بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Metabolism | Final 9

F.A. synthesis pt.2 + GPL pt.1

Written by : DST

Reviewed by : NST member
Malak Mksosi

وَلِلَّهِ الْأَسْمَاءُ الْحُسْنَى فَادْعُوهُ بِهَا

المعنى: الذي أحاط علمه بالظواهر والبواطن، والإسرار والإعلان، فلا يخفى عليه شيء من الأشياء، يعلم ما كان وما هو كائن.

الورود: ورد اسم العليم (١٥٧) مرة، أما اسم العالم فورد (١٣) مرة، واسم علام الغيوب (٤) مرات.

الشاهد: ﴿إِنَّ ٱللَّهَ وَٰسِعٌ عَلِيمٌ﴾ [البقرة:١١٥]، ﴿عَٰلِمُ ٱلْغَيْبِ وَٱلشَّهَٰدَةِ﴾ [الأنعام:٧٣]، ﴿إِنَّكَ أَنتَ عَلَّٰمُ ٱلْغُيُوبِ﴾ [المائدة:١٠٩].

اضغط هنا لشرحٍ أكثر تفصيلًا

The stoichiometry of palmitate synthesis

- Stoichiometry of palmitate synthesis:

$$\text{Acetyl-CoA} + 7\ \text{malonyl-CoA} + 14\ \text{NADPH} + 14H^+ \longrightarrow \text{palmitate} + 7CO_2 + 14NADP^+ + 8\text{CoA} + 6H_2O$$

One acetyl-CoA and seven malonyl-CoA molecules are required. Each malonyl-CoA loses one carbon during the process , resulting in a total of 2 carbons from acetyl-CoA and 14 carbons from malonyl-CoA , yielding a 16-carbon chain.
The fatty acid synthesis process involves seven cycles , with each cycle requiring 2 NADPH molecules. Therefore , 14 NADPH molecules are consumed in total and 14 H+ ions yielding 7 CO_2 molecules , 14 $NADP^+$ molecules , and 8 CoA molecules (seven from malonyl-CoA and one from acetyl-CoA).
During the process , 6 H_2O molecules are released. The seventh H_2O is not released because the final fatty acid retains one carbonyl group (Also , one H20 molecule is consumed in the release of the fatty acid)

- Malonyl-CoA synthesis:

$$7\ \text{Acetyl-CoA} + 7CO_2 + 7ATP \longrightarrow 7\ \text{malonyl-CoA} + 7P_i + 7H^+$$

- Overall stoichiometry of palmitate synthesis:

$$8\ \text{Acetyl-CoA} + 14\ \text{NADPH} + 7ATP + 7H^+ \longrightarrow \text{palmitate} + 14NADP^+ + 8\text{CoA} + 6H_2O + 7ADP + 7P_i$$

A total of 7 ATP molecules are required to synthesize a 16-carbon saturated fatty acid.

Sources of molecules

- **Aceytle Co A**

Source :Pyruvate

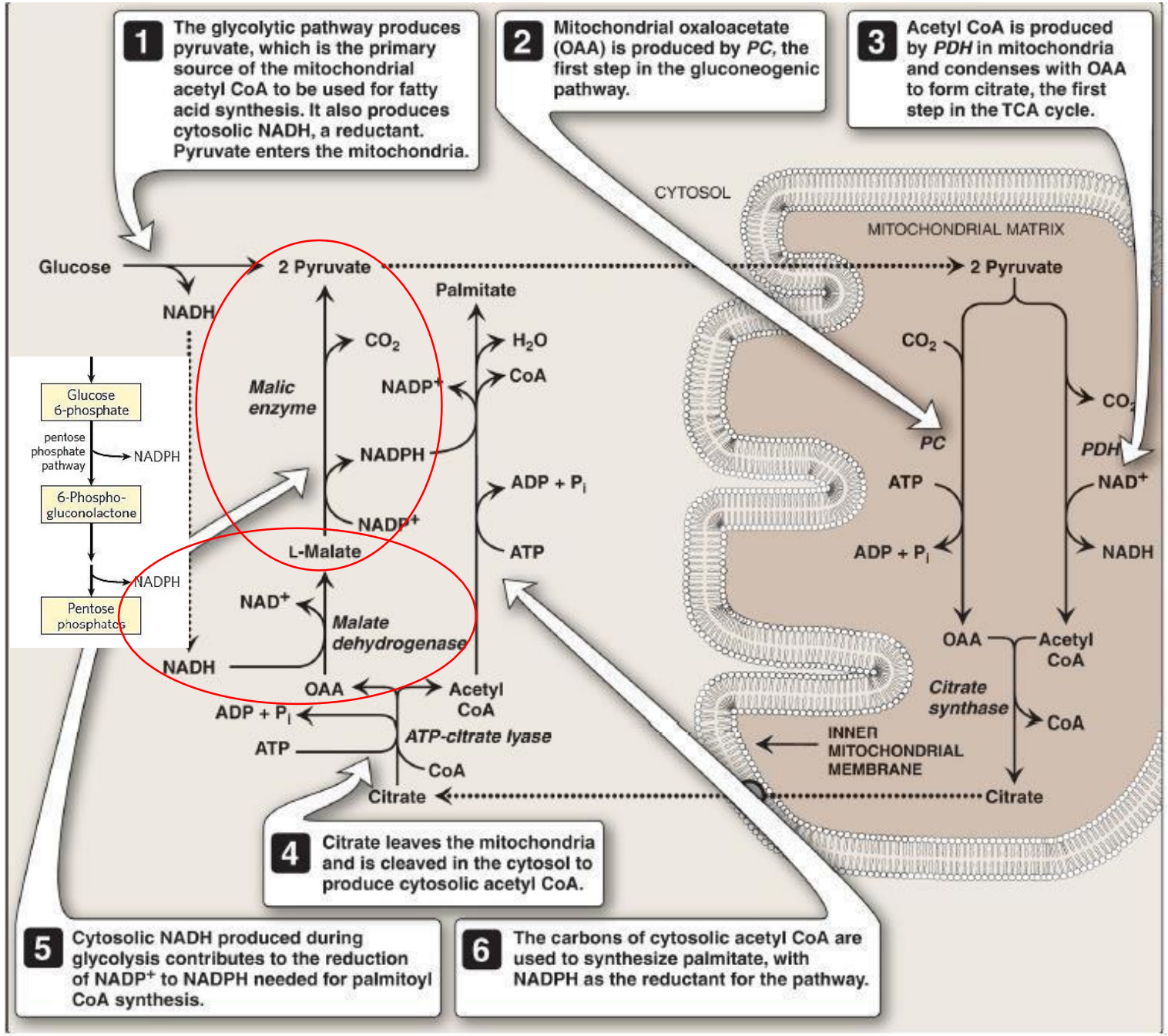
- **NADH** (*for oxaloacetate to malate)*

Source : Glycolysis

- **NADPH**

Sources :

- 1-Pentose phosphate pathway
- 2-Malate to pyruvate



Explanation for the previous slide

We can obtain the molecules that are needed for the synthetic pathway of fatty acids by the following:

- **Acetyl CoA:** under well fed state we can get it from pyruvate that comes from glucose as a major source of pyruvate and we won't mostly get it from other sources.So when we have high concentration of glucose in the well fed state we will break it down into pyruvate in the cytosol then the pyruvate will move to the mitochondria to form Acetyl CoA that reacts with oxaloacetate increasing the concentration of citrate so the citrate can exit through its transporter (citrate transporter) to the cytosol and then by citrate lyase it will be converted back into oxaloacetate and Acetyl CoA so then we will be able to use Acetyl CoA to start the fatty acids synthesis such as palmitate etc...

- **NADPH:** it comes from Pentose phosphate pathway that is also active in the well fed state and it happens in the cytosol so the NADPH is going to be produced there where the synthetic pathway of fatty acids also occur.
  NADPH can also be obtained from converting malate to pyruvate, after producing oxaloacitate from citrate we can reduce it to malate and then the malate can be converted to pyruvate by **malic enzyme** that will produce NADPH

- **NADH**: it is needed in malate dehydrogenase in the reduced form (NADH) for the conversion of oxaloacetate into malate and it comes from the glycolytic pathway (in the cytosol)) in the well fed state

Regulation of FA Oxidation & Synthesis

OXIDATION

- **Supply of Fatty Acids**
  From the adipocytes and degradation of triacylglycerols

  -Hormonal Control
  specifically glucagon and epinephrine
- **Entry into Mitochondria**
  long chain fatty acids are the most regulated

- **Availability of NAD^+**

SYNTHESIS

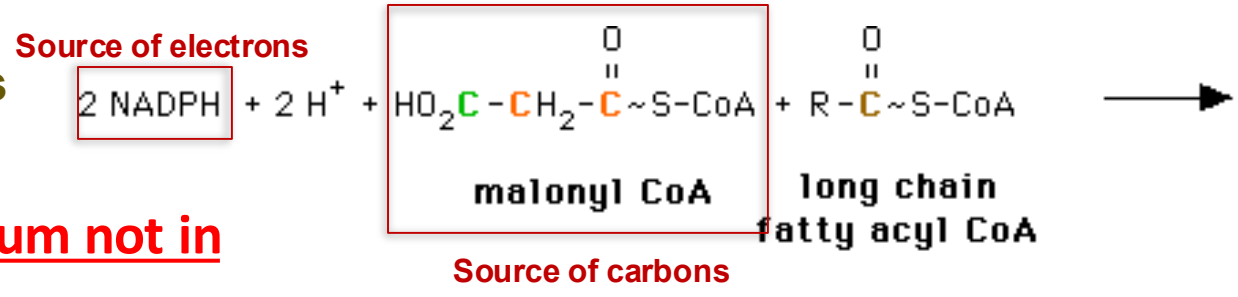
- **Regulation of ACC**
  to regulate the rate limiting step

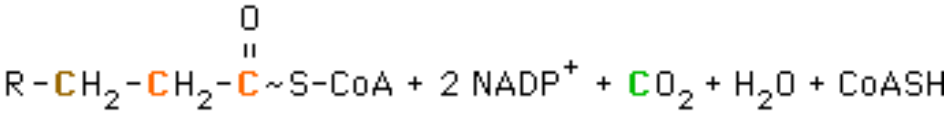
  -Allosteric Mechanism

  - Phosphorylation
  which is a covalent modification
- **Amounts of Enzymes**
  that are expressed by the binding proteins and the transcription factors that can affect the ACC

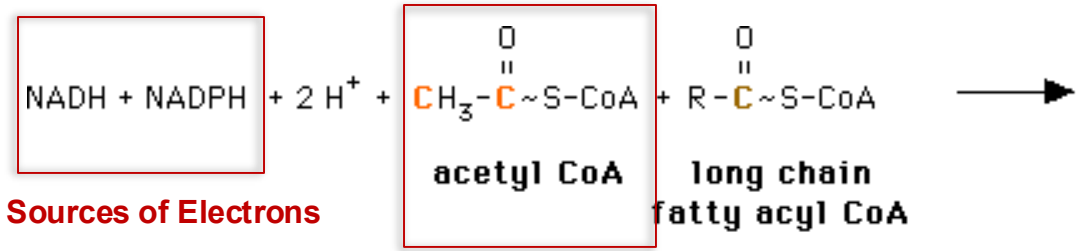
Further elongation of fatty acids

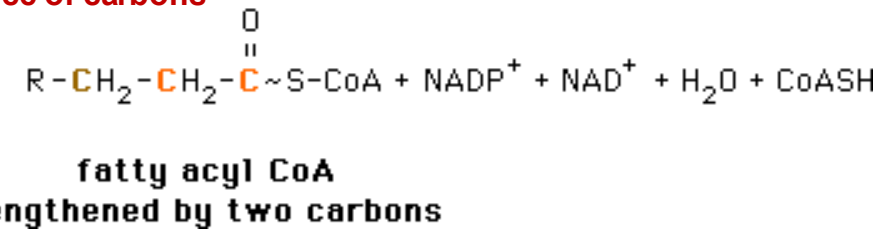
- **When we want to elongate the fatty acid chain such as palmitate which has 16 carbon we will use the following pathway**
- **Location: smooth endoplasmic reticulum not in the cytosol**





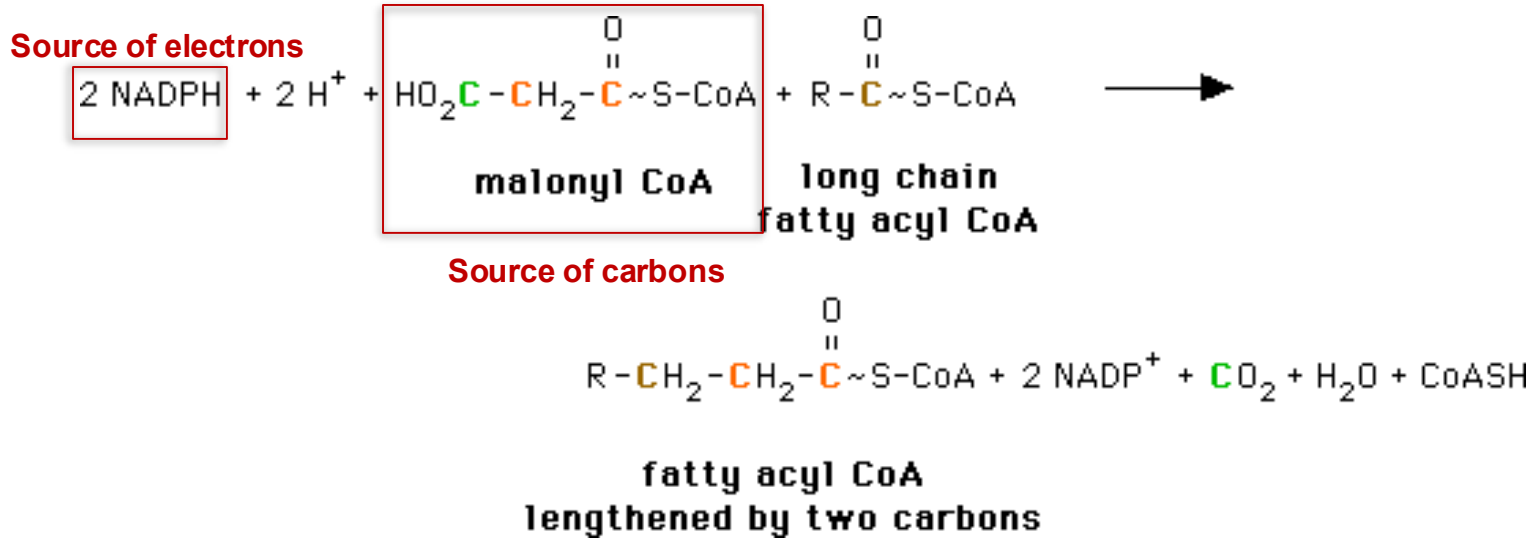
- **Different enzymes are needed but similar sequence of reactions.**(similar function)
- **Two-carbon donor**: Malonyl CoA (3 carbon molecule then we remove one of its carbons so that only 2c are added each time)
- **Source of electrons:** NADPH (will be oxidized)
- **No ACP or multifunctional enzyme is needed.**so no fatty acid synthase but there is other enzymes that are just like the components of this enzyme and perform



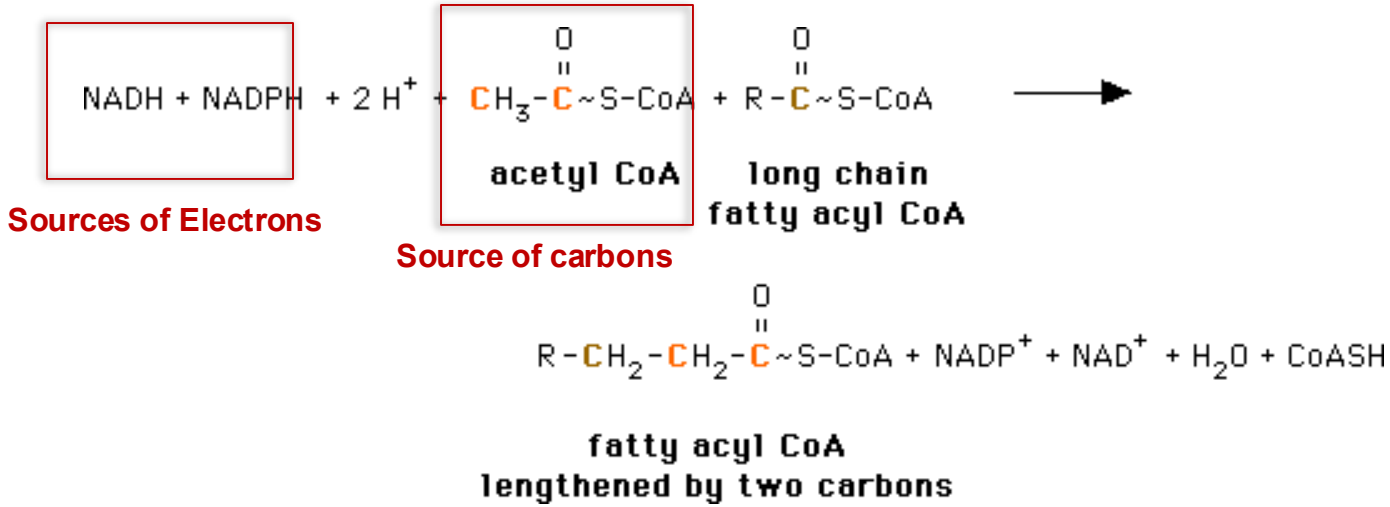


Further elongation of fatty acids

- **Note**: the **brain** has additional enzymes allowing it to produce the **very-long-chain fatty acids ([VLCFA] over 22 carbons)** as the brain is the most part that needs VLCFA

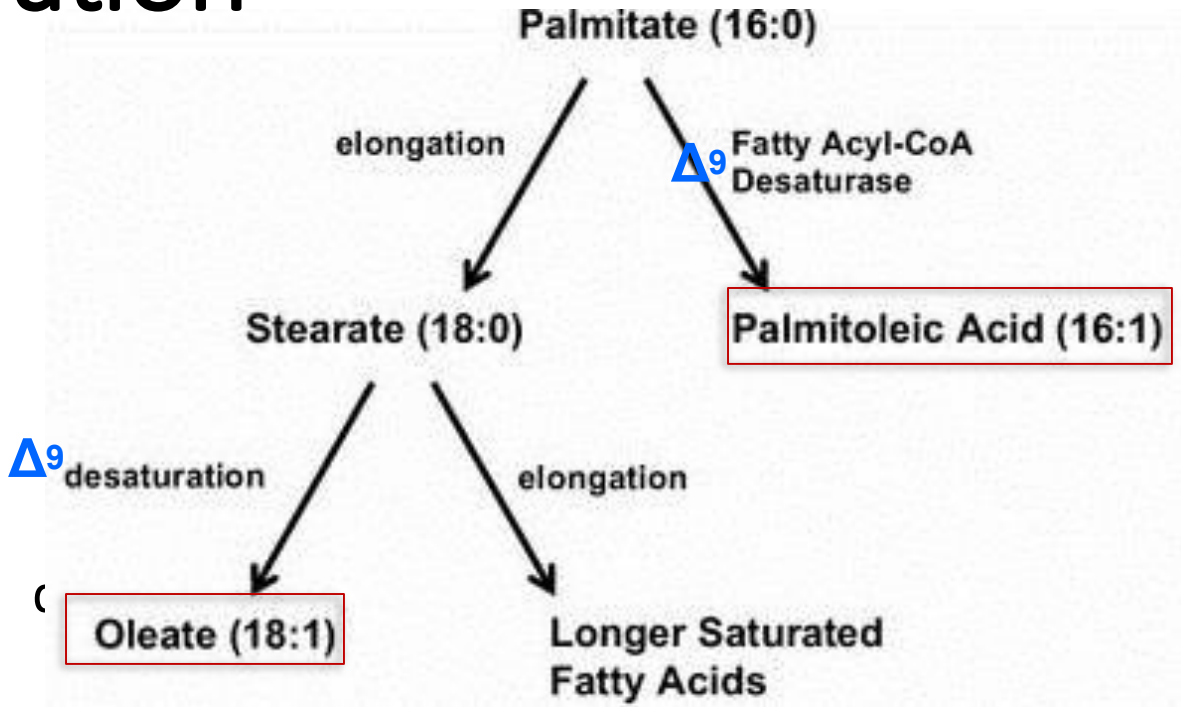


- Location: mitochondria it's where the brain cells make VLCFA and the SER can't make them they can only elongate the chain till 18-20C
- **Two-carbon donor:** Acetyl CoA
- **Source of electrons:** NADPH and NADH
- **Substrates**: fatty acids shorter than 16 (or medium **chains**)we are not going to start from the very beginning like 2c then 6c etc…



Chain desaturation

- **Enzymes:** fatty acyl CoA desaturases(they are multiple enzymes not only one depending on the location of the double bond for example Δ^9 Will form a double bond between c9 &c10)
- **Substrates:** long-chain fatty acids
- **Location: smooth endoplasmic reticulum**
- **Acceptor of electrons:** oxygen (O_2), cytochrome b5, and its FAD-linked reductase
- **Donor of electrons:** NADH
- The first double bond is inserted between carbons 9 an 10, producing oleic acid, 18:1(9), and small amounts of palmitoleic acid, 16:1(9).

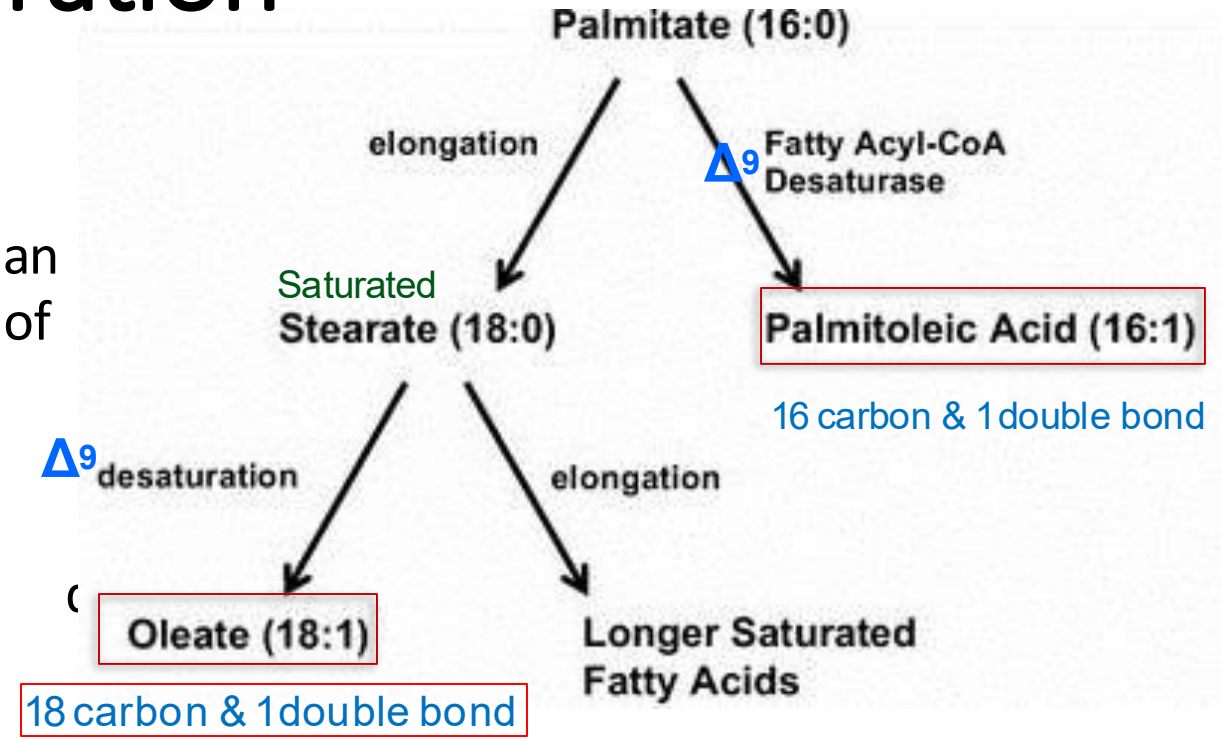


Humans have carbon 9, 6, 5, and 4 desaturases but cannot introduce double bonds from carbon 10 to the ω end of the chain. Therefore, the polyunsaturated ω-6 linoleic acid and ω-3 linolenic acid are essential.

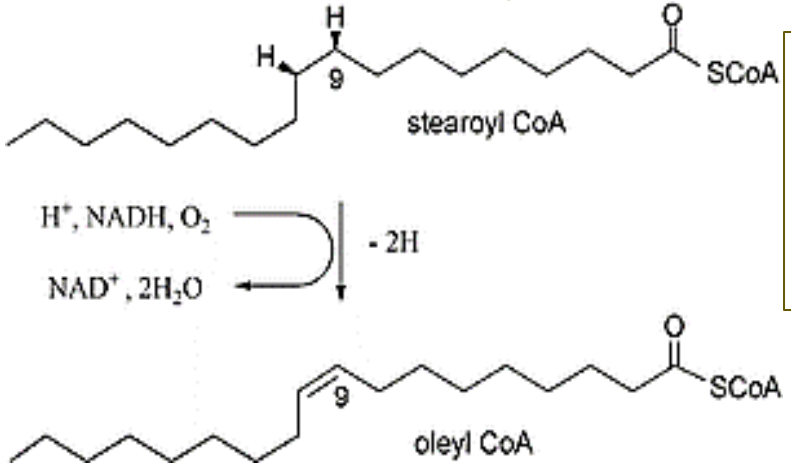
- ✓ Formation of polyunsaturated FA by elongation and desaturation
- ✓ Additional double bonds can be introduced by Δ^4 desaturase, Δ^5 desaturase and Δ^6 desaturase

Chain desaturation

- **Donor of electrons:** NADH
- The first double bond is inserted between carbons 9 an 10, producing oleic acid, 18:1(9), and small amounts of



- **The sites of desaturation are carbons number 4,5,6 and 9 in our body that's why we don't have enzymes that can introduce double bonds beyond carbon 10 and that's why we need the essential fatty acids like linoleic & linolenic who already have double bonds beyond carbon number 10 so we can use them as substrates to synthesize unsaturated fatty acids that have double bonds beyond carbon 10**



We have two oxidations one for the double bond and the other for NADH so they are the sources of electrons

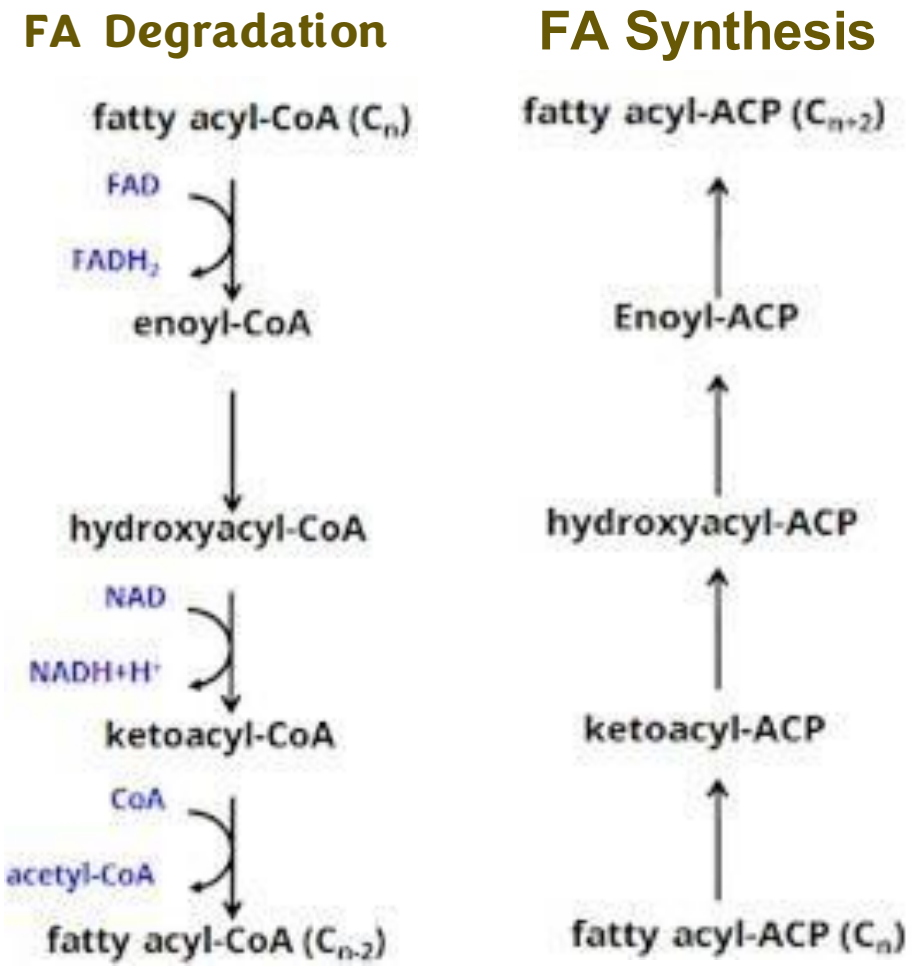
Humans have carbon 9, 6, 5, and 4 desaturases but cannot introduce double bonds from carbon 10 to the ω end of the chain. Therefore, the polyunsaturated ω-6 linoleic acid and ω-3 linolenic acid are essential.

- ✓ Formation of polyunsaturated FA by elongation and desaturation
- ✓ Additional double bonds can be introduced by Δ^4 desaturase, Δ^5 desaturase and Δ^6 desaturase

You need to memories this table :(

FA Synthesis vs. degradation

VARIABLE	SYNTHESIS	DEGRADATION
Greatest flux through pathway	After carbohydrate-rich meal	In starvation
Hormonal state favoring pathway	High insulin/glucagon ratio	Low insulin/glucagon ratio
Major tissue site	Primarily liver	Muscle, liver
Subcellular location	Cytosol	Primarily mitochondria
Carriers of acyl/acetyl groups between mitochondria and cytosol	Citrate (mitochondria to cytosol)	Carnitine (cytosol to mitochondria)
Phosphopantetheine-containing active carriers	Acyl carrier protein domain, coenzyme A	Coenzyme A
Oxidation/reduction coenzymes	NADPH (reduction)	NAD^+, FAD (oxidation)
Two-carbon donor/product	Malonyl CoA: donor of one acetyl group	Acetyl CoA: product of β-oxidation
Activator	Citrate	—
Inhibitor	Palmitoyl CoA (inhibits *acetyl CoA carboxylase*)	Malonyl CoA (inhibits *carnitine palmitoyltransferase-I*)
Product of pathway	Palmitate	Acetyl CoA
Repetitive four-step process	Condensation, reduction dehydration, reduction	Dehydrogenation, hydration dehydrogenation, thiolysis



In the mitochondria

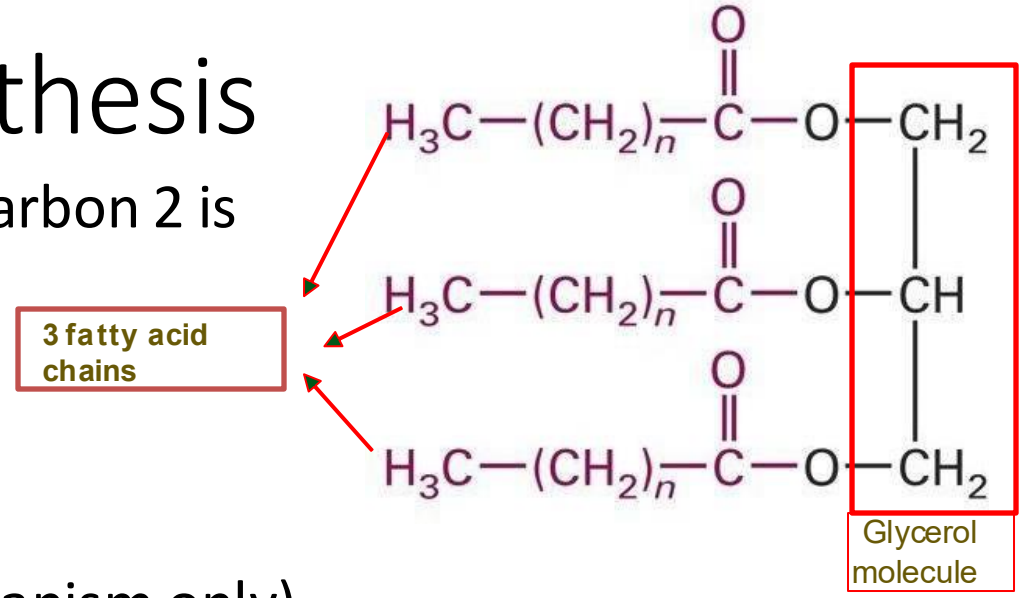
In the cytosol

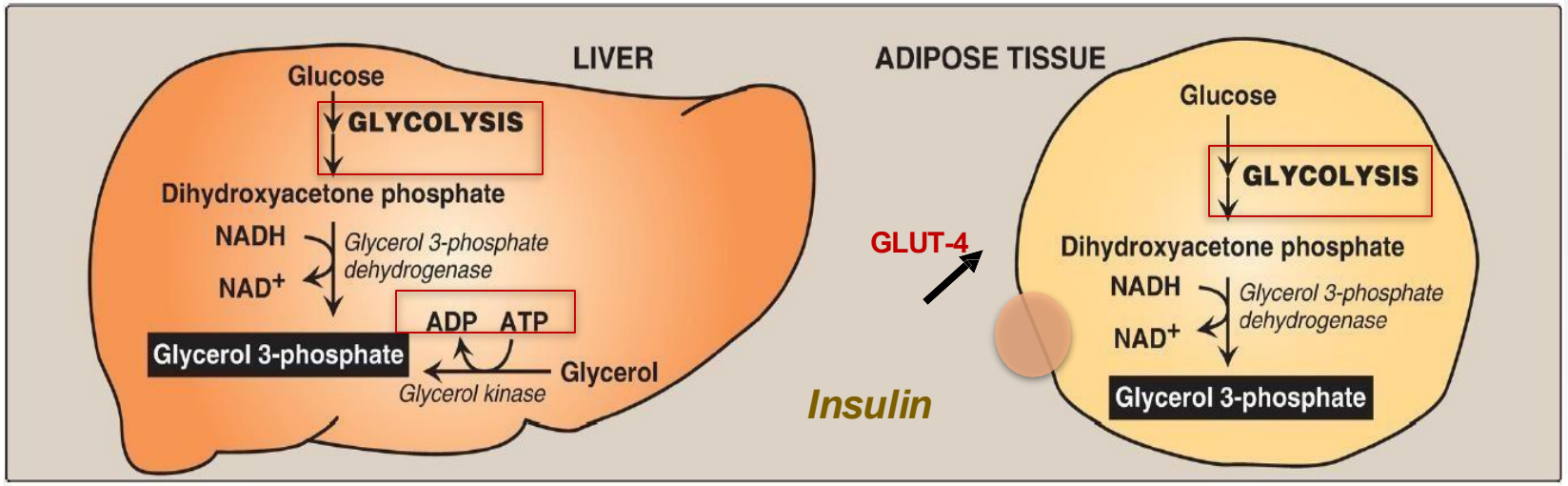
Whenever we have a high concentration of malonyl CoA in the cytosol it will inhibit the shuttling system that will transport the produced fatty acids in the synthetic pathway to the mitochondria for degradation

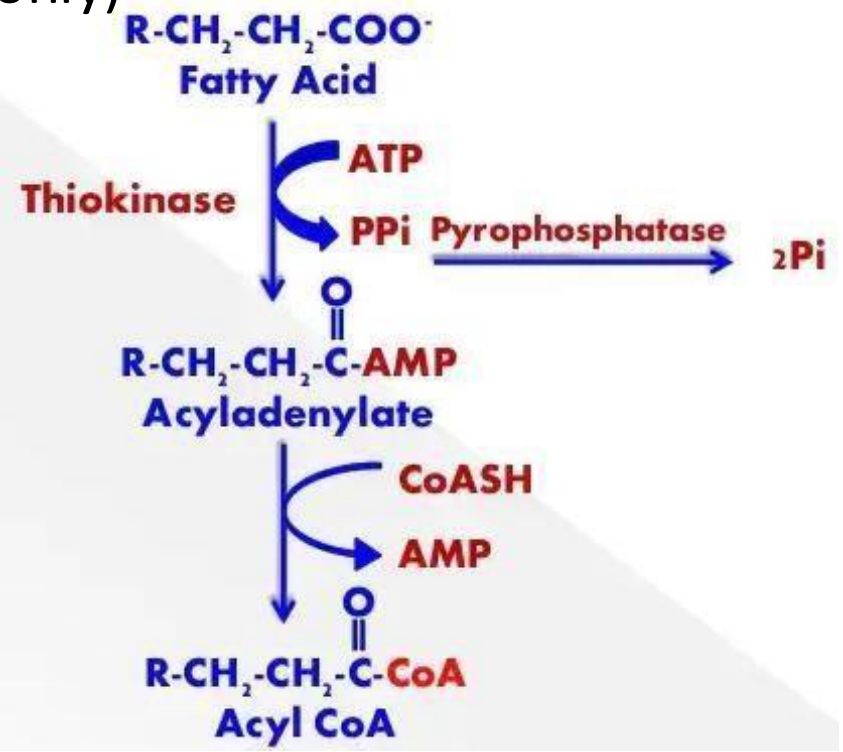
To be able to break down the bond between Acetyl CoA & the remaining structure of the fatty acids

Triacylglycerol structure and synthesis

- The fatty acid on carbon 1 is typically saturated, that on carbon 2 is typically unsaturated, and that on carbon 3 can be either.
- It's the typical but not the only form present
- **Synthesis involves three steps:**
  - Glycerol 3-phosphate synthesis
    - Liver (2 mechanisms) vs. adipose tissue (one mechanism only)
  - Activation of fatty acids
  - Synthesis of triacylglycerol



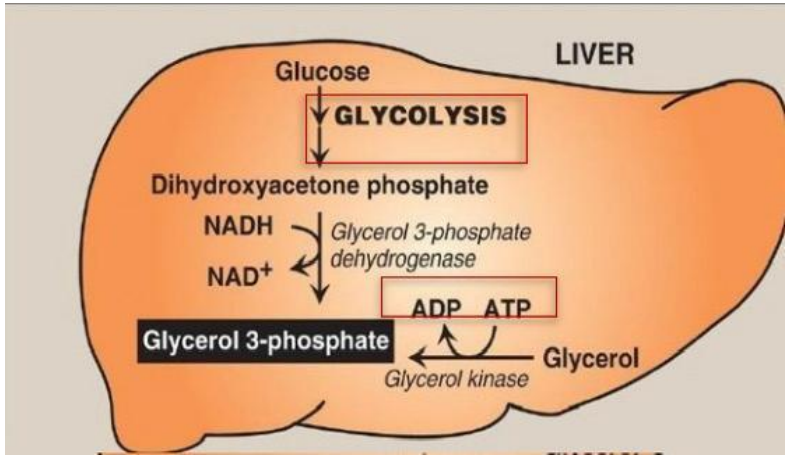




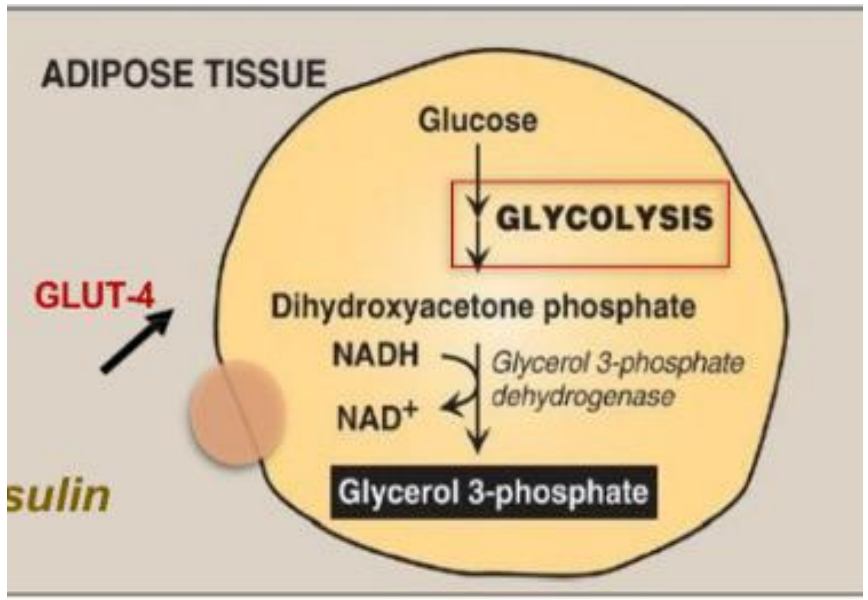
Explanation for the previous slide

- Whenever we synthesize fatty acids this means that we are in the well fed state after that we store them as triacylglycerols in the adipocytes and in the liver they can be used again to form triacylglycerols for the synthesis of different lipoproteins
- We are going to attach fatty acids to glycerol to make TAG

- To make TAG we need glecerol that must be activated by adding a phosphate to it forming glycerol 3 phosphate either by glycerol 3 phosphate dehydrogenase that can make dihydroxyacetone phosphate and then convert it into glycerol 3 phosphate by oxidation reduction reaction in the hepatocytes OR by the glycerol that can be up-taken from outside the liver and can be then phosphorylated by glycerol kinase which is only present in the liver to form glycerol 3 phosphate

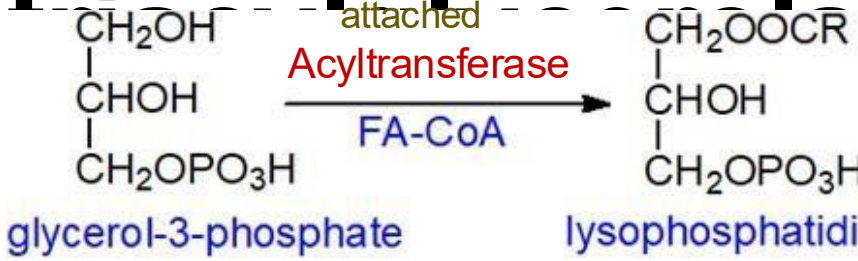


- In the adipose tissue there is only glycerol 3 phosphate dehydrogenase so they use the glucose that enters the adipocytes through glycolysis producing dihydroxyacetone phosphate and then it can be reduced into glycerol 3 phosphate after oxidizing NADH to NAD+
- Once we have glycerol 3 phosphate from either pathway we need to have the fatty acids in the active form by adding CoA group to them then we will start adding them sequentially by adding the 1st then the 2nd then removing a phosphate group to add the 3rd forming TAG



Synthesis of

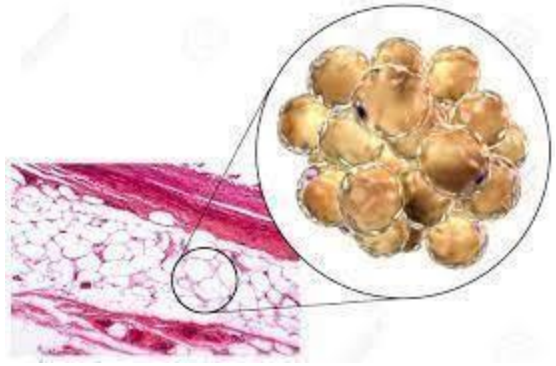
1st fatty acid will be attached



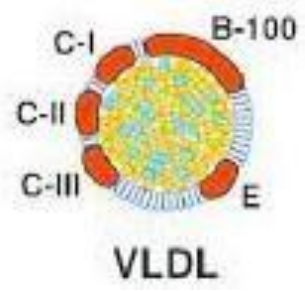
glycerol-3-phosphate — lysophosphatidic acid — phosphatidic acid → The parent molecule of glycerophospholipids

In liver and adipose tissue

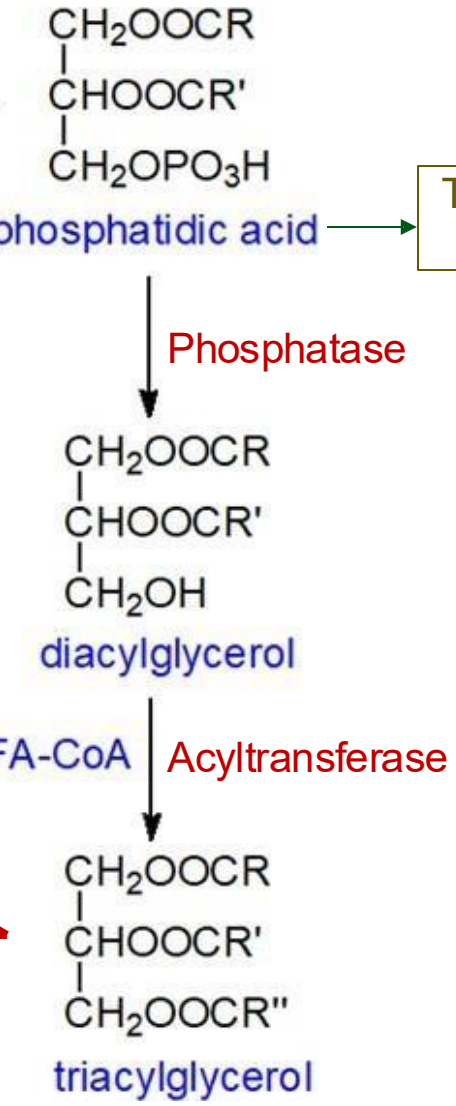
During esterification or forming an ester bond between the fatty acid and glycerol the CoA will be released forming lysophosphatidic acid



Adipose tissue
Stored as lipid droplets



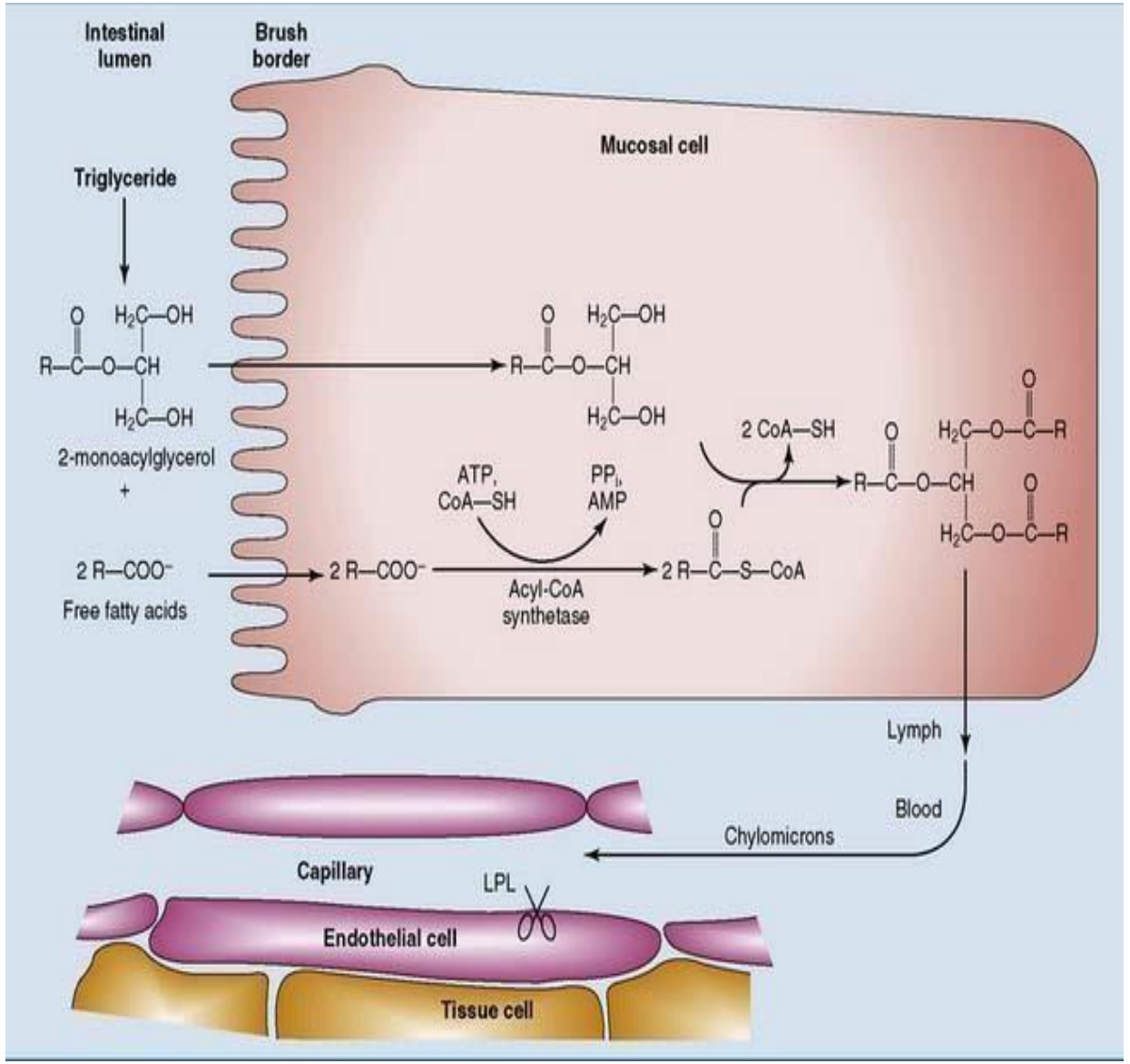
Liver
Little storage
Mainly packaged in VLDL



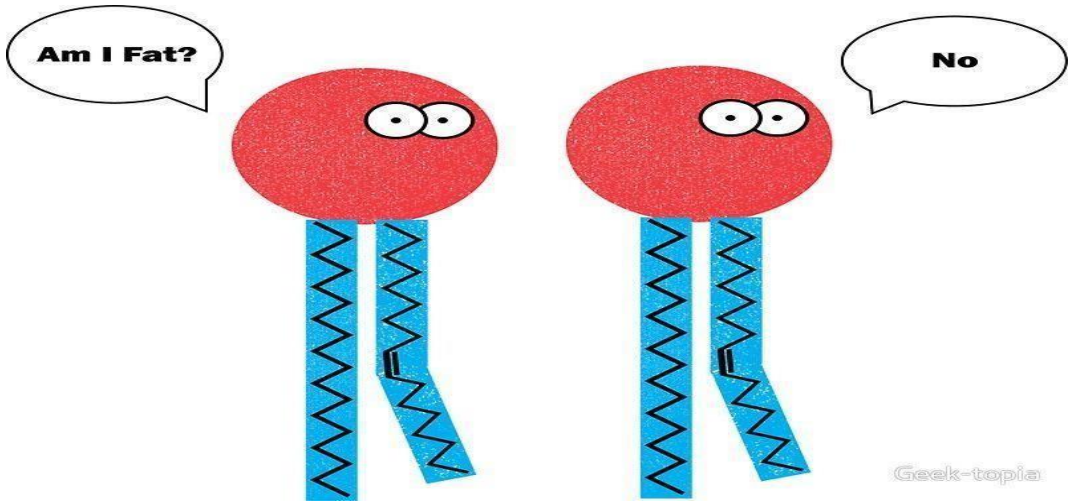
TAG resynthesis in intestinal mucosal cells

- In addition to these two pathways, TAG is synthesized via the MAG pathway in the intestinal mucosal cells during absorption.

- During TAG digestion they can't be absorbed as TAG they have to be digested and they become 2 free fatty acids and 2 monoacylglycerol which is a glycerol attached to carbon number 2
- If the free fatty acids are long chains they can be uptaken by proteins and by passive diffusion if they are short or medium chains but monoacylglycerol enter as a part of a mixed micelle to the mucosal cells
- Inside the mucosal cells the TAG are going to be resynthsized so they can be used to build the chylomicron that has the TAG as the major component so the acyleCoA synthatase will activate the fatty acids again into fatty acyleCoA then they can be attached again through this pathway to monoacylglycerol to make TAG that can be incorporated to the chylomicrons that will be released to the lymph then to the blood stream the TAG are going to be hydrolyzed by lipoprotein lipase which is the endothelial cell enzyme that reduces the content of them in chylomicrons making them chylomicron remnants then they will be uptake to the hepatocytes



Metabolism of Glycerophospholipids



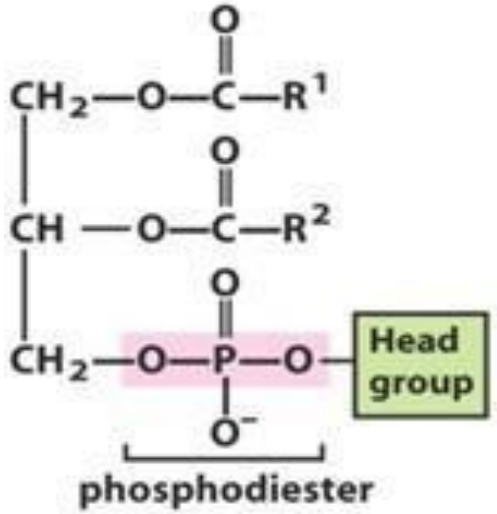
Dr. Diala Abu-Hassan

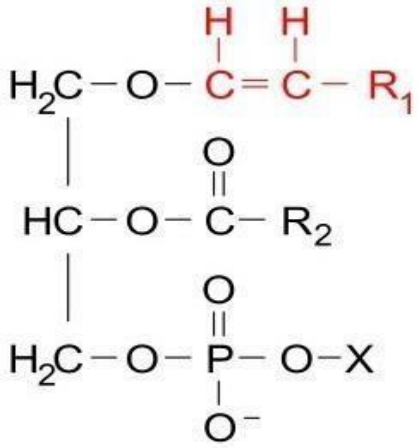
Lippincott's Biochemistry, Ch. 17

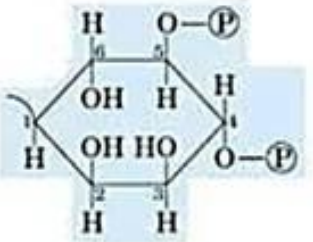
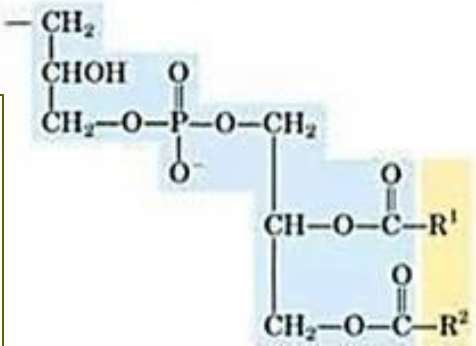
Structure and Classification of Glycerophospholipids

All glycerophospholipids share the same backbone (glycerol + 2 fatty acids + phosphate). Differences between them depend **only on the head group** attached to the phosphate.

- Phosphatidic acids **(the parent molecule)**
- Phosphatidylcholine (lecithin)
- Phosphatidylethanolamine
- Phosphatidylserine
- Phosphatidylinositol
- Cardiolipin
- Plasmalogens





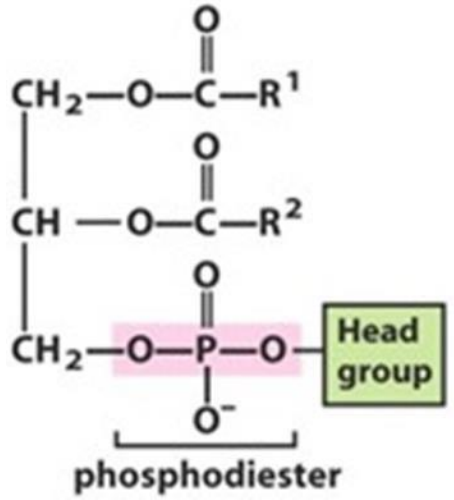
(I) Phosphatidic acid	—	— H
(III) Phosphatidylethanolamine	Ethanolamine	— CH_2—CH_2—$\overset{+}{N}H_3$
(II) Phosphatidylcholine	Choline	— CH_2—CH_2—$\overset{+}{N}(CH_3)_3$
Phosphatidylserine	Serine	— CH_2—CH(—$\overset{+}{N}H_3$)—COO^-
Phosphatidylglycerol	Glycerol	— CH_2—CH(—OH)—CH_2—OH
Phosphatidylinositol 4,5-bisphosphate	*myo*-Inositol 4,5-bisphosphate	
Cardiolipin	Phosphatidyl-glycerol	

By comparing the structures of choline and ethanolamine, it can be observed that ethanolamine has hydrogens (-$NH3^+$) in place of the methyl groups (- $N(CH3)3^+$) found in choline.

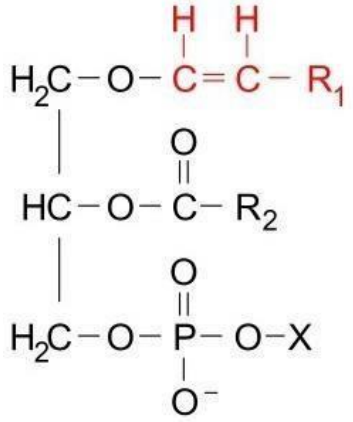
General structure of glycerophospholipids

- Glycerophospholipids are **membrane lipids** composed of:

1. Glycerol molecule (a poly alcohol).
2. **2** fatty acids attached to glycerol molecule on carbons 1&2 via **ester bonds**.
3. A phosphate group on carbon 3.



➢ the phosphate group has a **head group** attached via a **phosphodiester bond**; which can be as simple as a (I)**hydrogen** atom (phosphatidic acid) or a more complex structure as: (II)**choline** (phosphatidylcholine) or (III)**ethanolamine** (phosphatidylethanolamine), etc.



General structure of glycerophospholipids
Complex structures

1. **Cardiolipin** (inner mitochondrial membrane):

- Composed of 2 **phosphatidic acids** connected by a **glycerol** molecule.

➢ So, it has a PG; but it's not a PG itself.

2. **Plasmalogens:**

- Similar to GPs in structure, but **instead** of having a fatty acid on **carbon 1**, there's a **hydrocarbon chain** connected by an **ether** bond (but not ester).

✓ There's also modified GPs, including Phosphatidylinositol-4,5- Bisphosphate (**PIP2**) (and other inositol phosphates).

✓ PIP2 is involved in signaling, underneath the G-protein coupled receptors (**GPCRs**)- see slides 8&9.

- PG =phosphatidylglycerol
- GP =glycerophospholipids

Why do we need to make glycerophospholipids?

Important functions of glycerophospholipids other than their structural function in membranes

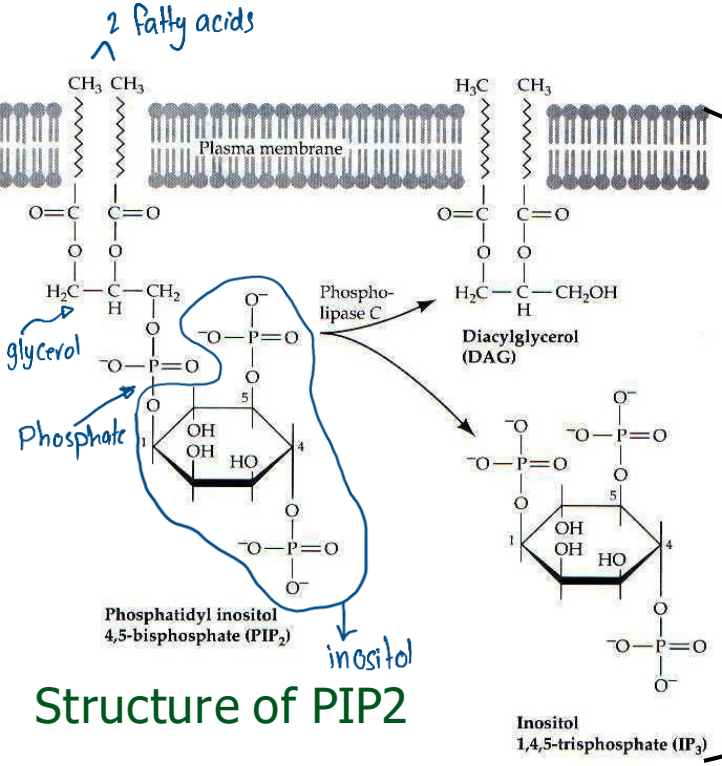
They are more common and abundant than sphingolipids

❖ Other functions of GPs:

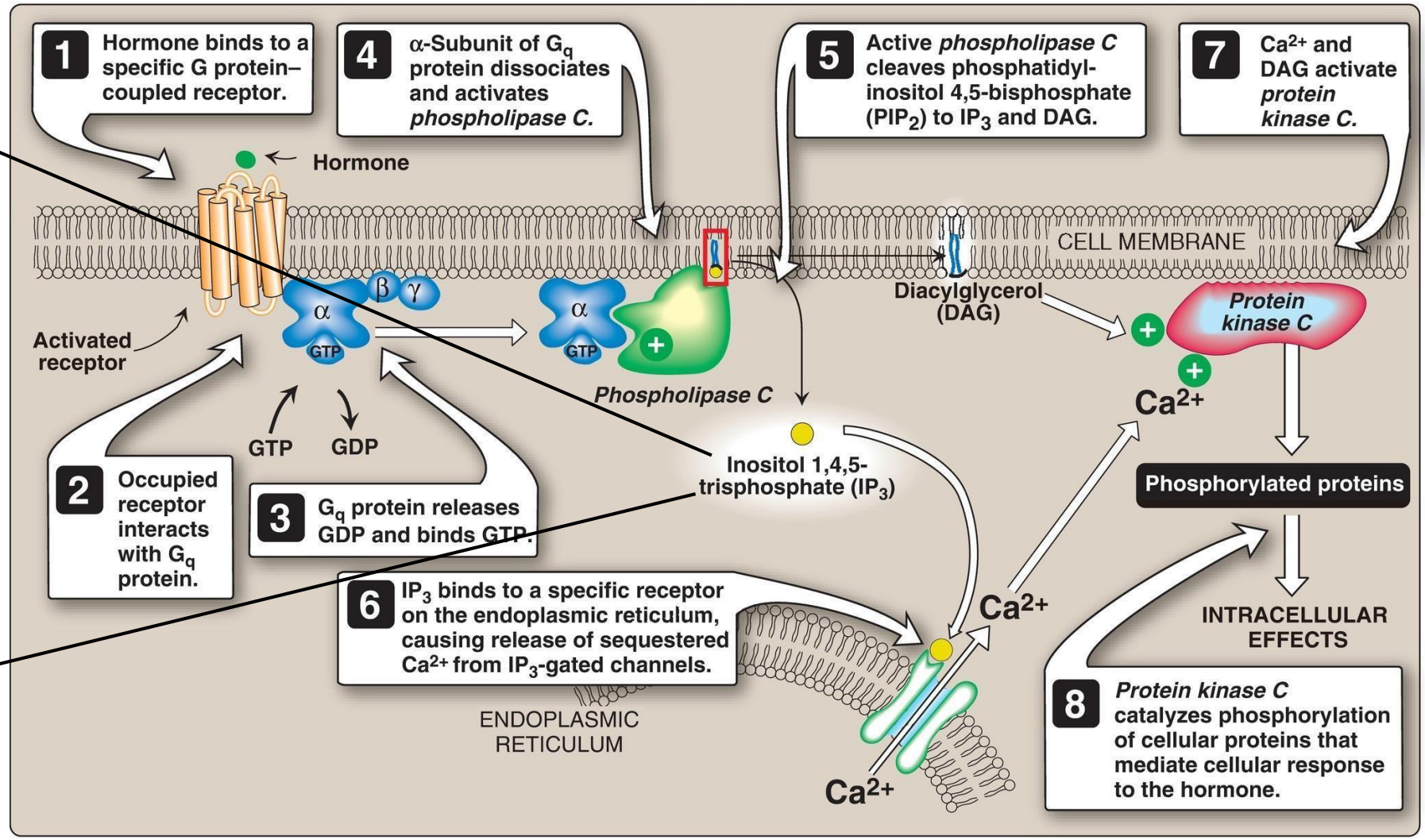
1. Signaling by specific types of GP, like PIP2 which is involved in GPCR signaling.

2. Membrane attachment (anchoring proteins to the membrane).

Signaling by PIP2 products



Structure of PIP2



Explanation- Signaling pathways

- Again GPCRs!

1. Activated by different hormones, growth factors, etc.
2. G-protein activation through the alpha subunit by exchanging GDP for GTP.
3. Alpha subunit is now active.
4. Eventually, alpha subunit activates downstream molecules.

➢ for example, the alpha subunit activates adenylyl cyclase which in turn activates another downstream molecules.

➢ But here the focus is on the activation of **phospholipase C**.

Explanation- Signaling pathways
PIP2 signaling

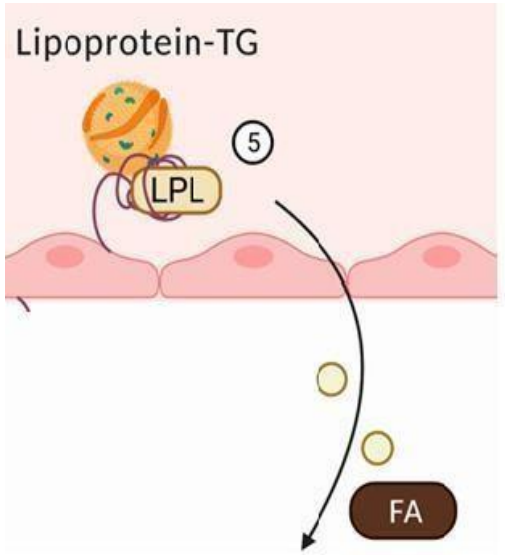
1. Following **alpha-subunit** activation, it **activates Phospholipase C.**
2. Phospholipase C is the enzyme that **degrades** membrane PIP2 into diacylglycerol (DAG, **hydrophobic**) and inositol triphosphate (IP3; negatively charged, thus **hydrophilic**).
    - Phospholipase C cleaves inositol with the phosphate groups (IP3), leaving the fatty acids associated with the glycerol molecule (DAG).
3. DAG remains in the membrane (because of its hydrophobic nature of the FAs), while **IP3** acts as a **second messenger** (leaves the membrane).
4. IP3 binds to the Ca^{2+} channels on the ER membrane (**IP3-gated calcium channels**).
5. Channels **open**, allowing **Ca^{2+}** to exit to the **cytosol**.
6. Ca^{2+} **activates** protein kinase C (**PKC**).
7. PKC **regulate** molecules in the **cytosol**.

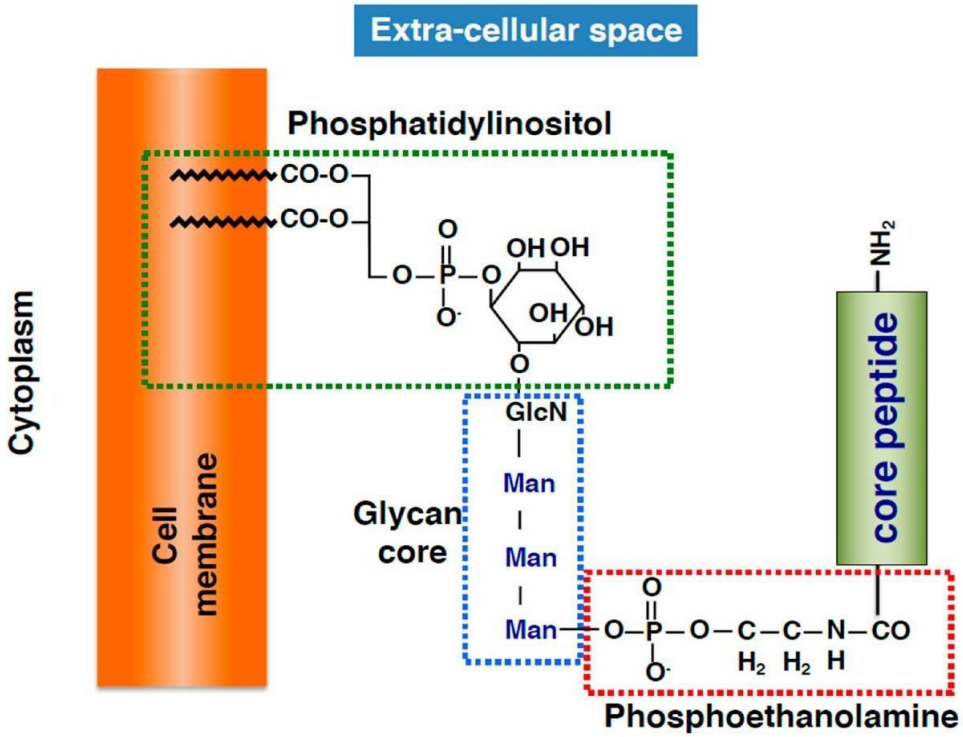
➢ The result, different cellular effects and responses.

GPI for membrane attachment

Glycosyl phosphatidylinositol (GPI) attaches proteins to the plasma membrane, **anchoring proteins via phosphatidyl inositol.**

- Advantage: lateral mobility
  - Example: lipoprotein lipase





✓ This is phosphatidylinositol (in membrane).
- The inositol is connected to sugars (**glycan core**).
- These sugars are attached to phosphoethanolamine.
- The phosphoethanolamine is attached to the protein (core peptide).

GPI for membrane attachment

❖ Advantages/ importance:

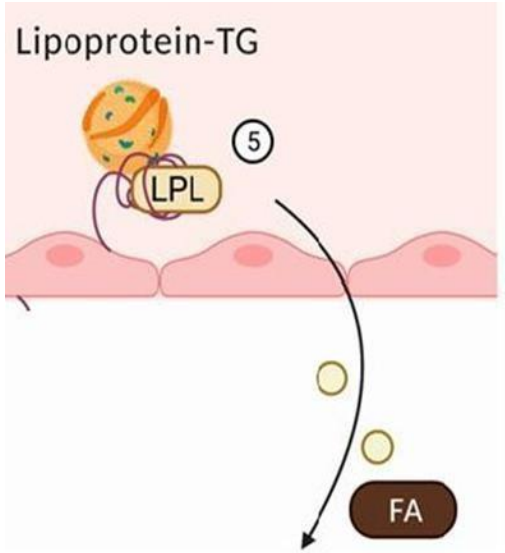
1. Connection is covalent **strong attachment.**
2. Provision of **flexibility** and ability to **move.**

✓ These proteins are more mobile within the lipid bilayer because they are attached to the outer leaflet via the GPI anchor, allowing for rapid lateral movement. This can facilitate quick interactions and signaling. On the other hand, transmembrane proteins embedded within the lipid bilayer can be less mobile due to their integral nature and interactions with the cytoskeleton.

❑ If this protein is inserted as an **integral membrane protein**, its movement is restricted to the **plane of the membrane** itself, where it continuously moves **laterally** within the lipid bilayer

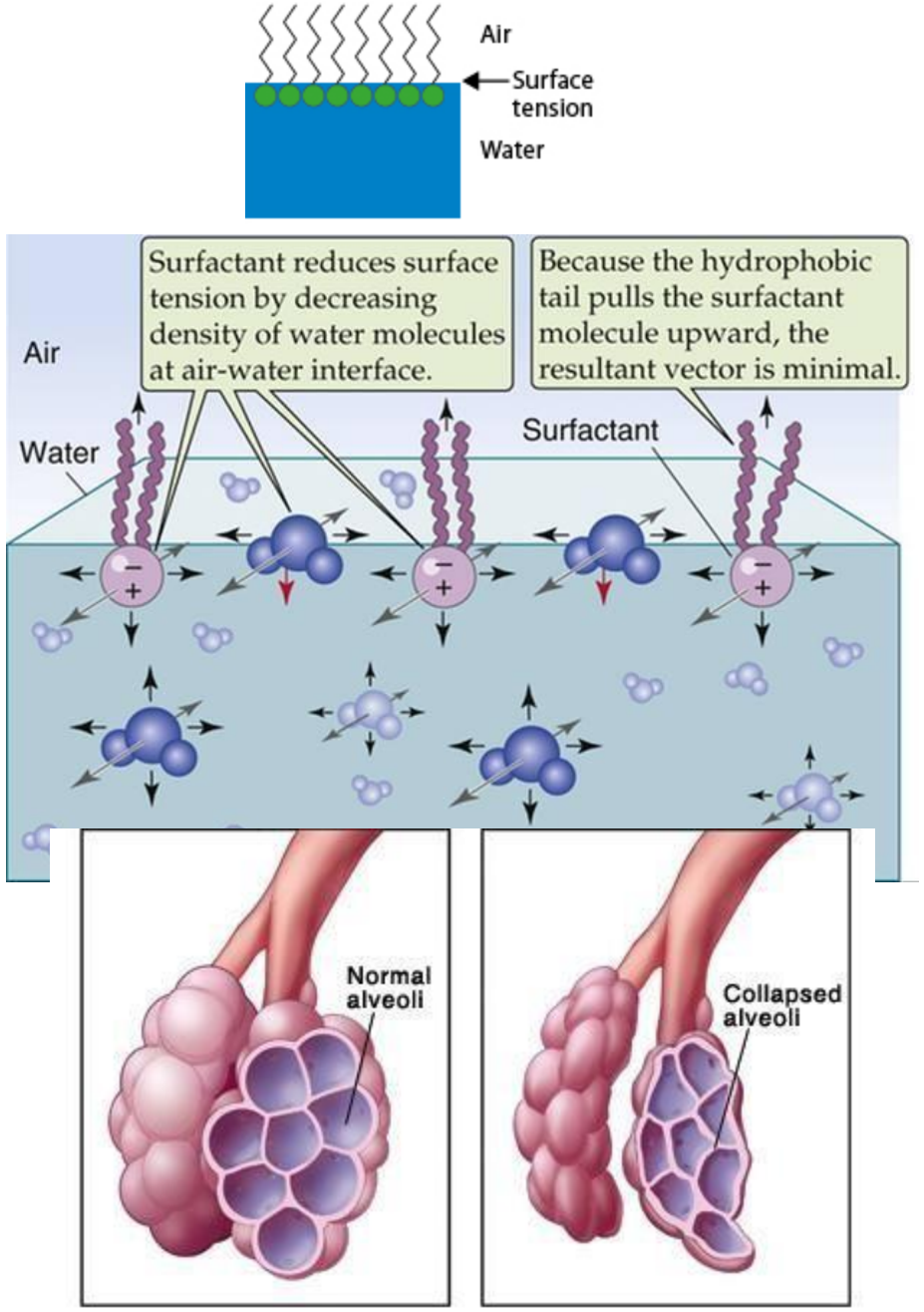
❖ **Lipoprotein lipase (LPL)** is an enzyme that:

1. **Originates** from the membrane of endothelial cells.
2. **Degrades triglycerides** in various types of circulating lipoproteins, converting them into different forms (into free fatty acids and monoacylglycerols which can the be taken up by tissues and used for energy production and storage).
3. Is **anchored** to endothelial cell membranes via **GPI anchors,** providing flexibility for its activity in blood vessels.



Application: Surfactants

- Surfactants are a complex mixture of lipids (90%) and proteins (10%) that make the extracellular fluid layer lining the alveoli and are secreted by type II pneumocytes in the lungs.
- Dipalmitoylphosphatidylcholine (DPPC) is the major lipid in surfactants.
- Surfactants serve to decrease the surface tension of the fluid layer allowing reinflation of alveoli and preventing alveolar collapse (atelectasis).
- Respiratory distress syndrome (RDS) in preterm infants is associated with insufficient surfactant production and/or secretion.
- Prenatal administration of glucocorticoids shortly before delivery to induce expression of specific genes.



Explanation- Surfactants

- The lungs are composed of a functional unit called the **alveolus**, which resembles a small sac with very thin walls.
- Inhalation makes the sacs **expand** while the opposite occurs in exhalation.
- During exhalation and **deflation** of the sacs, **surface tension** builds up inside the alveoli due to interactions between **water molecules.**
- **High surface tension** can cause the alveolar walls to **collapse**, leading to increased resistance during the next inhalation—much like inflating a balloon that's deflated – needs more effort due to surface tension.

➢ As a result, greater effort is needed to breathe; there's resistance.

- to counteract this, **type II pneumocytes** secrete a greasy material called **surfactant**, which reduces surface tension.

- Surface Tension: This is the force exerted by the liquid lining the alveoli that causes the surface to contract. It's due to the cohesive forces between water molecules.
- Role in Exhalation: During exhalation, the alveoli deflate, and the surface tension increases, helping to push air out of the lungs.

Explanation- Surfactants (Cont'd)

- Surfactant allows the alveoli to **slide easily** against each other, making inflation during breathing much easier.
- The key component of surfactant is **dipalmitoyl phosphatidylcholine** (**DPPC**), which is made of two palmitic acid chains attached to phosphatidylcholine.
- ➢ By reducing surface tension, surfactant ensures **effortless breathing** in healthy individuals.
- Premature babies often lack sufficient surfactant production because their lungs are underdeveloped, causing **respiratory distress syndrome** (**RDS**), where high resistance to breathing makes inhalation difficult.
- RDS can be treated with Dexamethasone.
- To address this issue, **glucocorticoids** like **dexamethasone** are administered to pregnant women at risk of preterm delivery, it **induces the expression** of genes responsible for producing surfactant, specifically DPPC; therefore, reducing the risk of respiratory distress in premature babies.
- Care is provided to premature babies if they still have insufficient surfactants, so they are placed in incubators to support breathing until lungs maturation.

Extra explanation

❑ Mechanism of Action:

Surfactants are **amphipathic** molecules. The hydrophobic ends of surfactant molecules insert themselves into the water layer lining the alveoli. This disrupts the **hydrogen bonds** between water molecules, which are responsible for the high surface tension.

❑ Benefits in the Alveoli:

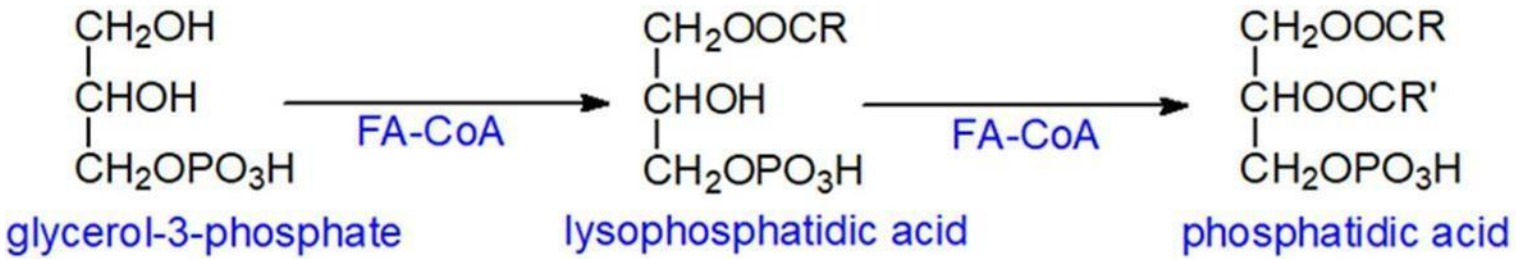
1. **Preventing Collapse:** Lower surface tension reduces the risk of alveolar collapse (atelectasis), especially during exhalation when the alveoli shrink.

2. **Ease of Re-inflation:** Reduced surface tension makes it easier for the alveoli to re-inflate during inhalation.

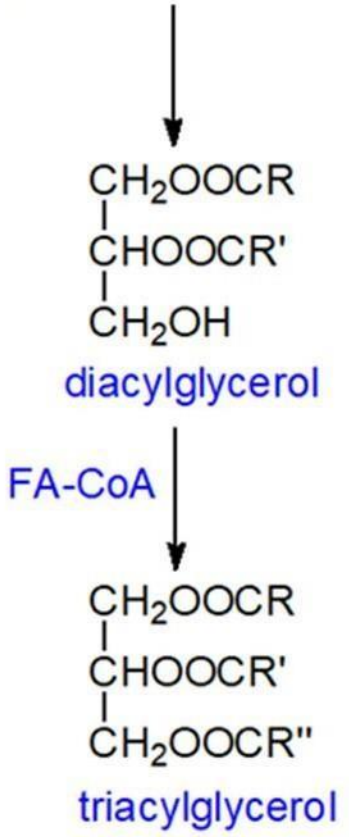
3. **Uniform Expansion:** Smaller alveoli would have higher internal pressure due to higher surface tension, but surfactant helps to equalize this pressure across alveoli of different sizes, which helps in maintaining uniform expansion of alveoli, which improves gas exchange efficiency.

- ✓ In preterm infants, a **deficiency** in surfactant can lead to respiratory distress syndrome (**RDS**). **Surfactant replacement therapy** is often used to treat this condition.
- ✓ Conditions like acute respiratory distress syndrome (**ARDS**) can benefit from treatments that enhance surfactant function.

Synthesis of phosphatidic acid (the parent GP)



Phosphatidic acid is the precursor of glycerophospholipids.

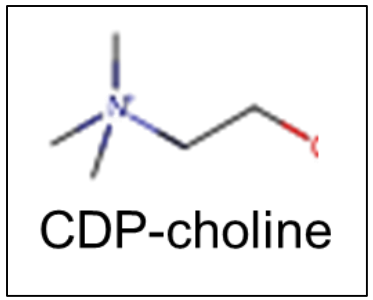


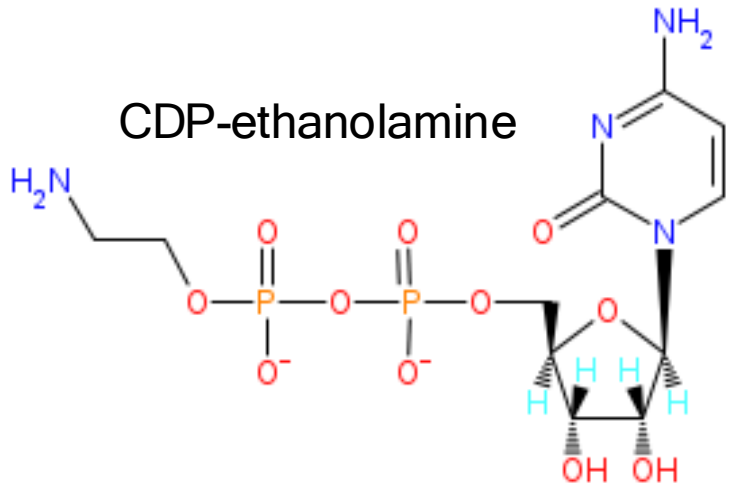
1. **Glycerol-3-phosphate** (G3P), obtained from sugar metabolism.
   - Directly as G3P or by the conversion of dihydroxy acetone phosphate (DHAP).
2. **Fatty acyl transferase enzyme** transfers a FA (activated) to the first carbon, producing **lysophosphatidic acid.**
3. Again, the transfer of the second fatty acid to the second carbon, producing **phosphatidic acid**.

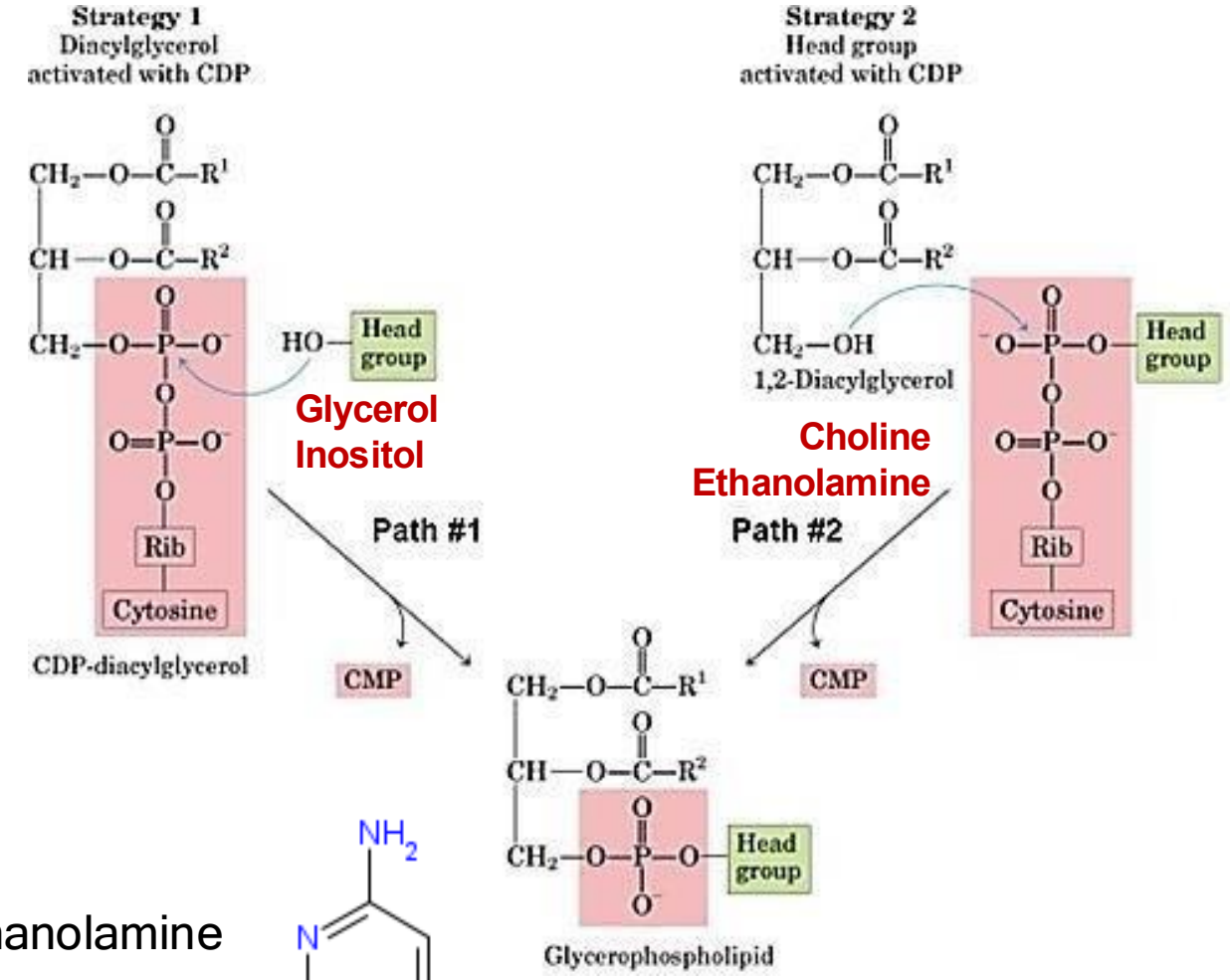
➢ For the storage of TAGs in adipocytes, the phosphate group can be removed to produce **diacylglycerol**, then the third FA is added to it, producing triacylglycerol (TAG). (synthesis!)

Synthesis

- Location: smooth ER
  - Except for ether lipids
- Activation by CDP is necessary. Either:
  - CDP-DAG (glycerol, inositol)
  - CDP-alcohol (choline, ethanolamine)
- Sources of choline and ethanolamine
  - diet
  - synthesis
  - re-cycling from the turnover of pre-existing phospholipids
- Diet is still essential since demand > supply







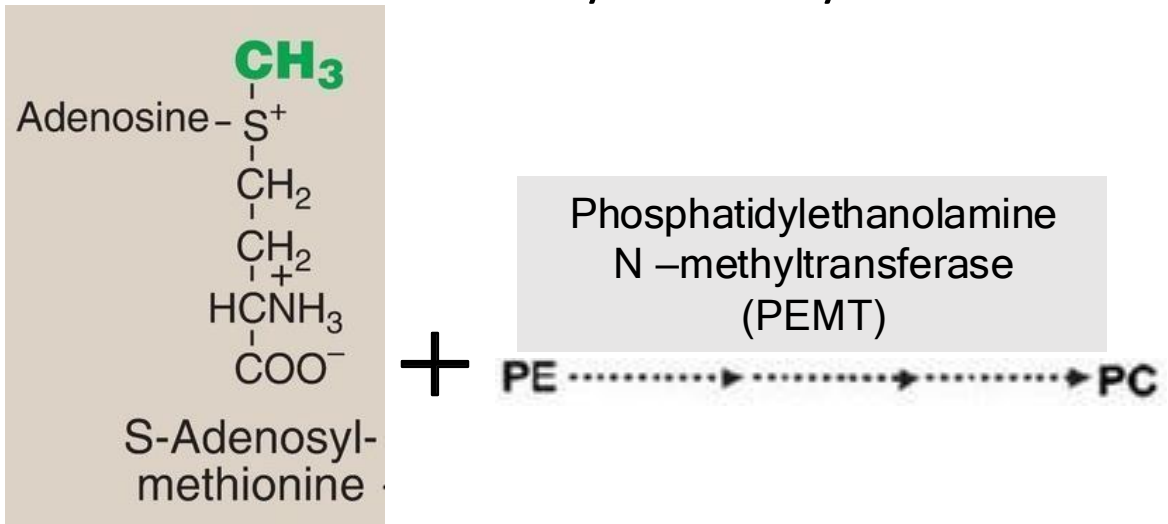
The nucleotide initially enters as CTP and then becomes CDP once added, just like addition of UTP.

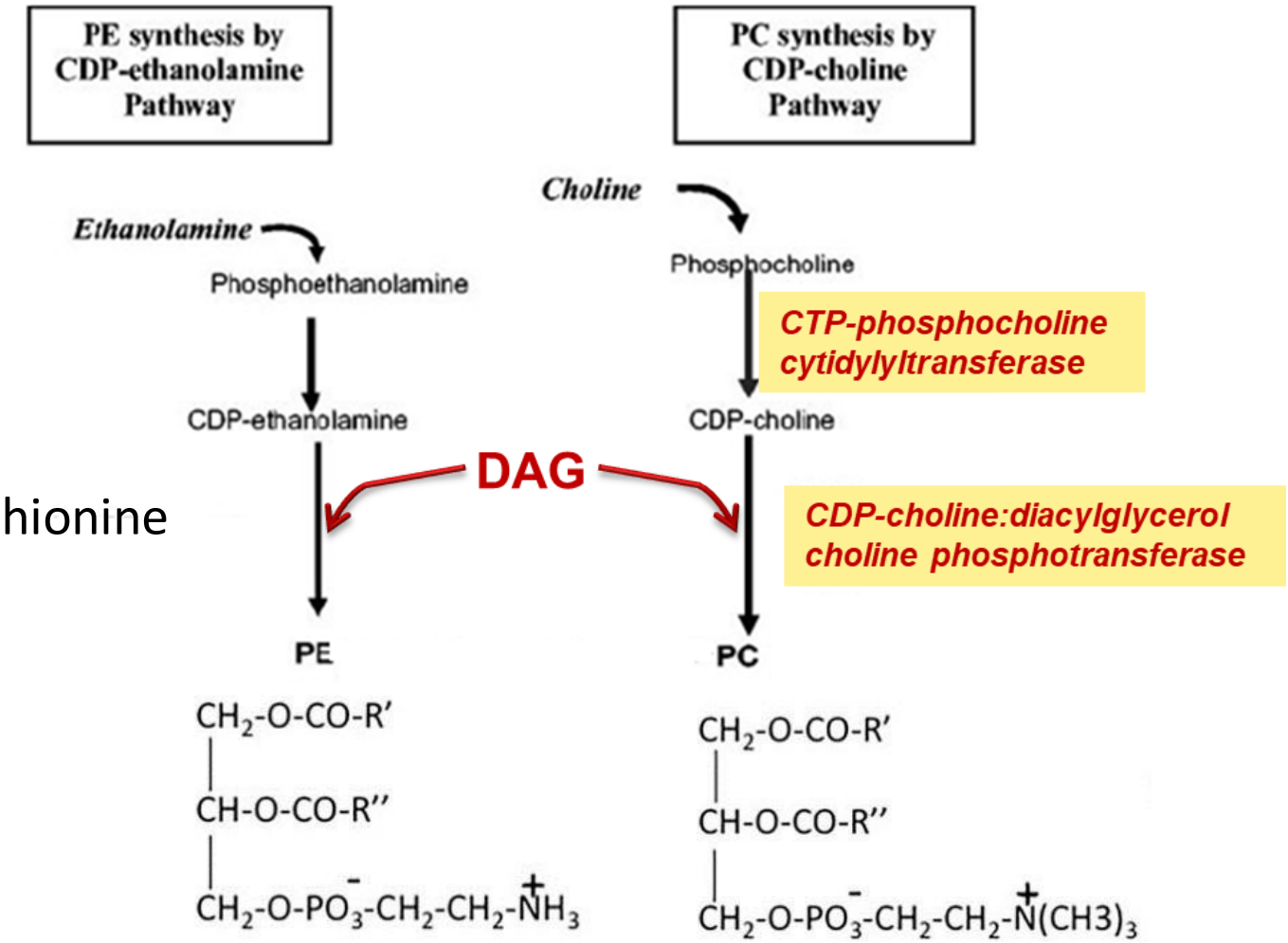
Synthesis of *ph*-choline and *ph*-ethanolamine

- Choline or ethanolamine are phosphorylated by *kinases*, then activated by *transferases* to form, CDP-choline or CDP-ethanolamine.
- Choline phosphate or ethanolamine phosphate is transferred from the nucleotide (releasing CMP) to DAG.

➢ Synthesis of ph-choline from ph-ethanolamine

- Methyl groups are donated by S-adenosylmethionine to convert PE to PC by PE methyltransferase.





Synthesis, generally and specifically(1).

Ph-choline and Ph-ethanolamine.

- The creation of phospholipids like **phosphatidylcholine** and **phosphatidylethanolamine** involves similar steps (as phosphatidic acid) but varies based on the specific head group used (either choline or ethanolamine).

❖ steps:

1. Head groups are added to CTP nucleotides by a **transferase**. (CDP-head group)
2. Diacylglycerol (DAG) is obtained.
3. The head groups are **transferred** to DAG using a **CDP nucleotide**, by the action of a **phosphotransferase**.
4. After the attachment of the head group, CDP nucleotide is **cleaved** (the cut of phosphate, ribose, and cytosine), producing **cytidine mononucleotide** (CMP).
5. Now, depending on the head group; either phosphatidylcholine or phosphatidylethanolamine is produced.

Synthesis, generally and specifically(2).

Others, ex. Ph-inositol and Ph-glycerol.

- For the synthesis of others, the process is similar but the order is different.

❖ Brief steps:

1. **CDP nucleotide**, but instead of carrying the head group, now it carries **DAG** (CDP-DAG).
2. Addition of the **head groups to DAG** by a transferase.
3. Cleavage and **removal** of **CMP**.
4. **Production** of GPs.

➢ Notes about synthesis:

1. The synthesis occurs primarily in the **SER**, but they can come from diet.
2. Phospholipid production doesn't always start from scratch; existing molecules can be **recycled**. For example, **phosphatidylethanolamine** can be converted into **phosphatidylcholine** when needed, which adds flexibility to the body's lipid synthesis process.

phosphatidylcholine is an emulsifier in different food products.

Explanation- Recycling Process.

- Recall structural differences between choline ($-N(CH_3)_3^+$) and ethanolamine ($-NH_3^+$).
- By a methylation reaction, PE can be converted to PC by the action of a **methyltransferase**.
- **Phosphatidylethanolamine N-methyltransferase** (PEMT), adds methyl groups to PE to be converted to PC.

- *From where do we get these methyl groups?*

➢ Addition of a single carbon unit, this carbon unit could be (1)Methyl group ($-CH_3$), (2)formyl group (-C=O) or (3)formimino group (-CHNH), etc.

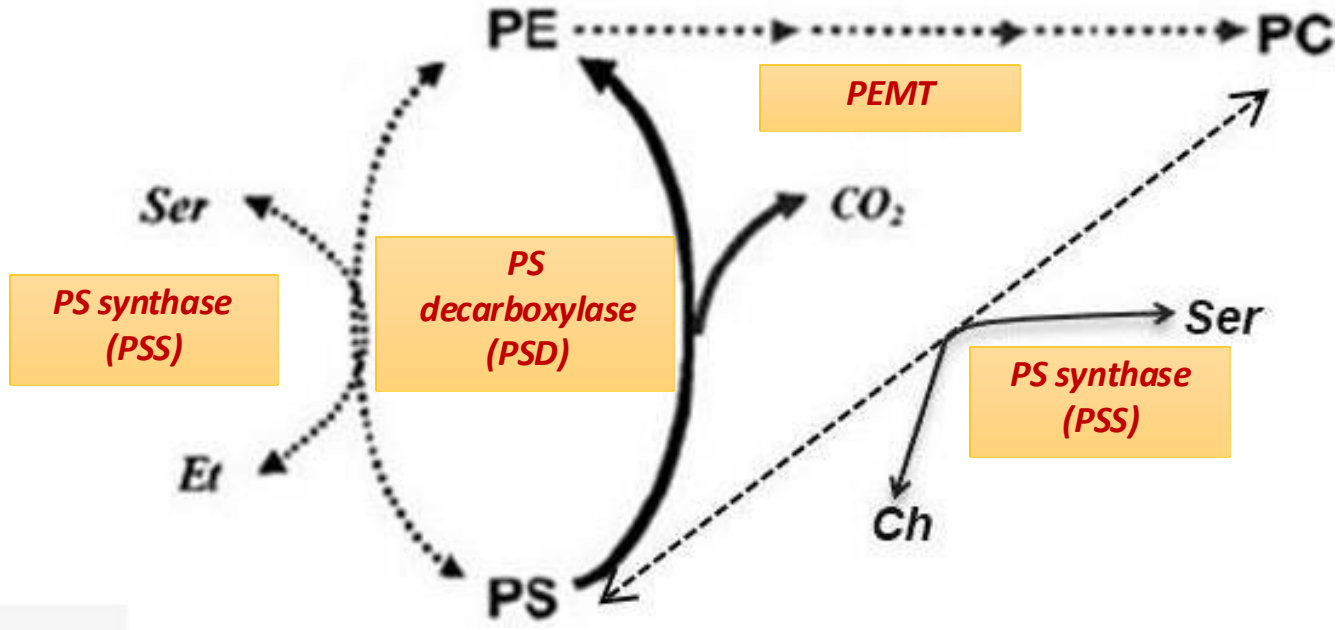
➢ **S-adenosylmethionine** (SAM) that comes from methionine metabolism, transfers **methyl** groups. That is the terminal carbon of methionine can be **cleaved** and used for this transfer of methyl group to a recipient.

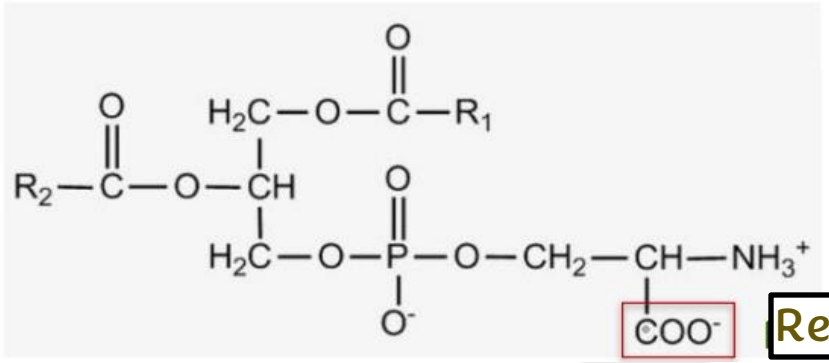
➢ Also, folic acid (**vit. B9**) can transfer methyl groups or other single carbon units More diversity.

PE =Phosphatidylethanolamine
PC =Phosphatidylcholine

Synthetic pathways for and from ph-serine

- The liver requires another mechanism to produce PC because it uses it to make bile and other plasma lipoproteins.
- PS is decarboxylated to PE by PS decarboxylase (PSD). It can be methylated by PEMT to PC
- PS is exchanged from PE or PC by PS synthases (PSS).





phosphatidylserine

Removal of the carboxyl group from PS, will yield PE.

Metabolism of phosphatidylserine(PS)

❖ exchange between PE and PS:

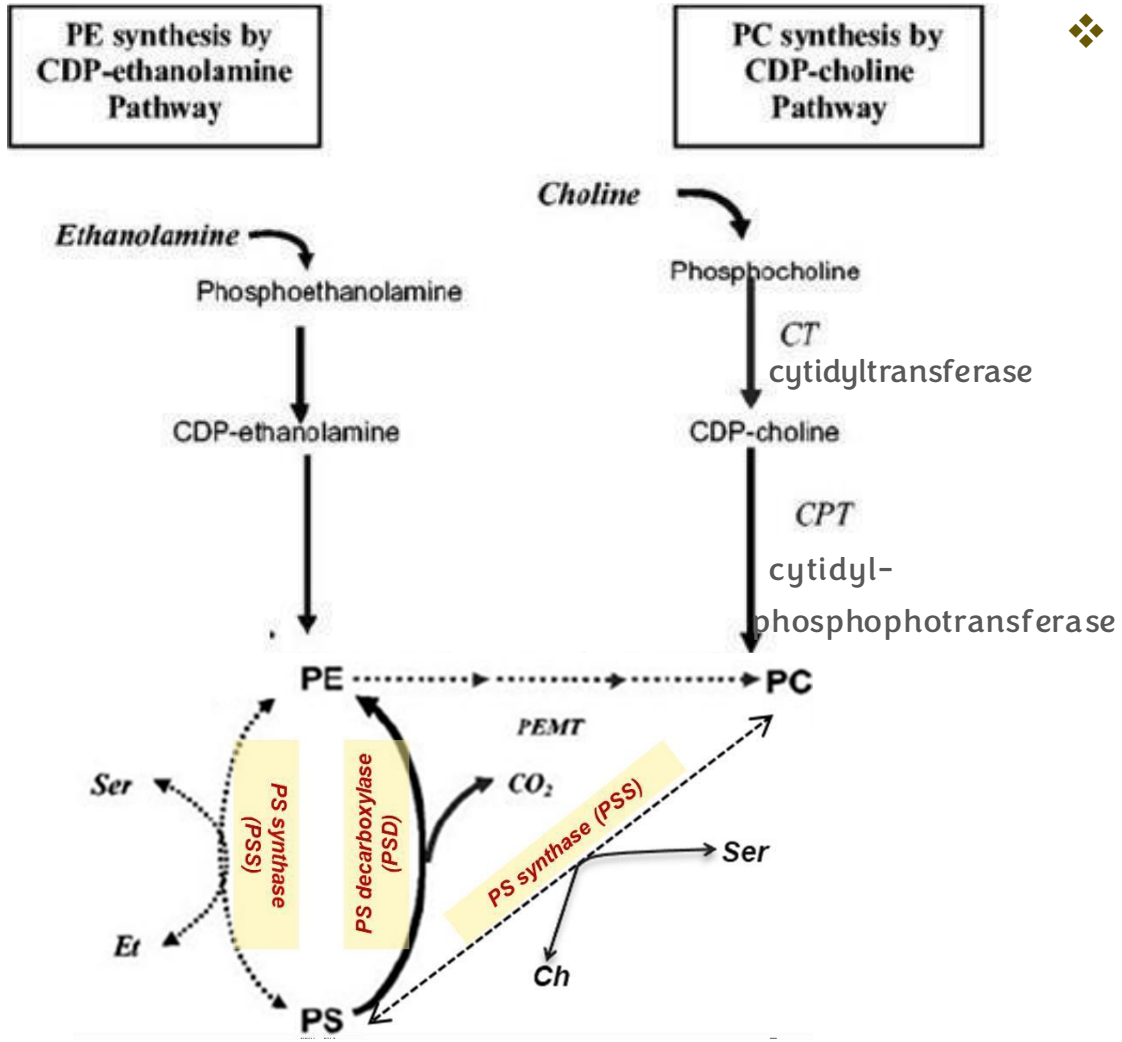
- By a **reversible** exchange reaction, PS can be produced from PE, by replacing ethanolamine with serine A.A using phosphatidylserine **synthase**, or the opposite, to produce PE instead.
- In addition, decarboxylation of PS gives PE.

❖ exchange between PC and PS:

- Phosphatidylserine synthase can also remove the choline and replace it with serine; producing PS from PC in a reversible manner.

Summary of synthesis pf PE, PC, and PS

1. Phosphorylation of the head group (choline or ethanolamine) by kinases.
2. Attach the head group to a CDP molecule (which entered as CTP) by a transferase.
3. CDP-head group (choline or ethanolamine) is transferred to a diacylglycerol using a phosphotransferase to produce PC and PE.



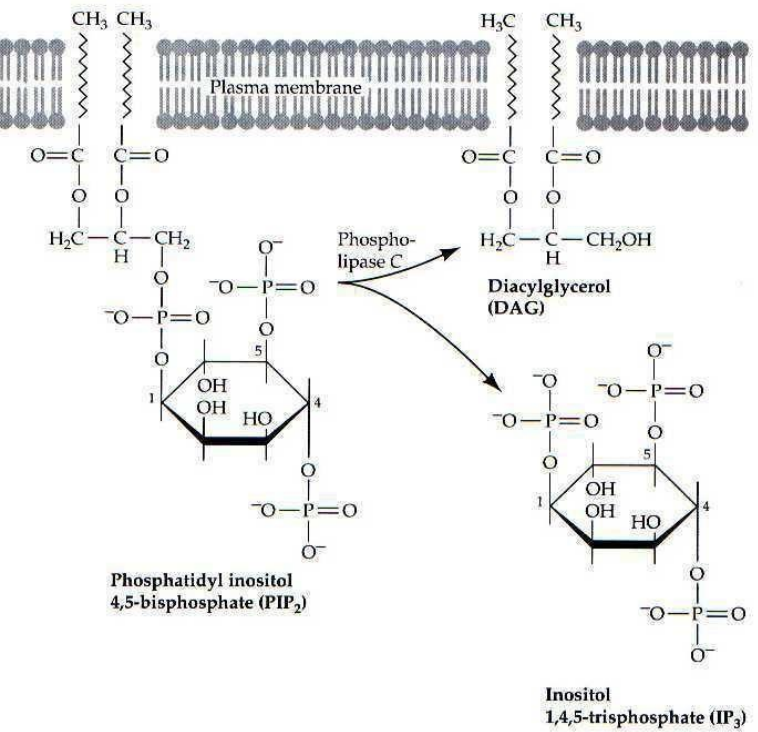
- Pathways connecting different types:
  1. Methylation of PE to make PC.
  2. Decarboxylation of PS to make PE.
  3. Exchange reactions by PS synthase:

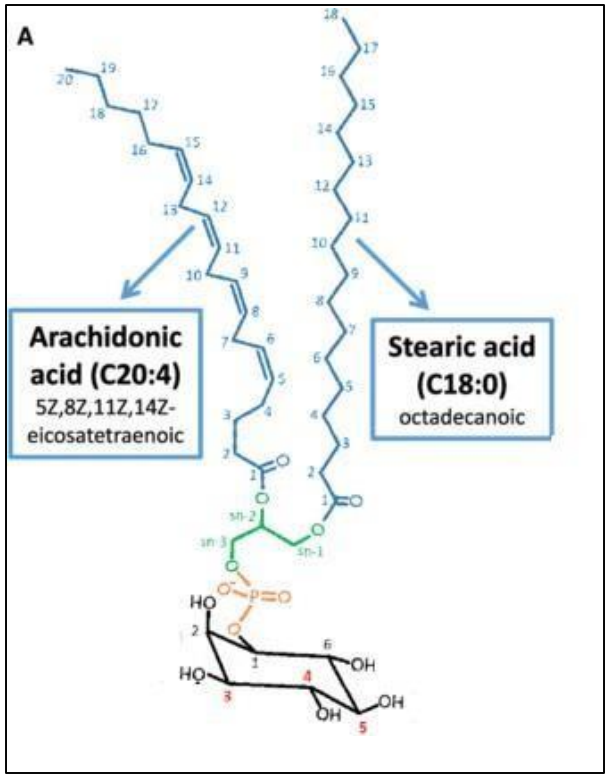
  a) Exchange of serine with ethanolamine (reversible)

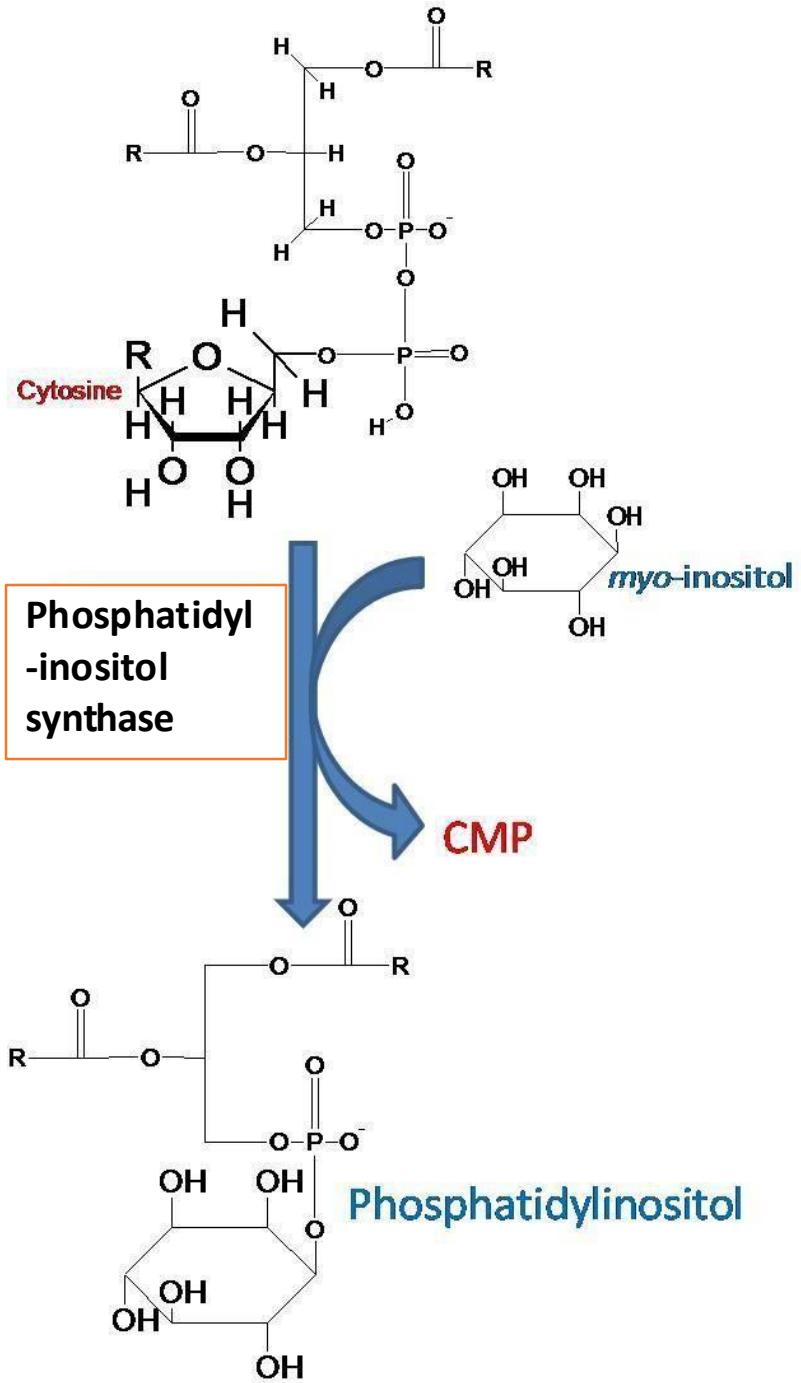
  b) Exchange of serine with choline (reversible)

Synthesis of ph-inositol (1st pathway)

- Inositol is combined with CDP-DAG by PI synthase to produce phosphatidylinositol.
- It is a reservoir of arachidonate.
- It also produces signaling molecules when cleaved by phospholipase C.







Phosphatidylinositol (PI) synthesis

❖ Steps of synthesis: same as before- repeated.

1. DAG is carried by **CDP**, the activated form: CDP-DAG.
2. Inositol is added to the phosphate group on DAG through the action of phosphatidylinositol synthase.
3. CMP is removed, and PI in produced.

➢ Roles of phosphatidylinositol:

a) Critical for forming GPI anchors, attaching proteins to the plasma membrane.
b) plays a key role in signaling pathways, particularly as a precursor for **PIP2** (Phosphatidylinositol 4,5-bisphosphate).
c) Arachidonic acid reservoir; as its FAs composition is majorly Arachidonic acid and steric acid.

Additional Resources:

رسالة من الفريق العلمي:

رغم ضغط الدراسة، وتراكم المسؤوليات، والتعب اللي نعيشه يوميًا، نؤمن أن الله لا يكلّف نفسًا إلا وسعها، وأن مع التوكّل عليه يهون كل صعب نمشي خطوة بخطوة، نعمل بالأسباب، ونترك النتائج على الله، واثقين أن ما بعد هذا الجهد يسرٌ وتوفيق

لأن كل خطوة ...بنعرف إن الضغط كبير، والتعب مو شوي نشتغل، نغلط، نتعلّم، ونكمّل تعبنا مو هدر، وطريقنا ماشي، والله دايمًا أكرم مما .صادقةاليوم، ربنا راح يسهّلها بكرة نتوقع.

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			