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Biochemistry 2

Doctor 2018 | Medicine | JU

◉ Sheet ○ Slides

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In the last lecture we discussed the synthesis of fatty acids, and we noted that it proceeds until it reaches 16 C long then it gets released. So, what about fatty acids that are longer than that?

Elongation of fatty acids occur in ER not in cytoplasm because they are insoluble there.

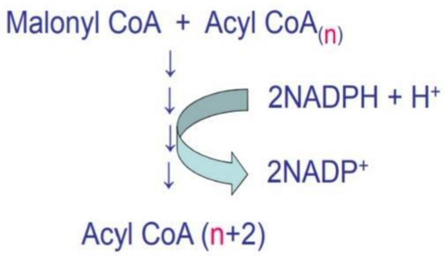
"any reaction involves fatty acids or any other insoluble substance will occur in ER "

- Similar Sequence to Reactions of synthesis. But, with different Enzymes → enzymes in the ER are different from **fatty acid synthase** that carries out the synthesis in cytoplasm.

- Elongation of fatty acids may occur in mitochondria, when we consume fatty acids that are shorter than **16C** (short or medium) because they can't be stored as such and they must be elongated.

Condensation start with:

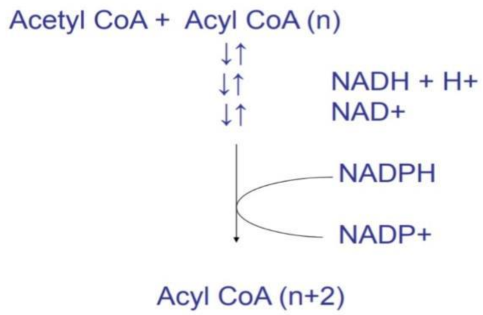
In the ER



n = 16 or more carbons

*longer than the original one

In the mitochondria



n = less than16 carbons

- The process occurs by **reversible Beta oxidation**, **3** of beta oxidation reactions can happen in both directions, but (the first one in oxidation = the last one in synthesis) happen by **different enzyme** and requires **NADPH not $FADH_2$.**

WHY??

Because the energy of **$FADH_2$** are directly transferred to **Co-enzyme Q**. We consider that $FADH_2$ is part of the enzyme's prosthetic group or part of the enzyme itself.

➢ Introduction of double bond:

Firstly: synthesis of monounsaturated fatty acids

An example:

Oleic Acid 18:Δ9

Palmitoleic 16:Δ9

As humans **can't** introduce double bond **beyond C9**, fatty acids with double bond on **C12 or C15** are essential fatty acids and we should take them from diet (from plants). So, animal fat is not considered a good source for polyunsaturated fatty acids.

This happen in the ER in a simple process that involves 2 reaction catalyzed by $\Delta 9$ Desaturase that form a complex with Cytochrome b_5, in ER.

1) introduction of hydroxyl group → O_2 molecule is required. one atom is added to the fatty acid and the other should be reduced by **NADPH.**

>> Even if the introduction of fatty acid is oxidation reaction, the reducing agent ***(NADPH) is required to:***

- Reduce the one O atom
- Activate the other one to be introduced to FA.

2)dehydration reaction → removal of H_2O from C_9 & C_{10}, catalyzed by Δ9 Desaturase.

Stearoyl CoA
$\downarrow$ NADPH + O_2 → $NADP^+$ + $2H_2O$
Oleoyl CoA

Palmitoyl CoA
$\downarrow$ NADPH+O_2 → $NADP^+$+ $2H_2O$
Palmitoleoyl CoA

Secondly: Formation and Modification of Polyunsaturated FA

Double bond can be introduced to fatty acid that already have a double bond between **the carboxyl group** and the **first double bond**. Of course, it requires additional ezymes.

Additional double bonds can be introduced by:

- Δ_4 Desaturase
- Δ_5 Desaturase
- Δ_6 Desaturase

The enzyme we use depends on the C that will be desaturated, which in turn depends on the existing double bond, because there should be a CH_2 separating the two double bonds

If we take linoleic acid as an example the process of the reaction will be:

1) Double bond is added to **C6** by **Δ6 Desaturase**.
2) Two C atoms are added to the carboxyl end.
3) Another double bond is introduced by **Δ5 Desaturase.**

18:2 Δ 9,12 Linoleic
$\downarrow$
18:3 Δ 6,9,12
$\downarrow$
20:3 Δ 8,11,14
$\downarrow$
20:4 Δ 5,8,11,14 Arachidonic

- *Linoleic acid is an essential fatty acid, but what about Arachidonic?*

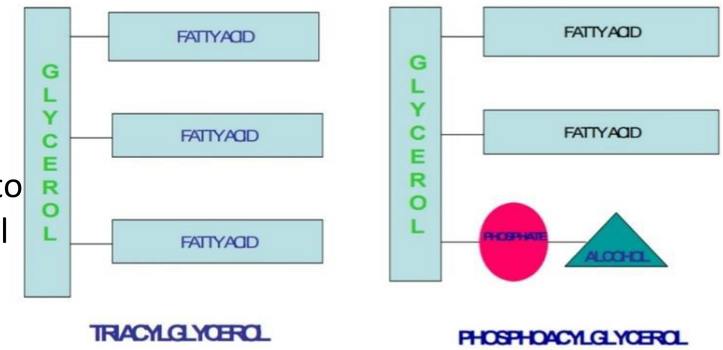
Essential → if linoleic acid intake is low.
Nonessential → if linoleic acid intake is high so it can be synthesized. We don't have to get it from food. But, it's derived from essential acid.

- **Omega classification** doesn't change with elongation or desaturation, that's why we have families according to it. Ex: omega 6 or omega 3.

✓ Now, we have finished talking about FA synthesis, elongation and desaturation and we are going to talk about another topic ^^.

➢ Biosynthesis of Triacylglycerol & Phosphoacylglycerol:

The structure of these two molecules have common part **(glycerol + two FA)** and they both contain ester bonds.
But what differ is that C3 of glycerol binds to phosphate + alcohol in Phosphoacylglycerol rather than binding to another FA.
So, the pathway of synthesis for them share common steps.



- phosphatidic acid is a common intermediate in their synthesis. It is formed from glycerol, 2 fatty acid + phosphate. The ionized form is called **phosphatidate.**

  - **Let's start with the biosynthesis of Triacylglycerol:**

✍ **The requirement of this biosynthesis:**
1) Glycerol Phosphate.
2) Acyl~CoA (Active form of FA) - produced by acyl CoA synthetase (require 2 ATP).

Why Active form?

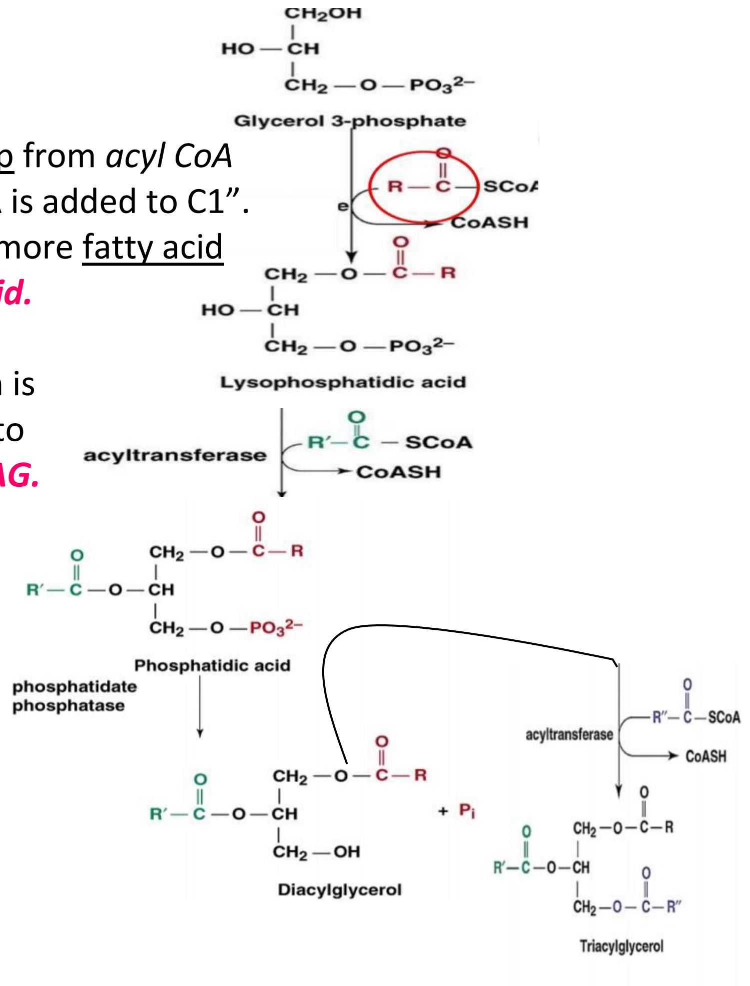
$$TAG + H_2O \longrightarrow DAG + FA \quad \Delta G\ -ve$$
$$DAG + FA \longrightarrow TAG + H_2O \quad \Delta G\ +ve$$

Look at this reaction:

$$DAG + Acyl{\sim}CoA \longrightarrow TAG + CoA \quad \Delta G\ -ve$$

The first reaction is an exergonic (hydrolysis), but if we want the reaction to go through the other way, it would be endergonic. What really happens that FA comes from acyl CoA, so DAG can accept acyl group to produce TAG and the energy will be <u>provided by</u> **the cleavage of the high energy thioester bond.**

✍ Steps of synthesis phosphatidic acid:



1) Glycerol 3-phosphate **accept** acyl group from *acyl CoA* to produce ***lysophosphatidic acid***. "FA is added to C1".
2) Lysophosphatidic acid can **accept** one more fatty acid from *acyl CoA to* give ***phosphatidic acid.***

Then we can make TAG BY:

1- Hydrolysis of phosphatidic acid, which is catalyzed by phosphatidate phosphatase to remove ***phosphate*** group and produce ***DAG.***

2- DAG can **accept** one more acyl group**.**

Note that:

- All acyl groups are transferred by ***acyl transferase.***

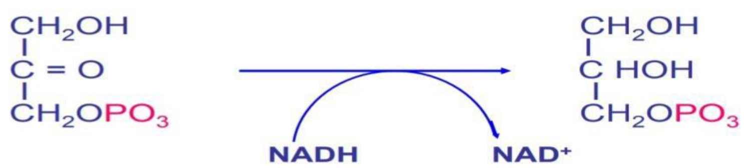
✍ TAG synthesis is active mostly in:

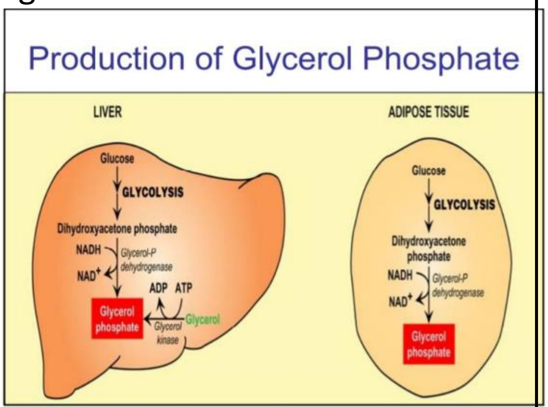
1) Liver: extra carbohydrates are Converted to TAG.
2) Adipose tissue: storage of TAG

- **production of glycerol phosphate:**

glycerol + ATP $\xrightarrow{\text{Glycerol kinase}}$ glycerol 3-phosphate +ADP

- This reaction does not occur in **adipose tissues** because the lack of the enzyme **glycerol kinase.** But, adipose tissue can obtain it through this reaction:





Dihydroxyacetone (glycolysis intermediate) get **reduced** (the ketone group) into ***glycerol phosphate*** by **glycerol phosphate dehydrogenase.**

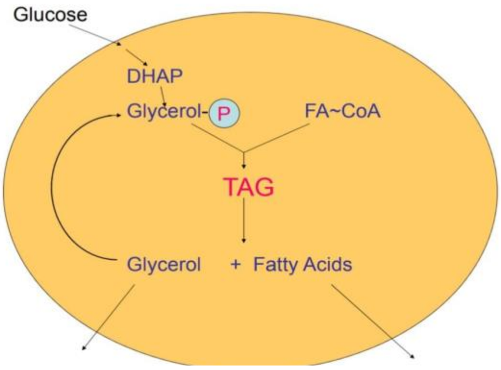
- The liver can produce TAG by **both ways**.

In adipose tissue:

✓ **TAG** is form about **85-90%** of the volume of adipocyte.

✓ When **energy is needed** → TAG will break down to 3 fatty acids and glycerol. Fatty acids will be transported to the plasma and used as source of energy to other tissue.

✓ If we have glycerol kinase in adipose tissue, we will only consume Energy.
How??



Glycerol that is produced by hydrolysis will be **rephosphorylated** and give ***glycerol phosphate***.
In this case, synthesis and degradation occurs at the same time and this represent just *loss of energy* (7 ATP will be lost → 2 for each FA (3*2) and 1 for glycerol)

✓ If there is DHAP (from glycolysis of glucose), there will be synthesis of ***glycerol phosphate.***

How glucose enter the adipose tissue in well fed state?

- In this case **insulin** level is high →**glucose** will enter to the adipose tissue by **GLUT4/insulin dependent** →glycolysis →DHAP →glycerol phosphate→with acyl CoA in the tissue →synthesis of TAG will take place.
- When **insulin** level is low (during hypoglycemia)→ hydrolysis of TAG. Glucose won't enter and synthesis won't occur.

- One of the early diabetes diagnostic symptoms is **sudden loss of weight** because no glucose is entering the adipose tissue, because insulin is not there→ no TAG synthesis.
- **Insulinoma:** tumor that produce insulin. Patients suffering from insulinoma gain weight.

➢ Digestion and Transport of TAG by Plasma Lipoproteins:

Lipids mainly are composed of a **nonpolar FA** and a **polar glycerol** that lose its polarity because of the ester bond, so **how lipids can be soluble in blood?**

The nonpolar part aggregate together forming a **micelle.**
Also, **phosphoacylglycerol** contains polar and nonpolar parts. The nonpolar part (2 FA chains) aggregate together, and the polar part (-ve charge on the phosphate group and +ve charge on alcohol "usually amino alcohol") interact noncovalently with water.

Micelle: spherical particle made of large number of phospholipids, its surface is polar and can interact with water noncovalently, while the rest of it is nonpolar (aggregation of side chain of FA).

Lipoproteins: multimolecular complexes of lipids and proteins forming **noncovalent interactions**.
✓ Lipoproteins are used for transport of lipids in the plasma.

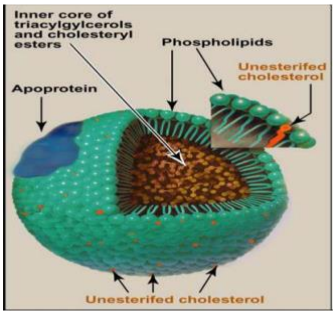
✓ *The lipids include:*

1- **TAG** Triacylglycerol
2- **CE** Cholesterol Ester

Highly nonpolar. So, they are **core component**

3- **CH** Cholesterol
4- **PL** Phospholipids

Amphipathic molecules. So, they **are surface component**



- **The polar head** in case of *cholesterol* is the hydroxyl group, while in *phospholipid* is the phosphate group binds to alcohol as we mentioned previously.

*The doctor noted that he may ask about the core and surface component ^^*

✍ Apolipoproteins:

The protein part of lipoproteins, they are considered as amphipathic molecules (part of it interact with lipid and the other part interacts with water) and they are important for binding to cell surface receptors.

Apo means protein that can bind to something else. Ex: apoenzyme is the protein without the Co-enzyme.

✓ **Include several classes**: Apo A, Apo B-48, Apo E….

✓ **Apolipoproteins play two important roles:**

- *Structural Role:* maintain the particle shape.
- *Regulatory Role:* regulate the enzyme activity.

▪ Lipoproteins are found in **plasma.**

✓ Can be separated by **centrifugation** and it end up with these **5 classes:**

Lipoprotein	Density	Protein	Major Lipid
Chylomicrons	<0.95	2%	TAG (85%)
VLDL	0.95- 1.006	9%	TAG (55%)
IDL	1.006-1.019	11%	TAG (26%) CE (30%)
LDL	1.019- 1.063	20%	CE (35%)
HDL	1.063- 1.21	45%	PL (25%)

We are required to know their order

▪ ***Some notes related to the previous table:***

⇨ ***Remember that:*** Density of water =1. So, anything less than this will be on the top of the tube forming a creamy layer.

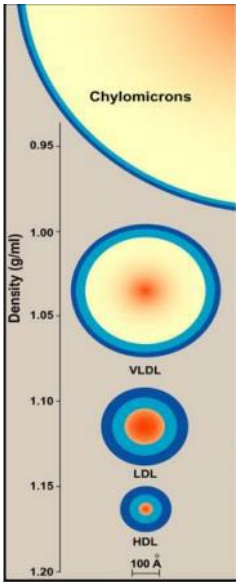
⇨ **HDL** in the *bottom* of the tube and **LDL** in the *top.*

⇨ The *lipid to protein ratio* determines the density of lipoprotein.

⇨ Lipids has lower density than water, while protein density is higher. So, as the ratio increase the density decrease.

⇨ **Chylomicrons** has the *highest* lipid to protein ration and the *larger* size related to the other lipoprotein.

⇨ **HDL** contain 25% ***PL*** and 45% ***protein*** which are considered as *surface component* and. So, more than 70% of its component are ***surface component.***



⇨ You should know that as the percentage of surface components Increases, the size of lipoprotein decreases.

- Newborn baby has high surface area relatively to their size, so they lose heat that's why they have brown adipose tissue.

The end ^^