بسم الله الرحمن الرحيم

METABOLISM

FINAL – Lecture 6

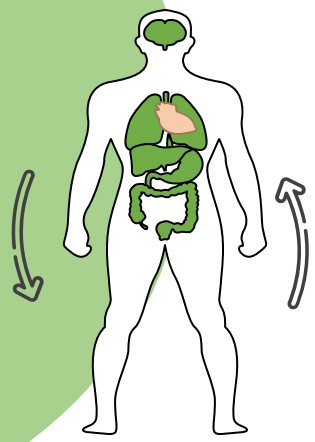
Degradation of Fatty Acid (Pt.2) & Synthesis of Fatty Acid (Pt.1)

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

Written by :

- Sadeel Al-hawawsheh



QUIZ ON THE PREVIOUS LECTURE

CLICH HERE

NOTES REGARDING THE PREVIOUS LECTURE

Last time, we discussed the process of beta-oxidation , which refers to the degradation of fatty acids under fasting conditions or during ketogenic diet.

- **Fasting Conditions and Hormonal Changes**

Under fasting conditions , hormonal changes play a key role. Specifically , there is an increase in glucagon levels , often accompanied by elevated epinephrine. These hormones bind to receptors on adipocytes , triggering the activation of lipolysis. This leads to the hydrolysis of triacylglycerols into fatty acids and glycerol. Fatty acids are then released into the bloodstream , taken up by cells , and oxidized through beta-oxidation to produce acetyl-CoA molecules. Meanwhile , the glycerol is utilized in gluconeogenesis by hepatocytes and kidney cells.

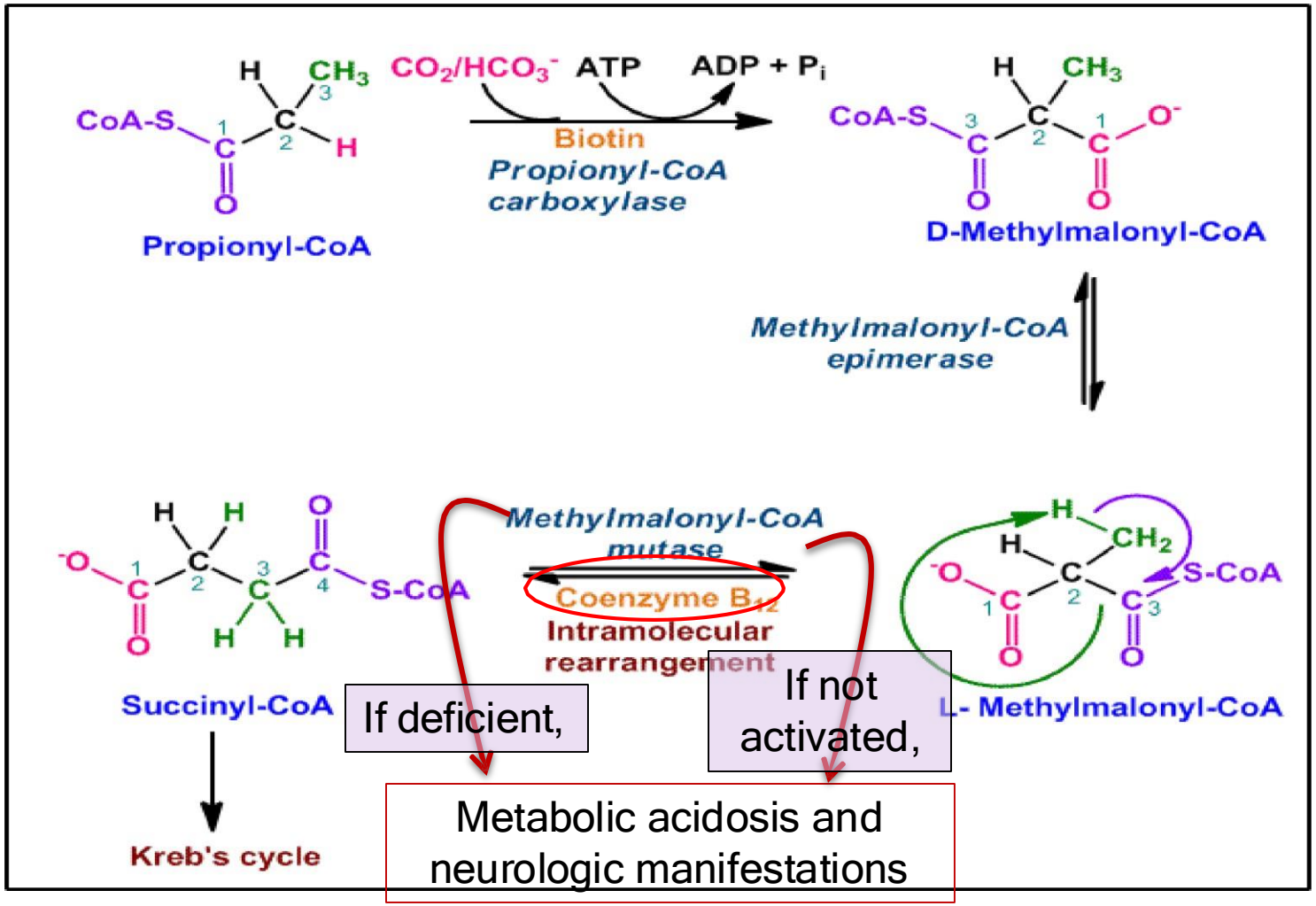
- **Beta-Oxidation**

Beta-oxidation derives its name because it involves the cleavage of fatty acid chains at the beta-carbon (the second carbon from the carboxyl group). This results in the sequential production of acetyl-CoA molecules. This pathway occurs in the mitochondria , so fatty acids must first be transported into the mitochondria to undergo degradation into acetyl-CoA.

In the previous lecture, we focused exclusively on saturated fatty acids with an even number of carbons. We have not yet addressed how beta-oxidation handles unsaturated fatty acids (whether mono- or polyunsaturated) or those with an odd number of carbons.

Oxidation of odd-numbered FAs

- Starts as cycles of beta-oxidation producing acetyl-CoA and propionyl-CoA



Oxidation of odd-numbered FAs / 1

Odd-chain fatty acids are found in various sources , including certain fish, algae, etc . Their oxidation begins similarly to the oxidation of even-chain fatty acids. Through beta-oxidation , two carbons are removed at a time , producing acetyl-CoA molecules.

- **The Unique Challenge of Odd-Chain Fatty Acid Oxidation**

In the final step of beta-oxidation for odd-chain fatty acids , a five-carbon molecule remains. This molecule undergoes cleavage , producing :

- A two-carbon molecule in the form of acetyl-CoA (no issues here).
- A three-carbon molecule called propionyl-CoA , which requires special handling to be metabolized efficiently.

- **Conversion of Propionyl-CoA to Succinyl-CoA**

To make propionyl-CoA usable for energy production , it undergoes a series of steps :

1) Carboxylation of Propionyl-CoA

- An additional carbon atom is added to propionyl-CoA in the form of bicarbonate (HCO_3^-).
- This reaction is catalyzed by propionyl-CoA carboxylase , an enzyme that requires biotin as a coenzyme and ATP as an energy source.
- The product of this reaction is D-methylmalonyl-CoA.

TO BE CONTINUED

Oxidation of odd-numbered FAs / 2

2) Epimerization to L-Methylmalonyl-CoA

· The D-methylmalonyl-CoA is converted into **L-methylmalonyl-CoA** by the enzyme **methylmalonyl-CoA epimerase**. This step involves reorienting the methyl group to produce the L-enantiomer.

3) Isomerization to Succinyl-CoA

- The **L-methylmalonyl-CoA** is rearranged (by transferring the branch - intramolecular rearrangement) to form **succinyl-CoA** , a linear four-carbon molecule that is an intermediate in the **Krebs cycle** (TCA cycle).
- This reaction is catalyzed by **methylmalonyl-CoA mutase** and requires **vitamin B12** (cobalamin) as a coenzyme.

▪ **Significance of Vitamin B12**

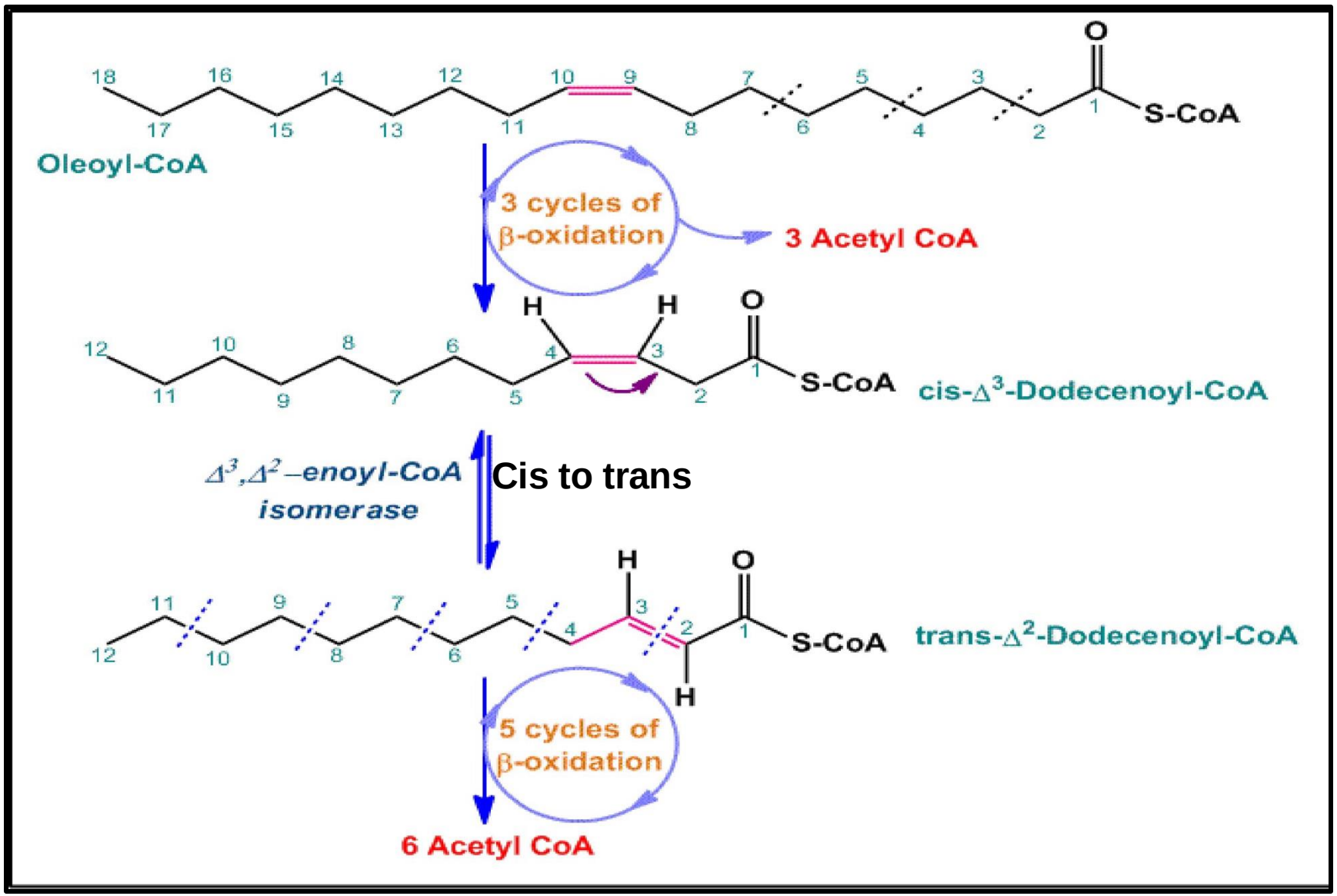
- Vitamin B12 is essential for only two reactions in our metabolism course , one of which is the conversion of odd-chain fatty acids into usable energy intermediates.
- By completing these steps , the three-carbon propionyl-CoA is effectively converted into succinyl-CoA , allowing it to enter the Krebs cycle and contribute to energy production.

Deficiency or Inactivation of Coenzyme B12 :

If Methylmalonyl-CoA mutase or Coenzyme B12 is deficient or inactive , the conversion to Succinyl-CoA is impaired , which leads to the accumulation of Methylmalonyl-CoA and related metabolites in the body , which causes :

- Metabolic acidosis : Excess acid in the bloodstream due to the buildup of organic acids.
- Neurologic manifestations : Potentially severe neurological issues , such as developmental delay , seizures , or intellectual disabilities.

Monounsaturated fatty acid β-oxidation



Monounsaturated fatty acid β-oxidation

Oleic acid, a monounsaturated fatty acid with 18 carbons and a single double bond between carbons 9 and 10 , undergoes beta-oxidation for energy production. Here's how the process proceeds:

- **Initial Rounds of Beta-Oxidation :**
- In the first cycle , beta-oxidation cleaves carbons 1 and 2 , producing the first acetyl-CoA.
- In the second cycle , carbons 3 and 4 are cleaved , generating the second acetyl-CoA.
- In the third cycle , carbons 5 and 6 are cleaved , producing the third acetyl-CoA.

- **Encountering the Double Bond :**
- At this stage , further cleavage would encounter the double bond between carbons 9 and 10. To proceed , the double bond must first be addressed.
- The enzyme enoyl-CoA isomerase shifts the double bond from its current position (between carbons 3 and 4 in the new molecule) to a new position (between carbons 2 and 3) , placing it at the beta-oxidation cleavage site.

- **Continuation of Beta-Oxidation :**

Then , beta-oxidation continues , generating additional acetyl-CoA molecules until the fatty acid is fully oxidized.

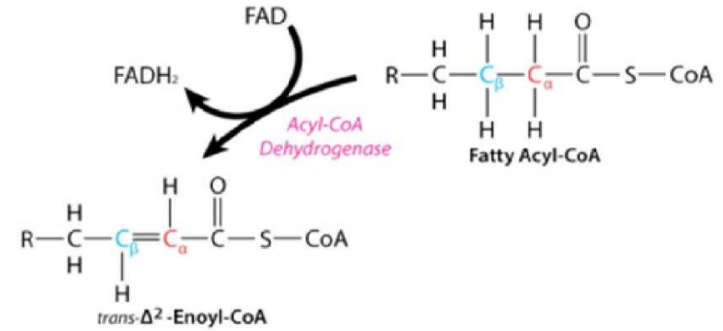
Polyunsaturated fatty acid β-oxidation / 1

Polyunsaturated FA will also need an *NADPH-dependent 2,4-dienoyl CoA reductase* in addition to the *isomerase*.

→ **loss of electrons**

For polyunsaturated fatty acids , which contain multiple double bonds , their processing during beta-oxidation involves two main strategies :

- **Isomerization : Similar to monounsaturated fatty acids , some double bonds can be shifted to the cleavage site using enoyl-CoA isomerase , allowing beta-oxidation to proceed normally.**
- **Reduction : For certain double bonds that cannot be directly isomerized , the enzyme 2,4-dienoyl-CoA reductase reduces them to a single double bond , to processed further in the beta-oxidation cycle.**



But this reaction is skipped resulting in one less $FADH_2$ → loss of electrons

PLEASE SEE NEXT SLIDE

- The molecule shown is a saturated fatty acid attached to Coenzyme A (CoA) through a thioester bond.

Cα (alpha-carbon) : The carbon directly attached to the carbonyl group (C=O).

Cβ (beta-carbon) : The carbon next to the alpha-carbon.

- The enzyme Acyl-CoA Dehydrogenase catalyzes the oxidation of the Cα-Cβ bond in the fatty acyl-CoA molecule.
- This step removes two hydrogen atoms , creating a trans double bond between the alpha and beta carbons.
- During this reaction , FAD is reduced to $FADH_2$ as it accepts the two hydrogen atoms removed from the fatty acyl-CoA.
- The product of this reaction is trans-Δ^2-enoyl-CoA , which now contains a double bond between the alpha and beta carbons.
- $FADH_2$ is generated and will later contribute to ATP production in the electron transport chain.

In saturated fatty acids , during β-oxidation , a double bond must be introduced before cleaving the acetyl-CoA units. This is necessary because the cleavage process must occur adjacent to a carbonyl group. Initially , the fatty acid contains only one carbonyl group , which is removed in the first cycle of β-oxidation. To enable further processing , a double bond is formed by oxidation of the Cα-Cβ bond , followed by the addition of a water molecule and a subsequent oxidation step to generate a new carbonyl group.

In unsaturated fatty acids, the presence of a pre-existing double bond eliminates the need to create one during a specific cycle of β-oxidation. Instead, the double bond is simply rearranged (isomerized) to the correct position. This isomerization step does not require energy and does not produce energy carriers like FADH2. Consequently , one cycle of β-oxidation for unsaturated fatty acids generates NADH but not FADH2, leading to reduced ATP production compared to saturated fatty acids of the same carbon length.

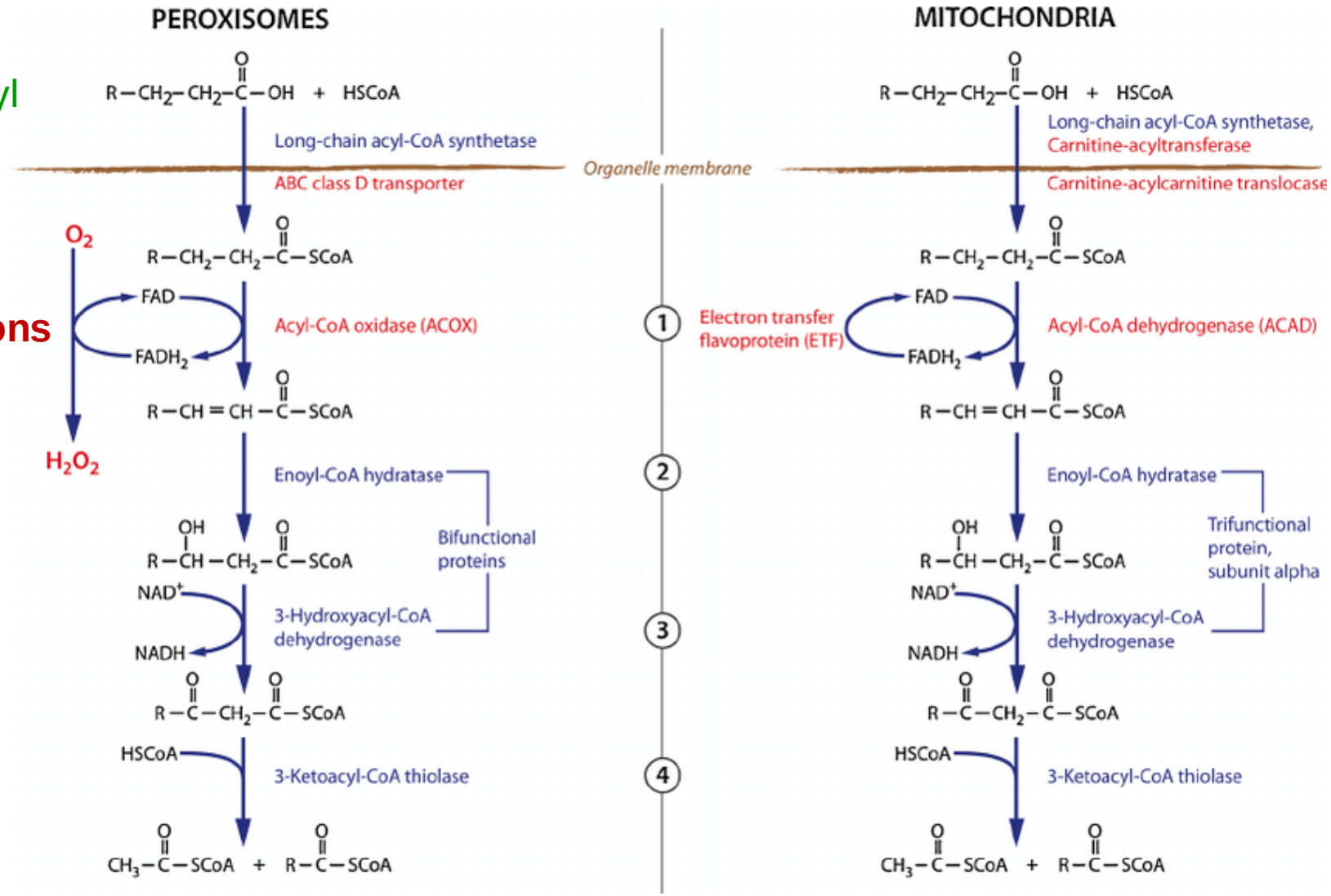
For polyunsaturated fatty acids, the absence of FADH2 production occurs multiple times due to the repeated presence of double bonds. This results in a greater loss of electrons , fewer electron carriers , and ultimately less energy production compared to saturated fatty acids with an equivalent number of carbons.

Peroxisomal β-oxidation

VLCFA ≥22

FAD Containing acyl CoA Oxidase

Loss of electrons



Peroxisomal β-oxidation / 1

Beta oxidation in the mitochondria can metabolize short- , medium- , and long-chain fatty acids. However, very long-chain fatty acids (VLCFAs) undergo beta oxidation in peroxisomes rather than mitochondria due to differences in their transport and enzymatic systems.

- **Transport of VLCFAs into Peroxisomes**

- VLCFAs cross the peroxisomal membrane through a specialized transport system distinct from that of mitochondria. In peroxisomes , the ABC class D transporter facilitates the entry of VLCFAs in an inactive form , accompanied by CoA (coenzyme A). Activation of VLCFAs through CoA addition occurs inside the peroxisome.
- In general, fatty acids must be linked to CoA to participate in metabolic reactions, as this activates the acyl chains for subsequent processing.

- **Beta Oxidation in Peroxisomes**

Once activated, the beta oxidation pathway in peroxisomes proceeds similarly to that in mitochondria but with key differences :

1) Oxidation :

- In mitochondria , acyl-CoA dehydrogenase catalyzes the first oxidation step, reducing FAD to $FADH_2$, which enters the electron transport chain to produce energy.
- In peroxisomes , the enzyme acyl-CoA oxidase performs this step. Instead of contributing $FADH_2$ to the electron transport chain , $FADH_2$ is re-oxidized to FAD, reducing oxygen to hydrogen peroxide (H_2O_2) , a reactive oxygen species.
- This distinction results in less energy production during beta oxidation in peroxisomes compared to mitochondria.

Peroxisomal β-oxidation / 2

2) Hydration :
The enzyme enoyl-CoA hydratase creates an alcohol group .

3) Second Oxidation :
3-Hydroxyacyl-CoA dehydrogenase catalyzes the oxidation of the alcohol group , reducing NAD to NADH. This step is similar to the process in mitochondria.

4) Cleavage :
3-Ketoacyl-CoA thiolase cleaves the fatty acid chain, adding another CoA molecule and producing a shortened fatty acyl-CoA chain.

- **Structural and Functional Differences between mitochondrial and peroxisomal oxidation**
- **Transport Process**
- **The hydratase and 3-hydroxacyle dehydrogenase enzymes in peroxisomes are bifunctional proteins , whereas in the mitochondria they are trifunctional proteins.**
- **The overall process is less energy-efficient in peroxisomes due to the generation of hydrogen peroxide instead of ATP from $FADH_2$.**

Diseases Associated with Peroxisomal Beta Oxidation

- **Zellweger syndrome : a peroxisomal biogenesis disorder**

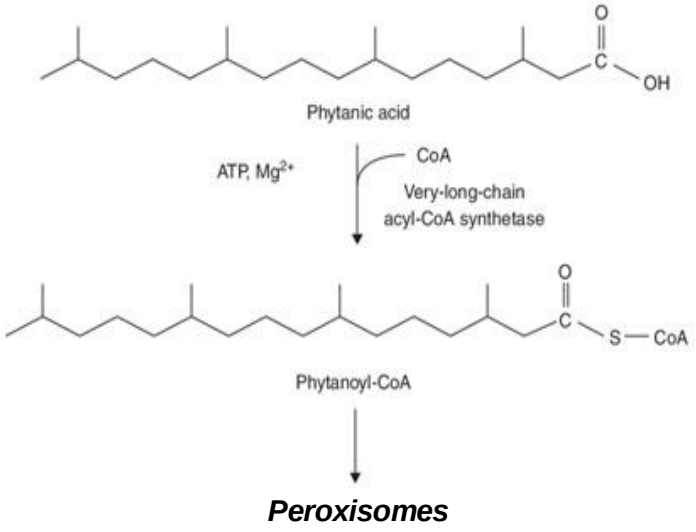
A disorder caused by defective peroxisome (which is a dynamic organelle) biogenesis. As a result, peroxisomal functions , including beta oxidation and detoxification of oxidative stress, are impaired.

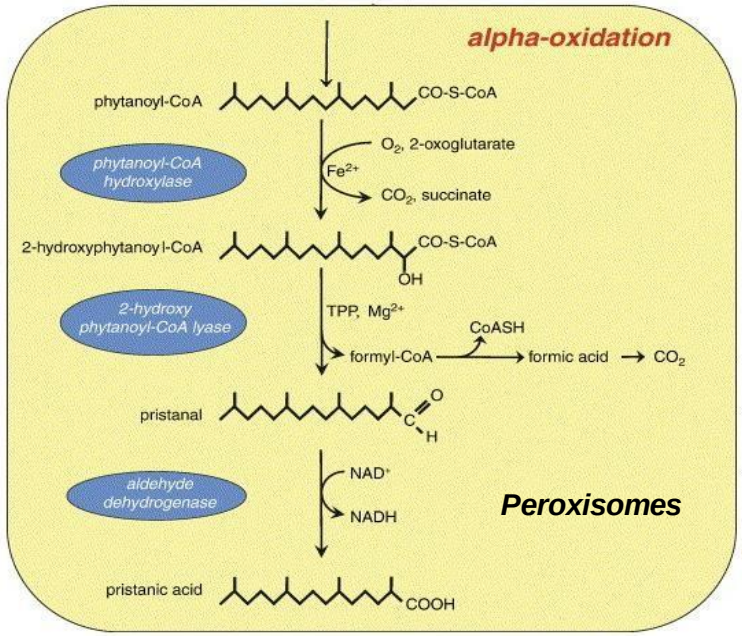
- **X-linked adrenoleukodystrophy: dysfunctional transport VLCFA across the peroxisomal membrane (Accumulation of VLCFAs)**

A genetic condition characterized by impaired transport of VLCFAs into peroxisomes due to defective ABC class D transporters. This leads to the accumulation of VLCFAs , causing cellular damage and neurological dysfunction.

Peroxisomal α-oxidation of branched chain FAs

- Phytanic acid is a breakdown product of Chlorophyll.
- It is activated by CoA , transported into peroxisome , hydroxylated by phytanoyl CoA α-hydroxylase (PhyH) and carbon 1 is released as CO2 (unlike beta oxidation) .
- When fully degraded , it generates formyl-CoA , propionyl-CoA , acetyl-CoA , and 2-methyl-propionyl- CoA.





Refsum disease is an autosomal-recessive disorder caused by a deficiency of peroxisomal PhyH.

PLEASE SEE NEXT SLIDE

Peroxisomal α-oxidation of branched chain FAs

This pathway is used for branched-chain fatty acids like phytanic acid , which is a product of chlorophyll breakdown. Although phytanic acid is saturated , it contains branches that make it unsuitable for beta-oxidation.

- **Activation:**

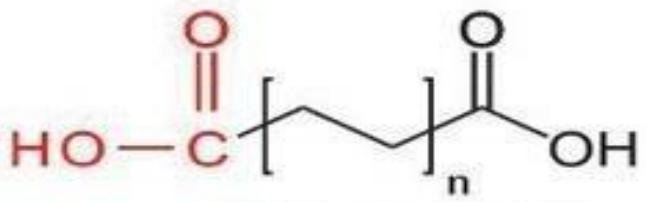
Initially , very-long-chain acyl-CoA synthetase activates phytanic acid outside the peroxisome by attaching a CoA group , forming phytanoyl-CoA , which is now active and ready for peroxisomal metabolism.

- **Alpha-Oxidation Process in Peroxisomes :**

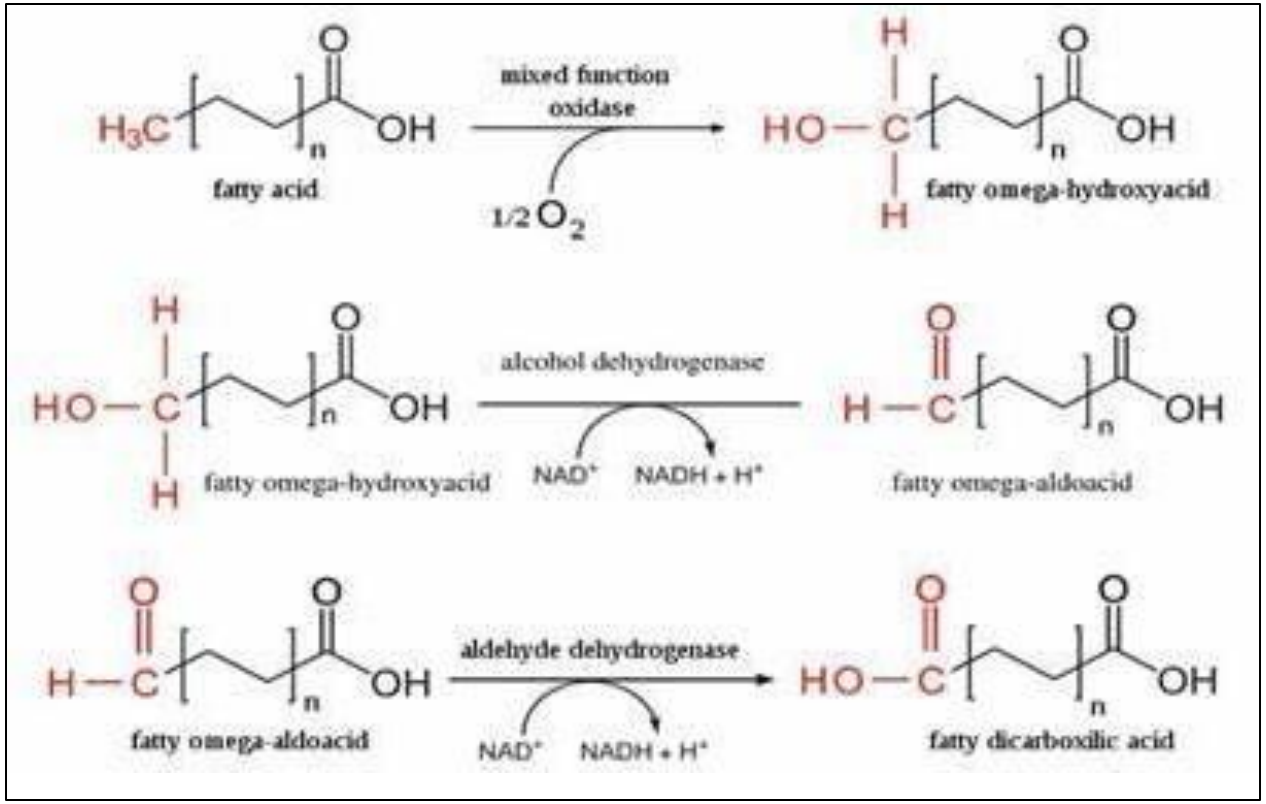
- Phytanoyl-CoA hydroxylase introduces a hydroxyl (-OH) group on the alpha-carbon
- This facilitates the cleavage of the carbonyl group with CoA by 2-hydroxy phytanoyl-CoA lyase , releasing it as formyl-CoA , which is further broken down (by removing CoA) to formic acid and then CO_2.
- The remaining hydroxyl group is oxidized to form an aldehyde via 2-hydroxy phytanoyl-CoA lyase , resulting in the production of pristanal.
- Pristanal undergoes further oxidation to a carboxyl group using aldehyde dehydrogenase , with NAD^+ reduced to NADH , forming pristanic acid.

- The cycle repeats until the fatty acid is completely metabolized. However, due to the branches , subsequent cycles may produce varying products , including formyl-CoA , acetyl-CoA , propionyl-CoA , or methyl-propionyl-CoA , depending on the structure of the acid.

ω-Oxidation



- ω-Oxidation is a minor pathway of the SER (smooth endoplasmic reticulum)
- It generates dicarboxylic acids.
- It is upregulated in certain conditions such as MCAD (medium-chain acyl-CoA dehydrogenase) deficiency.

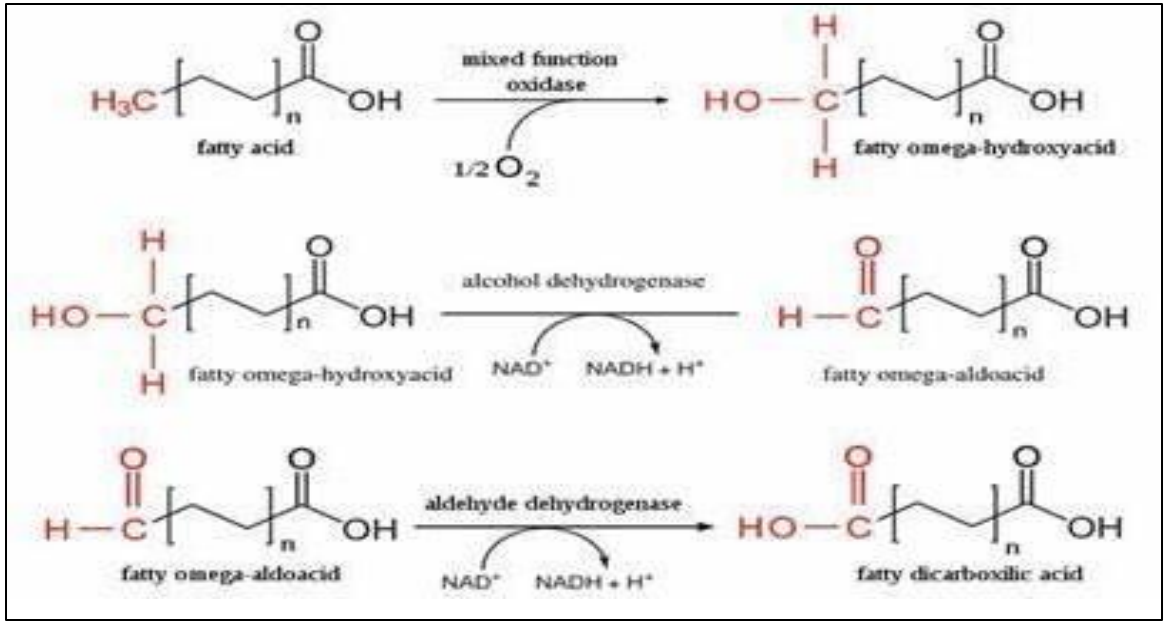


ω-Oxidation

This minor oxidation pathway targets the omega (last) carbons of the fatty acid chain , opposite the carboxyl group. It typically occurs in the SER as a minor pathway but becomes significant under certain conditions , such as (MCAD) deficiency.

- An oxidase introduces a hydroxyl (-OH) group at the omega carbon , converting it into an alcohol.
- Alcohol dehydrogenase oxidizes the alcohol to an aldehyde , producing NADH.
- Aldehyde dehydrogenase oxidizes the aldehyde to a carboxyl group , producing NADH .

Once the omega carbon is converted into a carboxyl group, the fatty acid is ready for cleavage from the omega side. The process repeats multiple times .



Lipids and energy

- TAGs are the body's major fuel storage reserve.
- The complete oxidation of fatty acids to CO2 and H2O generates 9 kcal/g of fat (as compared to 4 kcal/g protein or carbohydrate). Why?

	carbohydrates	lipids
Stored as...?	Starch - plants Glycogen - animals	Fats & oils (plants Fat (animals)
Long/short term storage?	Starch: long-term Gylcogen: short-term	Long term
Ease of digestion/ release of energy?	Easy to release energy	Harder to release energy (needs more oxygen)
Energy per gram?	17kJ/g	38kJ/g
Solubility in water? (and consequence)	Soluble	Not soluble
Use of oxygen in metabolism? (and consequence)	Needs less oxygen, useful for high-demand activity	Needs more oxygen, less efficient to release energy

Lipids and energy

- **Lipids : Each gram of lipids provides approximately 9 kcal (38 kJ) , making them energy-dense. However, lipid oxidation is a slower and more complex process , involving hormonal regulation and the release of fatty acids from adipocytes.**
- **Carbohydrates : Provide 4 kcal (17 kJ) per gram but serve as the body's first source of energy because their metabolism is faster and more efficient.**
- **Lipid oxidation during fasting is limited due to the diversion of oxaloacetate for gluconeogenesis. As a result , some acetyl-CoA from fatty acid oxidation is used for energy , while the rest contributes to ketogenesis.**

	carbohydrates	lipids
Stored as...?	Starch - plants Glycogen - animals	Fats & oils (plants Fat (animals)
Long/short term storage?	Starch: long-term Gylcogen: short-term	Long term
Ease of digestion/ release of energy?	Easy to release energy	Harder to release energy (needs more oxygen)
Energy per gram?	17kJ/g	38kJ/g
Solubility in water? (and consequence)	Soluble	Not soluble
Use of oxygen in metabolism? (and consequence)	Needs less oxygen, useful for high-demand activity	Needs more oxygen, less efficient to release energy

Exercise and sources of energy

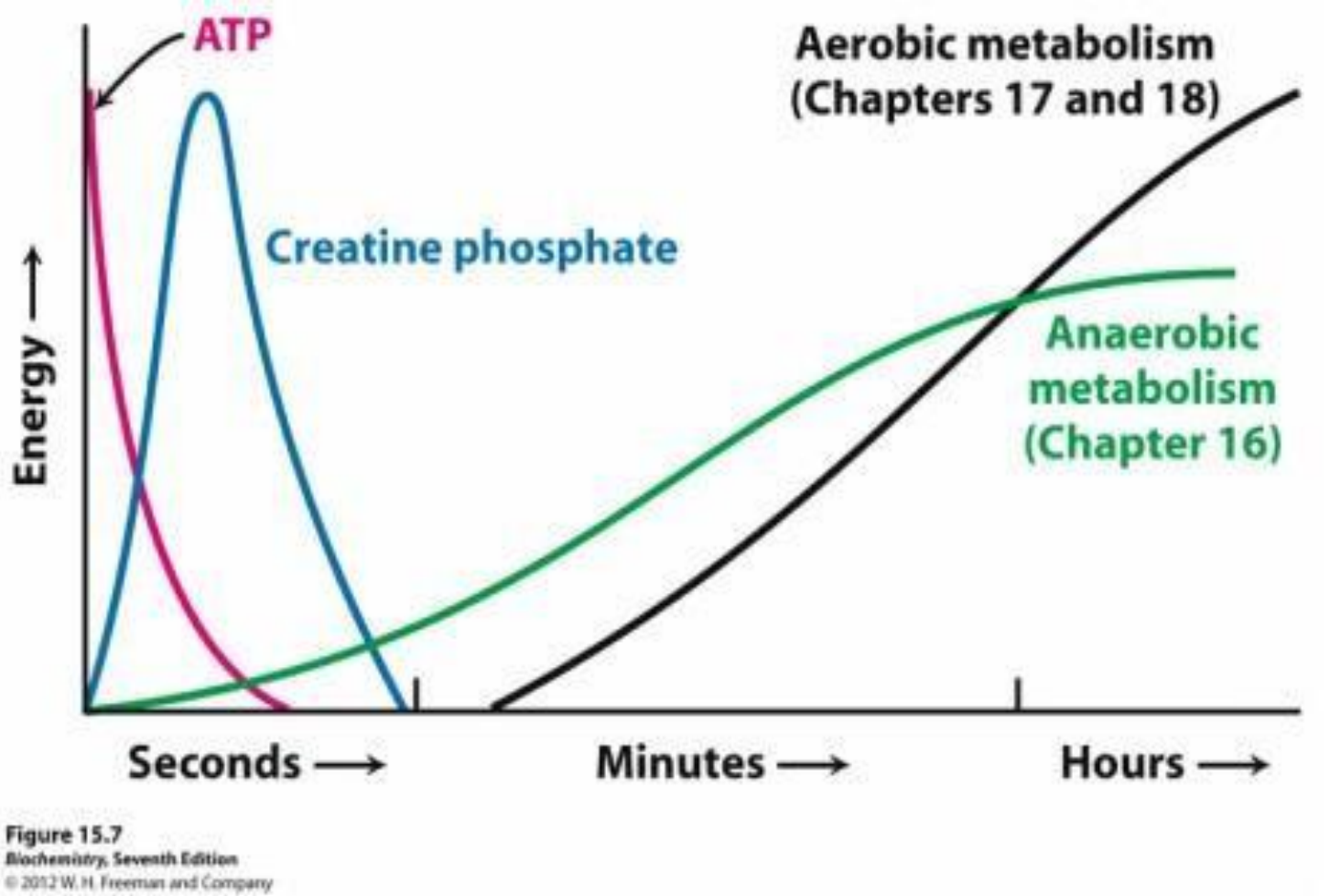
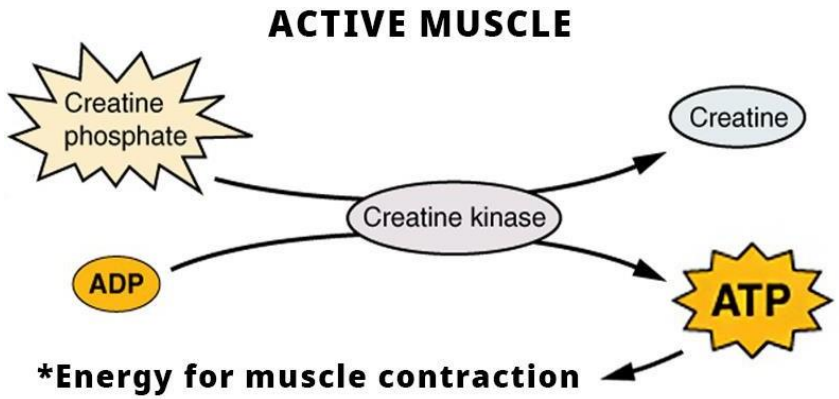


Figure 15.7
Biochemistry, Seventh Edition



Exercise and sources of energy

Muscle energy demands increase significantly during exercise . The sequence of energy utilization is as follows :

- **Immediate ATP Use :**

ATP already present in cells is consumed first , but its concentration rapidly decreases.

- **Creatine Phosphate :**

This high-energy phosphate compound provides a quick energy boost by hydrolysis , but its supply depletes rapidly within seconds.

- **Anaerobic Respiration :**

Activated before aerobic respiration , anaerobic metabolism provides a fast , albeit less efficient , energy source. This is because oxygen delivery to tissues delays as the heart and respiratory rates adjust to increased demands.

- **Aerobic Respiration :**

Once oxygen availability improves , aerobic respiration becomes the predominant energy provider. However , this shift requires time due to its dependency on oxygen delivery and transport mechanisms.

Thus , during exercise , energy initially relies on ATP , creatine phosphate , and anaerobic respiration before transitioning to the more sustainable aerobic respiration pathway.

Synthesis of fatty acids

Dr. Diala Abu-Hassan

Lippincott's Biochemistry , Ch. 16

Fatty Acid Synthesis

- Excess carbohydrates and proteins in diet will be used to synthesize fatty acids and stored as TAGs.
- Occurs in liver, lactating mammary glands and adipose tissue
- Requires :
  - Carbon Source : Acetyl CoA
  - Reducing Power : NADPH
  - Energy Input : ATP

Fatty acid synthesis is an anabolic pathway that involves the construction of fatty acids from smaller precursors , primarily acetyl-CoA. This process is essentially the reverse of fatty acid degradation , with distinct enzymes and regulatory mechanisms. It predominantly occurs during well-fed states when energy and nutrient levels are high, such as after consuming carbohydrates or proteins.

Fatty Acid Synthesis

- **Carbohydrates :**
- Excess glucose leads to increased glycolysis, generating acetyl-CoA through pyruvate oxidation.
- Acetyl-CoA enters the Krebs cycle, where high levels of citrate signal energy sufficiency. Citrate exits the mitochondria and contributes to fatty acid synthesis.
- The synthesized fatty acids are stored as triacylglycerols in adipocytes.

- **Proteins :**
- Amino acids from dietary proteins cannot be stored directly. They are either used for protein synthesis , converted into nitrogen-containing compounds , or catabolized for energy.
- Excess amino acids can be converted into acetyl-CoA (via specific pathways) , fueling fatty acid synthesis and subsequent storage as triacylglycerols.

- **Major Sites of Fatty Acid Synthesis**
- Adipocytes : Serve as primary storage sites for triacylglycerols.
- Liver : Synthesizes fatty acids for lipoproteins (e.g., LDL, cholesterol esters) and other metabolic needs.
- Lactating Mammary Glands : Under the influence of prolactin , fatty acid synthesis is upregulated to produce the short- and medium-chain fatty acids essential for breast milk.

- The raw material to be used is Acetyl-CoA. Since the degenerative pathway involves oxidation , the corresponding biosynthetic pathway is expected to follow a reductive process. In this pathway , the main substrate undergoes reduction , while the coenzyme NADPH is oxidized to NADP+. Conversely , during the degenerative pathway , NAD+ is reduced to NADH , or FAD is reduced to FADH2.

Why Energy ?

Fatty Acid

↓

↓

↓

↓

Acetyl CoA

ΔG^{o} : -ve

Acetyl CoA

↓

↓

↓

↓

Fatty Acid

ΔG^{o} : +ve

Acetyl CoA + n(ATP)

↓

↓

↓

↓

Fatty Acid + n(ADP)

ΔG^{o} : -ve

Energy is required in this process, as it is an anabolic pathway. In contrast, during fatty acid degradation, Acetyl-CoA is produced , and energy is not extensively consumed , except in a single step : the activation step , where CoA is added. This step requires 1 ATP , which is hydrolyzed to AMP (effectively breaking two phosphate bonds) . Overall, when summing the ΔG values of the degradation pathway , the reactions are negative , making it an energy-producing pathway.

On the other hand , the reverse process starts with Acetyl-CoA and leads to fatty acid synthesis. This is expected to have a positive ΔG , requiring energy input. To drive the reaction forward , coupling with ATP hydrolysis is necessary to make the overall ΔG negative , allowing the reaction to proceed efficiently.

Overview of fatty acid synthesis

- **The fatty acids are synthesized by:**
  1. **Production of malonyl CoA** ← Which is a three carbon molecule
  2. **Binding of acetyl CoA and malonyl CoA to the fatty acid synthase** ← Complex enzyme
  3. **Condensation of acetyl CoA and malonyl CoA** ← One carbon will be removed
  4. **Elongation of the acyl CoA by 2 carbons per round**
     - **Reduction, dehydration, reduction** ← The extra carbonyl group is removed
  5. **Binding of malonyl CoA**
  6. **Repeat steps 3 (acyl CoA), 4, and 5**
  7. **Release of the hydrocarbon chain by a thioesterase (TE)**

Don't worry if you don't understand this slide , it will be clearer when the entire pathway is explained

FA Degradation and Synthesis

Acyl CoA $_{(n)}$

↓ Oxidation

↓ Hydration

↓ Oxidation

↓ Thyolysis

Acyl CoA $_{(n-2)}$ + Acetyl CoA

Acyl CoA $_{(n+2)}$

↑ reduction

↑ dehydration

↑ reduction

↑ condensation

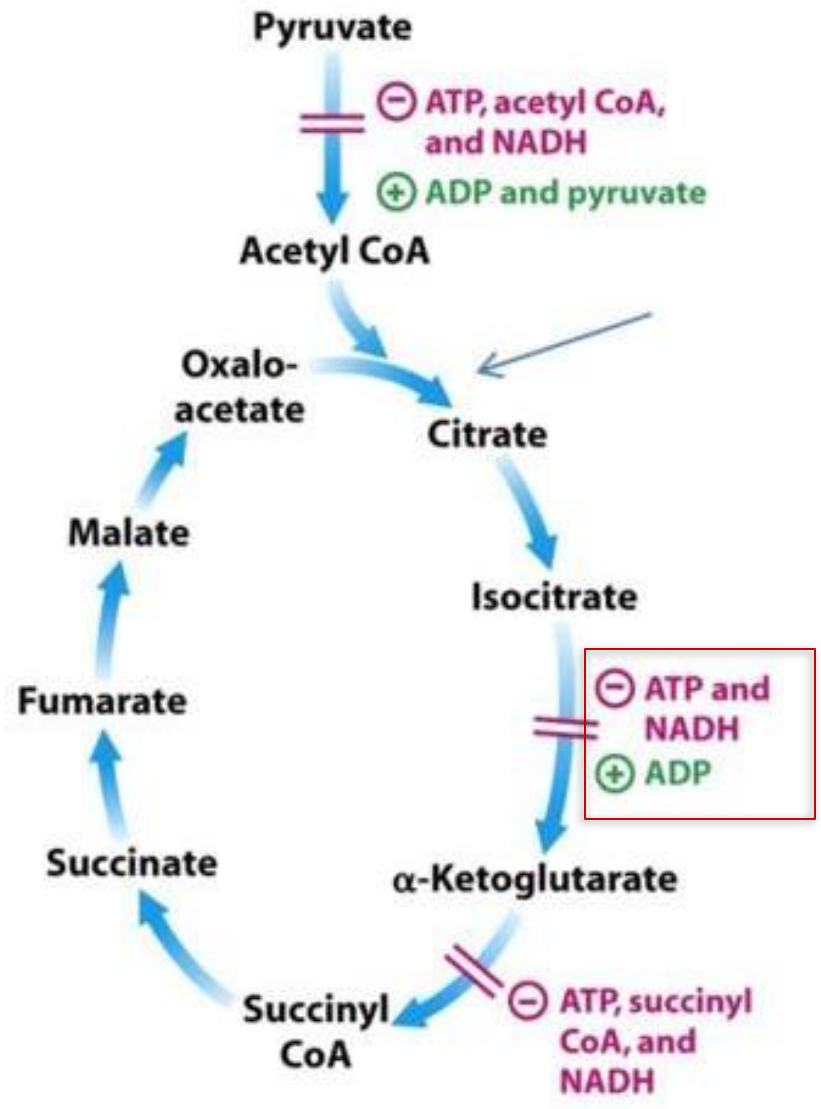
Acyl CoA$_{(n)}$ + Malonyl CoA

FA Degradation and Synthesis

	Degradation	Synthesis
Starting substrate	Acyl CoA $_{(n)}$	Acetyl CoA $_{(n)}$ + Malonyl CoA
First step	Oxidation : Formation a double bond	Condensation : Combining acetyl group with malonyl group followed by malonyl CoA binding
Second step	Hydration : Converting double bond to an alcohol	Reduction : Removal of oxygen and double bond
Third step	Oxidation : Converting alcohol to a carbonyl	Dehydration : Eliminating oxygen
Fourth step	Thyolysis : cleavage of acetyl CoA and reformating an acyl CoA $_{(n-2)}$	Reduction : Formation of Acyl CoA group (fatty acid)
Products	Acyle CoA (n-2) + Acetyl CoA	Acyl CoA $_{(n+2)}$

Fatty acid synthesis and degradation are excellent examples of spiral metabolic pathways, characterized by repeated cycles of similar reactions. These processes are highly regulated to ensure metabolic efficiency and adaptability to physiological conditions, such as energy demand or nutrient availability.

Transport of acetyl-CoA from mitochondria to cytoplasm



When ATP increases:

↓

ATP inhibits isocitrate dehydrogenase

↓

Citrate is transported into the cytosol

↓

Citrate is cleaved into oxaloacetate and acetyl CoA by ATP citrate lyase

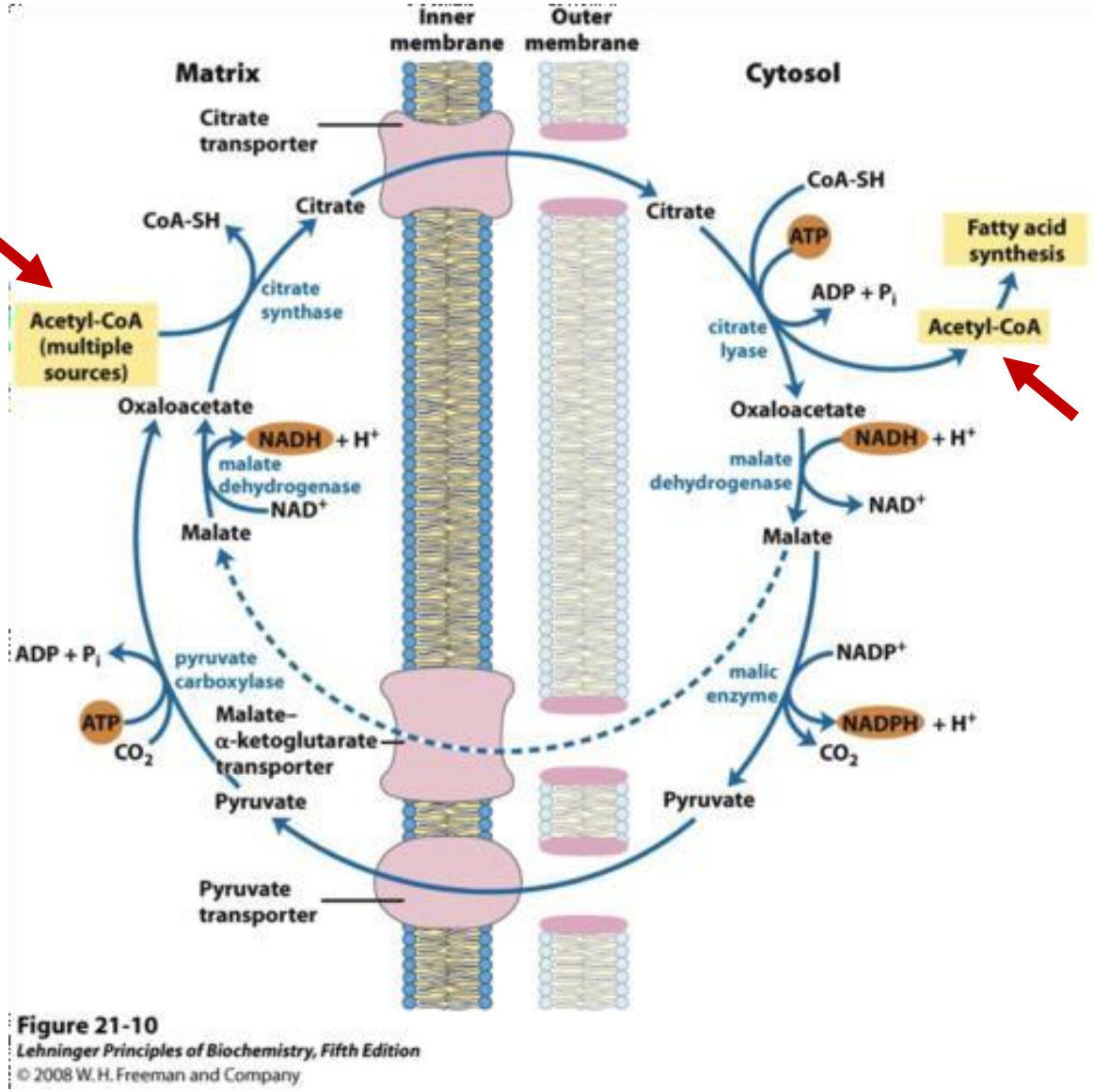


Figure 21-10
Lehninger Principles of Biochemistry, Fifth Edition

Glucose can be converted to fat, but fat cannot be converted to glucose.

Transport of acetyl-CoA from mitochondria to cytoplasm

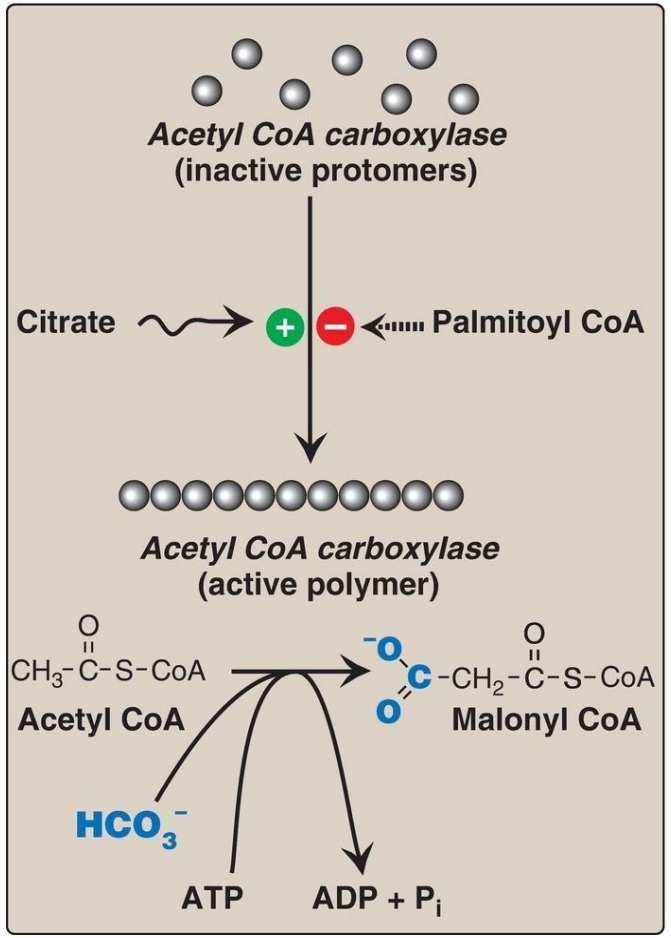
- **Cytosolic Acetyl-CoA Formation :**
- In the well-fed state , high glucose levels increase pyruvate and acetyl-CoA production.
- Citrate , generated in the Krebs cycle , exits the mitochondria via its specific transporter.
- In the cytosol , citrate is cleaved by citrate lyase into acetyl-CoA and oxaloacetate , utilizing ATP and CoA.

- **Oxaloacetate Recycling :**
- Oxaloacetate is reduced to malate via malate dehydrogenase.
- Malate re-enters the mitochondria to participate in the Krebs cycle.

- **Acetyl CoA now is available for fatty acids synthesis**

Synthesis of malonyl-CoA

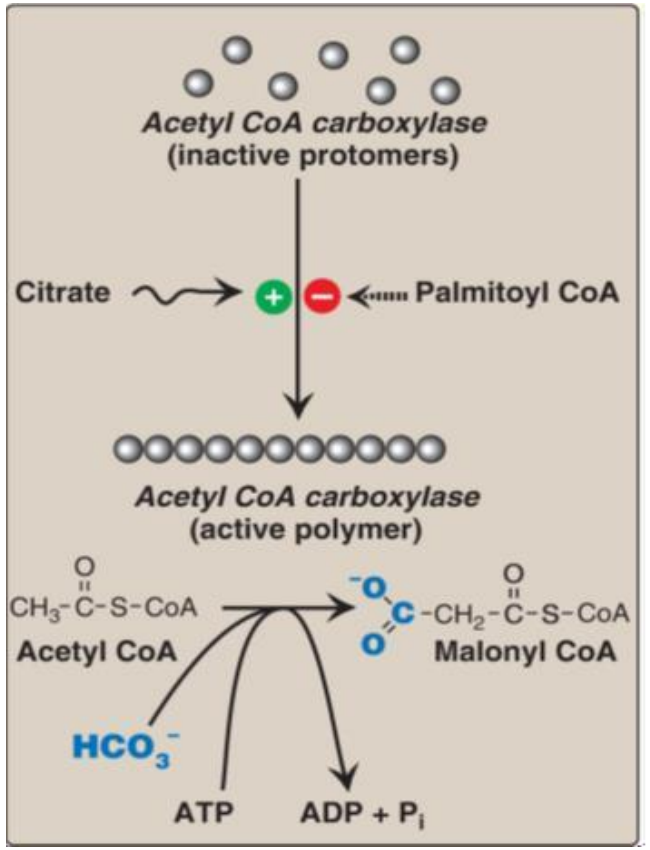
- Acetyl CoA carboxylase (ACC) transfers a carbon from CO2 (as a bicarbonate) via biotin (vitamin B7), which is covalently bound to ACC.
  - ATP is needed.
  - The reaction is the rate-limiting reaction.
  - ACC is an allosteric enzyme.

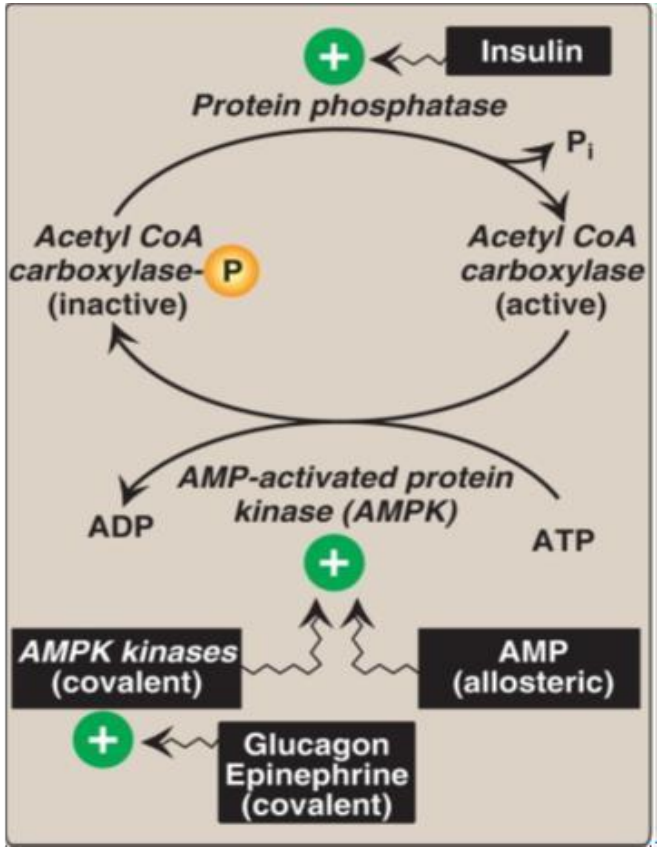


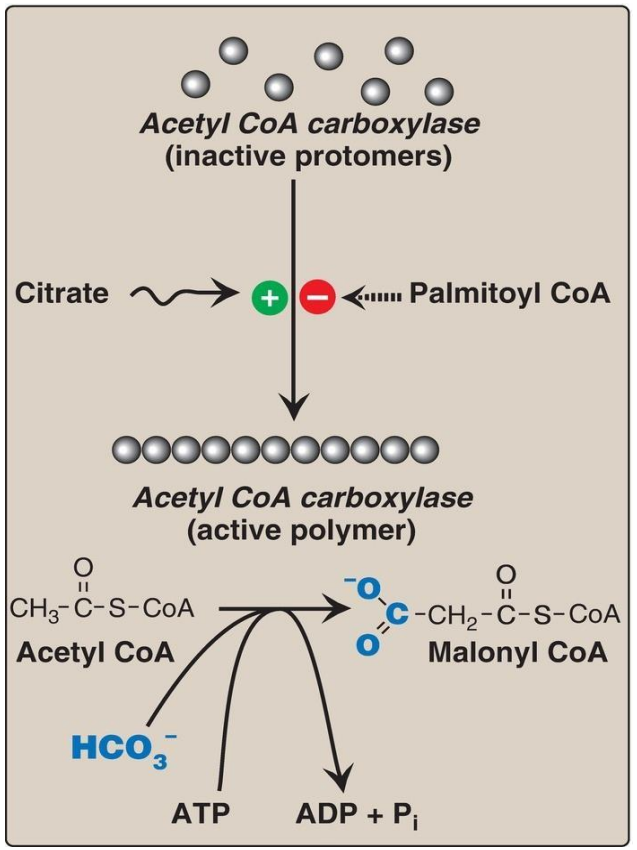
PLEASE SEE SLIDE 34

Regulation of ACC

- ACC is inactivated by :
  - Palmitoyl-CoA
  - Phosphorylation by AMPK, which is activated by glucagon and epinephrine.







PLEASE SEE SLIDE 34

Regulation of ACC / 1

- **Synthesis of Malonyl-CoA :**
- Acetyl-CoA is converted to malonyl-CoA by acetyl-CoA carboxylase (ACC).
- This carboxylation reaction requires ATP , biotin , and bicarbonate (HCO_3^-).
- Malonyl-CoA serves as a critical intermediate for chain elongation during fatty acid synthesis.

- **Reduction Reactions :**
- The synthesis pathway involves repeated reduction reactions , using NADPH as the reducing agent.
- Energy is provided by ATP hydrolysis to drive these thermodynamically unfavorable reactions.

- **Rate-Limiting Step :**
- Acetyl-CoA carboxylase (ACC) is the primary regulatory enzyme.
- It is regulated by allosteric interactions , covalent modifications , and hormonal signals.

- **Allosteric Regulation :**
- High citrate levels activate ACC by promoting its polymerization from inactive protomers (allosteric activator)
- Palmitoyl-CoA (a product of fatty acid synthesis) acts as a feedback inhibitor.

Regulation of ACC / 2

- **Phosphorylation (covalent modification) and Hormonal Control :**

This process involves an enzyme called AMPK (AMP-Activated Protein Kinase) , which phosphorylates acetyl-CoA carboxylase (ACC) , leading to its inhibition. As a result , fatty acid synthesis is suppressed.

- **Fasting State :**

- AMPK is activated under fasting conditions.
- This activation is mediated indirectly by glucagon and epinephrine through signaling pathways , including protein kinase A (PKA).
- PKA activates AMPK kinases , which phosphorylate and activate AMPK.
- Active AMPK then phosphorylates ACC , rendering it inactive and inhibiting fatty acid synthesis.

- **Well-Fed State :**

- In the presence of insulin , protein phosphatases are activated.
- These phosphatases remove the phosphate group from ACC , reactivating it and promoting fatty acid synthesis.

- This regulatory mechanism ensures that fatty acid synthesis is tightly controlled , occurring primarily during the fed state and being suppressed during fasting.

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			

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:

Lippincott’s Biochemistry , Ch. 16

[راجع] عبادتك **[راجع]** فكرتك ، مشروعك ، خطوتك ، **[راجع]** ، صدقك ، إخلاصك ، خبيئتك ، **[انظُر]** ما يُقوّيك ، يُضعِفُك ، يُعجزك ، يُبعِدك ، ينفعك ، **[تأمّل]** ما فعلت ، كَوّنت ، أنجزت ، أتممت ، **[أدرك]** مكانك ممّا تسير إليه ، **[انظُر]** مَن تُرافِق ، ما تُوافِق ، **[زِن]** ، ظهورك ، مرورك ، **[احتَرِم]** ضَعفَك ، عثرتك ، محاولاتك ، **[تقَبَّل]** خطأك ، بشريّتك ، نقصك ، **[قاوم]** ذَنبك ، **[بادِر]** توبةً ، قُربًا ، غرسًا، **[وكُن لله]**

"وَاللَّهُ غَالِبٌ عَلَى أَمْرِهِ وَلَكِنَّ أَكْثَرَ النَّاسِ لَا يَعْلَمُونَ"