بسم الله الرحمن الرحيم

METABOLISM

FINAL – Lecture 7

Synthesis of fatty acids (pt.2)

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

Written by :

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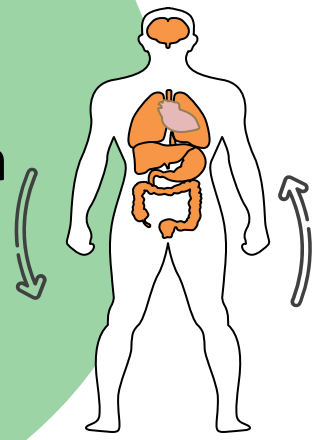

QUIZ ON THE PREVIOUS LECTURE

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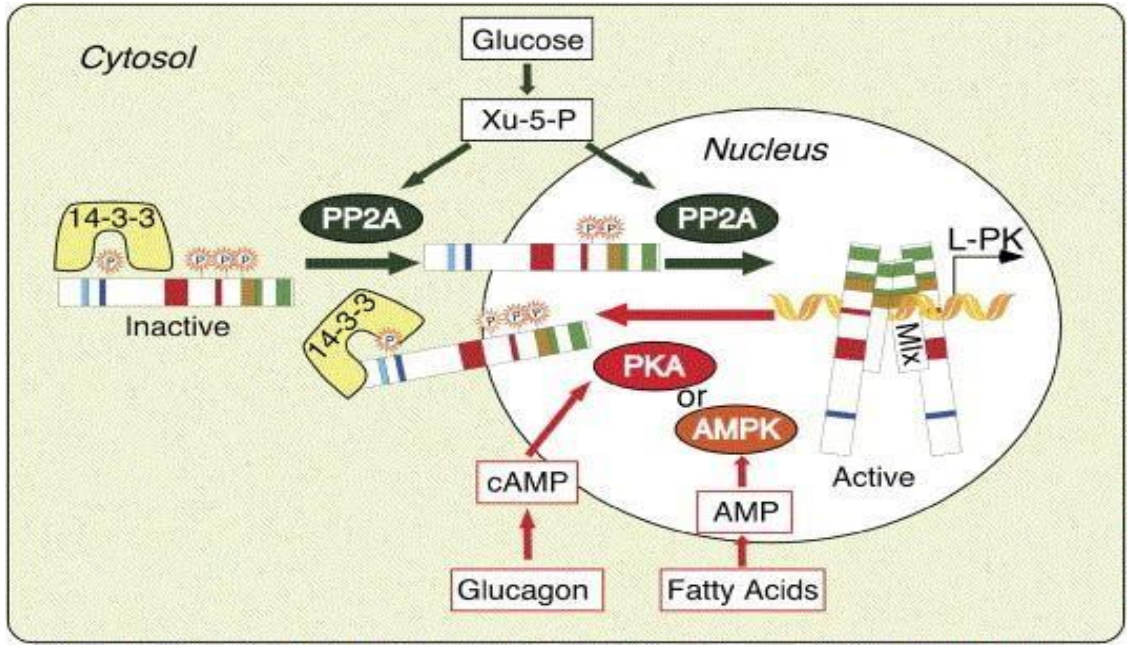
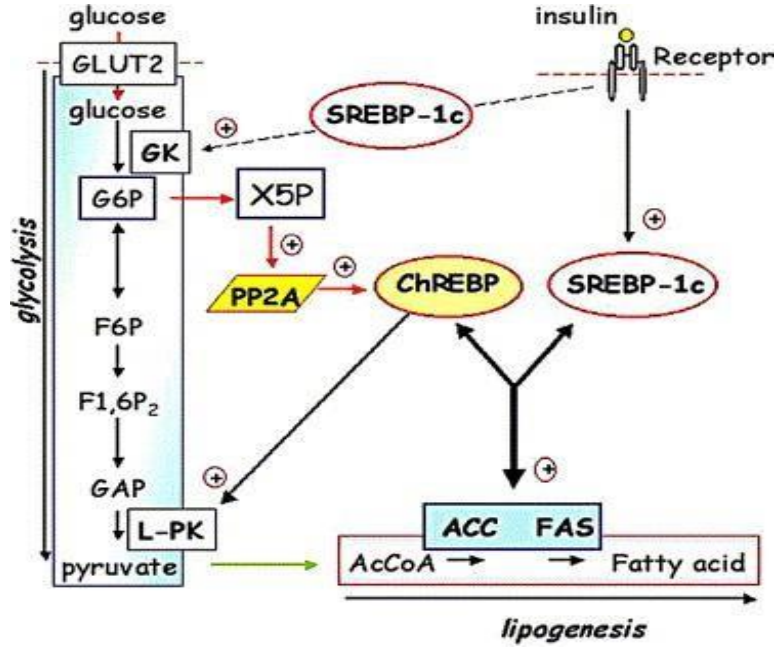
" اللهم لا تريني في دراستي هما يبكيني ولا عملا يلهيني، اللهم
وفقني في دراستي وكن لي عونا معينا، اللهم إني اسألك درجات
تشرح صدري وتفرح قلبي"
قول بسم الله وبدأ (=

Regulation of ACC synthesis by transcription factors

- The carbohydrate response element–binding protein (ChREBP)
  - ChREBP is inactivated by phosphorylation by PKA and AMPK preventing its nuclear localization.
  - It is dephosphorylated by excess glucose.
- The sterol regulatory element–binding protein-1c (SREBP-1c)
  - SREBP-1 is activated by insulin.





Regulation of ACC synthesis by transcription factors / 1

Fatty acid synthesis begins with the production of malonyl-CoA , a three-carbon molecule formed from acetyl-CoA through the action of the enzyme acetyl-CoA carboxylase (ACC). This step represents the rate-limiting stage of fatty acid synthesis and is subject to multiple levels of regulation.

- **Regulation of Acetyl-CoA Carboxylase (ACC)**

Another key regulatory mechanism involves controlling the synthesis of ACC itself. By modulating the concentration of the enzyme , the reaction rate and the Vmax can be altered. This regulation is achieved through the activity of transcription factors that influence the expression of ACC. Two major transcription factors involved are ChREBP (Carbohydrate Response Element Binding Protein) and SREBP-1c (Sterol Regulatory Element Binding Protein 1c).

ChREBP (Carbohydrate Response Element Binding Protein)

- **Inactivation by AMP Kinase (AMPK) :**

Under fasting conditions , ChREBP is phosphorylated and inactivated by AMPK. This phosphorylation prevents ChREBP from increasing ACC synthesis , thereby reducing fatty acid synthesis.

- **Activation by Insulin :**

In the well-fed state , insulin activates phosphatases that dephosphorylate ChREBP , restoring its active form. Active CHREBP can then enter the nucleus and stimulate the expression of ACC.

- **Role of AMPK :**

AMPK plays a dual role by phosphorylating and inhibiting both CREBP and ACC directly . This inhibition occurs during fasting or energy-deprived states when glucagon levels are elevated.

Regulation of ACC synthesis by transcription factors / 2

SREBP-1c (Sterol Regulatory Element Binding Protein 1c)

Activation by Insulin :

In the well-fed state , elevated insulin levels activate receptor tyrosine kinases , leading to the activation of SREBP-1c. Active SREBP-1c promotes the transcription of ACC . This , in turn , leads to higher enzyme concentrations and enhanced fatty acid synthesis.

- **Hormonal Regulation**
- **Insulin :**
- **Directly activates SREBP-1c , increasing ACC expression.**
- **Indirectly activates ChREBP by dephosphorylation via phosphatases.**

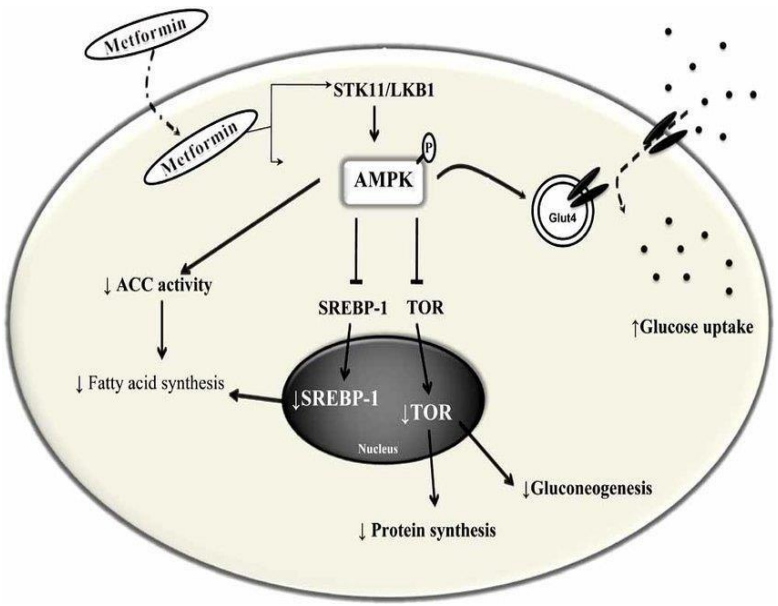
- **Glucagon:**

Activates AMPK , which inhibits ChREBP and ACC activity , reducing fatty acid synthesis.

In summary , both ChREBP and SREBP-1c enhance the expression of acetyl-CoA carboxylase , but their activity is regulated by distinct hormonal and metabolic signals. Insulin promotes ACC expression through both transcription factors , while glucagon and energy deprivation inhibit fatty acid synthesis via AMPK activation.

Application : Metformin

- Metformin lowers plasma TAG by :
  - Activation of AMPK, resulting in inhibition of ACC activity (by phosphorylation) and inhibition of ACC and fatty acid synthase expression (by decreasing ChREBP and SREBP-1c).
- It lowers blood glucose by increasing AMPK-mediated glucose uptake by muscle.



Application : Metformin

One application related to fatty acid synthesis involves the medication metformin , commonly known by Glucophage. While metformin is widely used for the treatment of diabetes , some individuals misuse it as a weight-loss aid , despite its potential for severe and even fatal side effects. Therefore , its use should always be carefully supervised and not taken haphazardly.

Metformin primarily acts by activating AMPK (AMP-activated protein kinase) , mimicking fasting conditions in the body. This activation leads to the phosphorylation of several proteins , resulting in significant metabolic effects. For example :

- Inhibition of fatty acid synthesis and storage : AMPK phosphorylates binding proteins (ChREBP and SREBP 1c) and enzymes like acetyl-CoA carboxylase (ACC) , inhibiting their activity. By reducing the synthesis of fatty acids , the formation of triacylglycerols , which are stored in adipocytes, is also minimized.

- Reduction in blood glucose levels : Metformin lowers blood glucose levels through AMPK-mediated mechanisms. It enhances glucose uptake into cells , reducing its presence in the bloodstream. This increased glucose uptake allows for its utilization in glycolysis while simultaneously inhibiting gluconeogenesis.

Overall , these mechanisms result in a reduction of fatty acid and protein synthesis , decreased gluconeogenesis , and increased glucose uptake , making metformin effective for managing blood sugar levels in diabetic patients.

Application : ACC2 inhibitors

- Challenges related to efficacy , selectivity and safety

Another application related to the acetyl-CoA carboxylase (ACC) enzyme dates back to earlier studies involving the development of ACC inhibitors as a potential method for weight loss. Historical reports have highlighted genetic engineering experiments in mice where ACC activity was modified , demonstrating its effects on reducing fat accumulation. Although this concept shares similarities with metformin's mechanism , the inhibitors are still under study. Despite their initial promise , no ACC inhibitors have yet been approved for clinical use due to concerns over efficacy and safety.

It is worth noting the age of some of these reports , which underscores the long-standing research interest in this area. However , until now , no ACC inhibitors have been confirmed to provide substantial benefits without significant side effects.

اكتشاف مثير ضد البدانة

لندن – قدس برس اكتشف الباحثون علاجا مثيرا وقويا ضد البدانة قد يسمح للأشخاص بتناول ما يشاؤون من الطعام دون أن يكتسبوا وزنا إضافيا، بل على العكس يمكنهم تخفيف أوزانهم الزائدة.

وقال الباحثون من كلية بايلور الطبية في تكساس، قالوا إنهم اكتشفوا إنزيما يضعف قدرة الجسم على حرق الدهون، وبالتحكم في هذا الأنزيم، فسيكون بالإمكان السماح للجسم بحرق دهون أكثر.

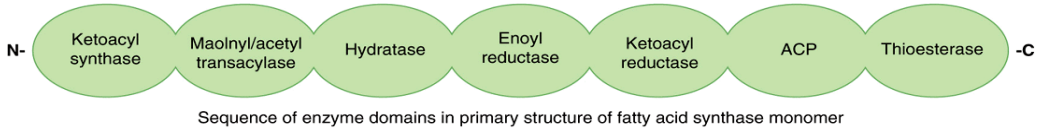
وقال الباحثون إن الفئران المهندسة وراثيا، التي ينقصها إنزيم «أسيتل – كو ايه كاربوكسيليز ٢» أو ما يعرف اختصارا بـ ACC2, تستطيع تناول كميات أكثر من الطعام بحوالي ٤٠ في المائة، وتزن أقل بنحو ١٥ في المائة، مقارنة مع غيرها من الحيوانات.

وسجل الدكتور صالح وكيل، كبير الباحثين، في مجلة «العلوم» الأمريكية، أن هذا الأنزيم ACC2 قد يكون هدفا لإنتاج أدوية تنظم حرق الدهون في الجسم، لذلك فقد يلعب دورا مهما في عمليات تنظيم البدانة، وعلاج السكري، وحتى في حالات استخدام وتراكم الدهون التي تزيد خطر الإصابة بتصلب الشرايين، مشيرا إلى أن الفئران التي ينقصها ذلك الجين تبدو سعيدة وحيوية وتتناسل بشكل جيد.

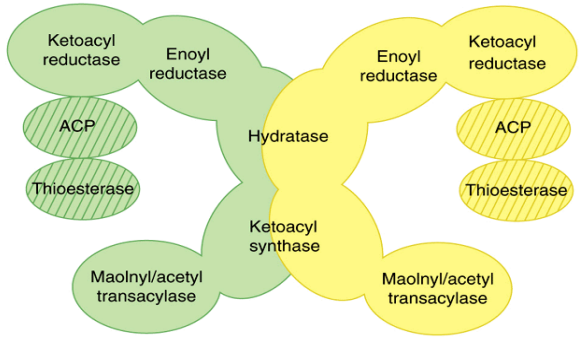
Fatty acid synthase (FAS)

- A multifunctional, homodimeric enzyme complex
- Each FAS monomer is multicatalytic with six enzymic domains and a domain for binding a phosphopantetheine-containing acyl carrier protein (ACP) domain.

The fatty acid synthesis pathway begins with the production of malonyl-CoA by the enzyme acetyl-CoA carboxylase (ACC). The next critical player in this process is fatty acid synthase (FAS) , a multifunctional enzyme complex. FAS performs seven enzymatic functions, including ketoacyl synthase , malonyl/acetyl transacylase , hydratase , enol reductase , ketoacyl reductase , acyl carrier protein (ACP) , and thioesterase. Structurally , it is a homodimer , meaning it consists of two identical subunits. Each subunit possesses all seven enzymatic functions , providing a total of 14 active sites (two identical sites for each enzymatic function)



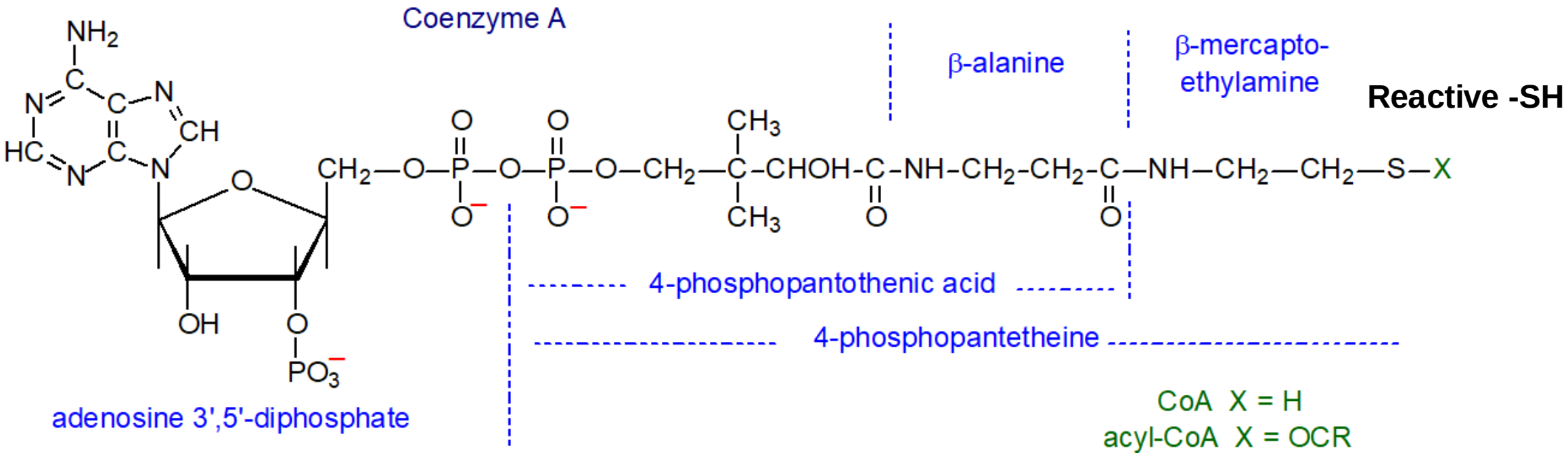
Sequence of enzyme domains in primary structure of fatty acid synthase monomer



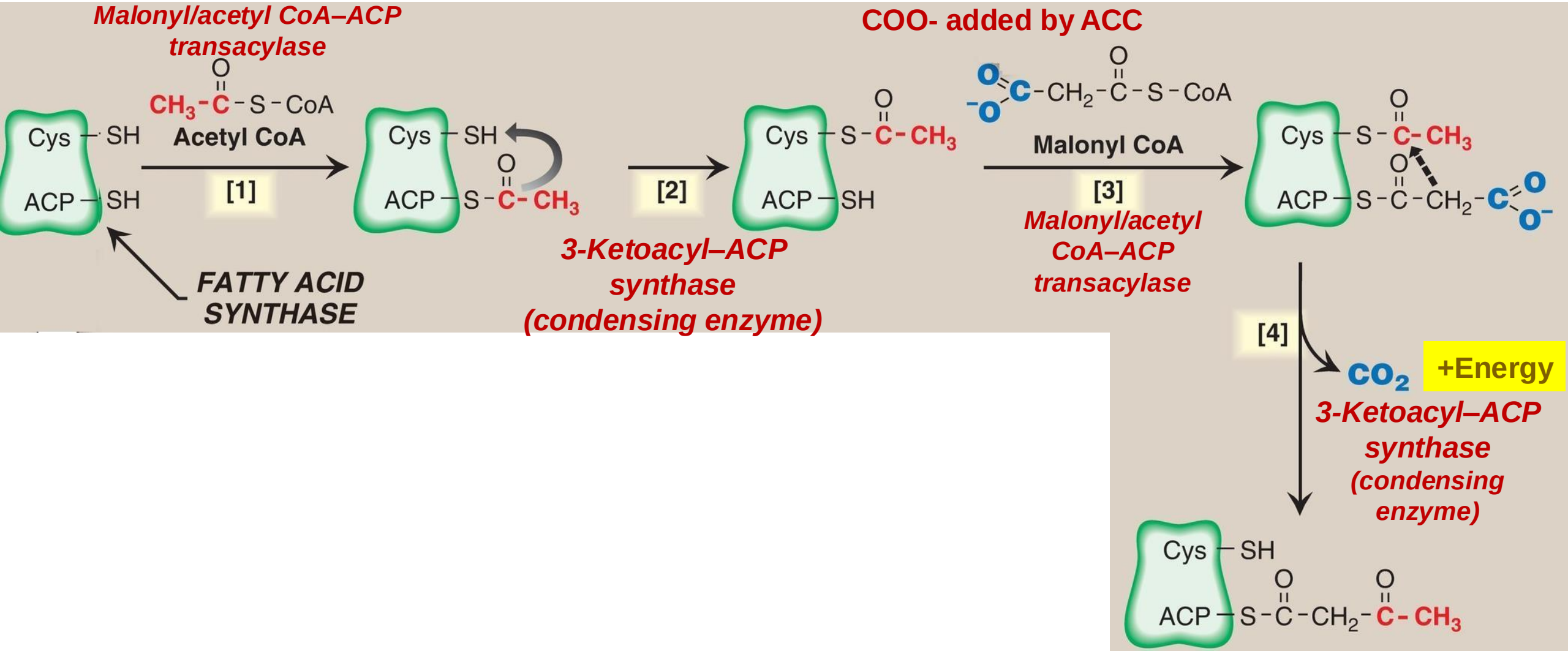
Fatty acid synthase homodimer

Fatty acid synthase (FAS)

- Phosphopantetheine, a derivative of pantothenic acid (vitamin B5), carries acyl units on its terminal thiol (–SH) group and presents them to the catalytic domains of FAS.
- It also is a component of CoA.

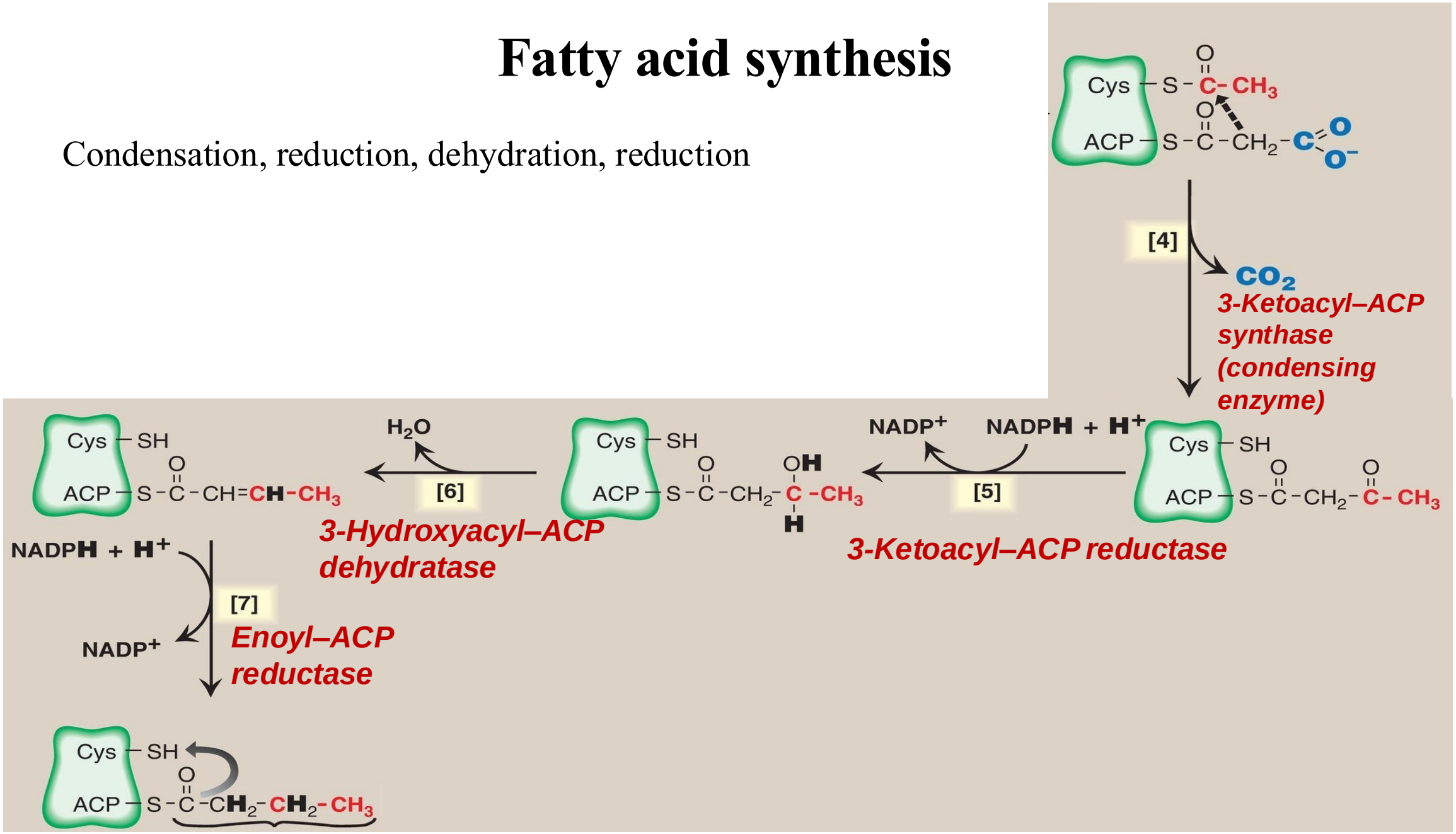


Fatty acid synthesis



Fatty acid synthesis

Condensation, reduction, dehydration, reduction



Fatty acid synthesis / 1

The synthesis pathway begins with one molecule of acetyl-CoA and one molecule of malonyl-CoA , which are processed in the following steps :

- **Attachment of Acetyl-CoA to ACP :**

Acetyl-CoA is attached to the ACP region of FAS through its reactive sulfhydryl (-SH) group . This step is catalyzed by malonyl/acetyl-CoA ACP transacylase (MAT) , which transfers the acetyl group to ACP.

- **Transfer of Acetyl Group to Cysteine :**

The acetyl group is transferred from ACP to a cysteine residue within FAS by the enzyme ketoacyl ACP synthase (KS) , leaving the ACP region available to bind malonyl-CoA.

- **Conversion of Acetyl-CoA to Malonyl-CoA**

Acetyl-CoA is carboxylated to malonyl-CoA by ACC , with the addition of a bicarbonate (HCO_3^-) group. This conversion prepares the molecule for elongation.

- **Attachment of Malonyl-CoA to ACP**

Malonyl-CoA is attached to the ACP region of FAS by malonyl/acetyl-CoA ACP transacylase, which previously attached acetyl-CoA. This creates a setup for condensation reactions.

Dr. Diala said that it is sufficient to understand the category of the enzyme (reductase, dehydratase) rather than memorizing its full name.

TO BE CONTINUED

Fatty acid synthesis / 2

- **Condensation Reaction**

A decarboxylation reaction removes the carboxyl group from malonyl-CoA , allowing the two carbons from acetyl-CoA (on the cysteine residue) to attach to the remaining two carbons of malonyl-CoA on ACP. This step is catalyzed by ketoacyl ACP synthase (KS) – the condensing enzyme , resulting in a four-carbon chain attached to ACP.

- **Reduction of the Carbonyl Group**

Fatty acids possess only a single carboxyl group , which is located at the terminal carbon (carbon number one). To achieve this , the non-terminal carbonyl group is reduced to an alcohol by the enzyme 3-ketoacyl ACP reductase. This reaction involves the oxidation of NADPH to $NADP^+$.

- **Dehydration**

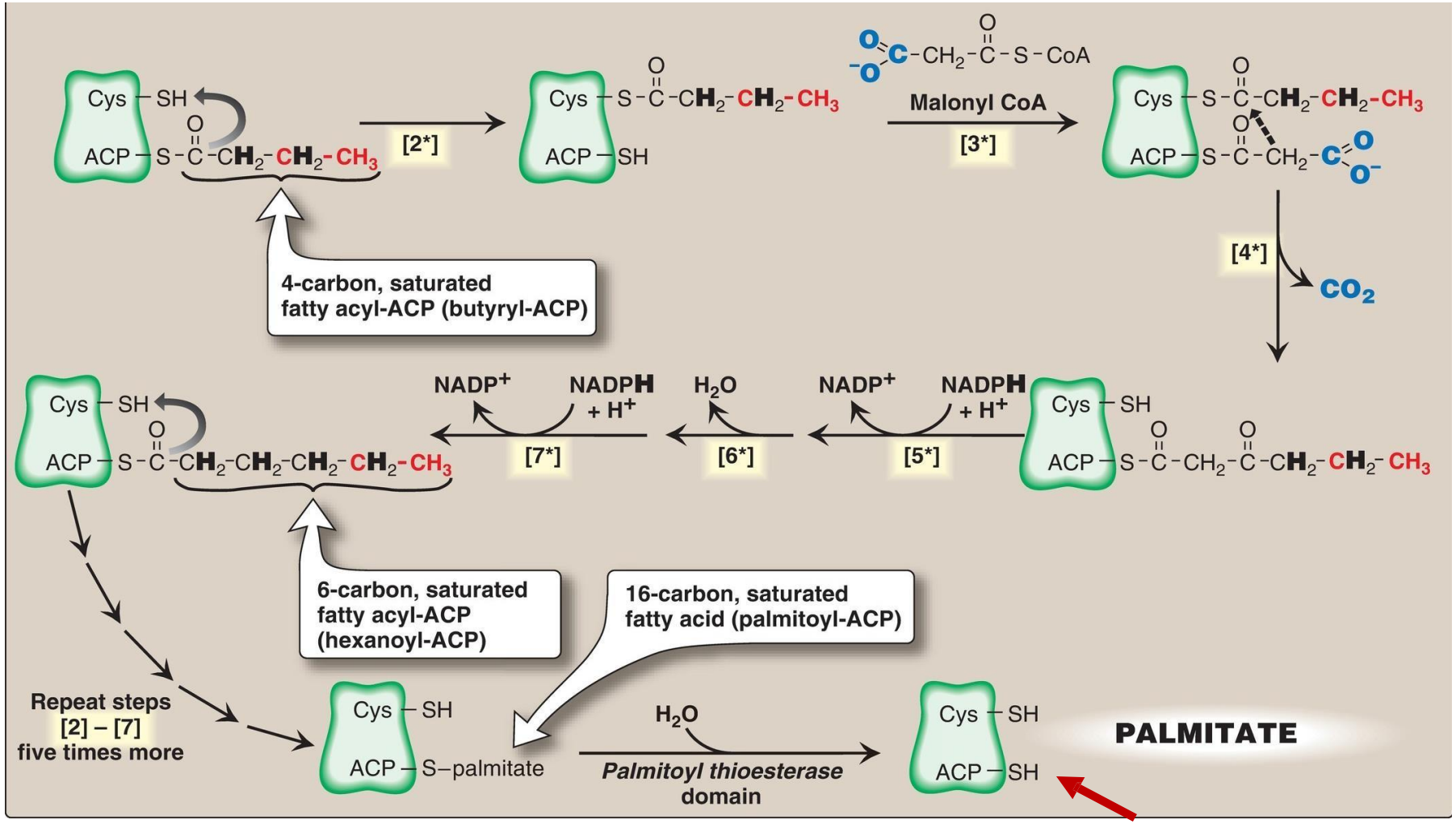
The alcohol group is removed via dehydration , resulting in the formation of a double bond. This step is catalyzed by 3-hydroxyacyl ACP dehydratase , which eliminates a water (H2O) molecule.

- **Reduction of the Double Bond**

The double bond is reduced to form a saturated hydrocarbon chain. This reaction is catalyzed by enoyl-ACP reductase , with NADPH serving as the reducing agent and being oxidized to NADP+.

At this stage , the chain consists of four carbons , including one terminal carbonyl group and a fully saturated hydrocarbon chain. Additional elongation cycles will repeat these steps to extend the fatty acid chain until the desiresd length is achieved. Desaturation , if needed , can occur later in a separate pathway

Fatty acid synthesis



✓ *The lactating mammary gland terminates lengthening the chain EARLY.*

Fatty acid synthesis

To synthesize palmitic acid , a 16-carbon saturated fatty acid , the previously mentioned steps (resulting in a 4-carbon chain) must be repeated six additional times. Each cycle extends the fatty acyl chain by 2 carbons , as one carbon from malonyl-CoA is lost during decarboxylation.

Steps for Palmitic Acid Synthesis :

- Initial 4-Carbon Chain Preparation

After completing the initial steps , the fatty acyl chain (4 carbons) is attached to the ACP (acyl carrier protein) region of the fatty acid synthase (FAS).

- Transfer of Fatty Acyl Chain to Cysteine Residue

Using the same enzyme as before , ketoacyl ACP synthase (KS) , the fatty acyl chain is transferred from ACP to the cysteine residue of FAS , leaving ACP empty to accept a new malonyl-CoA molecule.

- Addition of Malonyl-CoA

A new malonyl-CoA , produced by acetyl-CoA carboxylase , is attached to the empty ACP. Following this , a decarboxylation reaction occurs , enabling the fatty acyl chain on the cysteine to combine with the 2 carbons from malonyl-CoA. This results in a 6-carbon chain attached to ACP.

TO BE CONTINUED

Fatty acid synthesis

- **Reduction , Dehydration , and Second Reduction**
- The new carbonyl group on the 6-carbon chain undergoes reduction to an alcohol by ketoacyl ACP reductase, with NADPH oxidized to NADP+.
- The alcohol group is then dehydrated by 3-hydroxyacyl ACP dehydratase , forming a double bond.
- Finally , the double bond is reduced by enoyl-ACP reductase, again using NADPH, resulting in a saturated 6-carbon chain.

- **Repetition of the Cycle**

This process (transfer , malonyl-CoA addition , decarboxylation , reduction , dehydration , and reduction) is repeated , adding 2 carbons with each cycle. After six more cycles , the chain reaches 16 carbons , forming palmitic acid.

- **Release of Palmitic Acid**

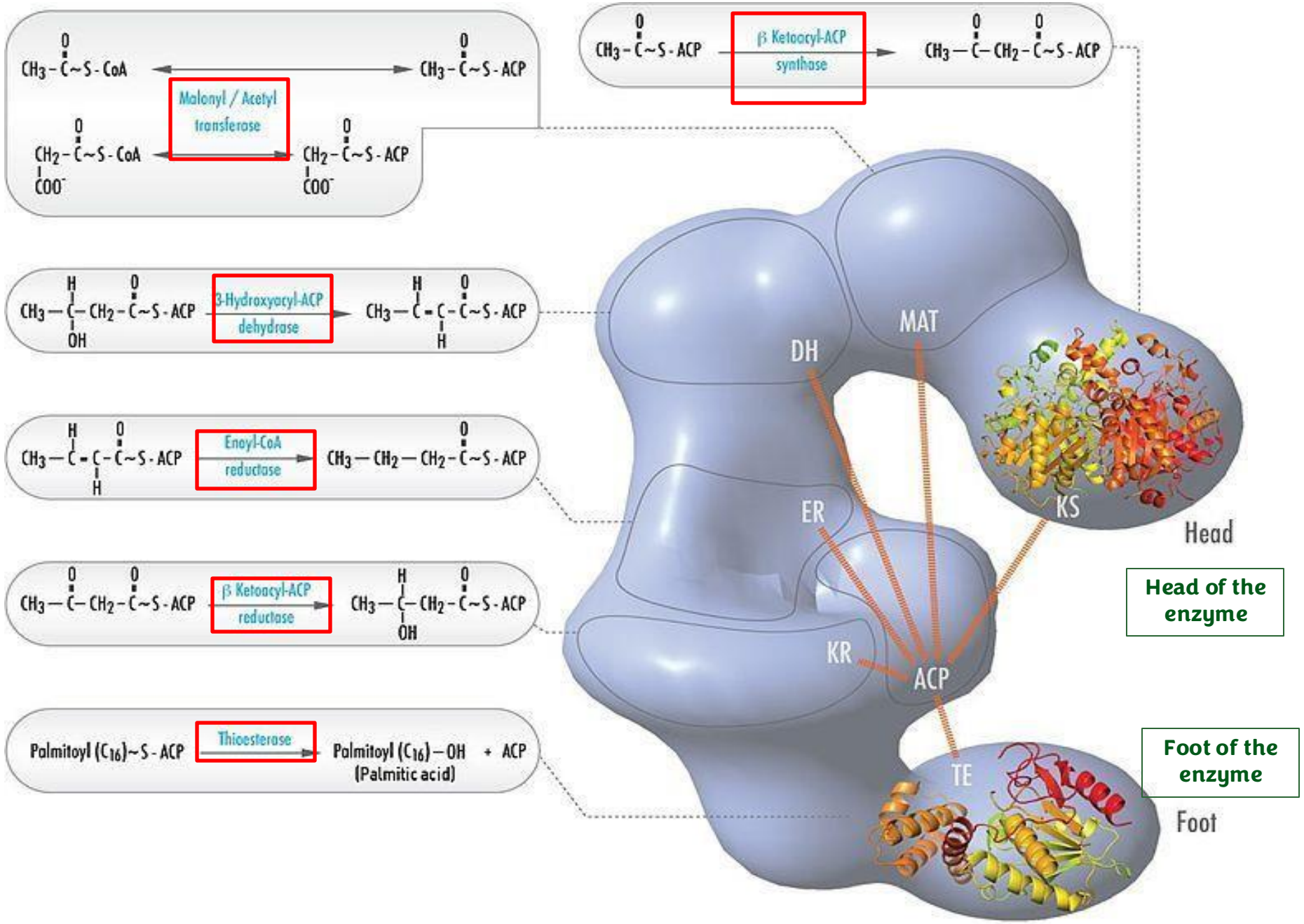
Once the 16-carbon chain is complete, palmitoyl thioesterase catalyzes the hydrolysis of the fatty acid from the FAS complex by adding a water molecule. This releases palmitic acid.

Variations in Fatty Acid Length :

In specific tissues , such as the mammary glands, the synthesis of shorter fatty acid chains (e.g. short- and medium-chain fatty acids -mainly medium-) is prioritized. This is achieved by terminating the elongation process early , after fewer cycles of the spiral pathway. These shorter chains are particularly abundant in milk fat.

Fatty acid synthesis

This highlights how the seven functional regions of the enzyme are positioned adjacent to one another , enabling seamless transfer of intermediates between them. Each step in the process transitions the substrate to the next neighboring region of the enzyme , ensuring the reactions proceed in an efficient and coordinated manner.



Fatty acid synthesis

This slide features a video on fatty acid synthesis

To watch it please CLICK HERE

Ketoacyl synthase (KS) Malonyl/acetyltransferase (AT) Dehydrase (DH)

Enoyl reductase (ER) Ketoacyl reductase (KR) Thioesterase (TE)

Acyl carrier protein (ACP)

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 , yielding 14 H+ ions , 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 H2O molecule is consumed in the release of the fatty acid)

- Malonyl-CoA synthesis:

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

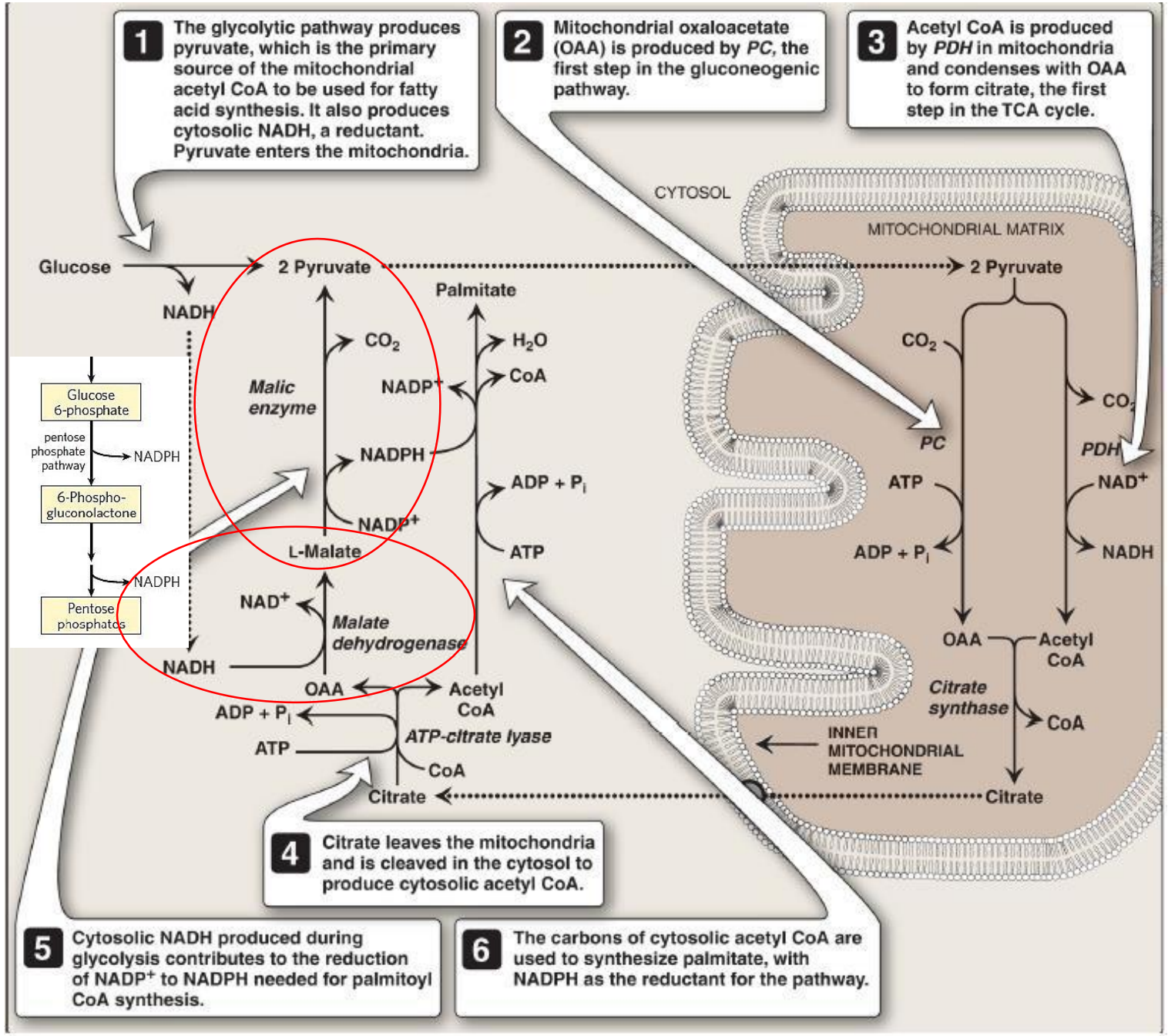
- Overall stoichiometry of palmitate synthesis:

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

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

Sources of molecules

- Acetyl CoA
  - Pyruvate
- NADH (for *oxaloacetate to malate)*
  - Glycolysis
- NADPH:
  - Pentose phosphate pathway
  - Malate to pyruvate



Go to the next slide for explanation

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 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

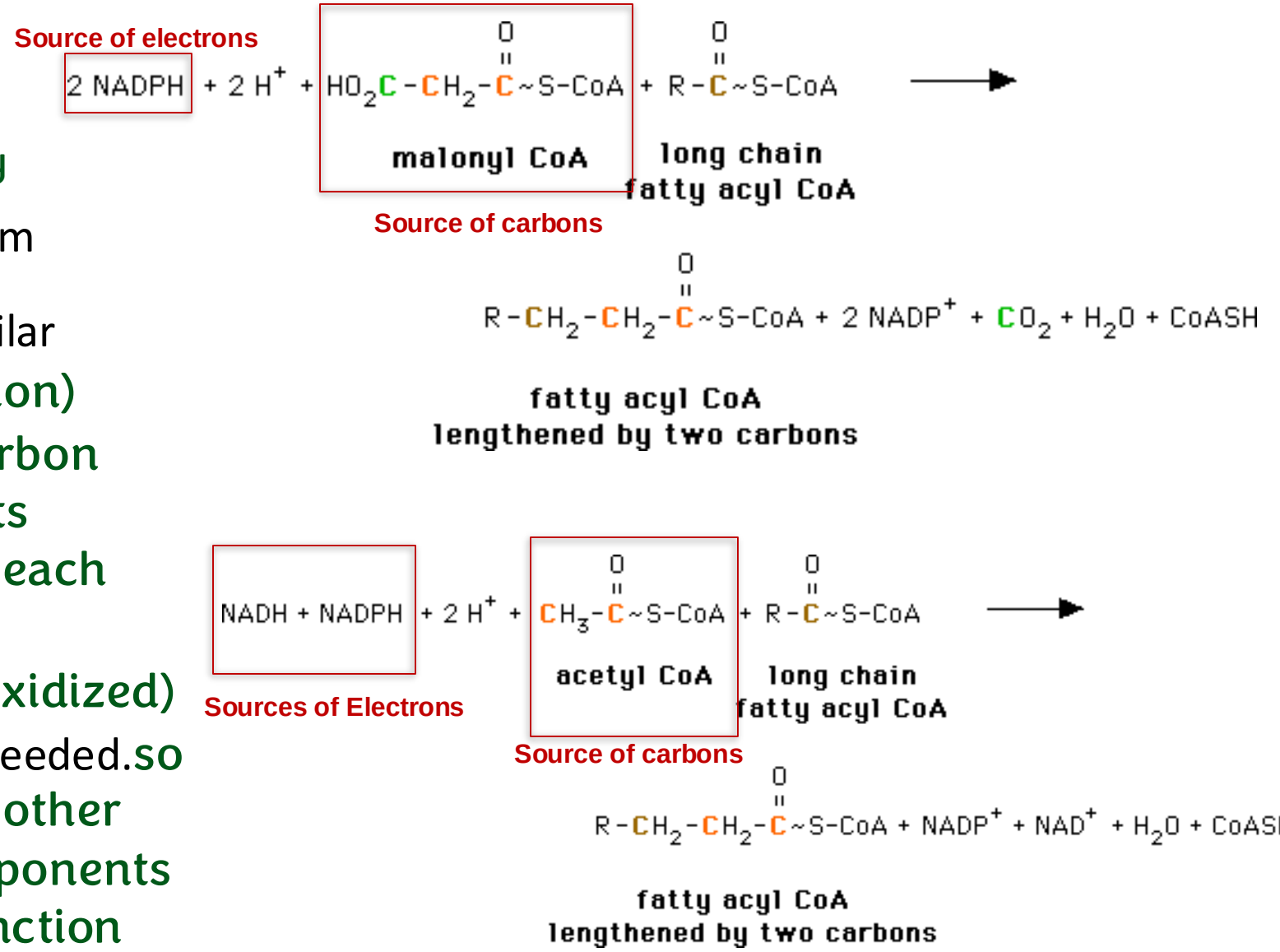
- **Regulation of ACC**
  to regulate the rate limiting step

  -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

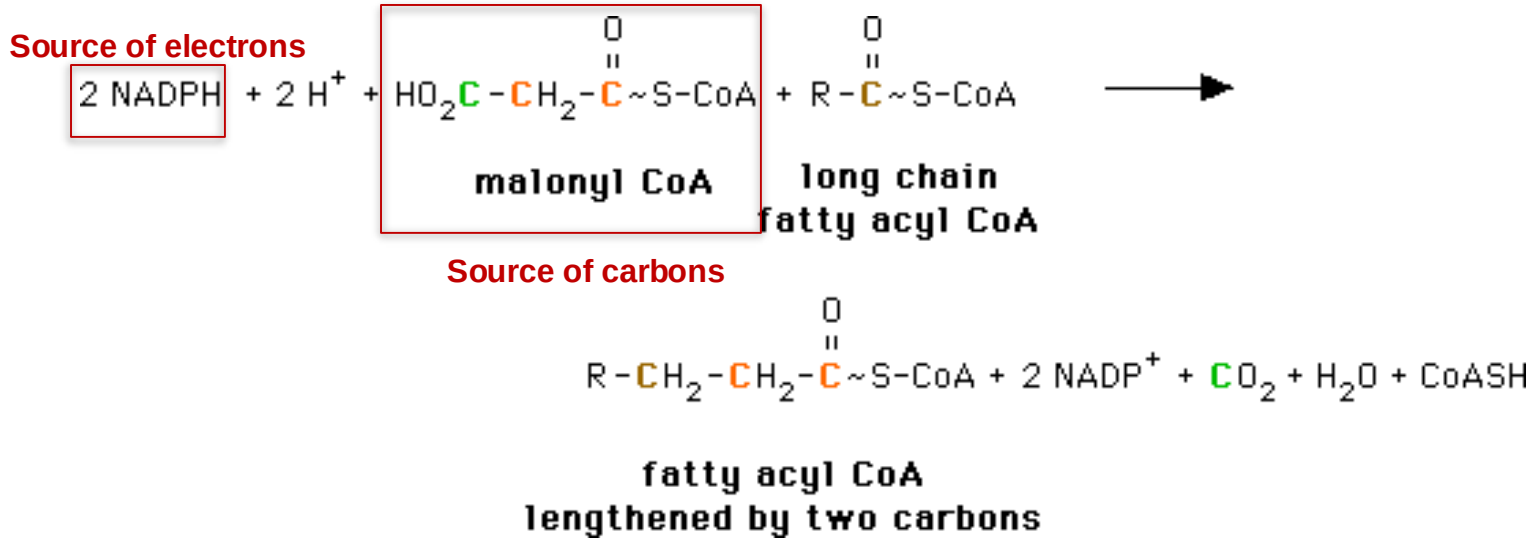
- When we want to elongate the fatty acid chain such as palmitate which has 16 carbon we will use the following pathway
- Location: smooth endoplasmic reticulum
- Different enzymes are needed but similar sequence of reactions.(similar function)
- Two-carbon donor: Malonyl CoA (3 carbon molecule then 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 its function

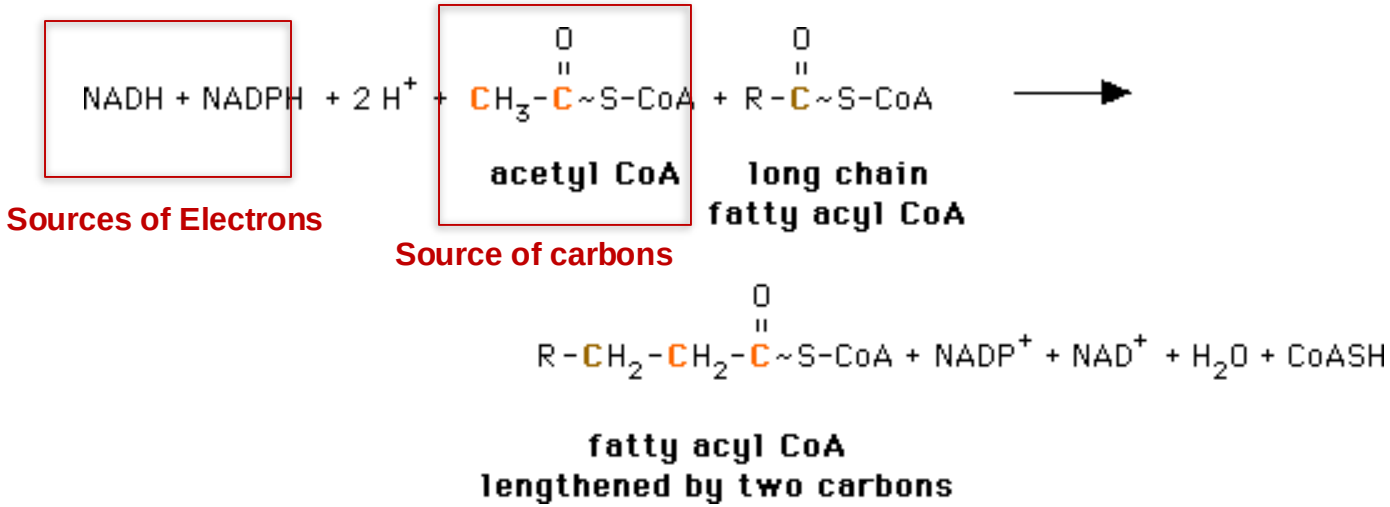


Further elongation of fatty acids

- 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

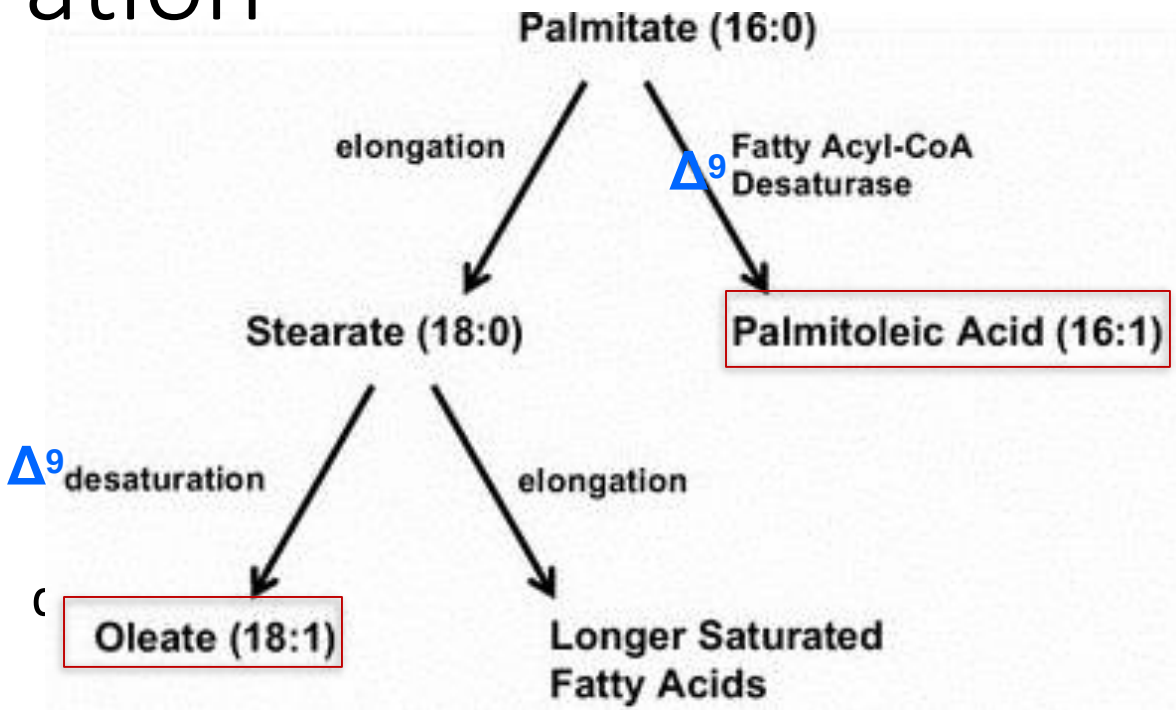
- Location: mitochondria it's where the brain cells make VLCFA and the SER can't make them they can only elongate the chain till 18-20C
- Two-carbon donor: Acetyl CoA
- Source of electrons: NADPH and NADH
- Substrates: fatty acids shorter than 16 (or medium chains)we are not going to start from the very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

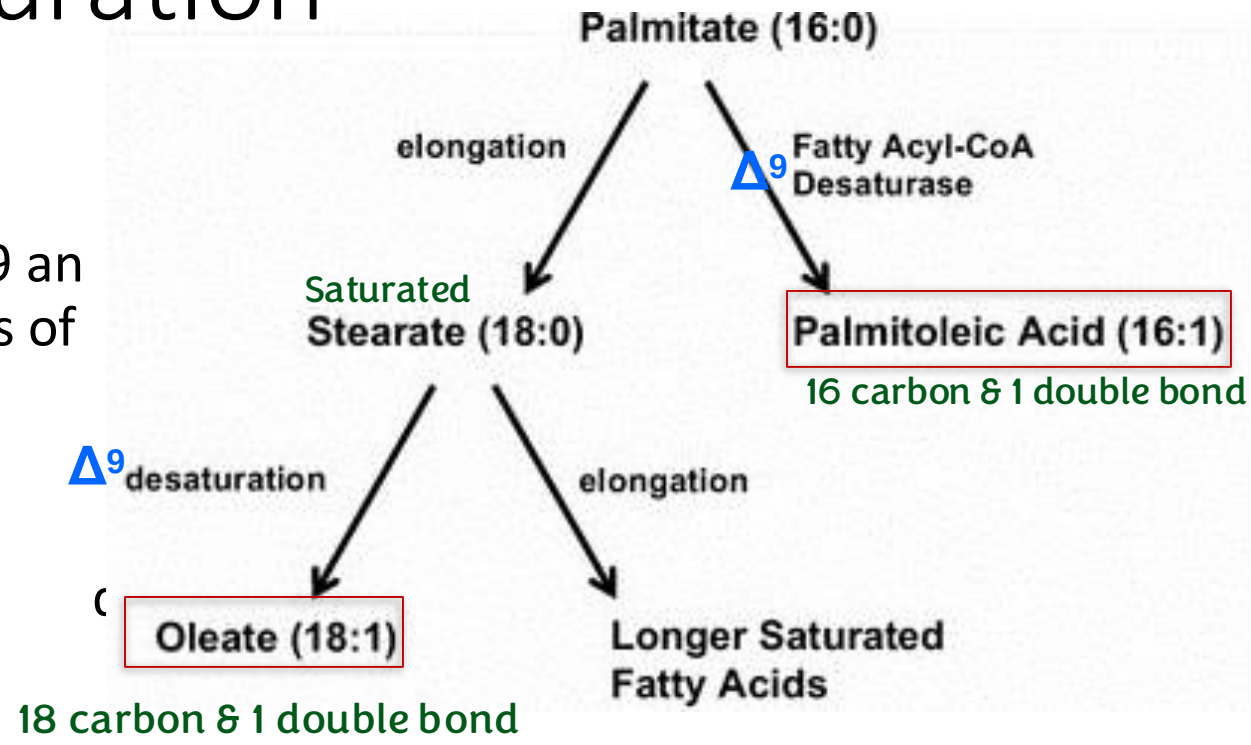


Humans have carbon 9, 6, 5, and 4 desaturases but cannot introduce double bonds from carbon 10 to the ω end of the chain. Therefore, the polyunsaturated ω-6 linoleic acid and ω-3 linolenic acid are essential.

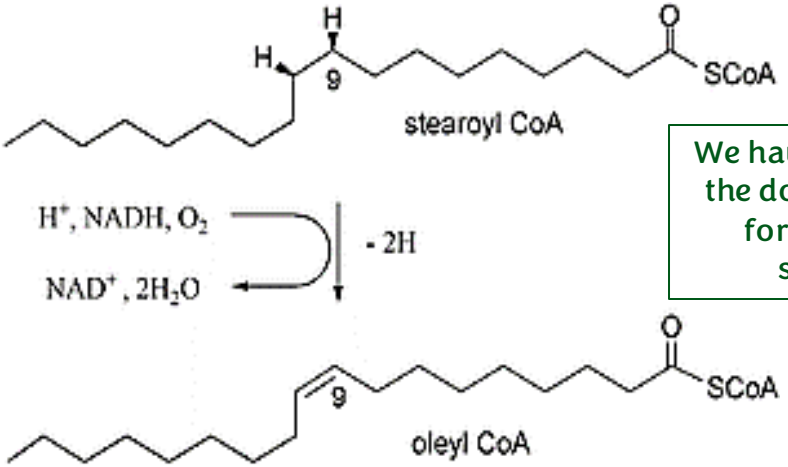
- ✓ Formation of polyunsaturated FA by elongation and desaturation
- ✓ Additional double bonds can be introduced by Δ^4 desaturase, Δ^5 desaturase and Δ^6 desaturase

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

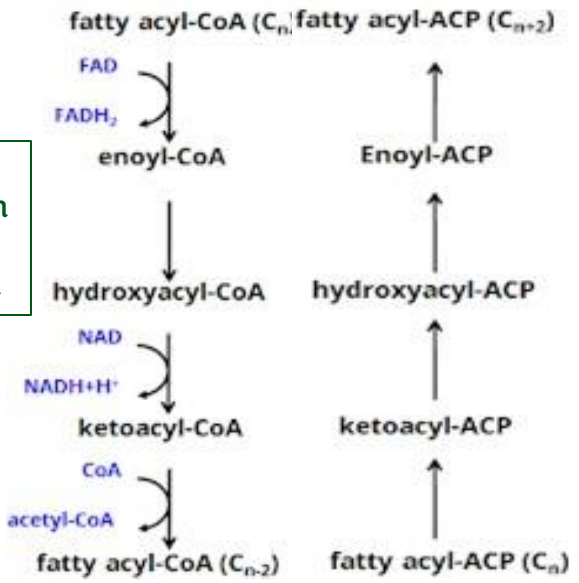
FA Synthesis vs. degradation

Anabolic

Catabolic

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 ,Mammary glands and adipocytes	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 The main allosteric regulator	—
Inhibitor	Palmitoyl CoA (inhibits *acetyl CoA carboxylase*)	Malonyl CoA (inhibits *carnitine palmitoyltransferase-I*)
Product of pathway	Palmitate 16c	Acetyl CoA
Repetitive four-step process	Condensation, reduction dehydration, reduction	Dehydrogenation, hydration dehydrogenation, thiolysis

The main one which is beta oxidation



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

Like malonyl CoA and acetyl CoA

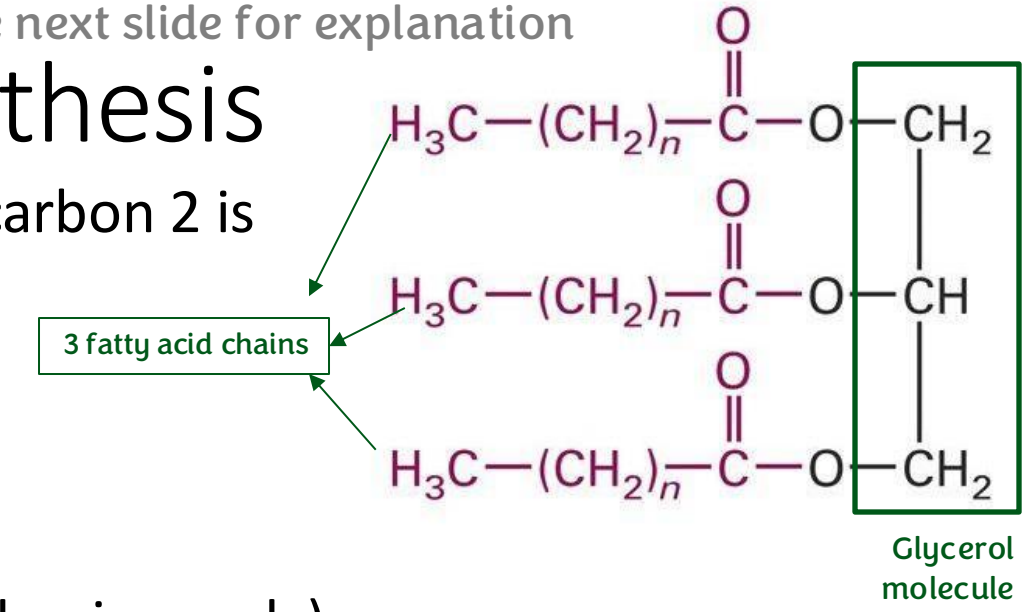
Or oxidation

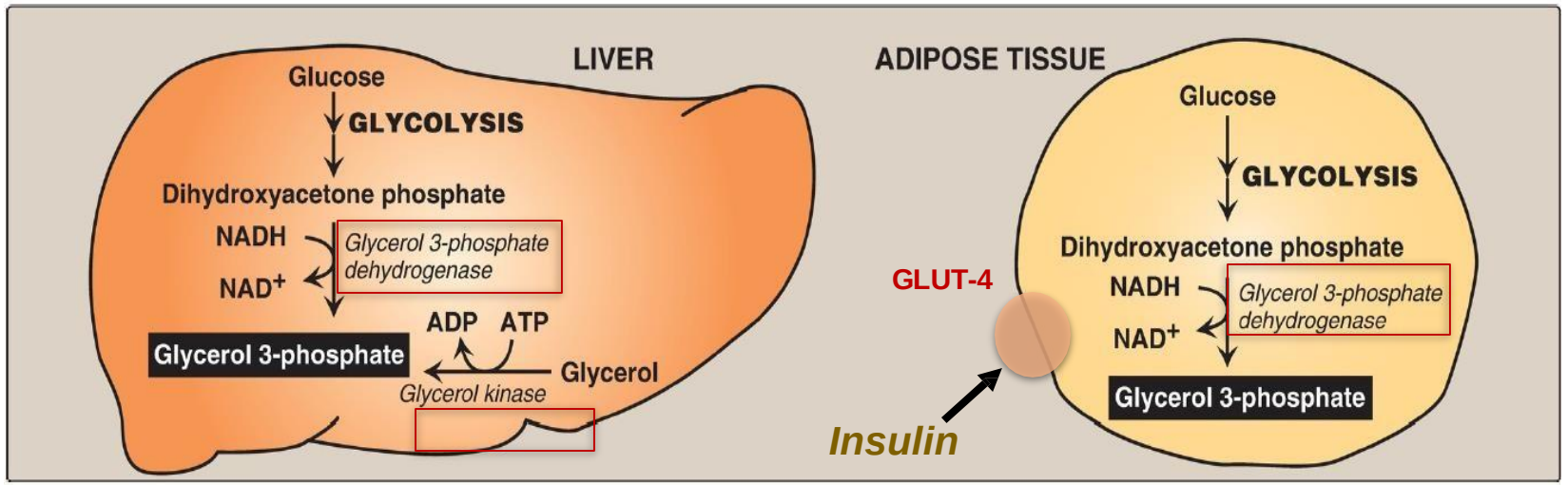
To be able to break down the bond between Acetyl CoA & the remaining structure of the fatty acids

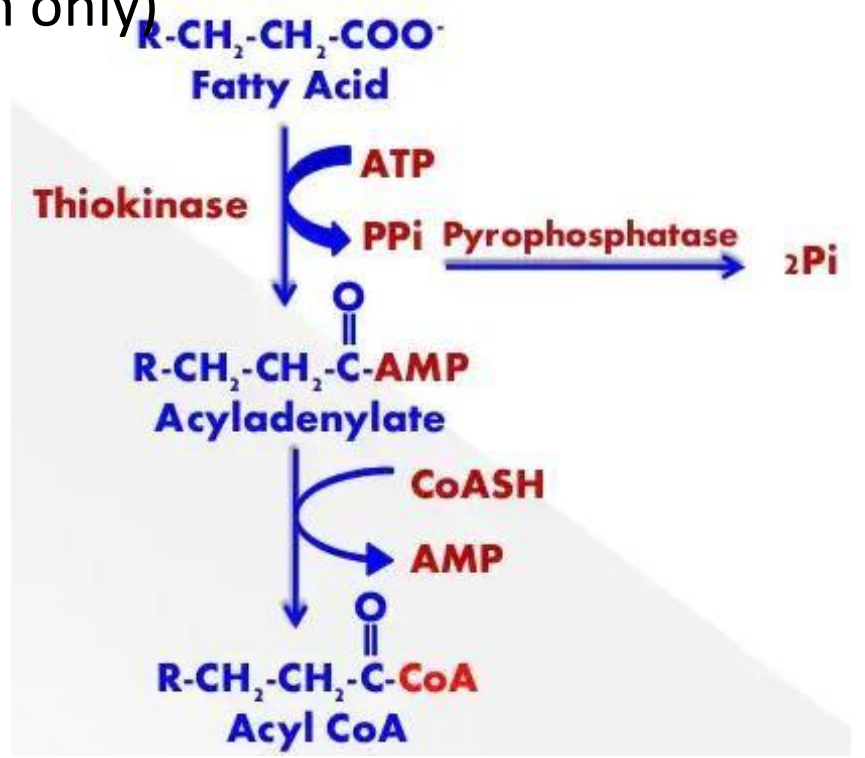
Go to the next slide for explanation

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





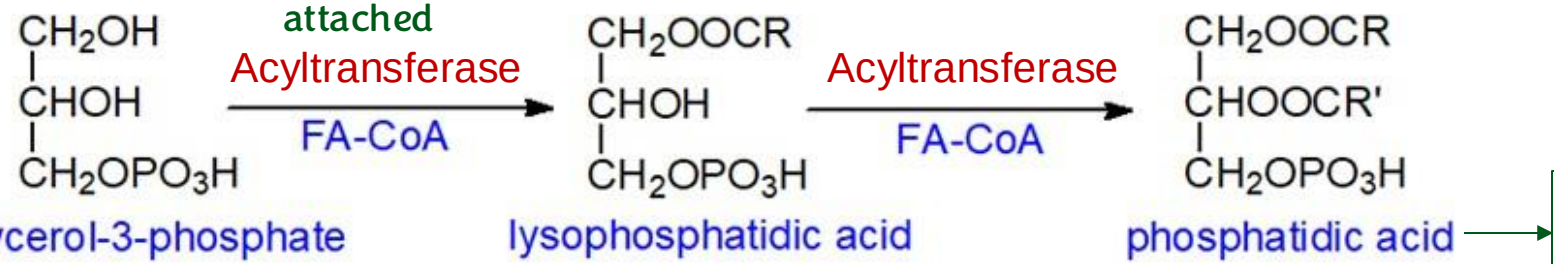


Explanation for the previous slide

- 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 triacylglycerols

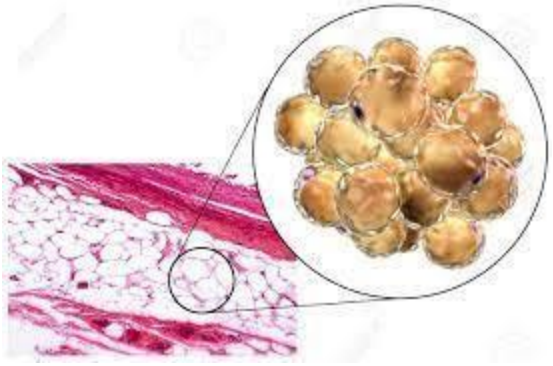
1st fatty acid will be attached



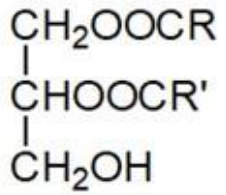
glycerol-3-phosphate — lysophosphatidic acid — phosphatidic acid → The parent molecule of glycerophospholipids

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

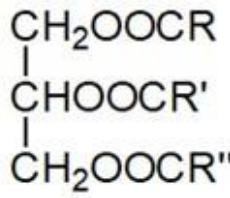


Phosphatase



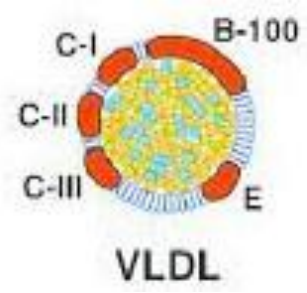
diacylglycerol

FA-CoA | Acyltransferase



triacylglycerol

Adipose tissue
Stored as lipid droplets

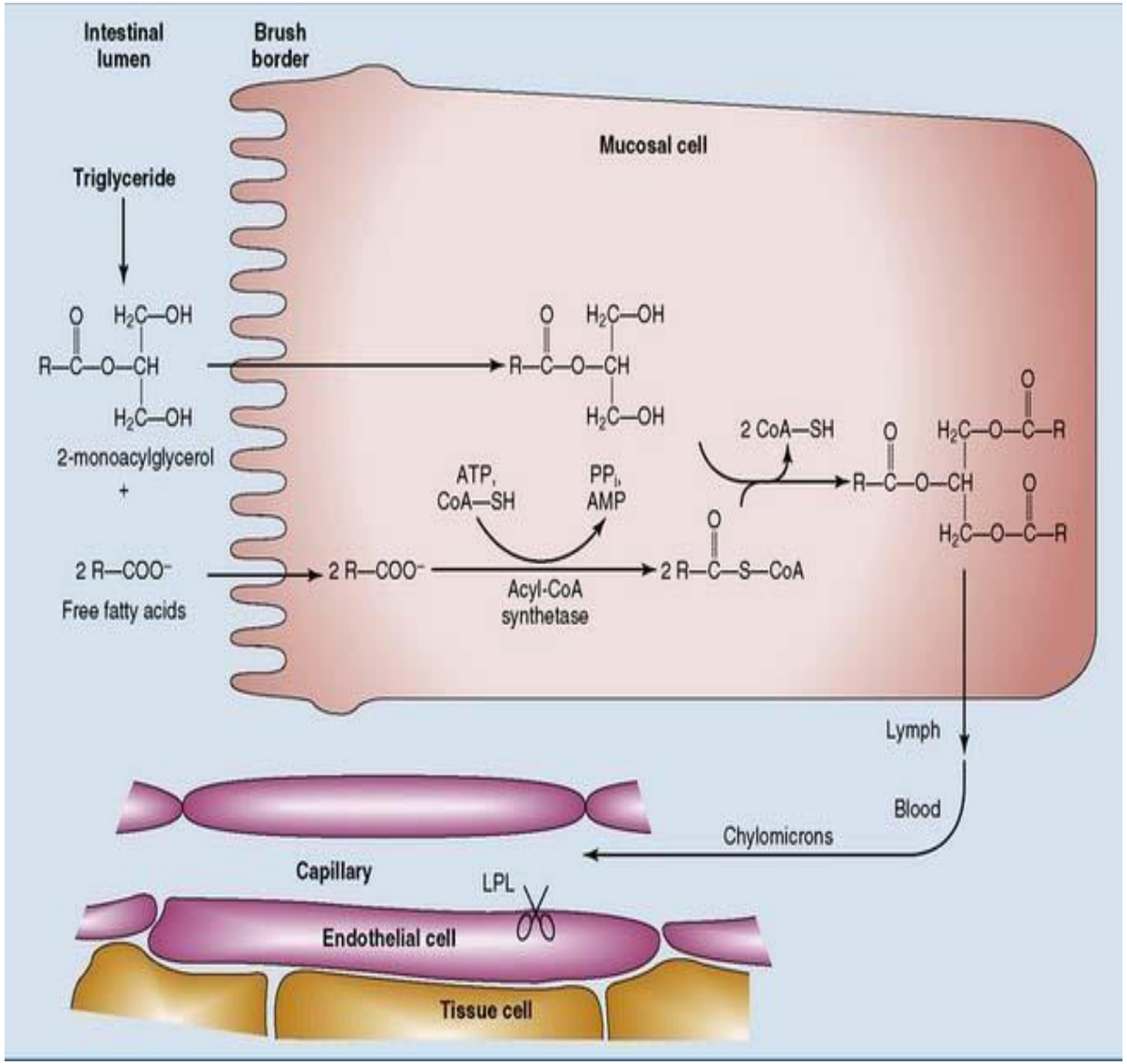


Liver
Little storage
Mainly packaged in VLDL

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



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	32	If the free fatty acids are long chains they can be uptaken by proteins **or** passive diffusion if they are short or medium chains but monoacylglycerol enter as a part of a mixed micelle to the mucosal cells	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
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

كلما صعب عليك الأمر، وعز عليك حلمك،
استند يقينك بأن الله لا يكلف نفسا ما لا تطيق،
ولكن :"الله يعطي أصعب المعارك لأقوى
جنوده"
أعدك ستصل.