



SHEET NO. 18



METABOLISM

DOCTOR 2019 | MEDICINE | JU

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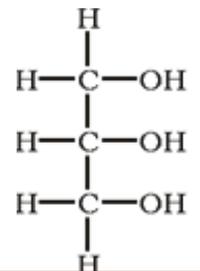
These topics are covered in chapters: 15, and 18.
ENJOY 😊

In this lecture we will talk about four main topics:

- Introduction about plasma lipoproteins.
- Digestion of dietary lipids.
- Digestion of TAG with short/medium chain fatty acids.
- Metabolism of sphingolipids.

on the right you can see the structures of:

- **Glycerol**, have 3 hydroxyl groups, thus it is polar.



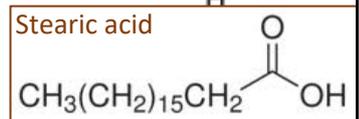
- **Stearic acid** (18 carbons fatty acid), has a hydroxyl group which is polar, in addition to the hydrocarbon chain which is non-polar, both make the acid

amphipathic.

(having both hydrophilic and hydrophobic parts), thus FAs can form

MICELLES due to their amphipathic property.

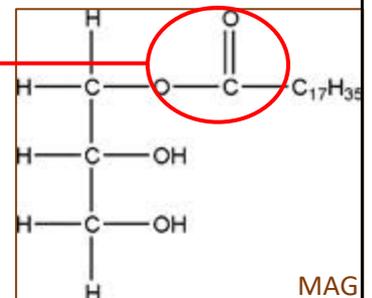
fatty acids are able to form micelles because they have the polar group.



- **MAG** (monoacylglycerol) shows Glycerol binding to 1 fatty acid (Stearic acid) through an **ester bond**.

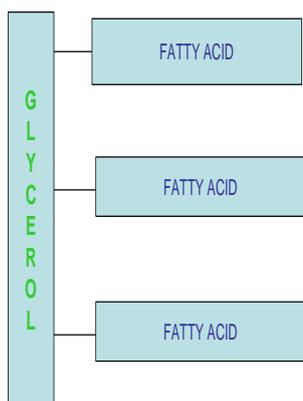
→ The **polar carboxyl group** upon ester bond formation, **loses** its polarity.

If 3FAs (fatty acids) bound to glycerol → TAG forms.

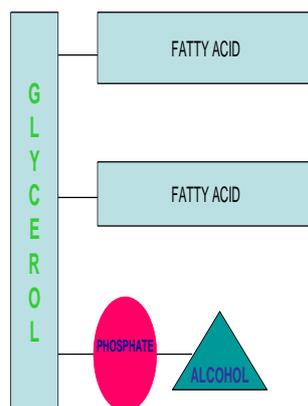


- **TAG** has 3 ester bonds thus it is: -completely non-polar. -insoluble in water.

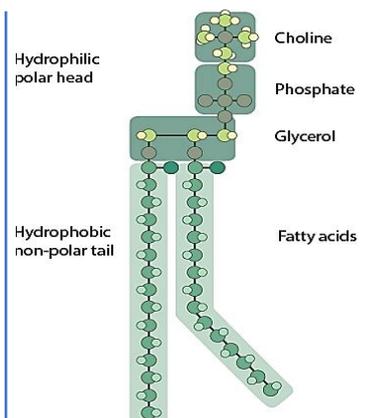
- **Phosphoacylglycerol/phosphoglyceride** has a hydrophilic polar head (alcohol and phosphate groups) and a hydrophobic non-polar tail, thus it is amphipathic, and can form micelles.



Triacylglycerol (TAG)



Phosphoacylglycerol/phosphoglyceride



INTRODUCTION ABOUT PLASMA LIPOPROTEINS

- ❖ Lipids are any biological molecule that is insoluble in water, non-polar, hydrophobic, and soluble in organic solvents. Lipids are not only fats or TAGs, they could be Steroid hormones, or cholesterol, or eicosanoids or CoQ.
 - ❖ How are lipids transformed from tissue to another?
 - Through plasma. But how, when lipids are hydrophobic and plasma contains 92% water?
 - Since lipids are hydrophobic and plasma is composed mainly of water, then there must be an agent which is soluble in plasma, that carry's lipids and transport them through plasma from tissue to another, such as; from small intestine (from where they are absorbed) to the targeted tissue.
- This agent is: **LIPOPROTEIN**

LIPOPROTEINS

❖ What are Lipoproteins?

Lipoproteins: Multimolecular (large number of molecules of lipids and proteins) complexes of lipids and specific proteins (**apolipoproteins**). They are distinctive in being amphipathic.

❖ Lipoproteins and Glycoproteins:

the bond connecting lipids with proteins is a NON-covalent bond,
the bond connecting carbohydrates with proteins is a Covalent bond (glycosidic).

❖ what is the function of Lipoproteins?

keeping their component-lipids soluble, while transporting them through plasma,

❖ Lipids (completely non-polar) of a lipoprotein, include:

- **TAG (Triacylglycerol)**,
- **CE (Cholesterol Ester)**,
- **CH (Cholesterol)**, free cholesterol has OH group, thus it has a small polar group, so it could be called amphipathic.
- **PL (Phospholipids)**, phospholipids have OH group, thus it has a small polar group, so it is called amphipathic.
- **And the polar group in both, cholesterol and phospholipids can interact with water.**

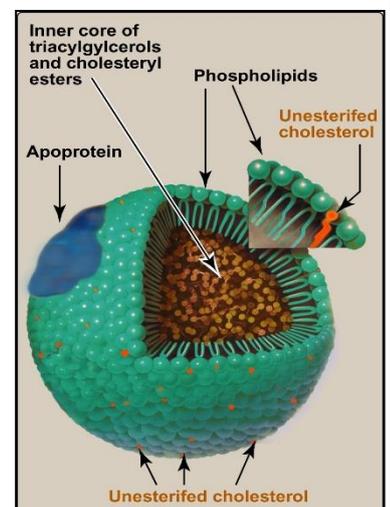
❖ Schematic representation of the lipoprotein particle, we can distinguish two types of components:

1. Surface component → a layer of phospholipids (green circle with two tails), which contains Free cholesterol (unesterified cholesterol).
2. Inner component → TAG and cholesterol ester and they are inside the core; because they are both hydrophobic.
3. Apoprotein → it is integral, and has two parts, one is on the surface (polar), and the other is interior in the core of lipoprotein, which is non-polar that interacts with the lipids in the core, thus they are amphipathic.

Micelle is not the same as Lipoprotein

→ Micelle is an aggregation of amphipathic molecules, forming a well-defined concentration.

→ Lipoprotein is a large group of complexes of proteins and lipids



APOLIPOPROTEINS

❖ What are Apolipoproteins?

the protein part of lipoproteins (The word APO in Apolipoprotein, represents the protein part of a complex lipoprotein). i.e., all of the structure, except the NON-protein part, is an Apoprotein

examples:

-transferrin is a protein that plays a role in transporting iron, the protein part of this transporter is an Apo transferrin/Apoferritin.

-the protein part of the enzyme.

❖ Apolipoproteins are **amphipathic**; thus, they are capable to interact with lipids and water.

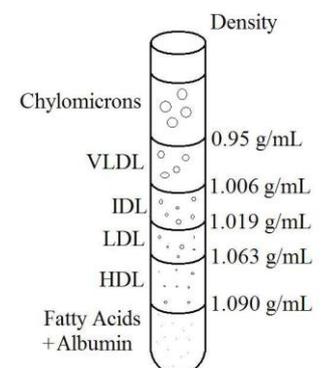
❖ They include **several classes** called: Apo A, Apo B, Apo B-48, Apo C, Apo E...

❖ Functions:

1. Structural Role: to maintain the integrity of lipoproteins,
2. Regulatory Role: they serve as activators or coenzymes for enzymes involved in lipoprotein metabolism,
3. Binding Role: Providing recognition sites for cell-surface receptors, for further purposes such as; getting into a cell, or transporting specific components to a cell.

Lipoprotein's lipid and protein composition, size and density explanation lipoproteins differ in ↑

- Lipoproteins circulate in the plasma, and they can be separated by **ULTRACENTRIFUGE**.
- **What is the principle of ULTRACENTRIFUGE?**
 - ULTRACENTRIFUGE separates components based on their **density**.
 - We put plasma in tubes and put those tubes in a machine that rotates at a very high-speed generating acceleration as high as 1,000,000 g (reaching gravity force and more). → Separating plasma lipoproteins by this method will separate lipoproteins into 5 major components, based on their density.
- Lipoproteins that are separated using ULTRACENTRIFUGE are:
 1. Chylomicrons.
 2. VLDL (very low-density lipid).
 3. LDL (low-density lipid).
 4. HDL (high-density lipid).
- Separating lipoproteins using ULTRACENTRIFUGE allows us to distinguish their density.



- What to know from this table?

- Chylomicron's density is less than 1 (density of water=1) thus it will float in water.

- LDL's density is like water or less a little bit.

- for each of them there is a range of density.

- What makes the density high in HDL and low in chylomicron?

→ the concentration of protein in the lipoprotein.

- If the protein percentage is high, then density is high; because proteins density is higher than fats and lipids (مثلا حطينا قطعة لحم اللي هي عبارة عن بروتينات، وقطرات زيت، في كوب ماء، ما الذي سيطفوا؟، الزيت سيطفوا لأنه أقل كثافة)

Higher protein percentage → Higher density

- chylomicrons have the lowest protein content because their density is the lowest on the other hand, HDL has the most protein content since it is high in density

- PL stands for: PhosphoLipid.

Lipoprotein	Density (g/ml)	Protein percentage	Major lipid
Chylomicrons	<0.95	2%	TAG (85%)
VLDL	0.95-1.006	9%	TAG (55%)
IDL	1.006-1.019	11%	TAG (26%)
LDL	1.019-1.063	20%	CE (35%)
HDL	1.063-1.21	45%	PL (25%)

Not for memorization, just know the points on the left

Composition of plasma lipoprotein:

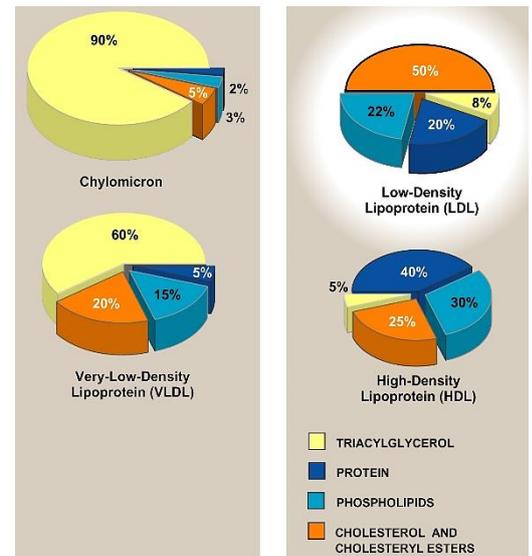
- Numbers in the previous table, help us in recognizing the composition of lipoproteins.

- percentages in the figure on the right, may differ a little bit from the table; because components can be variable and they have a wide range

- TAG is in the core of lipoproteins.

- Phospholipids are on the surface of lipoproteins.

→ so there are surface (phospholipid and Apoprotein and cholesterol) and core (TAG) components.

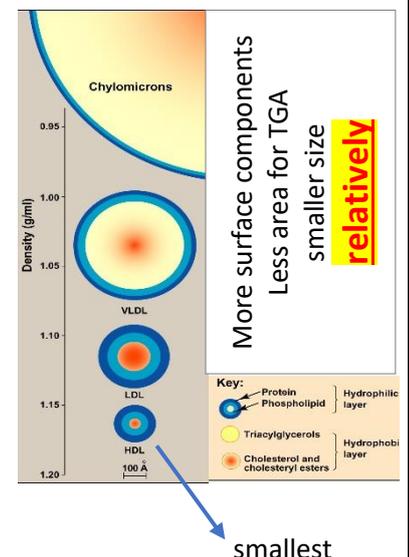


What is the relation between surface components (PL, CH) percentage and the overall size of the lipoprotein?

→ increasing PL percentage, will **relatively** decrease lipoprotein's size. HOW?

when surface components are **relatively** high in percentage → more phospholipids, smaller size

i.e., A large, 12K watermelon, and 4 others small, 3K watermelons, which of the two groups has more surface



components than core components **relatively**?

Answer: smaller ones.

The apolipoprotein part:

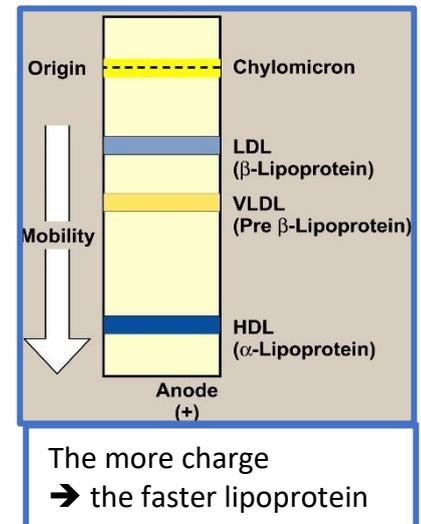
- **Apo B** is found in all except in HDL.
- **Apo A** is only found in HDL
- Function:
 - **Chylomicrons**: Dietary lipids: responsible for delivering dietary lipids for different tissues.
 - **VLDL**: endogenous TAG: they transport endogenous TAG
 - endogenous: TAG synthesized in the liver (major place to synthesis TAG from excess carbs).
 - exogenous: TAG obtained from diet, transported from small intestines to different tissues.
 - **LDL**: cholesterol: transport cholesterol to tissues, resulting in high cholesterol percentage in tissues.
 - **HDL**: to transport cholesterol back to the liver from different tissues, where it will be converted into bile acids. Also, it acts as a circulating reservoir of Apo C and E.

<u>Lipoprotein</u>	Apo Protein Types	function
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
مش مطلوب نحفظه لأنه مع نهاية المادة رح نلاقي حالنا حافظينه		

- Now, after understanding density and protein composition and size, let us watch the response of lipoproteins under electrophoresis:
- We use electrophoresis because; it is **cheap** and **effective** for daily/laboratory use/**routine** separation, unlike Ultracentrifuge.
- **Electrophoresis Separation is based on charge and size** rather on density,
- any type of electrophoresis can be used either; serum-protein electrophoresis, or plasma-protein electrophoresis.
- Process of separating plasma proteins in electrophoresis: you put a sample of plasma on a filter paper and put it in an electric current. we use a buffer PH more than 8.5, so almost all proteins have negative charge. They start running on the electrophoresis, proteins will migrate to the positive electrode (anode). After this, we use a dye that specifically color the lipid, so we can visualize lipoproteins.
 - more negative charge → faster running toward anode.
- so, the mechanism of regular separation in electrophoresis, is the same in lipoproteins separation **but the only difference is** that we need specific stain that

stain lipids rather than proteins.

- → chylomicrons
although they are negative, they remain at the origin and do not move; Because they are too big, thus relatively they pose little charge (since charge is on proteins, and proteins percentage in chylomicrons is too little, thus charge: mass ratio is small)
 - LDL
β-Lipoprotein.
 - VLDL
pre β: a little bit faster than LDL. (the reason isn't imp)
 - HDL
the fastest, called α-lipoprotein; because it comigrates with the α-fraction which is faster than β/preβ-fraction.



DIGESTION OF DIETARY LIPIDS

digestion is important for dietary lipids before absorption, those are the main reaction of digestion:



digestion of TAG involves hydrolysis producing 2FAs and MAG (glycerol that is esterified to 1 acyl group)



digestion of CE (cholesterol ester) involves the hydrolysis of the **ester bond** to produce one fatty acid and cholesterol.



Hydrolysis of TAG:

Digestion is hydrolysis reaction that:

- ✓ Occurs with water.
- ✓ It is exergonic and all you need is an **enzyme (lipase)**.
- ✓ The problem in digestion reaction is that, TAG is non-polar and cannot be mixed with water, thus we have a solubility problem, so how can TAG interact with water when they cannot be mixed together?
 - this solubility problem is solved by adding an **emulsifier/solubilizing agent**.
- ✓ **Emulsifier: an additive which helps two liquids mix.** For example, water and oil separate in a glass, but adding an emulsifier will help the liquids mix together. Some examples of emulsifiers are egg yolks and mustard.
Here our emulsifiers are: **CHOLIC ACID, AND CHENODEOXYCHOLIC ACID.**

✓ Those are the emulsifying agents:

→ cholic acid has **3 hydroxyl groups**, and a side chain that ends with a **carboxyl group** → thus it is a **carboxylic acid**

→ we can notice that cholic acid looks like cholesterol; because both have a steroid nucleus, but they differ in:

1. Number of hydroxyl groups:

cholic acid has two additional hydroxyl groups compared to cholesterol (which has a single hydroxyl group).

2. Carboxyl group:

cholic acid has a taller side chain of carboxyl group compared to that in cholesterol.

→ presence of these 4 polar groups and on the other hand the

non-polar steroid nucleus, makes the cholic acid an amphipathic acid because it has hydrophobic and hydrophilic parts.

→ what does this dashed line mean?

it means that those dashed hydroxyl groups are behind the screen (Imagine that the structure is on one plate, then solid line: in front of the screen).

→ although the **bond of the carboxyl group** is ionizable, it is relatively weak, and since then, it **can increase the hydrophilicity of cholic acid (but it stays as an amphipathic)**, by interacting with an amino acid called glycine (smallest and simplest amino acid), forming an amide bond. See the figure.

comments about the figure:

○ Pay attention that the **new carboxyl group** side chain (of the glycine), is **stronger** acid than the original one of the cholic acid, why is it stronger?

because it is almost totally ionized

○ The new acid formed is called **Glycocholic acid**, it is a **bile salt, it is amphipathic**.

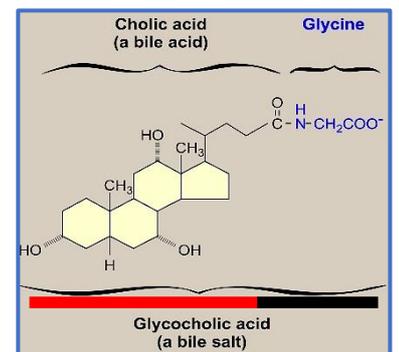
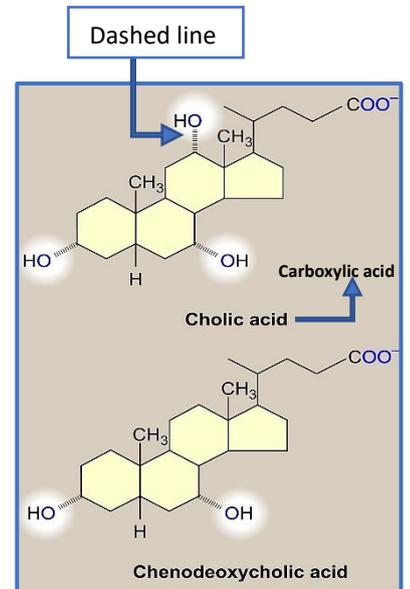
○ A bile salt has stronger acidity (due to the new carboxyl group).

○ Even though we can use the terms acid and salt interchangeably, we need to know that **the acid is the protonated form** and **the salt is the ionized form**

○ the red region represents the hydrophobic region and the black represents the hydrophilic region

○ **bile salts** are excreted in the bile and they can aggregate forming micelles:

- The interior of the micelle is hydrophobic, and can accommodate TAG
- TAG is not digested neither in the mouth (like carbs) nor in the stomach (like proteins), but in the small intestine, with the help of Bile salts. How? ↓



When adding salt and TAG in water and shake them very well, TAG molecules find their way to the core of the **micelles**. Thus, micelles like: lecithin are considered as detergent agents

- Bile salts solubilize TAG, and enzymes start hydrolyzing:

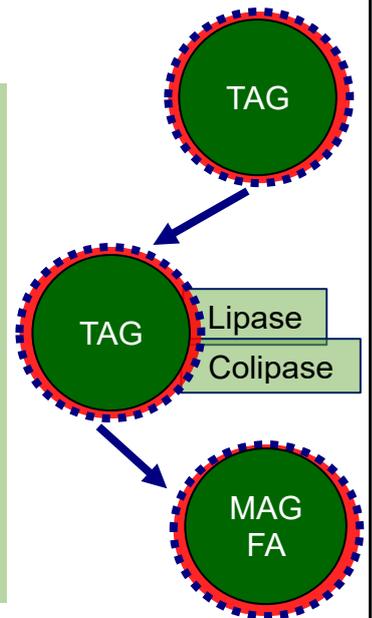
TAG molecules are very large in number and small in size, thus after solubilizing them in the bile salt's micelles in intestine, the surface area that is close to water is greatly increased.

BY THIS TAGs are ready for the hydrolytic enzymes: **LIPASE**, which is excreted from the pancreas along with a protein required for the enzymes function called **COLIPASE**.

they bind to the micelle and start the hydrolysis process:

TAG → 2 fatty acids and the 3rd FA remains attached to carbon 2 in glycerol giving 2-MAG (an acyl group on carbon 2 of glycerol)

→ digestion requires lipase from pancreas and bile salts from the liver.



- if the bile salts are not available, TAG won't be digested. If Lipase or Colipase were not available, TAG won't be hydrolyzed, so we need pancreas and liver to produce Lipase & Colipase and bile salts, respectively.

Hydrolysis of CE:

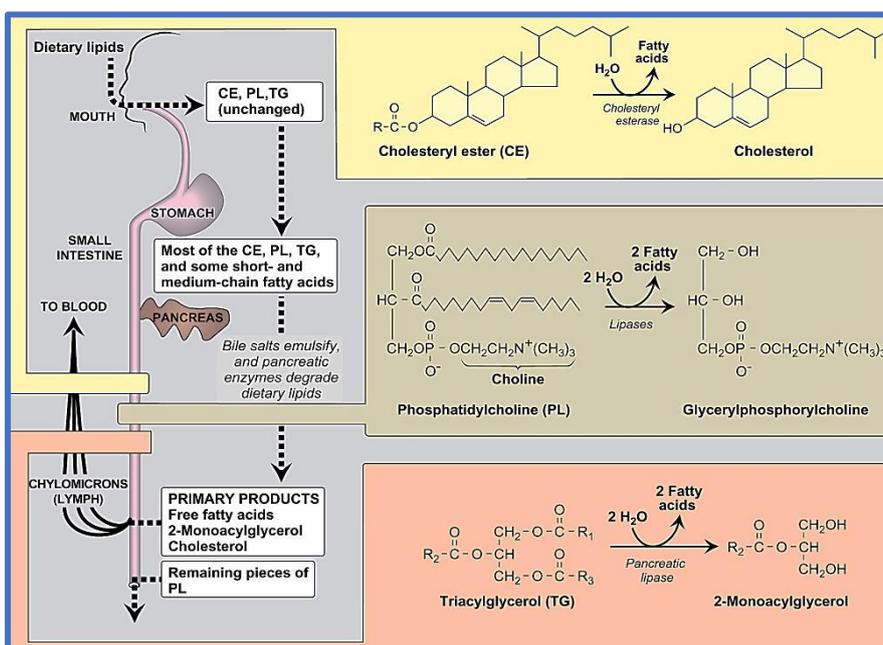
Digestion is hydrolysis reaction that:

- requires solubilization by **cholesterol esterase**, producing 1 FA, and Cholesterol.

Hydrolysis of PL:

Digestion is hydrolysis reaction:

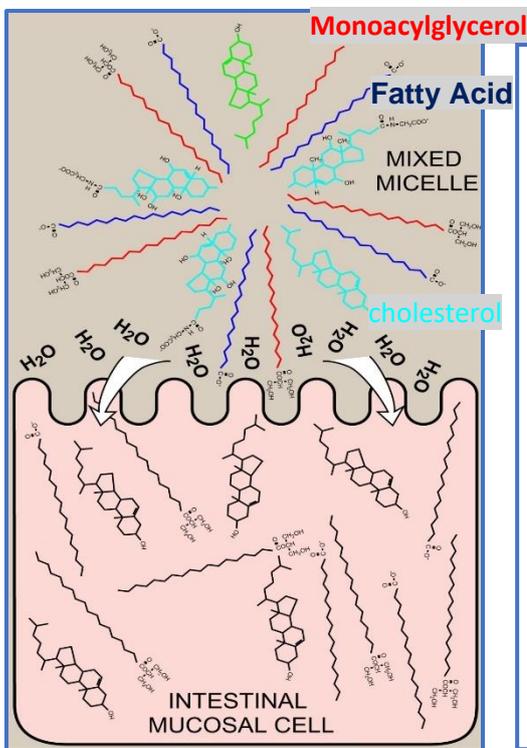
- phosphatidylcholine is digested by **phospholipases** (phospholipase A and B) Producing glycerophosphocholine



scientists always wanted to find an inhibitor of the pancreatic lipase → to lose weight, but how?

We gain weight when we eat lipids (سمن ازیت زبده), but if you take the substance that inhibit TAG digestion, thus it won't be absorbed or digested, and it will pass by and go out with stool producing fatty stool.

actually this drug exists: orlistat



Now these are the products of digestion, we said that digestion occur on micelles, after digestion they will be called **mixed micelles**; which contain a mixture of amphipathic lipids (FA, MAG, cholesterol) that unite with their hydrophobic groups inside and their hydrophilic groups on the outside).

Those mixed micelles go through the small intestine, and when they get in touch with the intestinal mucosal surface brush border the product of digestion can be diffused through the membrane of the microvilli (projections of small intestine, they provide large surface for absorption) thus when mixed micelles get in touch with the brush border, the product of digestion can pass to the intestinal mucosal cell by simple diffusion → no specific transporter

DIGESTION OF TAG WITH SHORT/MEDIUM CHAIN FAs

- Short & medium FAs are found in the dairy products.
- They are digested in the stomach, with the participation of lipase.
- Lipases are:
 1. Are Produced by: The stomach (gastric lipase), The glands in the posterior of the tongue (lingual lipase).
 2. **Are acid stable**, i.e., when they reach the stomach (high acidity) they can function.
- **What is their significance?**
 - **neonates** (حديثي الولادة), because they depend on milk; and milk contain TAG with short and medium chain fatty acids. Therefore, they can digest it without having to go to small intestine → then the digestion is **faster** and this is good for the baby (that is why the baby saturates quickly).
 - **pancreatic insufficiency**, since digesting these TAGs doesn't require bile acids or pancreatic lipases (so they're significance in pancreatic insufficiency).

Secretion of lipids from intestinal mucosal cells

After mixed micelles reach the small intestinal cells:

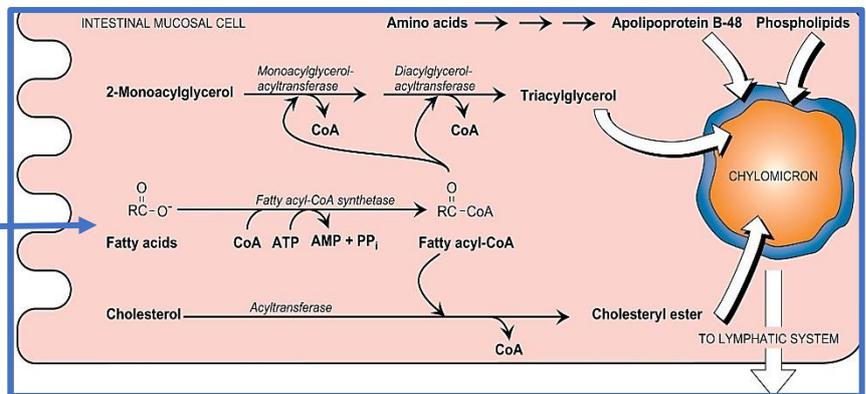
- TAG will be resynthesized from 2-MAG & FAs.
- cholesterol (By using acyl transferase) will be re-esterified to CE (cholesteryl esters).
- Then TAG, CE, phospholipids, & Apo B-48 are used to produce chylomicrons (**large particle**). These large particle chylomicrons cannot pass directly to the capillaries

Meaning: if they are transfer to the capillaries, they are large in size, they may block the capillaries since they are narrow 😊. What will happen?

→ chylomicrons will be released into **lymph vessels** and migrate slowly until they reach thoracic duct that will release them into the **subclavian vein**.

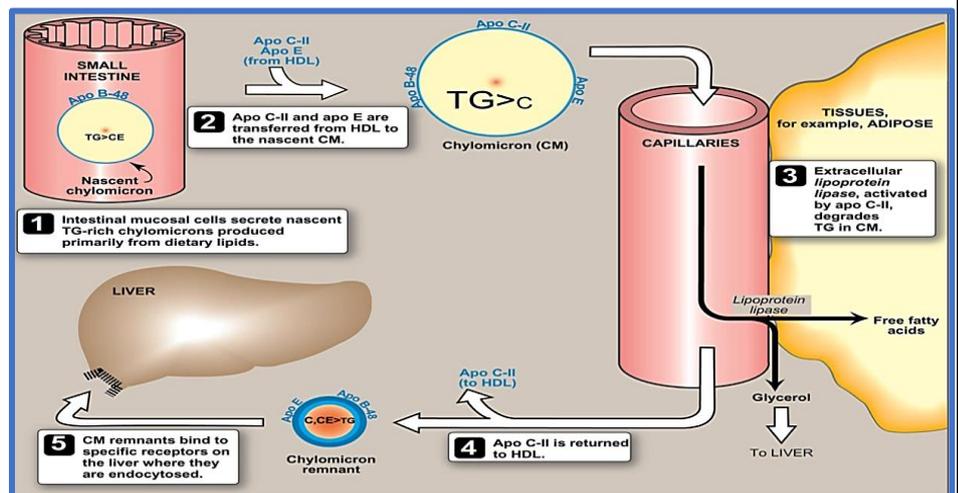
*Why are chylomicrons released into lymph vessels instead of capillaries? To prevent the blockage of capillaries.

Fatty acids are converted into the active form: fatty acyl-CoA, then it is added to MAG forming DAG and TAG



Transfer of TAG from chylomicrons to different tissues

- **Nascent chylomicron:** (newly synthesized CM) They are secreted through the lymph and they reach to blood through the subclavian vein. When they circulate in the blood, they require **APO C-2** and **APO E** from HDL (which is source of APO C-2 and APO E). after transferring Apolipoproteins to the **nascent CM**, it become **mature CM** particles.



These mature CM circulate in the blood, when they reach capillaries in different tissues (they are diluted (مش عم يمشوا بكثافه عاليه)), they pass to that tissue.

- we have in the capillaries an enzyme called **lipoprotein lipase**; an extracellular enzyme that acts on TAGs which are embedded in specific lipoproteins: It acts on CM and VLDL.
- **Apo C-2** (in CM and VLDL) is required to the activation of lipoprotein lipase that will convert TAG to **free FAs (diffuse into tissues) & glycerol (turn back to the liver)**.
- As a result of the hydrolysis of TAG, chylomicron will be smaller and called: **chylomicron remnant**, containing **APO E and APO B-48** (they → are small in size, → increase protein in CM → increase density).
- chylomicron remnant lacks Apo C-2 (it will turn back to HDL).
- Apo E is necessary for binding to cell surface receptors of hepatocytes "liver" (this binding is followed by endocytosis).
- Muscles tissue have higher affinity to get diffused-FAs than adipose tissue, why? Since there are different lipoprotein lipases that differ in their affinity to chylomicrons, and **muscle lipoprotein lipases have higher affinity** than that in adipose tissue.

TAG is delivered to different tissues and Cholesterol is taken by the liver by the small CM remnant (بقايا chylomicrons).
 this process occurs in the blood and it takes several hours, so if a doctor needed laboratory analysis of cholesterol, they should ask the patient to fast for at least (12-14) hours.
 In order to Remove cholesterol that is from food. If the **lipoprotein lipase is defective** for some reason CM remains in the circulation for a long period of the time, and because CM is very large and there is numerous of them, → it gives the plasma milky appearance
 Plasma in normal case: yellow, diaphanous (شفاف).

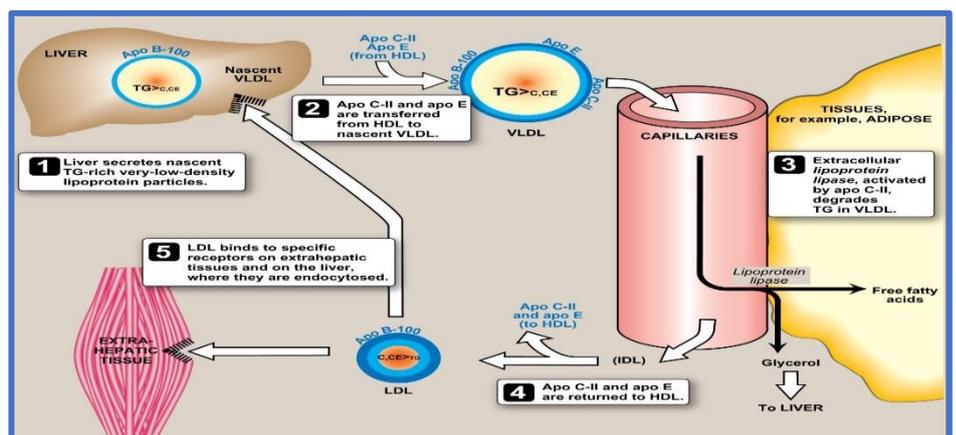
Transfer of TAG from VLDL to different tissues

This process is very similar to the previous one.

1. VLDL is synthesized in the liver (to carry TAG produced in the liver from excess carbohydrates).
2. VLDL is secreted into the blood (they acquired APO C-2 and APO E from HDL) and they circulate in capillaries.
3. Lipoprotein produce free fatty acids and glycerol; because TAG is removed continuously, and converted to fatty acids which are taken by tissues.
4. What happens for densities if we remove TAG continuously?

it Increase because we are removing component that has very small density. Therefore, there are more proteins relatively.

note: Apolipoprotein B-100: Apo B-100 is synthesized in the liver and is the major structural component of VLDL, IDL, and LDL. LDL in the liver contains APO-B100 that is important for binding to cell surface receptors. LDL in the small intestine contains APO-B48. The difference between them is that : mRNA for "APO-B48" is processed and cut into piece. Almost half of these in the liver. So, The amino acid sequence of apoB-48 represents 48% of the initial sequence of apoB-100. ApoB-48 is synthesized only by the intestine in humans, while apoB-100 is synthesized primarily by the liver.



Read these comments and see the figure above

→ TAG hydrolysis → lower TAG content → lower size (in micelles)

→ the remnants are Mainly: **Cholesterol & CE** → the density will keep changing, as it continues hydrolysis, in this order: VLDL → IDL → LDL.

Explanation:

- If we continue increasing density, it becomes LDL.
- If the rate becomes intermediate, density variation gives two options:
 - 1-complete to LDL.
 - 2-return back the APO C-2 to HDL
- The density now increases more and more; due to the continuous removal of TAG. And now it is LDL, where the only the apolipoprotein that is found in, is **APO B100**.

*Notice that the **size of LDL** compared with the VLDL is **smaller**.

*Notice that **VLDL** has **TAG** more than cholesterol ester, while **LDL** has **cholesterol ester** more than TAG.

- LDL is rich in cholesterol, it can transport it to cells by binding of its **APO B100** specific receptor in liver tissue or muscular tissue, by endocytosis.

Summary:

- TAG hydrolysis = lower TAG content = lower size = the remnants are Mainly Cholesterol & CE = the density will change as follow: VLDL IDL LDL.
- IDL can be taken by cells by endocytosis (50%) or continue to become LDL (50%).
- LDL contains only **apo B-100** that's important for binding to cell surface receptors of the liver & extra-hepatic tissues (in muscles).
- Notice that apo C-2 & apo E will turn back to HDL.

METABOLISM OF SPHINGOLIPIDS (SPHINGOPHOSPHOLIPIDS/ GLYCOSPHINGOLIPIDS)

There are two kinds of sphingolipids:

1-Sphingophospholipids, contain phosphate.

2-glycosphingolipids, contain carbohydrate.

SPHINGOPHOSPHOLIPIDS

-The structure of the **sphingosine** (amino alcohol):

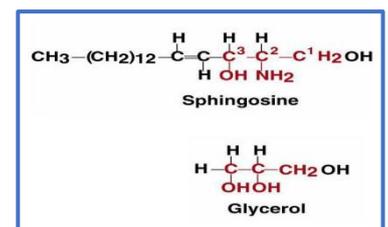
functional groups and long hydrocarbon chain.

Look at the functional groups on **C**:

At **c1**: hydroxyl group. At **c2**: amino groups. At **c3**: hydroxyl group
"ine" in sphingosine means: means that it contains amino group

-The structure of **glycerol**: It is part of sphingosine.

glycerol has the same functional groups in sphingosine, but in **c2** there is a hydroxyl group, instead of amino group.

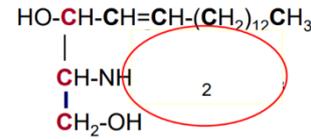


Sphingosine can be angle shaped (similar to DAG),

- Number of carbon atoms is 18, it is long amino alcohol.
- Only the first 3 carbons have polar groups.

Ceramide: Fatty Acid joined to Sphingosine

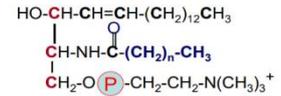
→ Sphingosine can be joined to fatty acids, how?
 joining the fatty acids through c2 to form called **ceramide**.
 What type of bond between fatty acids and sphingosine?



These is amide bond. (much resistance to hydrolysis than ester bond).

→ Ceramide can join phosphocholine:

Phosphatidylcholine + ceramide → sphingomyelin



Phosphatidylcholine contains phosphocholine

Sphingomyelin is an amphipathic molecule ↓

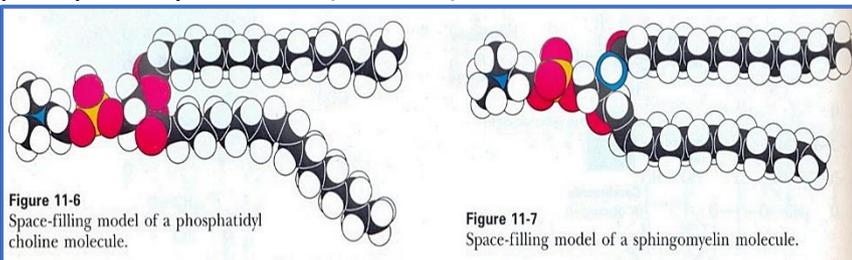
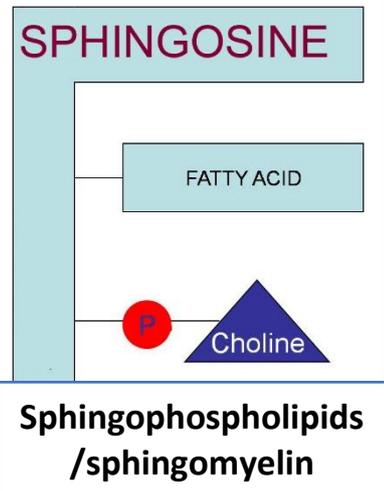
-It has 2 long hydrocarbons chains (one from FAs and one from sphingosine)

-it has a phosphate group + positive charge +choline

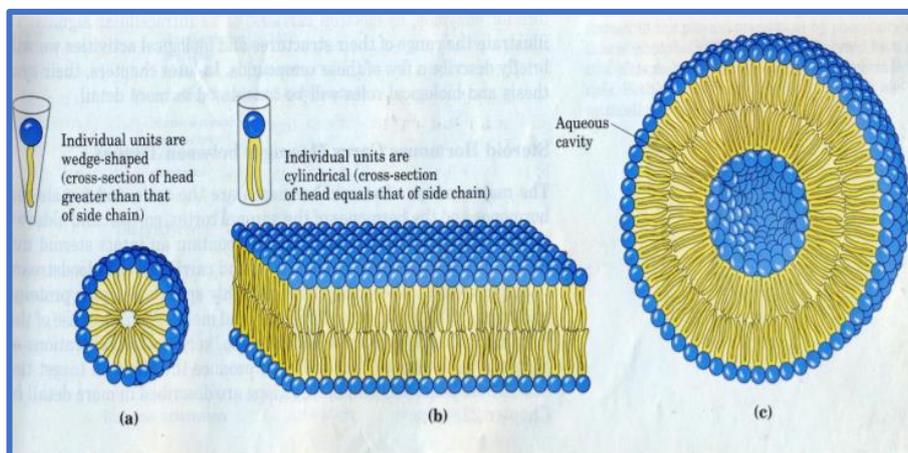
-Sphingomyelin's structure is similar to phosphatidylcholine's:

*Space-filling model of phosphatidyl choline molecule.

2 long hydrocarbons chains, polar in group, these is similar phosphatidyl choline (lecithin)

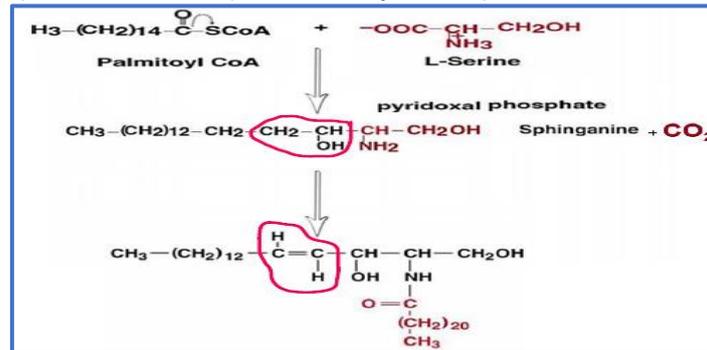


-Sphingomyelin is found in plasma membrane of all cells even in RBCs sphingomyelin, and specifically **myelin sheath** (around the axons of neurones to protect them) is rich of sphingomyelin.



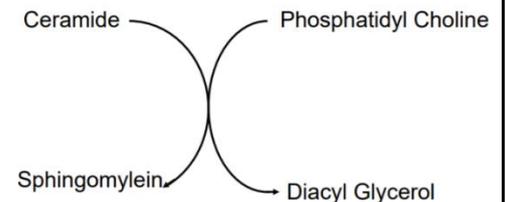
Synthesis of ceramide:

- Initially, condensation of serine and palmitoyl CoA gives a derivative of sphingosine called sphinganine (ما فيها رابطة ثنائية) composed of 2c from serine and 16c from palmitoyl CoA= 18 c. And this reaction requires an enzyme called **Pyridoxal Phosphate** (a derivative of vitamin B6).
- Then, Sphinganine is acylated at the amino group with a long-chain fatty acid.
- What drives the reaction forward? Dissociation of: CoA from palmitoyl CoA, and the carboxyl group (**CO₂**) from serine (decarboxylation).



Transfer of phosphocholine

transfer of phosphocholine group from phosphatidyl choline to ceramide, produces sphingomyelin and diacyl glycerol



GLYCOSPHINGOLIPIDS/GLYCOLIPIDS

glycolipids are Formed by Linking one or More Sugars to Ceramide:

- Ceramide +
1. Glucose or Galactose => Cerebroside
 2. Sulfated Galactose => Sulfoglycosphingolipids
 3. Oligosaccharide => Globoside
 4. Oligosaccharide with NANA => Gangliosides

-Cerebroside means: the molecule has glycosidic bond (between sugar and non-sugar).

-NANA: is acidic 9 carbon sugar (**structure** isn't imp)

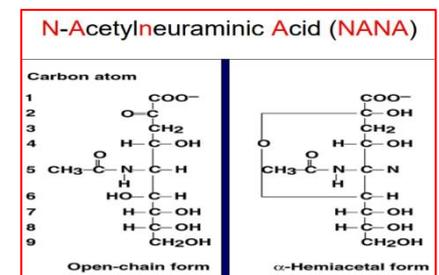
→ Building glycolipids requires sugar in its active form.

Activation requires UDP which will carry the sugar

Activated Donors in Glycolipids Synthesis

- UDP-Glucose
- UDP-Galactose
- UDP-N-Acetylgalactosamine
- **CMP-N-Acetylneuraminic Acid**

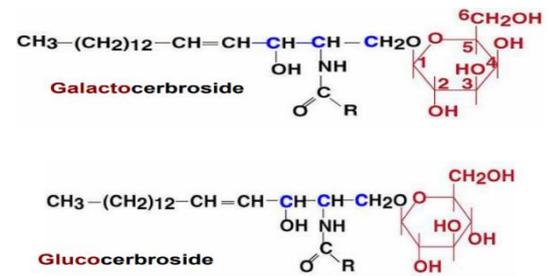
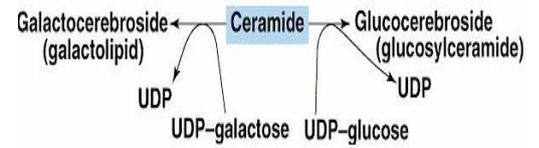
UDP-galactose and UDP-glucose are available



- Building glycolipids is done by adding activated sugars, but what decides which activated donors are used? → Enzymes

→ Differences between Galacto-/Gluco- cerebroside:

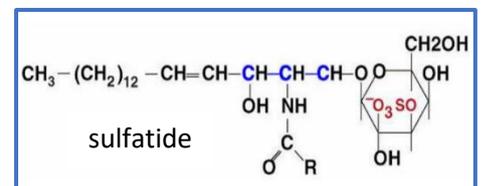
- Galactocerebroside and Glucocerebroside look similar to each other, with one difference: the orientation of the hydroxyl group which is:
 - up in galactocerebroside
 - down in glucocerebroside
- Both can be found in membranes, since they are both hydrophobic molecules
- The enzyme used to transfer glucose is different from the enzyme used to transfer galactose.



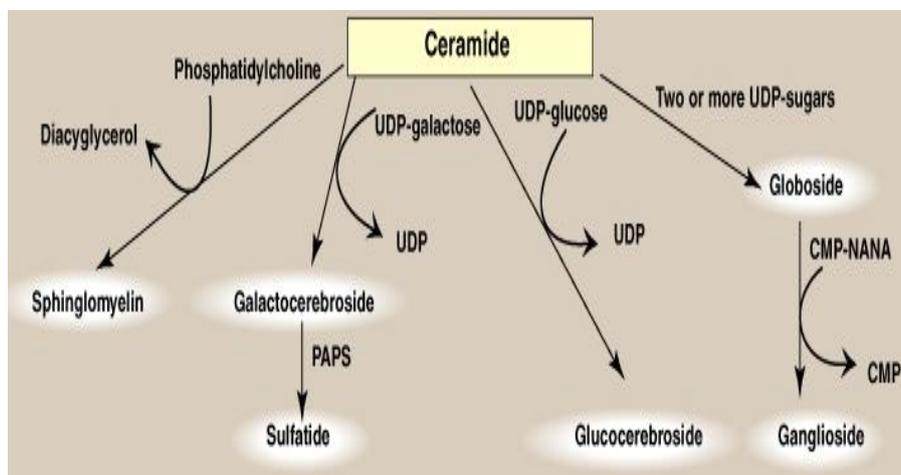
→ glycolipids are important:

They are on the outer leaflet of cell surfaces; to give identity, to differentiate cells, to receive and contact, to let viruses in. They're not just there for the sake of having a sugar, they're there in a carefully organized manner, and chosen to indicate certain information. The ABO blood groups are dependent on glycolipids. Sugars-adding Enzymes are specific for sugars, for the substrate to which the sugar is added, and for the sequence. The sequence is determined by many enzymes, each is specific for one sugar at a time

→ Transfer of sulfate group to galactocerebroside: production of sulfogalactocerebroside (sulfatide)



Summary:



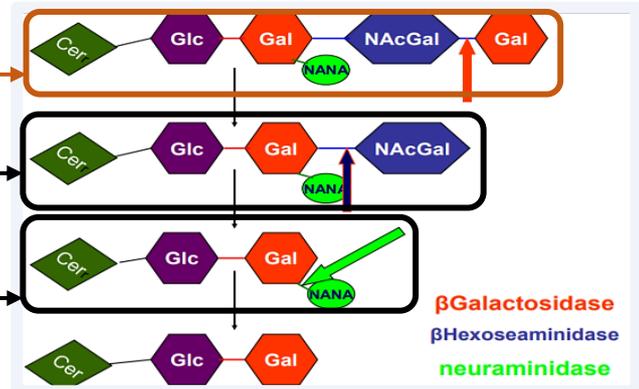
Degradation of Sphingolipids

The synthesis is not important as much as degradation is; because most clinical significance (degeneration) is due to abnormal degradation of sphingolipids. Moreover, no defect has been identified in the synthesis, but there's a defect in the degradation of sphingolipids

- ❖ The degradation of sphingolipids occurs by: **hydrolytic enzymes**, these are specific for the sugar and the substrate.
- ❖ Hydrolytic enzymes involved in lipids degradation are:
 - ⦿ α -galactosidase ⦿ β -galactosidase ⦿ neuraminidase ⦿ hexoaminidase
- ❖ each sugar requires different enzymes.
- ❖ Degradation occurs in lysosomes, since hydrolytic enzymes are found there, and they bound firmly to lysosomal membrane, they are not released; to ensure that no degradation occurs outside the lysosomes (عشان ما تهضم الخليه نفسها).
- ❖ Lysosomes in addition to degrading glycolipids, they degrade excess proteins, excess molecules, and membranes.
- ❖ Lysosomes environment is acidic (**pH between 3.5-5.5**)
- ❖ This process is very slow it is not for energy production, it isn't randomly process.
- ❖ **the last sugar to be added in synthesis, is the first sugar to be removed in degradation.**

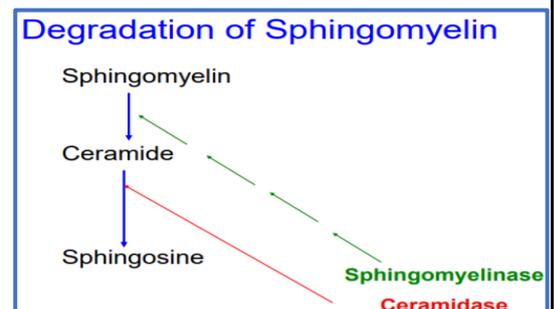
❖ In the figure:

- The first glycolipid is **GM1** (the one with the longest oligosaccharide chain).
- **Galactose** is removed by **β Galactosidase**, producing **GM2**.
- **N-Acetylgalactosamine (NANA)** is removed by **β Hexosaminidase**, producing **GM3**.
- **Neuraminidase** catalyzes the removal of **N-Acetylneuraminic acid**.



❖ Degradation of Sphingomyelin:

- **Sphingomyelin** is degraded by **sphingomyelinase**, that converts sphingomyelin into ceramide and phosphocholine.
- **Ceramide** is degraded by **ceramidase** that hydrolyzes the fatty acid to produce sphingosine.



Sphingolipidoses

- ✦ Sphingolipidoses are group of diseases. The termination (ses) refers to a disease state. When they were first identified, they were called “**lipid storage diseases**” because they thought that the presence of lipids is the storage form, but in fact they’re present in the lysosomes for degradation not as a storage form. Thus, the nomenclature has changed.
- ✦ Sphingolipidoses result from a defect in one of the **hydrolytic enzymes**, which leads to the accumulation of a lipid that is the substrate of that defected enzyme.
- ✦ They’re inherited as **autosomal recessive diseases**, i.e., they don’t appear if an individual has only one defected allele from one parent, because having one normal gene is sufficient for preventing the occurrence of the disease, and this can be understood by the fact that the process of degradation is a very slow process, and even having 10% of the enzyme activity could be sufficient for preventing the appearance of the disease.
- ✦ **The disease occurs when the enzymatic activity is almost zero.**
- ✦ The brain is **the most** affected; because the **accumulation of lipids in the cell leads to its destruction**. Moreover, once the neuronal cell is damaged, it cannot be replaced. So, the individual might be born normal, but with time the accumulation occurs, and the disease starts to appear. The extent of enzyme deficiency is the same in different tissues, but the generation of neuronal tissues isn’t the same as other tissues. Once they’re destructed, they cannot be replaced. **This is important for the diagnosis: we can take a cell sample from different tissues and measure the enzyme activity to diagnose the condition.**
- ✦ Manifestations of CNS disease include mental retardation and movement problems.
- ✦ The diseases that we have to know are:
 - 1. TAY-SACHS DISEASE:**
 - A classic example of lipidoses that affects Jewish population (Because of marriage among relatives and the same ethnic groups).
 - Accumulation of gangliosides (GM2)
 - Rapid, progressive, and fatal neurodegeneration.
 - Blindness, cherry-red macula, muscular weakness and seizures.
 - Deficiency of activator protein (GM2 ACTIVATOR) in some cases.

2. GAUCHER DISEASE:

- **The most common lysosomal storage disease.**

- Accumulation of glucocerebrosides. Causes hepatosplenomegaly, osteoporosis of long bones.
- CNS involvement in rare infantile and juvenile forms, enzyme-replacement therapy can be used.

3. NIEMANN-PICK Disease (A+B)

- Accumulation of sphingomyelin. Causes hepatosplenomegaly, cherry-red macula
- Neurodegenerative course (type A)

"وأنا في كل ضائقةٍ أخشع لهذا الصوت: واصبر وما صبرك إلا بالله"

هذا الجهدُ لله.