol in HDL is a good sign. In females, the level of HDL cholesterol is higher than it is in males. Therefore, **females have lower risk of getting MI** especially when they are young.

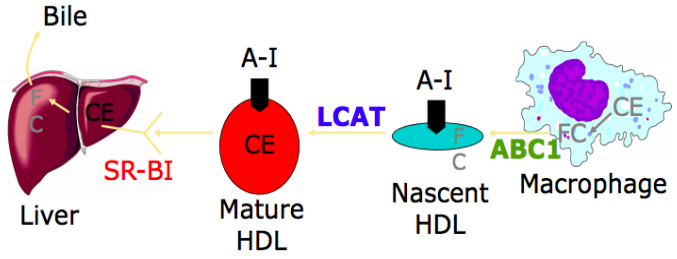
Exchange of Cholesterol ester



Within the plasma, there is an exchange of CE with TAG from HDL2 to VLDL.
Then, the newly synthesized VLDL becomes LDL and ends up in tissues or the liver.

WHY exchange?
To prevent product inhibition of an enzyme that is carrying on the esterification. CE can act as an inhibitor, and when it moves to different particles such as VLDLs, it's no longer an inhibitor.

Fate of HDL cholesterol



ABC1 = ATP-binding cassette protein 1;
A-I = apolipoprotein A-I; CE = cholesteryl ester;
FC = free cholesterol; SR-BI = scavenger receptor class BI
LCAT = lecithin:cholesterol acyltransferase;

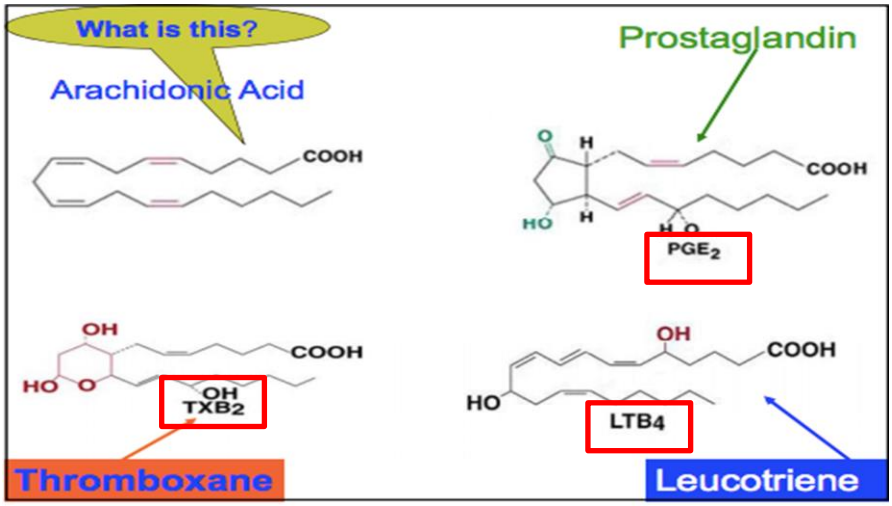
- Uptake by liver; binding to specific receptor on hepatocytes (HDLRs).
- Transfer of cholesterol into cells scavenger receptor **SR-B1**
- found on many cell types
- Can be **upregulated** if cholesterol is needed
- **Not down regulated**
- Interaction with other particles (exchange)

Bear with me through this part, the following 3 pages are mostly pictures, not many things to memorize

Eicosanoids (Eicosa = 20)

Several Classes of Signal Molecules: Prostaglandins, Thromboxanes, Leukotrienes:

- Synthesized in the form of a 20 carbon FA that is **unsaturated**
- Produced in Almost **all Tissues**
- **Wide Range of Responses**
- **Local Hormones:** produced in cells and affect neighboring cells, they don't circulate in the blood like other hormones.
- **Very Potent:** active at very low concentrations
- **Short Half Life:** rapidly degraded
- **Not Stored:** synthesized in response to some signals and released directly

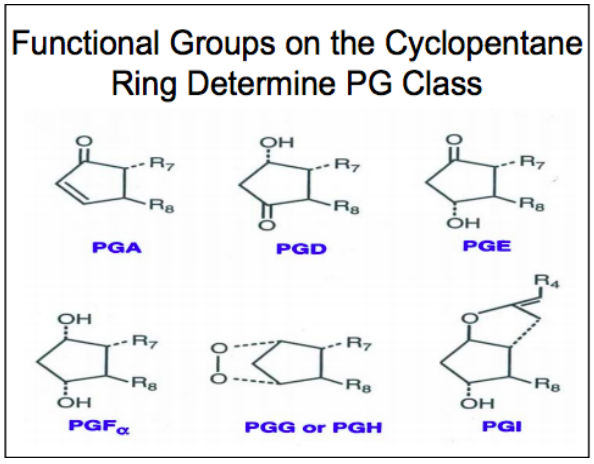


Arachidonic acid or EICOSATETRANOIC acid: **20 carbons, 4 double bonds (polyunsaturated FA).** *Eicosanoids structures are related to arachidonic acid*.

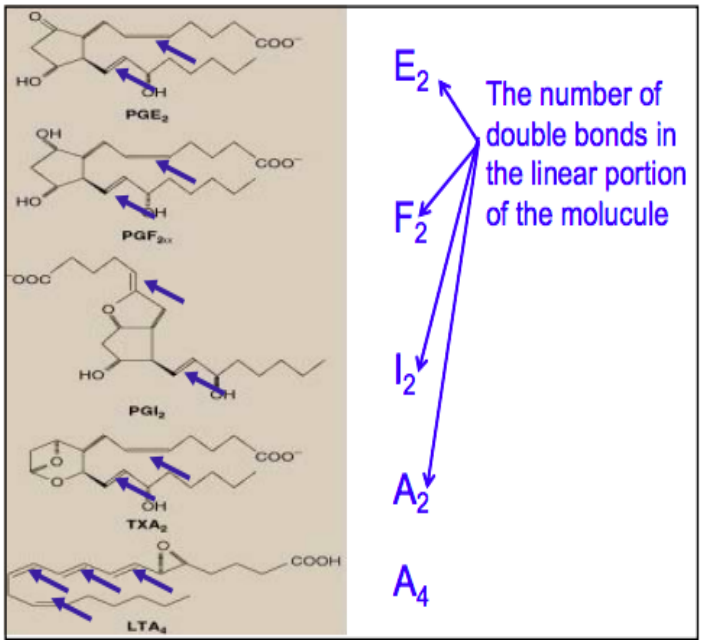
Thromboxanes: 6-membered ring, one of the molecules is **oxygen** in the ring.

Leukotrienes: no ring, **3 conjugated** double bonds (alternation of double-single bonds) and hence the name tri---3; enes---double bonds.

Prostaglandins: 5-membered ring called **cyclopentane**



- There are several classes of PGs that differ in the functional group on the 5-membered ring. Each class is synthesized by a different enzyme, so whether the hormone is synthesized or not depends on the presence of the hormone. *we are not required to know the classes.*
- The number at the end of a PG name indicates: **How many double bonds are in the linear portion** *(see the figure below)*



The last one is **LK-A4**: all linear with 4 double bonds

Functions of Prostaglandins and Thromboxanes

PGI_2, PGE_2, PGD_2

- Increase
  - Vasodilation, cAMP
- Decrease
  - Platelet Agregation
  - Leucocyte Aggregation
  - Lymphocyte Migration

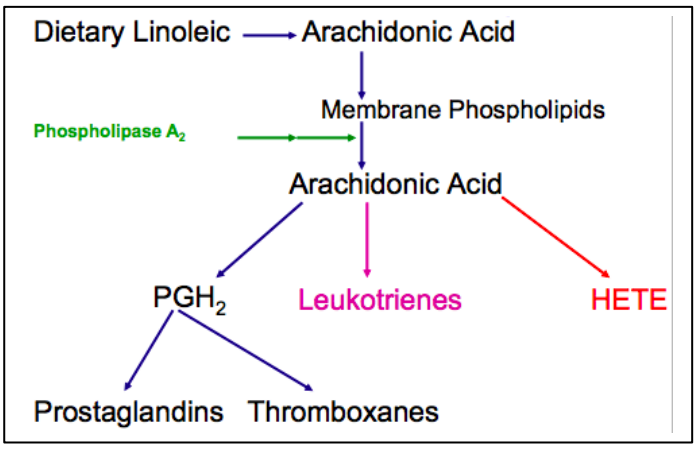
$PGF_{2\alpha}$ Increses
- Vasoconstriction
- Bronchoconstriction
- Smooth Muscle Contraction

Thromboxane Increases
- **Vasocostriction**
- **Platelet Agregation**
- **Lymphocyte Proliferation**
- **Bronchoconstriction**

NOT FOR MEMORIZATION. Very different functions, some are related to inflammation. Just know that they affect many things and their **effects may contradict each other**: TXs increases platelet aggregation, PGs decrease platelet aggregation.

Overview of Eicosanoids synthesis

1- dietary phospholipids are converted into arachidonic acid, which gets incorporated into membrane phospholipids.
2- By the action of **phospholipase A2,** FA at number 2 is released.



3- When arachidonic acid is released, it will **rapidly be converted into LKs, HETE (HYDROXYEICOSATETRANOIC), or PG-G then PG-H2 then different PGs, and TXs.**

- The **rate limiting step is the release of arachidonic acid**.

Inhibition of arachidonic acid release

- Steroids inhibit release of arachidonic acid by inhibiting phospholipase A, thus inhibiting PGs synthesis → ANTI-INFLAMMATORY.
- Nonsteroidal ANTI-INFLAMMATORY: aspirin; acetylation of COX OR irreversible binding to the enzyme. This is the basis of **low dose aspirin** (100mg daily); aspirin inhibits platelet aggregation by inhibiting TX synthesis.

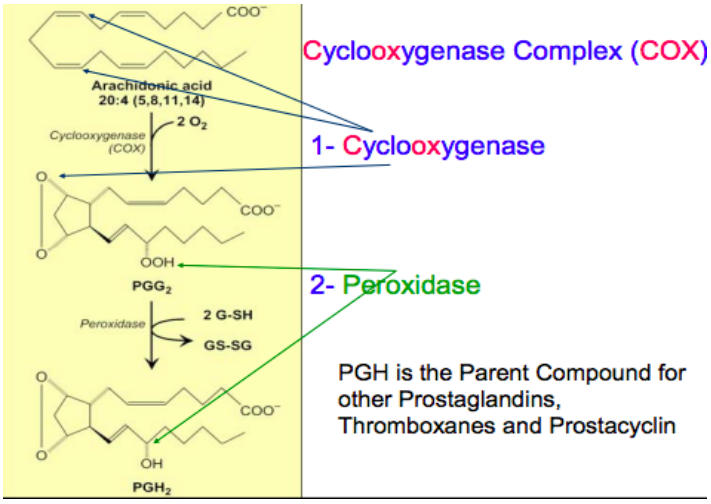
Cyclooxygenase complex

(includes cox and peroxidase)

COX catalyzes the formation of the ring

Cyclo→ causes formation of ring

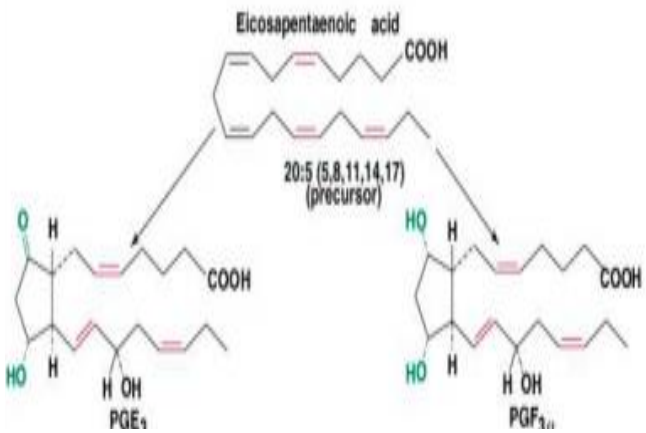
Oxygenase→ introduces oxygen to substrate (depends on presence of oxygen)



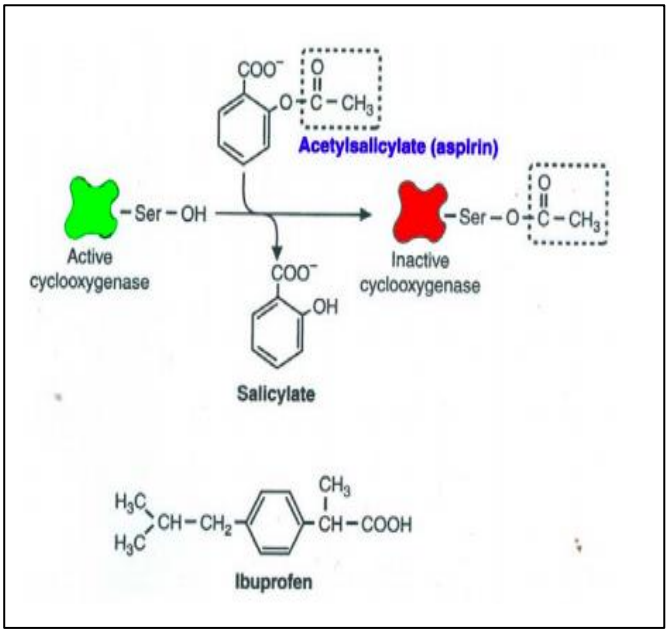
If synthesis is started with EICOSA**TETRA**NOIC (arachidonic) acid which has 4 double bonds, 2 of them will remain in the linear portion resulting in the series of 2.

If synthesis started with EICOSA**TRI**ANOIC which has 3 double bonds, only one double remains in the linear portion resulting in the series of 1.

If synthesis started with EICOSA**PENTA**NOIC acid **[20:5 (5,8,11,14,17) → omega-3]** as a precursor, the resulting series of PGs would end in number 3. Some of these PGs are inhibitors of platelet aggregation, that's why omega-3 has an important role in preventing MI due to inhibition of platelet aggregation.



These are slides that weren't mentioned in detail by the doctor

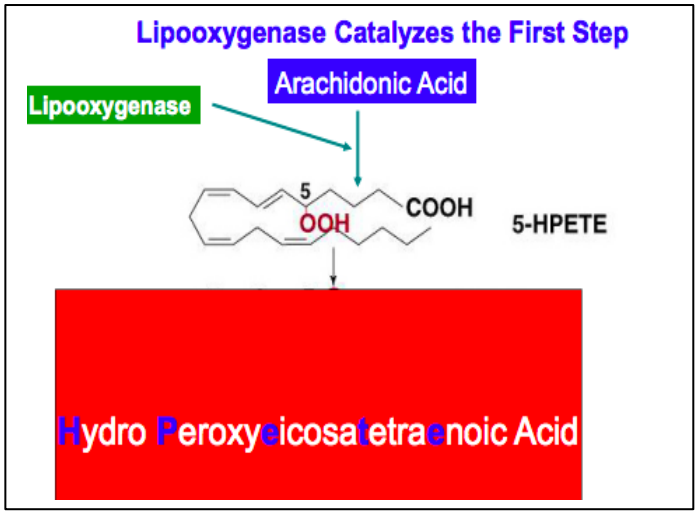


Leukotrienes and (LT) Hydroxyeicosatetraenoic acid(HETE)

- Signal Molecules
- Produced from Arachidonic Acid
- Linear Molecules; No Ring
- LT Contain 3 Conjugated Double Bonds

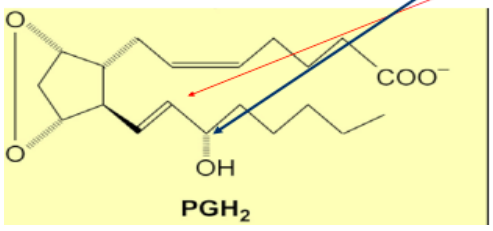
Cyclooxygenase exists in two Forms

- Cox 1
  - Constitutive
  - Gastric Mucosa, Kidney, Plateletes
- Cox 2
  - Inducible; in Response to inflamation signals
  - Monocytes, Macrophages, Smooth Muscle



Inactivation of Prostaglandins

Rapid
Oxidation of Hydroxyl group at C15
Reduction of Douple bond at C13



Please refer to that last 2 slides/ pages, Lippincott