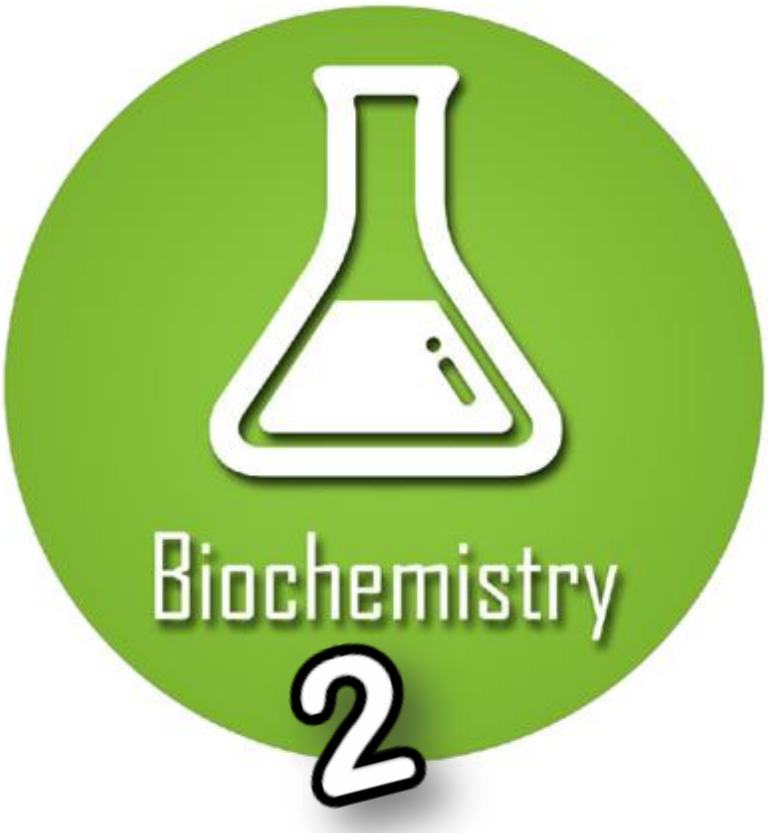

◉Sheet ○Slides

Number: 18

Done by: Ahmad Fo2ad

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Subject: Glycolipids and Lipoproteins

Doctor: Faisal Al-Khateeb

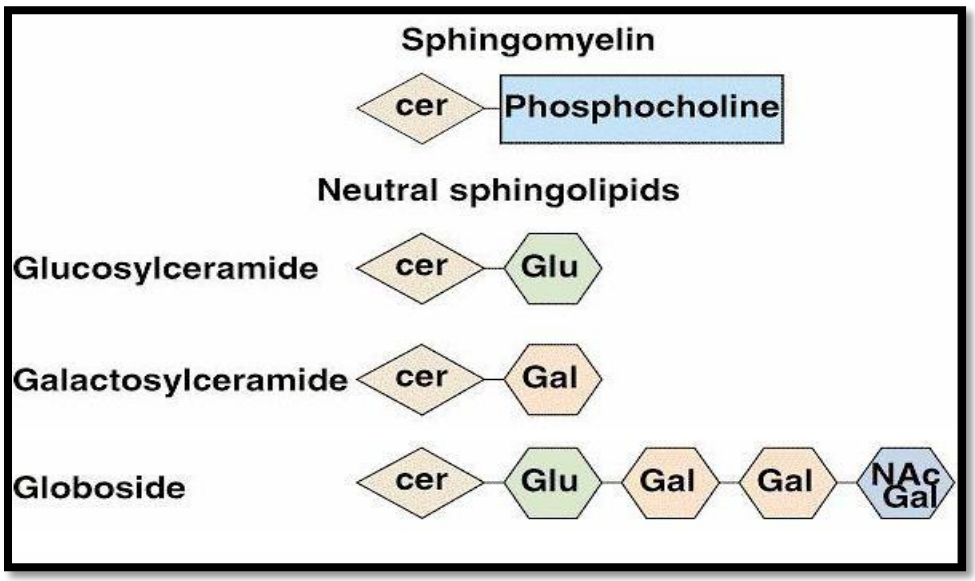
9/12/2015

Overview :

Glycolipids are composed of Ceramide that is connected to **one** sugar or **oligosaccharide.**

If ceramide is connected to one sugar, The sugar could be either *glucose* or *Galactose* .

If ceramide is connected to oligosaccharide, the oligosaccharide is *Glucose-Galactose-Galactose-NAcGal.*

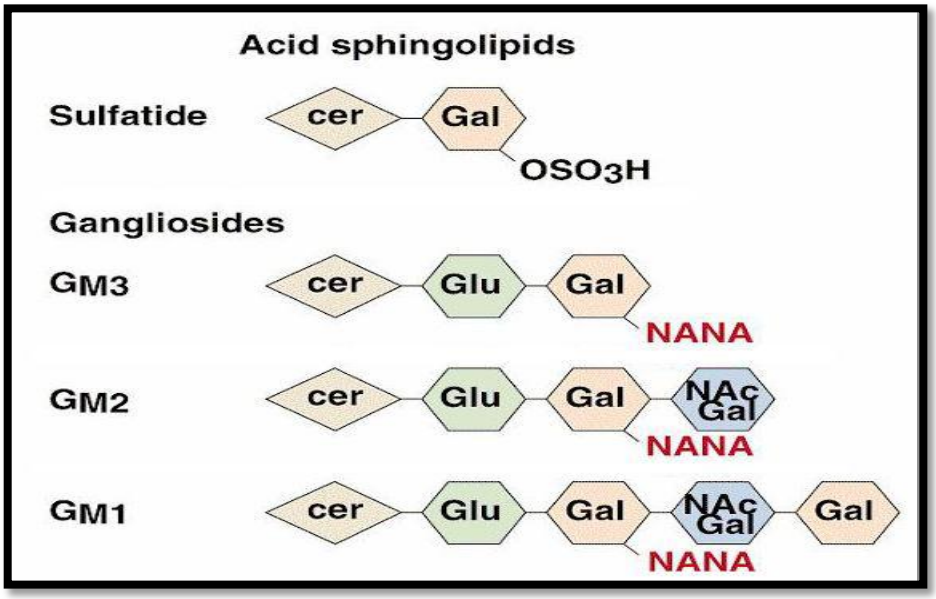


These are <u>neutral sphingolipids</u>, Since there is no charge on the carbohydrates.

Some sphingolipids have Galactose that is connected to *sulphate group*, the sulphate group is negatively charged, So it is **<u>Acidic sphingolipid</u>**. The presence of the negative charge(in the polar head portion) allow it to interact with other molecules in the membrane, Usually these are found outside in the outer leaflet of the membrane. Or galactose may be connected to N-Acetylneuraminic Acid (NANA). Which is from its name indicates that it contains –Ve charge. These sphingolipids which contain NANA are called *Gangliosides.* Gangliosides are known with different names. GM1,Gm2,GM3.

G= Ganglioside M= mono(because it has one NANA)

1,2 and 3 = are the sequence.



conclusion: Nuetral sphingolipids→ contain no charge.

Acidic sphingolipids → contain either Sulfate or NANA.

Review is over

Synthesis of sphingolipids

1-addition of sugars

Synthesis occurs by adding one sugar at a time. However , the sugar is not added as a single molecule , it must be activated .

General rule : the activated form of sugar is **UDP-sugar** (UDP is the universal donor of sugars , remember glycogen , lactose and glycoproteins synthesis)

Exception : N- acetylneuraminic acid it's not attached to a UDP molecule, but it's attached to a CMP (cytidine monophosphate) so the final donor is CMP-NANA.

So , The sugar derivatives are: (the Active donors)

- UDP-**Glucose**
- UDP-**Galactose**
- UDP-**N-Acetylgalctoseamine**
- CMP- **N-Acetylneuraminic Acid** **(exception)**

This process occurs by specific enzymes called **glycosyl transferases** (they transfer sugars from the active donor form to the ceramide) .

Note : the **sequence** of sugars is determined by the **presence or absence** of a specific glycosylic tranferase . for example , if **galactosyltransferase** is found, **galactose** will be added to the ceramide, whereas if **glucosyltransferase** is found , **glucose** will be added , moreover these enzymes are specific to **the sugar molecule that's added** in addition to the **molecule to which the sugar molecule is added** (specific for donor and acceptor) .

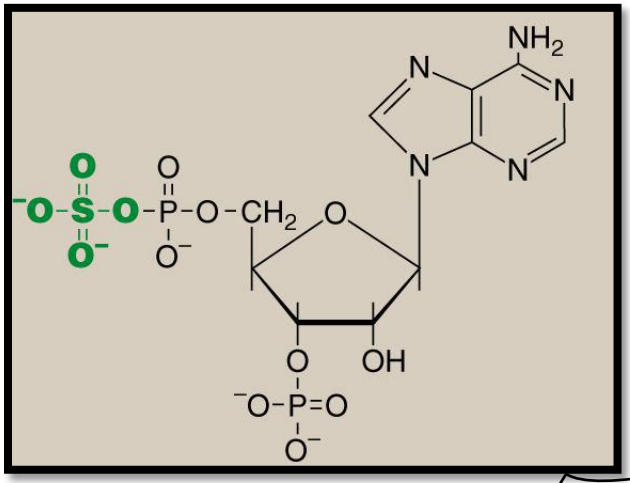
The strong question now , why to have so many enzymes to repeat similar reactions 4 or 5 times ? Why to have so many enzymes to make a molecule with 4 or 5 sugars?

A: Actually because they carry **important information** about the protein and about the interaction as we said (they are signaling molecules) .

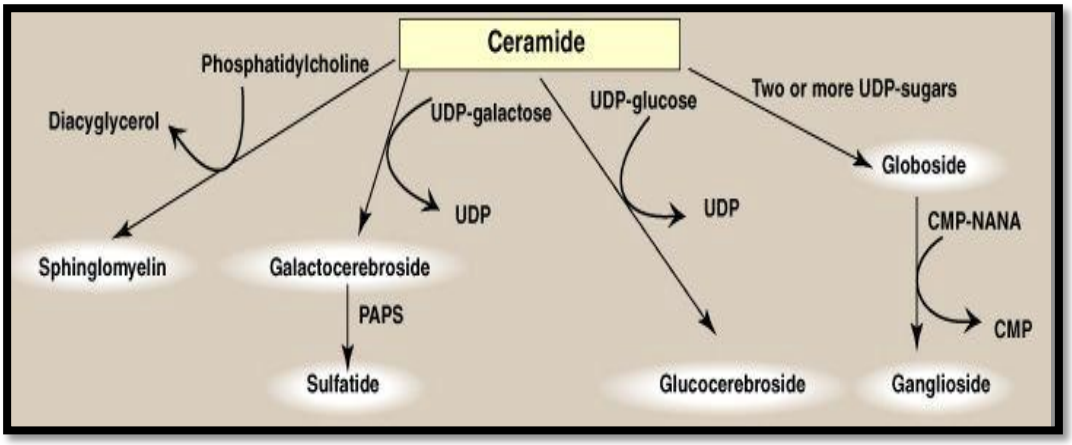
2- addition of sulfate groups :

We have also a Transfer of Sulfate Group to Galactocerbroside to Produce **Sulfogalatocerbroside** (Sulfatide).

The donor of sulfate group is **3-phosphoadenosine-5-Phosphosulfate "PAPS"** (it has adenine, ribose, sulfate, phosphate , as seen in the figure) it's similar to ADP but the group is **Phosphosulfate** rather than pyrophosphate, so it's the donor of sulfate, it also acts in the synthesis of glycosaminoglycans which have sulfated sugar.



Last but not least , we have a figure (seen in the next page) that summarizes the synthesis of various sphingolipids. Ceramide is the parent compound where we can add phosphocholine from phsphatydylcholine to produce sphingomylin. Or we can add galactose from UDP-Galactose to produce Galactocerebroside, and further addition of sulphate group produces sulfatide. we can add one sugar at a time to produce globoside, and further addition of NANA produces Gangliosides.



Degradation of sphingolipids

Degradation occurs by hydrolytic enzymes which catalyze the hydrolysis of the sugars, and they are **specific** for the sugar they degrade. These enzymes are found in the **lysosomes**, which degrade substances taken up by endocytosis.

Hydrolytic Enzymes

- α Galactosidase → galactose which is linked by α configuration
- β Galactosidase →galactose which is linked by α configuration
- neuraminidase → neuraminic acid
- Hexoaminidase → N-acetylgalactosamine)

So according to the sugar to be removed, there is specific enzyme.

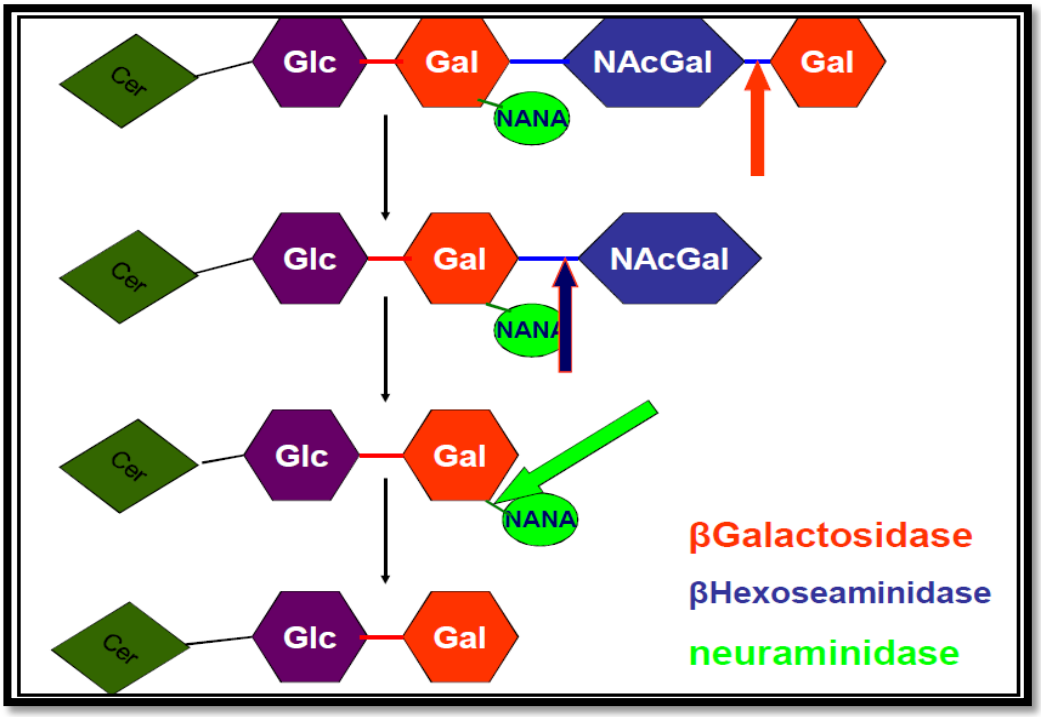
The enzymes are usually firmly bound to the **lysosomal** membrane.{they should be in the lysosomes, otherwise they will degrade the cell}. Since the lysosomal PH is acidic, these enzymes act better at low PH medium 3.5-5.5. This is important in regulation, if they are found outside the lysosome, they are no longer functioning. Degradation occurs by stepwise sequential process(step after step).

Here in degradation, the last one (sugar) to be synthesized (added) in synthesis is the first one to be degraded and vice versa. For example Cer- Gal-Gal-Gal-Glc (seen in the next page) . the last one to be synthesized here is Glucose therefore it will be the first one to be degraded, and the first to be synthesized is the galactose therefore it is the last to be degraded.

So , By the presence of β-galactosidase, it will remove the sugar by attacking the bond connecting it to the rest of the compound.

Then hexoseaminidase will act, then neuraminidase, then galactosidase, and finally glocosidase.

β-galactosidase→ hexoseaminidase→ galactosidase→ glocosidase



Previously, in GM1, GM2 and GM3 we said that the numbers refer to the sequence. And the shorter the chain, the higher the number it is given, that's because we call them according to the degradation pathway. The longer one is the one which comes the first in the degradation, so it is given number 1→GM1. The very next compound is given number 2→ GM2, and so on.

Sphingolipidoses

Actually synthesis isn't important from a clinical point of view because **any defect in synthesis will yield an individual that is not consistent with life**, whereas defects in degradation is important clinically because any problem will yield a family of disease called Lipid Storage Diseases

Spingolipidoses: are diseases of the lipids. Also called *Lipid storage diseases*.

There is either *total* deficiency or *partial* deficiency. In this case(deficiency) the absence of the enzyme leads to accumulation of specific lipid, Which is the substrate of the deficient enzyme.

The lipids will accumulate in the lysosomes→ accumulation in the cell→ the cell enlarges→ tissue damage→Cell death.

Lipid storage diseases are inherited as autosomal *recessive* diseases.

It is not dominant but recessive. If it was dominant→ if there is one defective gene, the disease appears. But it is actually recessive, which means if there is a defective gene → the disease doesn't appear, and the person is considered as carrier.

Why Sphingolipidoses/LSD (Lipid storage diseases) are recessive?

If there is problem in the gene, there will be a deficiency in the enzyme. And if there is only one gene is defective, and the other one is normal, this will lead to the synthesis of 50% of the enzyme amount. This 50% of the enzyme are sufficient to catalyze the degradation, because the degradation is very slow process. So **even low amount of the enzyme is present, it is sufficient to make the person normal.**

The **brain** is mainly affected, because the sphingolipids (cerebrosides, Gangliosides…etc) as their names imply, are rich in the brain. But also they are found in different tissues like RBCs. When RBCs die they only require 120 days to be regenerated. On the other hand, brain cells can't be regenerated. As a result the organ that is mainly affected is the brain. This will lead to mental retardation (sometimes appear early in children, when the extent of brain damage is high)

Degradation of sphingomyelin

Spingomylin = *(Ceramide + Phosphochline)* by the action of *sphingomyelinase* it is degraded to ceramide and phosphocholine.

Ceramide is also degraded by *ceramidase*, converting it into sphingosine and fatty acid.

There are 9 Lipid storage diseases→ related to deficiency in one of the enzymes of the degradation pathway of sphingolipids, the most important ones are:

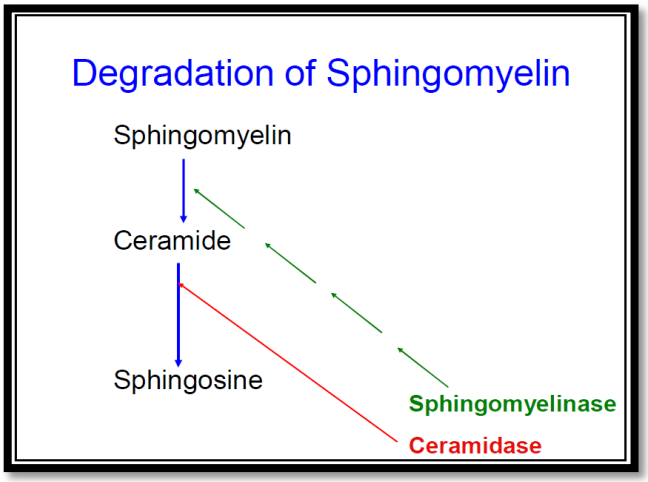
1-Tay-Sachs Disease (common)

2- Gaucher Disease (common)

3- Farber Diseas

4- Niemann-Pick Disease

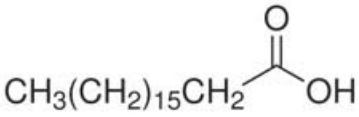
These diseases are very <u>rare.</u>



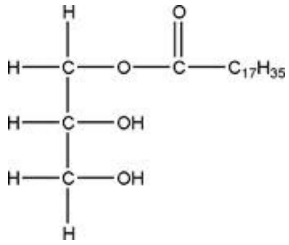
Digestion and Transport of TAG by Plasma Lipoproteins

The Digestion part is self-study, the doctor will give us hand out about this portion (you can refer to chapter 15 in Lippincott)

Transport of TAG by Plasma Lipoproteins

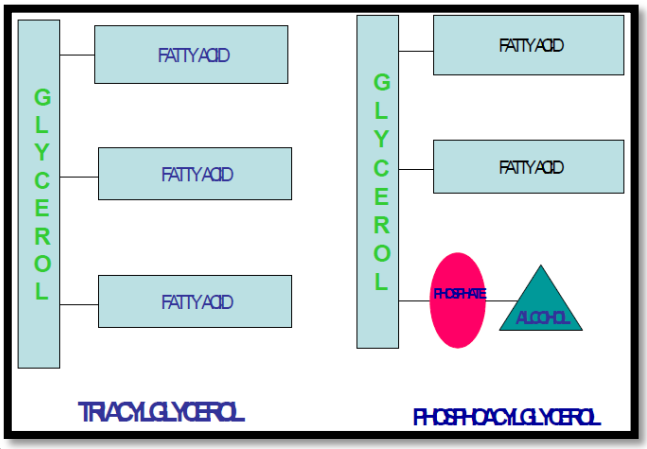


Fatty Acid ⇒ Found in the ionized form→ more soluble



monoacylglecerol ⇒ Not ionized→less soluble

When the fatty acid is joind to the glecerol by ester bond, the negative charge is no longer found→ the solubility of TAG is very poor(since it has 3 ester bonds→ no negative charge).



On the other hand, Phosphoacylglecerols are amphipathic molecules, they can form micelles, and they can enhance the solubility of lipid in water because of the presence of charges.

Lipoproteins

Lipoproteins: Multimolecular complexes of lipids and proteins.

Important note: There is no protein called lipoprotein. Lipoproteins are actually *aggregations of many lipids and proteins together.* Their function →transport lipids in the plasma.

The lipids of lipoproteins include:

- **TAG** Triacylglycerol
- **CE** Cholesterol Ester
- **CH** Cholesterol
- **PL** Phospholipids

TAG and Cholesterol ester→ insoluble(nonpolar)

Cholesterol and phospholipids→Amphipathic molecule

Apolipoproteins

•The protein portion of lipoproteins is called *Apo-lipoprotein*.

Apo prefix means protein with no nonproteinous part.

Ex: Apo-enzyme → means the protein part of the enzyme, whereas the enzyme may contain many parts other than the protein, such as coenzyme.

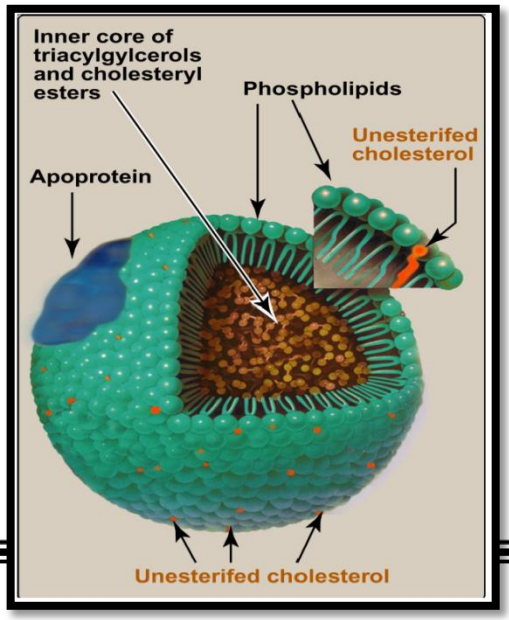
{*Conclusion*: apo-protein→ the protein part of the lipoprotein}.

• Amphipathic
• Include Several Classes Apo A, Apo B-48, Apo E..etc.
•It serves Structural Role {maintain the structure of the lipoprotein} Regulatory Role and Binding to Cell Surface Receptors.

The picture to the right represents Lipoprotein.

The Core(interior): contains TAG and Cholesterol ester because they are none polar(hydrophobic).

The exterior: contains phospholipids, unesterified cholesterol and the proteins.



To sum up :

1- Lipoproteins are aggregates of lipids and proteins, to make the lipids soluble. Lipids become soluble because the surface is completely hydrophilic.

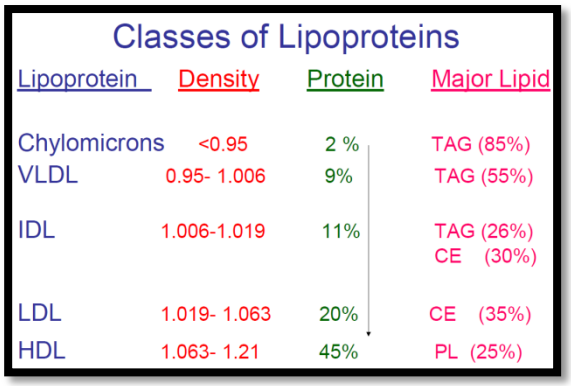
2- Lipoproteins structure is crucial for the transport of TAG and CE.

Classification of Lipoproteins

1- According to the type of lipoprotein.
2- According to the density(classical method used between doctors).

Based on their density, lipoproteins are classified into:

1- Chylomicrons
2- VLDL(Very Low Density Lipoproteins)
3- IDL(Intermediate Density Lipoproteins)
4- LDL(Low Density Lipoproteins)
5- HDL(High Density Lipoproteins)



Density= mass/volume. The density of water equals 1 g/ml. anything that has density above 1 will sink, and anything that has density below 1 will float.

The highest density lipoprotein is HDL(1.21), while the lowest density is for chylomicron(<0.95).

The reason why they vary in their density is that they differ in the *protein/lipid ratio*. {Higher % of proteins→the density increases}{Higher% of lipids→the density decreases}, this is because the lipids have lower density than water, lipids float on water.

The higher the protein content the higher the density , and vice versa. (Refer to the picture above).

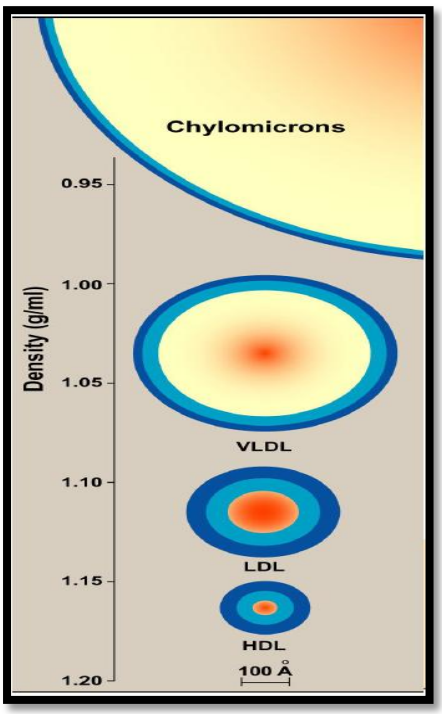
What are the major lipids carried in these lipoproteins ?

- The major lipids of chylomicrons and VLDL are TAG.
- The major lipids of HDL are phospholipids 25%. Notice that phospholipids are found in the surface, and the proteins

45% are also found in the surface, by addition 45+25=70%, so 70% of the components of HDL are surface components.

General rule: When the percentage of the surface components is higher, the volume decreases. Here we are talking about the relative size which means the volume compared to the surface area, the higher the surface area the lower the relative size.

(The doctor mentioned the watermelon **example** here, if we have 1 large watermelon which weighs 12kg and 4 smaller watermelons each weighing 3kg, both cases have 12kg. So if we peel the watermelons, we'll find that the 4 small will produce more peel, therefore more surface area, so as the relative mass decrease the surface area increase and vice versa. The doctor gave another example about the surface area of adults and babies, which has a higher relative surface area, the answer is the baby because he has a lower volume/mass)



The picture to the right shows that the smaller the volume (e.g; HDL), the greater the surface component. And the larger the volume (e,g; chylomicron), the lesser the surface component.

Types of Apo-lypoproteins (apo-proteins)

Lipoprotein	Apo Protein Types	
Chylomicrons	Apo B, Apo C, Apo E	Dietary Lipids
VLDL	Apo B, Apo C, Apo E	Endogenous TAG
IDL	Apo B, Apo E	
LDL	Apo **B**	Cholesterol
HDL	Apo **A**, Apo C, Apo E	Cholesterol Return to Liver

Only memorize the following:

- Apo A is only found in HDL
- LDL contains only Apo B
- Apo B is found in all lipoproteins except HDL

The **function** of each Lipoprotein:

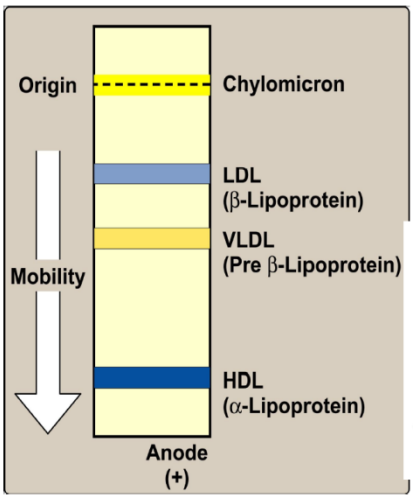
Chylomicrons: transport of **dietary lipids**. After digestion and absorption of these lipids into the intestinal cells, they will form chylomicrons.{90% of chylomicron is composed of TAG, so clearly they function in the transport of TAG).

VLDL: transport of **endogenous TAG** that is synthesized in the body(liver).

LDL: transport of **cholesterol**. (LDL is composed mostly of cholesterol, so clearly it functions in the transport of cholesterol).

HDL: transport of **cholesterol bach to the liver**.

To separate lipoproteins according to their density, we require expensive instruments. But we can separate them easily- Cheap way- by electrophoresis(movement in electrical field). We can see the proteins of plasma (albumin and globulins) by using stains that are specific for the proteins. On the other hand, if we use stains that are specific for the lipids, we can see the lipoproteins.



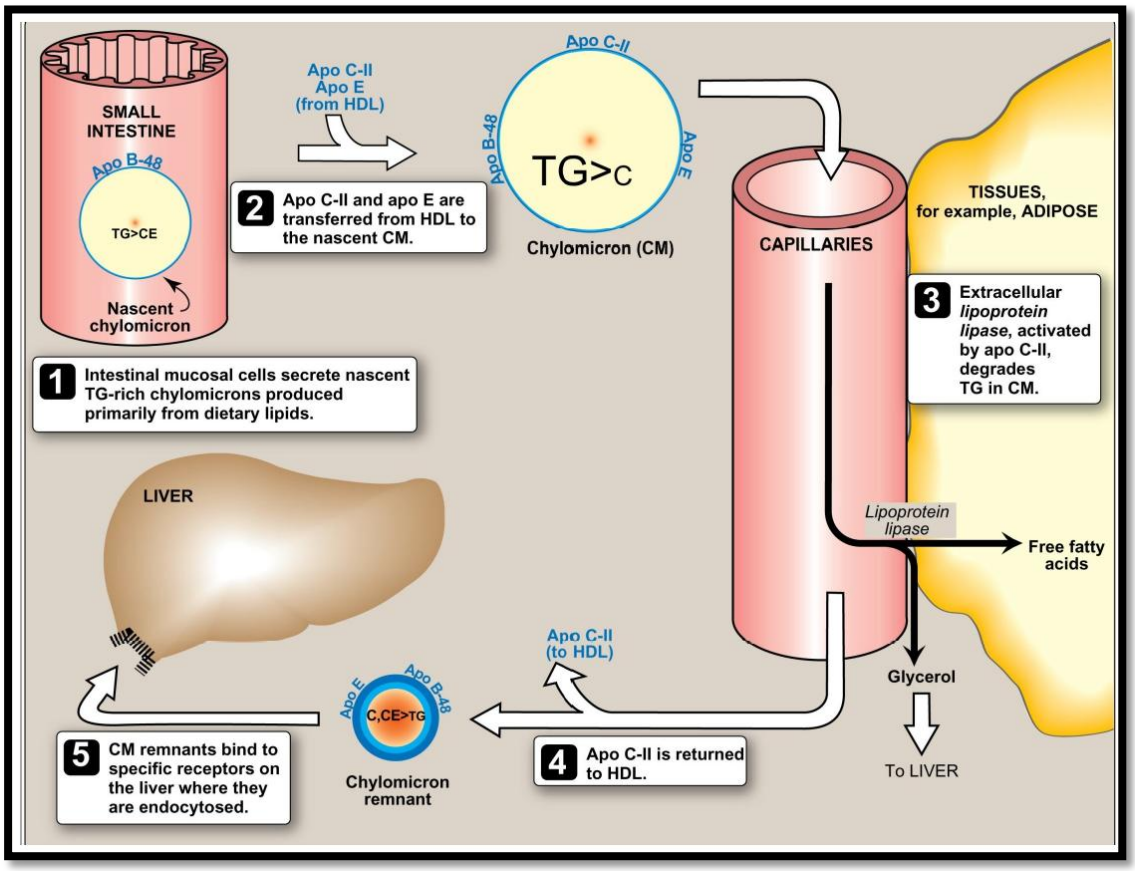
The lipoproteins are put at the cathode (-) site, and they will move in the downward direction toward the Anode (+). The mobility is due to the charge of the proteins in lipoproteins (notice that lipoproteins carry charges , even though they contain high amount of lipids . Because , at least , each protein carry two charges , due to ionization in aqueous environment) .

- Chylomicrons: Don't move→because protein content is low.
- HDL (also called α-Lipoprotein): the fastest, and migrates the furthest.

- VLDL (also called **pre**β-Lipoprotein): slower than HDL. {Note: pre means in precedes the β lipoprotein}.
- LDL: slower than VLDL.

Important note: Mobility is not totally based on density, since VLDL precedes LDL. It is based on charge/mass ratio (charge depends on the type of proteins in the lipoprotein).

Pathway of Dietary TAGs



Digestion (breakdown) of dietary lipids (e.g TAG) occurs in the GI tract, then they are absorbed into the intestinal cells. The TAGs that are hydrolysed by a lipase are resynthesized in the intestinal cells. Hydrolysis of TAGs produces fatty acids and produces monoaclyglecerols, they are joined together to reform triacylglycerol, these TAGs that have been resynthesized in the intestinal cells, need to be transported to different tissues. They can't be transported as such, because they are insoluble in water, therefore there must be chylomicrons to transport them. Chylomicrons are synthesized in the intestinal cells.

The chylomicron is formed by phospholipids and Apo B-48, together they form the chylomicron (called Nascent Chylomicron).

Chylomicrons(CM) are large particles , so they can't be released directly to the capillaries, otherwise it will block the capillaries. Instead, **they are released to the lymphatic system**, and from the lymphatic system to the blood through a large vain which is the subclavian→ inters the circulation.

In the blood Apo C-II, and Apo E are transferred from HDL to the nascent CM.

- If we isolate serum from the blood → it is transparent
- If serum contains high quantity of CM → Milky appearance, you can't see through it.

Chylomicrons will be transported through the blood to different tissues. In the capillaries of different tissues, there are enzymes called *lipoprotein lipase*. This lipoprotein lipase is extracellular enzyme that is attached to the endothelial cells of the capillaries. The substrate of this enzyme is TAG that is found in the chylomicrons. Lipoprotein lipase requires Apo C-II as an activator. Lipoprotein lipase hydrolyzes TAG into free fatty acids and glycerol, free fatty acids enter directly into the cells. {Note: Lipoprotein lipase acts on TAG in chylomicron not any other part of chylomicron}. Lipoprotein lipase is extracellular enzyme, it acts on TAG in the capillaries, fatty acids will enter the cells but chylomicron remains in the capillaries, since they are large.

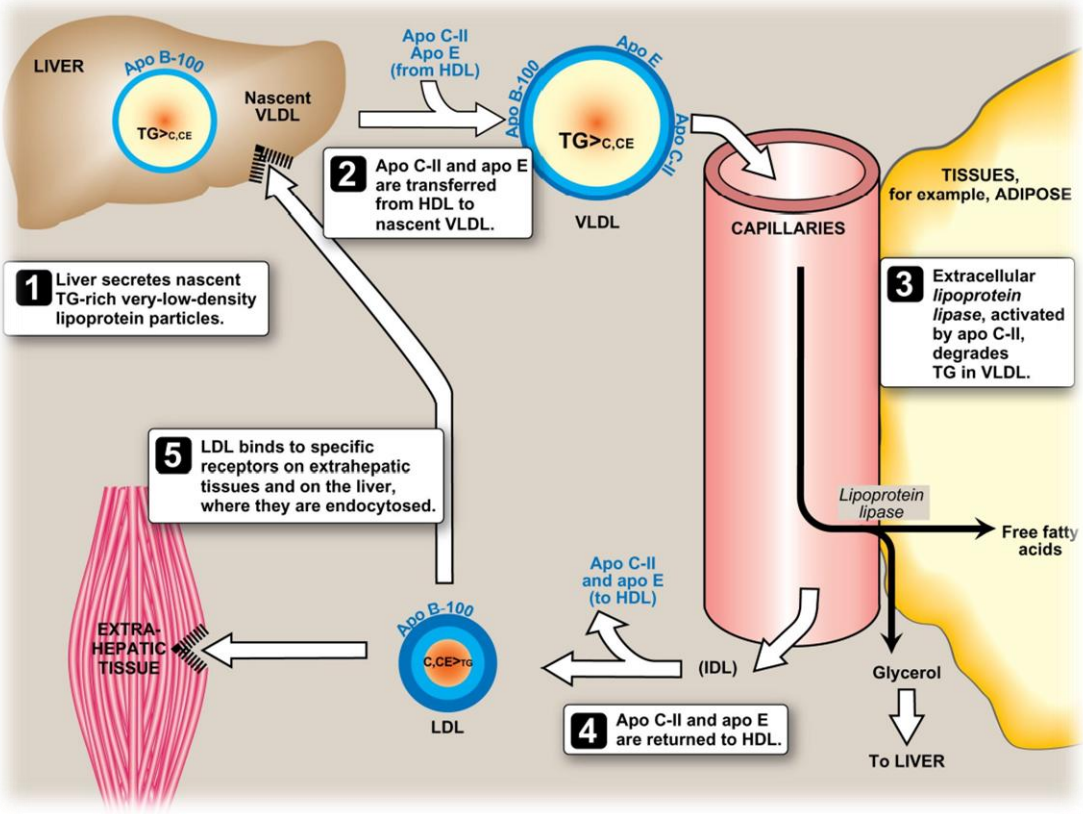
Consequences of the action of Lipoprotein lipase on chylomicrons:

- The amount of TAG is greatly reduced TAG< CE. Henceforth it is termed to as Chylomicron Remnant.
- Apo C-II will return back to HDL

Apo B-48 and Apo E will bind to cell surface receptors on the liver cells. Apo E is required for this binding. So chylomicron remnant reaches the liver, carrying mainly cholesterol.

Pathway of TAGs synthesized in the liver

Same things go with VLDL. But VLDLs are synthesized in the liver. Not from the small intestines as in the case of CM.



- Function: Transport of TAGs <u>synthesized in the liver</u> itself.
- It is released <u>directly</u> into the blood.
- It takes Apo C-II and Apo E from HDL.
- Travel through the capillaries.
- TAGs are acted on by *lipoprotein lipase*.
- After losing great quantity of TAGs→ it becomes IDL then LDL.
- Apo B-100 is the Apo-lipoprotein that remains, they are taken by the extra-hepatic tissues and the liver. {so they carry cholesterol to different tissues and to the liver}.

Done by: Ahmad Fo2ad

Sorry for any mistake

The End ☺ ☺ ☺ ☺