METABOLISM

This lecture
Lippincott's Biochemistry, Ch. 16

"100% of students should watch the lec" ... Dr said

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Now we will talk about degeneration of fatty acids; it seems like the reverse of synthesis with some differences

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TAGs are the body's major fuel storage reserve.

TAGs (triacylglecerides) are the main source of energy because;

1. The amount of lipids is good in the body (substantial) .

2. More energy is produced from fatty acid (lipids in general) than sugars and proteins,
the complete oxidation of fatty acids to CO2 and H2O generates 9 kcal/g fat (as compared to 4 kcal/g protein or carbohydrate).

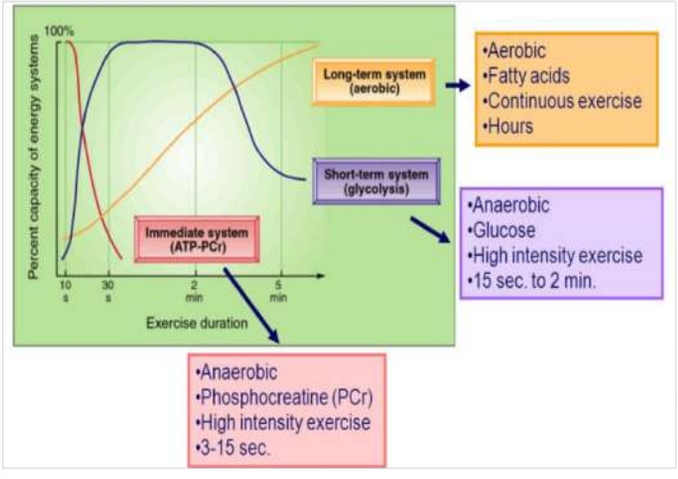
***why one gram of lipids produces much more energy than carbohydrates and proteins?*
The reason is that the lipids are saturated, they have relatively large amounts of covalent bonds (a lot of energy) compared with carbohydrates and proteins.

What does the body utilize to produce energy?

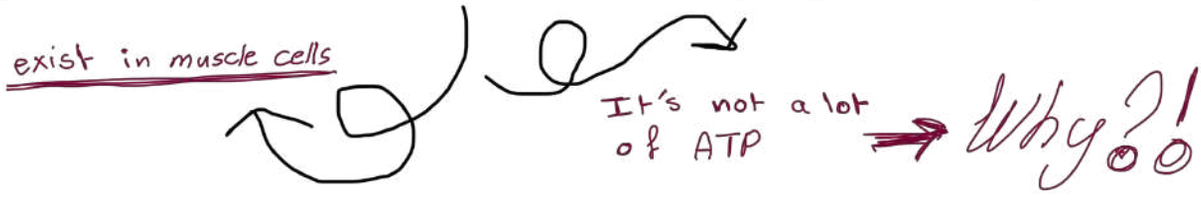
Actually there are a number of sources (it depends on what you are doing), for example (look at the photo while you're reading)

All pathways happen in order, memorize them in order, we don't use the second pathway until the first pathway is depleted.

Let's say that you start to jog (هرولة) or walk fast ➡️ your body needs energy (but your body doesn't predict what you want to do) it doesn't know if you are going to just walk or you are going to run fast for 10 seconds or 2 minutes or 2 hours ➡️ your body start to utilize (produce) energy that will enable you to do what you want to do ➡️ it is looking forward energy from:



💡 *First: the energy comes from ATP molecules in the cells (they are existing in the cells)*



Remember what Dr Nafez said about why cells don't store a lot of ATP !!! That's because if we stored enough ATP for a whole day we will be really fatty, so body must generate ATP when it needs.

So, we used all ATP in the cells

💡 second : we start to produce energy (ATP)

How we do that? What are the pathways that produce energy (ATP).

1. The cells use a molecule that is known as "phosphocreatine" it is phosphorylated creatine.

There is an enzyme ➡️ it transfers phosphate group from phosphocreatine to ADP and that will generate some ATP molecules that will sustain the movement and action of muscles, but there is a problem (the phosphocreatine is depleted within 10 seconds.

So Now after utilizing all phosphocreatine molecules we don't have ATP existing in the cells and we don't have phosphocreatine, so we should find another way to produce energy.

2. Then the body will use the Anaerobic metabolism.

Glucose → pyruvate → lactate

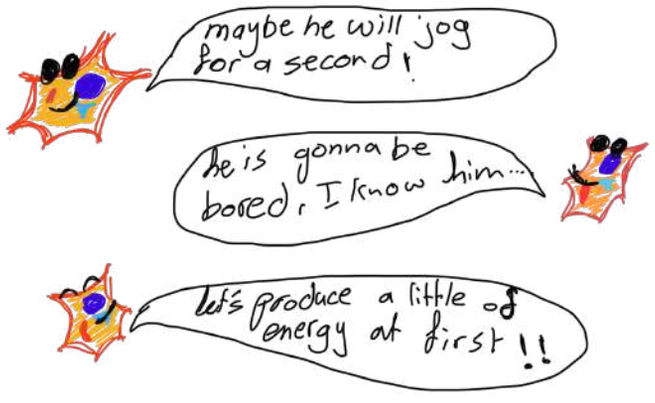
↓

producing some Energy (ATP)

That allow muscles to do action and that will last for few minutes, but you still running (doing action)

Remember, our bodies can't predict what will be going on, maybe you will ask you self, why we don't use the anaerobic or aerobic metabolism that produce more energy than existing ATP or phosphocreatine, but our cells don't know if you need a little energy for walking for a few seconds or a large amount of energy for running for hours, so cells start to produce energy from pathways that produce a little of energy then it will be converted to the pathways that will produce a large amount of energy for relatively a long time of action.

3. Aerobic metabolism to produce a lot of energy (again the body can't predict what you will be doing)



For aerobic metabolism (glycolysis) we have these sources

Glucose

Oxidizing of glucose producing H_2O and CO_2 and a lot of ATP

Lipids (fatty acids)

The excellent source of energy (remember 9 kcal/g)

In order to oxidizing fatty acids (oxygen is needed)

To maintain the metabolism (breaking down of fatty acids)

Matching with our daily life .

A. Aerobic exercise basically maintain O_2 in your body, you will exercise slowly in periods so you have interruptions in between in order to burn fat, this is an excellent way to lose weight (you should exercise aerobically and not to do hard or strenuous exercise).

Runners 🏃 for example have different exercises depending on the races that they participate them, runners (who run for about 100m/ in 10 seconds they relay a lot on ATP and phosphocreatine and anaerobic glycolysis (attention: the duration is 10 seconds, it is too short).

Marathon runners 🏃 they take a lot of time jogging, they exercise while they are breathing to make sure that they have oxygen in their body to maintain the oxidation reaction from fats and sugars .

B. When you wake up in the morning and then you have a breakfast (you break your fast…that's it) You ate your breakfast ➡️ you came to the university ➡️ now you are depending on the glycogen store (depleted in 3 hours) ➡️ after depletion of glycogen, the body turns to another thing which is the lipids (fatty acids).

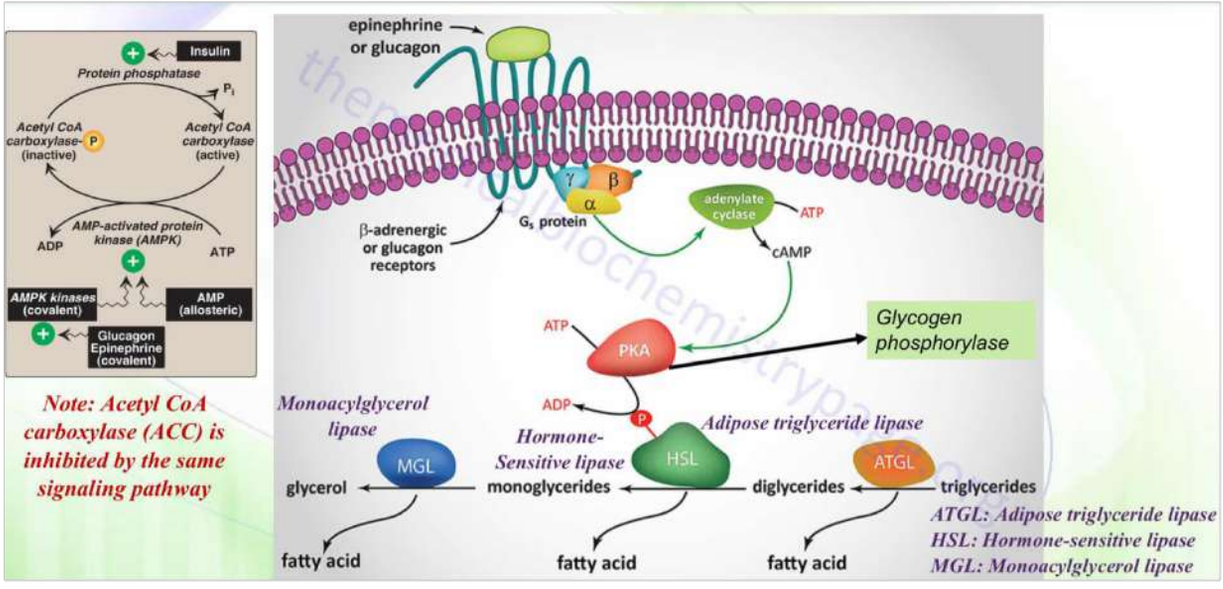
This table shows the differences between carbohydrates and lipids as sources of energy

	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

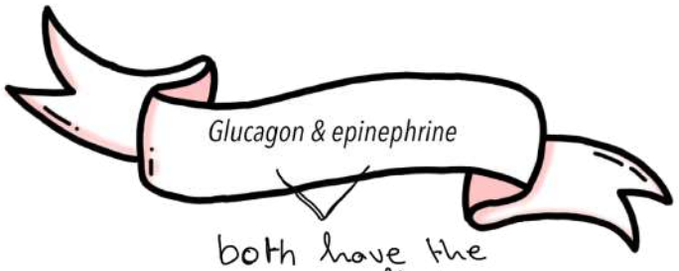
All previous metabolism reactions are regulated by hormones

Pay attention for this important topic … the doctor focused and talked a lot about it 🔥🔥🔥

Try to make matching between the following paragraphs and this slide from doctor



All previous metabolism reactions which are concerned with the utilization of energy are regulated by hormones especially



both have the same effects

In terms of epinephrine/glucagon وضع الطوارئ، محتاجين طاقة
They activate fatty acids breaking down (oxidation of fatty acids).

Epinephrine/Glucagon bind with GTA-protein coupled receptor GPCR (it's a receptor associated with G-protein) ➡️ the binding will cause the releasing of Alfa subunit ➡️ Alfa subunit binds to adenylate cyclase [it will be activated] ➡️ it will produce cAMP ➡️ cAMP binds to protein kinase A (PKA) ➡️ PKA phosphorylates many enzymes and proteins including:

1. "Glycogen phosphorylase" the enzyme that is responsible for releasing of glucose from glycogen.
2. a lipase enzyme "Hormone Sensitive Lipase HSL"

what is the exact role of HSL ?!

↓

HSL is one of three lipases that participate in the release of fatty acids from triacylglycerols TAGs

So we have now a glycerol back bone with a three fatty acids
You have the action of the first enzyme called " adipose triglyceride lipase" ➡️ it releases the first fatty acid from the TAG ➡️ so the triglyceride is converted into diglyceride and one free fatty acid ➡️ the diglyceride is the substrate of the second lipase which is HSL that we have just talked about, this enzyme removes the second fatty acid from the diglyceride ➡️ so now we have monoglyceride with 2 free fatty acids (one from the first lipase and the other is from the second lipase) ➡️ the monoglyceride is the substrate of the third enzyme "monoacylglycerol lipase" that releases the third fatty acid molecule ➡️ so finally we have a glycerol molecule + three free fatty acids in adipocytes.

We are talking about the hormonal regulation of the metabolism reactions? So why we mentioned this story?!
We mentioned that because the lipase 2 which is in the middle and called HSL is sensitive -as the name implies- to the insulin + epinephrine/glucagon.

Glucagon/epinephrine pathway is the same pathway that regulates Acetyl CoA Carboxylase that is involved in the fatty acids synthesis (it inhibits the synthesis of fatty acids and activate the degradation of lipids) … Two birds 🧿 by one stone 🪨 ، it makes a sense, who wants to synthesis something and consuming energy however at the same time he is degrading it?!

So, whenever you activated a pathway, you should be sure that the opposite pathway is inhibited, to maintain your energy

Glucagon/epinephrine activates fatty acids breaking down and inhibits the synthesis of fatty acids …. The great harmony in metabolism 🧠

AGAIN!

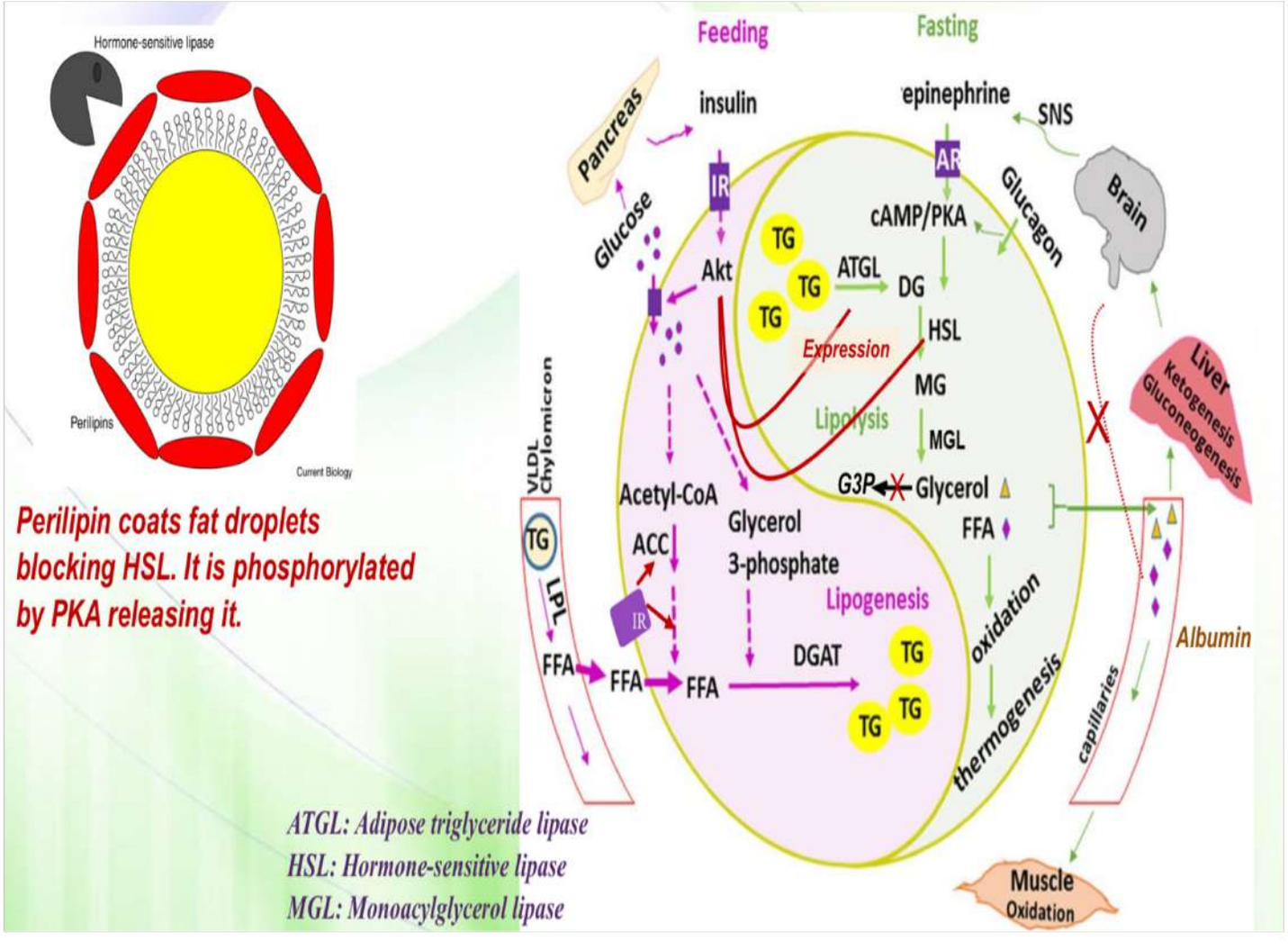
Epinephrine/Glucagon acts via PKA pathway generating glycerol and 3 fatty acids (fatty acids will leave adipocyte and enter the blood stream

Fatty acids will bind Albumin (the main carrier) and they are taken to the peripheral tissues like muscle cells which are utilizing fatty acids to generate energy.
*But glycerol has another route, it goes to the liver and it doesn't need a carrier, also it can be used for another thing ****

**** we will talk about it later on, when you see these *** 3 stars, remember that we are talking about the routes of glycerol*

Let's talk about Insulin

Insulin on the other hand is released in the feeding state…
When insulin binds to its receptor, then a number of events will take place, including:
1. Increase in glucose uptake by the cells (adipocytes).
2. You have the production of Acetyl CoA, that can be used to generate fatty acids.
3. You have the production of glycerol 3 phosphate from a dihydroxy acetone phosphate.
4. The generation of the glycerol backbone that carries the fatty acids forming TAG.
5. Insulin decreases the expression of the first lipase that participate in the breaking down or releasing of fatty acids from the TAG [insulin acts at the transcriptional level right here].
6. Insulin activates the phosphates that removes the phosphate group from the Hormone Sensitive Lipase [the second reaction is blocked by insulin].



Protein

Peri=around

lipin = lipids

Perilipin

It coats the fatty acids droplets in adipocytes, why? It prevents the HSL from accessing the TAG.

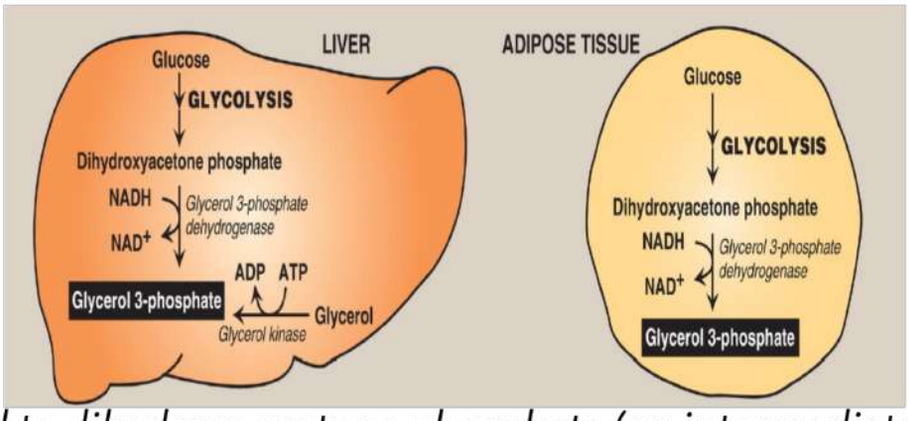
Perilipin is phosphorylated by PKA and when it is phosphorylated it get released, it disassociates from the fatty acids droplets and now the fatty acids droplets will be accessible to HSL

The time of glycerol

****remember the three stars*

Glycerol leaves the adipocyte to the liver and when it goes to the liver, it can be used for 2 things:

1. Glycerol go to the cells and can be phosphorylated by glycerol kinase, when it gets phosphorylated, it can be used as a back bone to store some fatty acids, but this glycerol kinase doesn't exist in the adipose tissue, so that glycerol leaves the adipocytes.



2. It can be converted to dihydroxy acetone phosphate (an intermediate in glycolysis which will follow one of two pathways:

Either goes all the way to form pyruvate (completion of glycolysis)

It goes back to produce glucose in (gluconeogenesis) and finally, glucose leaves liver cells to other tissues

In adipocytes, If there isn't glycerol and there are fatty acids, there is a pathway that is called (glyceroneogenesis)

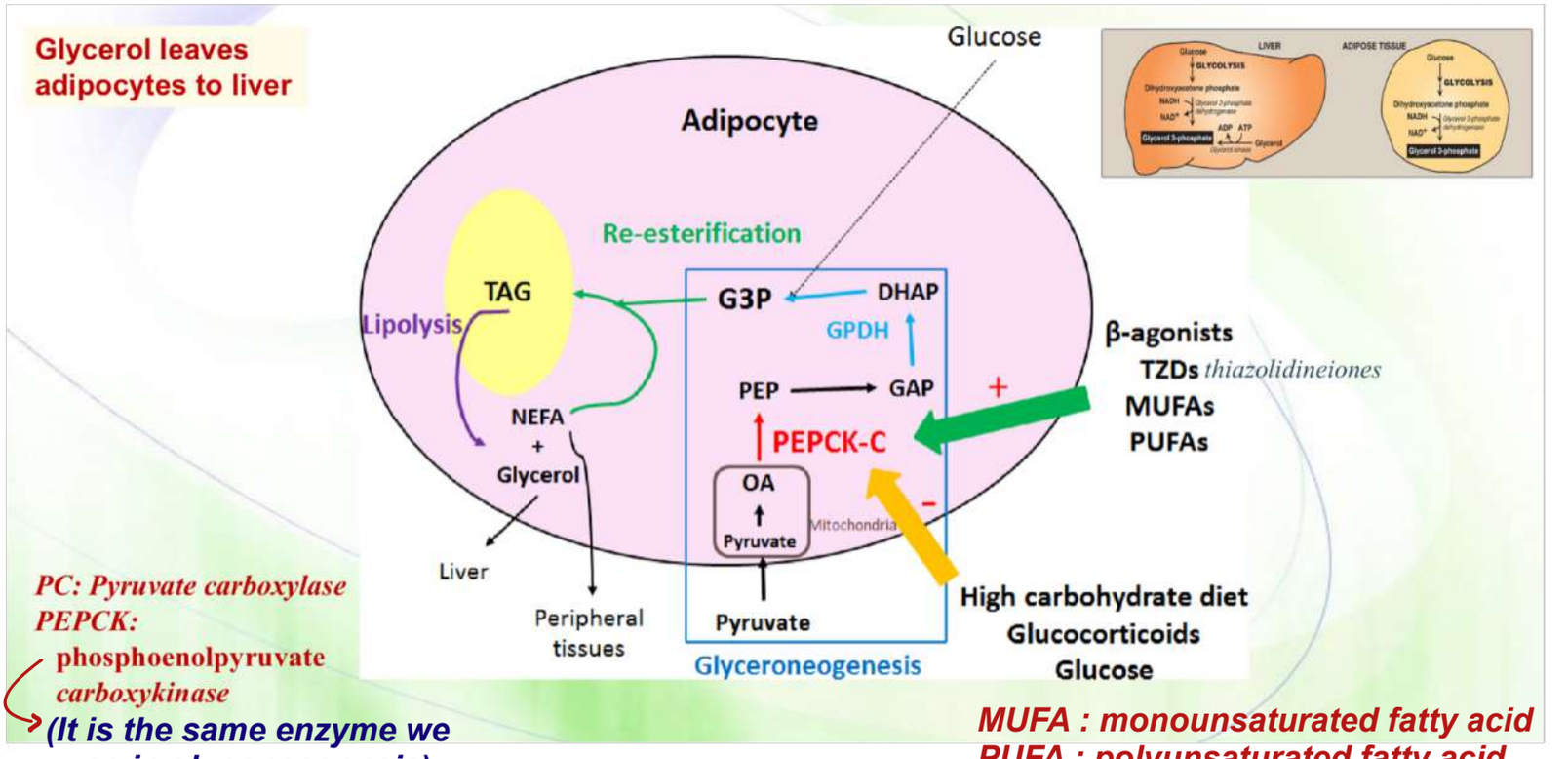
Glyceroneogenesis : formation of glycerol from pyruvate in adipocytes.

Pyruvate is converted to oxaloacetate OA ➡️ OA is converted to phosphoenolpyruvate PEP ➡️ PEP is converted to glyceraldehde 3 phosphate ➡️ glyceraldehyde 3 phosphate is converted into dihydroxy acetone phosphate ➡️ dihydroxy acetone phosphate is converted into Glycerol 3 phosphate which is used as a back bone for fatty acids.

The enzyme phosphoenolpyruvate carboxykinase (converts OA into PEP) is regulated by :

1. Activated by monounsaturated and polyunsaturated fatty acids .

2. It gets inhibited by high carbohydrate diet or glucose.



In another words…. Whenever there are fatty acids available, you have production of glycerol to carry these fatty acids

Fatty acids oxidation…Beta oxidation

Means breaking down of fatty acids

Previously, we talked about degradation of TAG which is the process for cleavage and separation of fatty acids from glycerol in a TAG molecule…. Now we get these fatty acids and we want to break them down

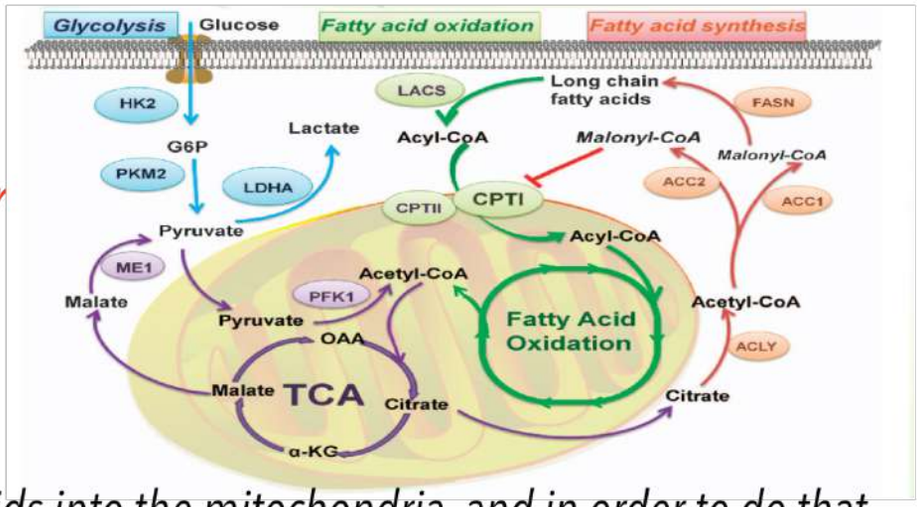
The idea here is when you have beta oxidation, you have the release of 2 carbons in a form of Acetyl CoA and this takes place in the mitochondria (mitochondrial matrix), fatty acid synthesis takes place in the cytosol (there is a separation of these two opposite pathways, it is a mode of regulation, one way of regulation is compartmentalization: separation of opposite pathways)

So, beta oxidation is regulated by:

1. Compartmentalization 2. At the level of transport (later on)

So we have the production of Acetyl CoA from the breaking down of fatty acids, and this Acetyl CoA goes to the Kreb's cycle (you know the pathway 🙏)

Let's talk in details about beta oxidation



1. It starts with transporting of fatty acids into the mitochondria, and in order to do that, fatty acids are activated be attaching CoA to them (the enzyme that is important for that is called Acetyl CoA synthetase, it's also called thiokinase) …. So now we have long chain fatty acid that is activated by the attachment with CoA … Notice: energy is required from ATO which is hydrolysed to AMP and you have the release of pyrophosphate…
By converting ATP to AMP, it is like hydrolysing 2 ATP molecules

ra

2. After the activation of fatty acids,fatty acids need to be transported to the intermembranous space of the mitochondria, once it reaches the intermembrane space it should cross the inner membrane of the mitochondria, but they can't, because fatty acids are attached to CoA.

3. CoA is replaced by a molecule that is known as *carnitine*, a small molecule with a hydroxyl group, fatty acid is now attached to carnitine, this is an enzymatic reaction catalyzed by an enzyme that is present in the outer membrane of the mitochondria (carnitine palmitoyl transferase I (CPT I)) which is inhibited by malonyl CoA (it is an intermediate for the first reaction of fatty acid synthesis) … that makes a sense!!! Because you don't want to get fatty acids into mitochondria if you have enough malonyl CoA (the rate limiting step in fatty acid synthesis), it means there is enough energy in the cells (there is no need to break down more fatty acids)

CPT I is inhibited by Malonyl CoA

4. Then the fatty acyl carnitine is transported into the mitochondrial matrix by (tranlocase) so you have a transporter (carrier).

5. Once it is inside the mitochondrial matrix, you have another enzyme known as (carnitine palmitoyl tranferase II) that releases carnitine and places CoA (exchange reaction right here).

So the whole function or purpose of carnitine is to transport the fatty acid across the inner membrane.

The transport of the fatty acyl carnitine into the mitochondrial matrix is done in exchange of a free carnitine (it is really an exchanger!)

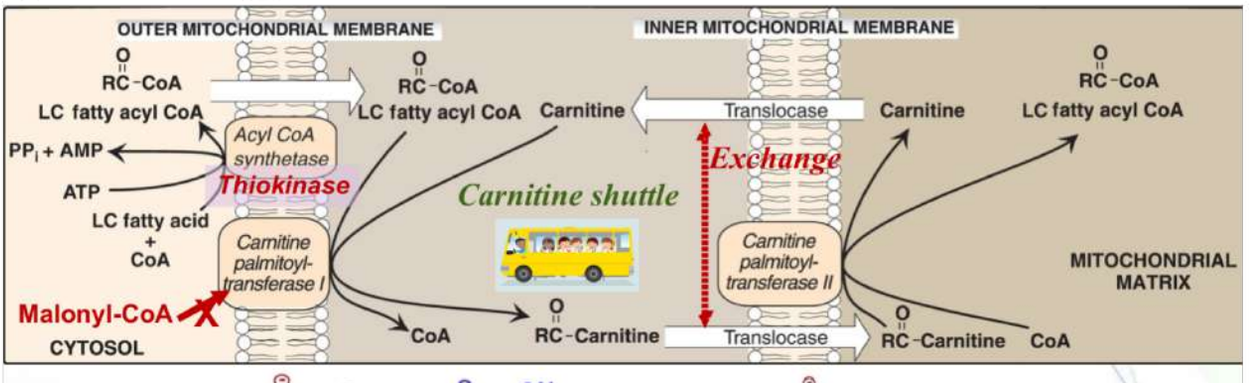
It takes the fatty acid inside and instead of that you have a transport or exchange of carnitine out of the mitochondrial matrix, this is known as carnitine shuttle…. It is like the bus

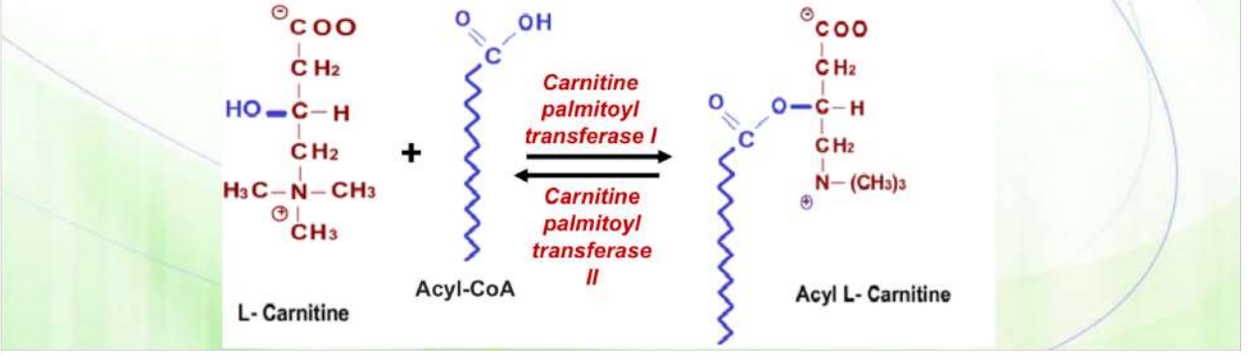
All 5 points are related to the first step of beta oxidation, after talking about the second step, let's talking about carnitine 🧠

first step :-

Transport of fatty acids (cytosol → Mitochanderial Matrix)

Try to make matching between the paragraph and photo beside

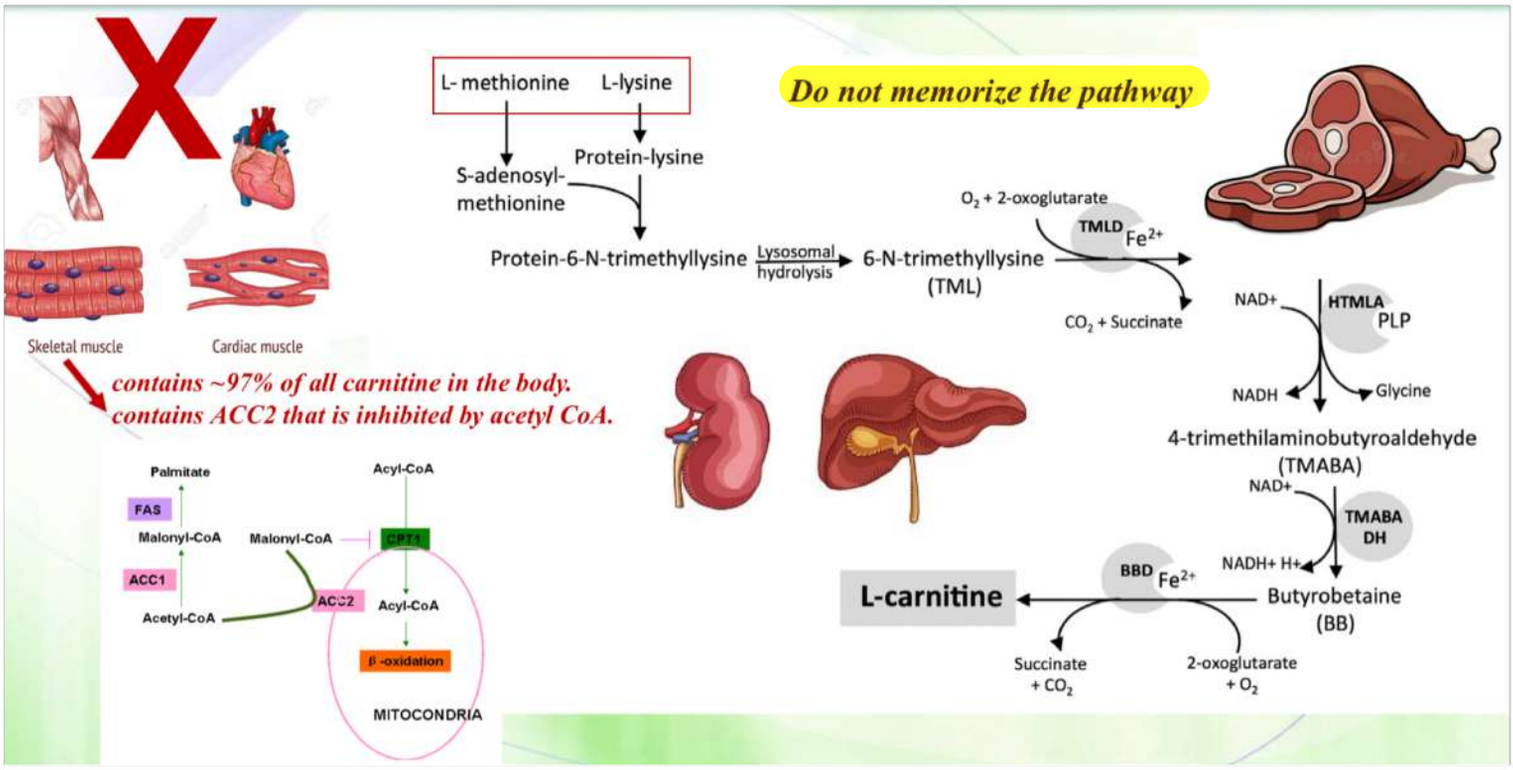




Carnitine: small molecule, there are2 sources of carnitine:

1. Meat 🥩 (diet) excellent source of carnitine.

2. It is synthesized in the cells starting from 2 amino acids (L-Lysine / L-Methionine) … the pathway isn't required, it takes place in the liver & kidney, carnitine leaves liver and kidney and it is mainly stored or existing in skeletal and cardiac muscle…. 95%-97%=of carnitine existing in the skeletal muscle, but these muscles can not synthesize carnitine, so the only source of carnitine really is liver and kidneys.



So, skeletal muscles also have an (enzyme/ isoenzyme) for Acetyl CoA carboxylase, it is the enzyme that catalyzes the carboxylation of Acetyl CoA forming malonyl CoA, even though skeletal muscles can't synthesis fatty acids the do have Acetyl CoA carboxylase…. Purpose: if you have Acetyl CoA carboxylase it means that you can synthesize malonyl CoA ant this will inhibit CPT I, so skeletal muscles regulate the transport of fatty acids into the mitochondrial matrix.

Again, if there is enough Acetyl CoA in the cells that means that we will have high level of malonyl CoA, so there is no need to break down fatty acids in skeletal muscles, so let's keep these fatty acids in the cytosol.

Acetyl CoA carboxylase is used for regulatory purposes not really to synthesis fatty acids in skeletal muscles.

There are pathological conditions related to carnitine deficiencies , and either they can be :

1. primary (it is related to carnitine itself or to beta oxidation) as a result carnitine will be eliminated from the body

2. secondary results from :

a. taking carnitine medications like valproic acid - it is anti seizure medication, it decreases renal absorption of carnitine,

b. Defective fatty acids beta oxidation, it means acyl carnitine will accumulate in the cells and it will be eliminated from the body in urine.

C. Carnitine liver disease (damage to liver cells can also decrease carnitine synthesis.

D. CPT II deficiency or CPT I deficiency can also result in carnitine deficiency as well.

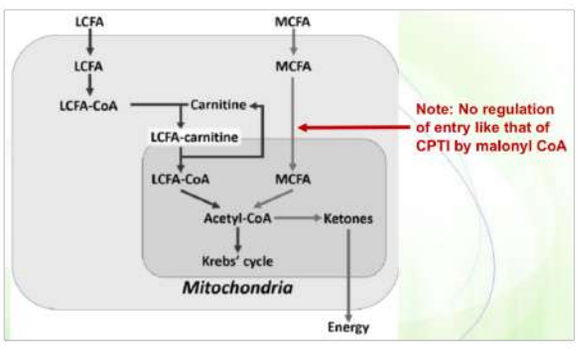
important

- Primary carnitine deficiency
  - Defects in a membrane transporter: No uptake of carnitine by cardiac and skeletal muscle and the kidneys, causing carnitine to be excreted.
    - Treatment: carnitine supplementation.
- Secondary carnitine deficiency
  - Taking valproic acid (antiseizure) → decreased renal reabsorption
  - Defective fatty acid oxidation → acyl-carnitines accumulate → urine
  - Liver diseases → decreased carnitine synthesis
  - CPT-I deficiency: affects the liver; no use of LCFA, no energy for glucose synthesis during a fast → severe hypoglycemia, coma, and death
  - CPT-II deficiency: affects the liver, cardiac muscle, and, less severely, skeletal muscle
    - Treatment: avoidance of fasting and adopting a diet high in carbohydrates and low in fat but supplemented with medium-chain TAG.

because they can be transported into the mitochanderia without the need of Carnitine.

long chain TAGs depend on Carnitine, so Medium chains are a good source of energy in these abnormalities

because during fasting the body depends on the fatty acids metabolism (oxidation)

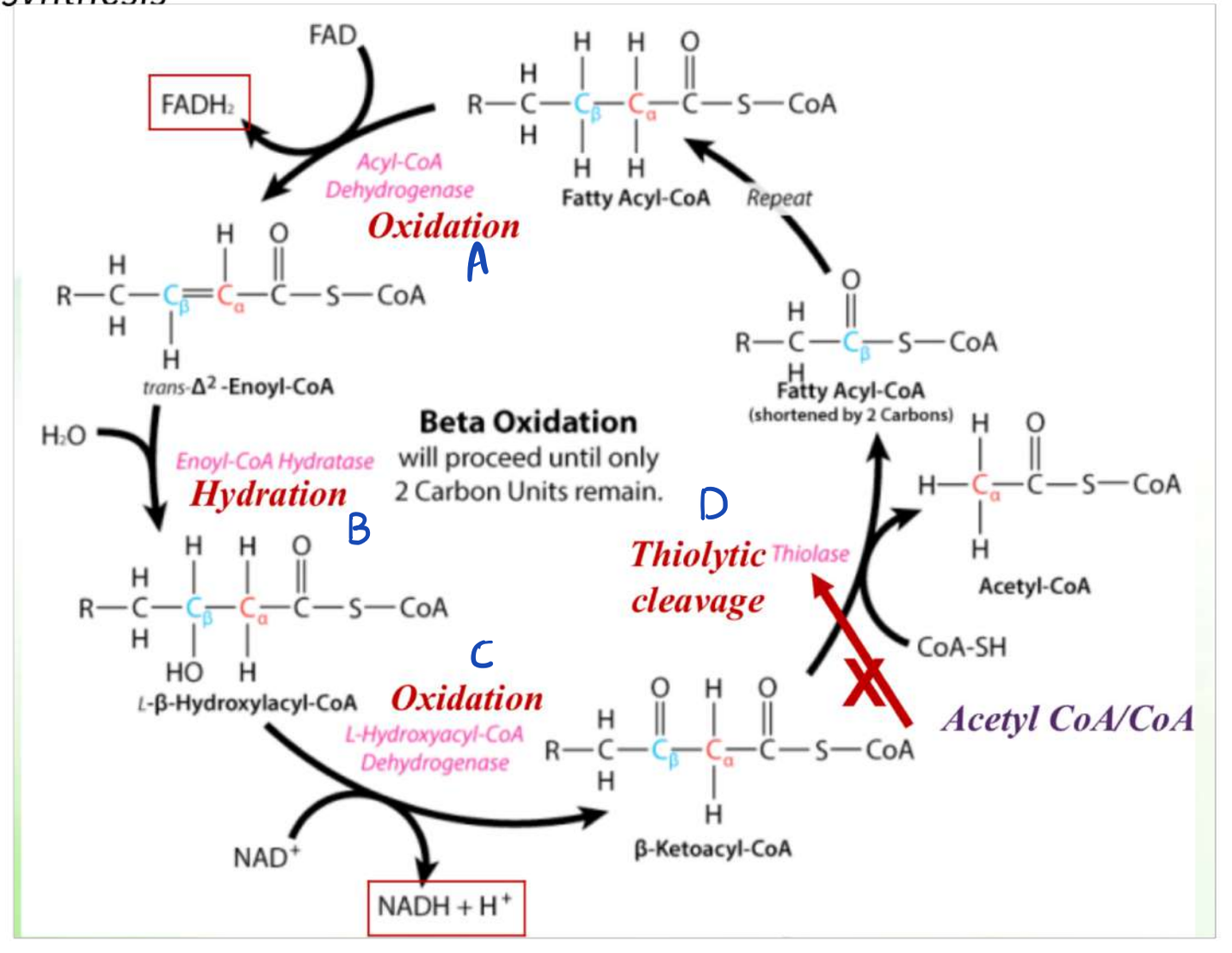


2. The real beta oxidation reaction starts from the second step where we have fatty acyl CoA in the mitochondrial matrix.

The reactions in order are:

1. Oxidation reaction
2. Hydration reaction
3. Another oxidation reaction
4. Thiolytic cleavage

So these reactions really sort like a reverse of fatty acid synthesis



The fatty acid that we focus on is palmitate (16 carbon saturated fatty acid)

A. The first reaction is oxidation reaction by dehydrogenase, you have the production of FADH2 (the result is a compound with double bond)

B. Hydration reaction (now you will get a compound with a hydroxyl group that is attached to fatty acid.

C. Another oxidation reaction, you have the production of NADH. (Hydroxyl to keto group)

D. Thiolytic cleavage (CoA attacks the fatty acid by using its terminal reactive group "Thiol group SH-" and it results in the releasing of Acetyl CoA (2carbons). (Breaking the bond between alpha and beta carbons)

So you end up with a fatty acid that is shorter by 2 carbons (they are lost in a form of Acetyl CoA).

So the result of beta oxidation of palmitate is 14 carbon fatty acid

The electron carries (FADH2 / NADH) can be used in electron transport chain to produce energy

Why it is called beta oxidation? Because it involves beta carbon (the covalent bond between beta carbon and Alpha carbon is broken.

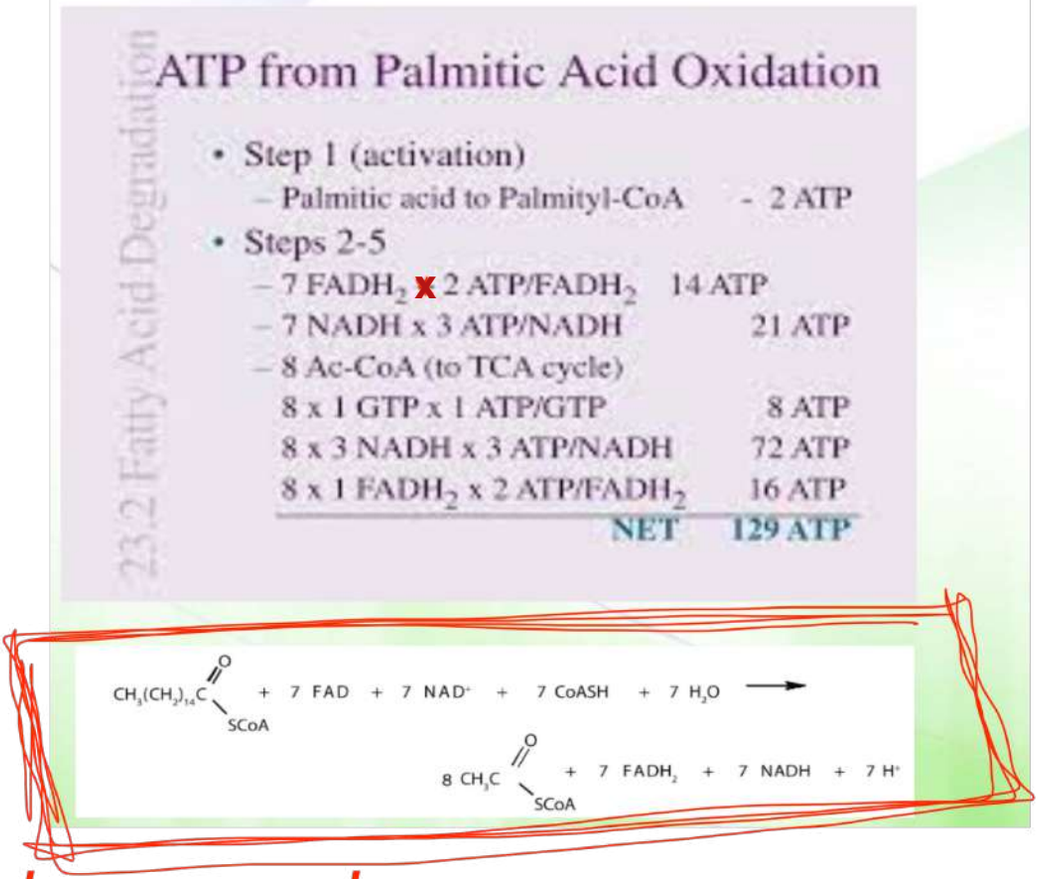
For a palmitate molecule, how many cycles do we need? We need 7 cycles.

Why not 8 (it is 16 carbons) ?

Because at the end we have the production of butyrate (4carbons molecule), when it is cleaved you have the production of 2 Acetyl CoA molecules. Try to draw a chain with 16 carbons and cleave it several times in the way to get the whole 16 carbons are separated in segments each one contains 2 carbons and you will notice that we need to cut 7 times.

So you have the production of 8 Acetyl CoA molecules + 7 NADH + 7 FADH2

- **Number of cycles: (n÷2)-1**



So how much energy can we produce?

Remember: we have 8 Acetyl CoA that will enter Kreb's cycle (every thing takes place in the mitochondrial matrix, so each Acetyl CoA produce 3NADH+1FADH2 + 1GTP that can be converted to ATP

You can multiply each NADH by 3 and each FADH2 by 2 however :

1 FADH2= 1.5 ATP

1 NADH = 2.5 ATP

So a lot of ATP is produced.

But remember that the first reaction involves activation of fatty acids (palmitate or palmitic acid is converted into palmitoyl CoA that consumes ATP which gets converted to AMP like hydrolysing 2 ATP molecules , so it is -2 for that reaction).

Why 2 ATP not just one?

Because you convert ATP to AMP without passing through ADP , reducing 2 phosphate groups, so in order to regenerate this ATP from AMP you need 2 phosphate groups.

The source of CoA is vitamin B5.

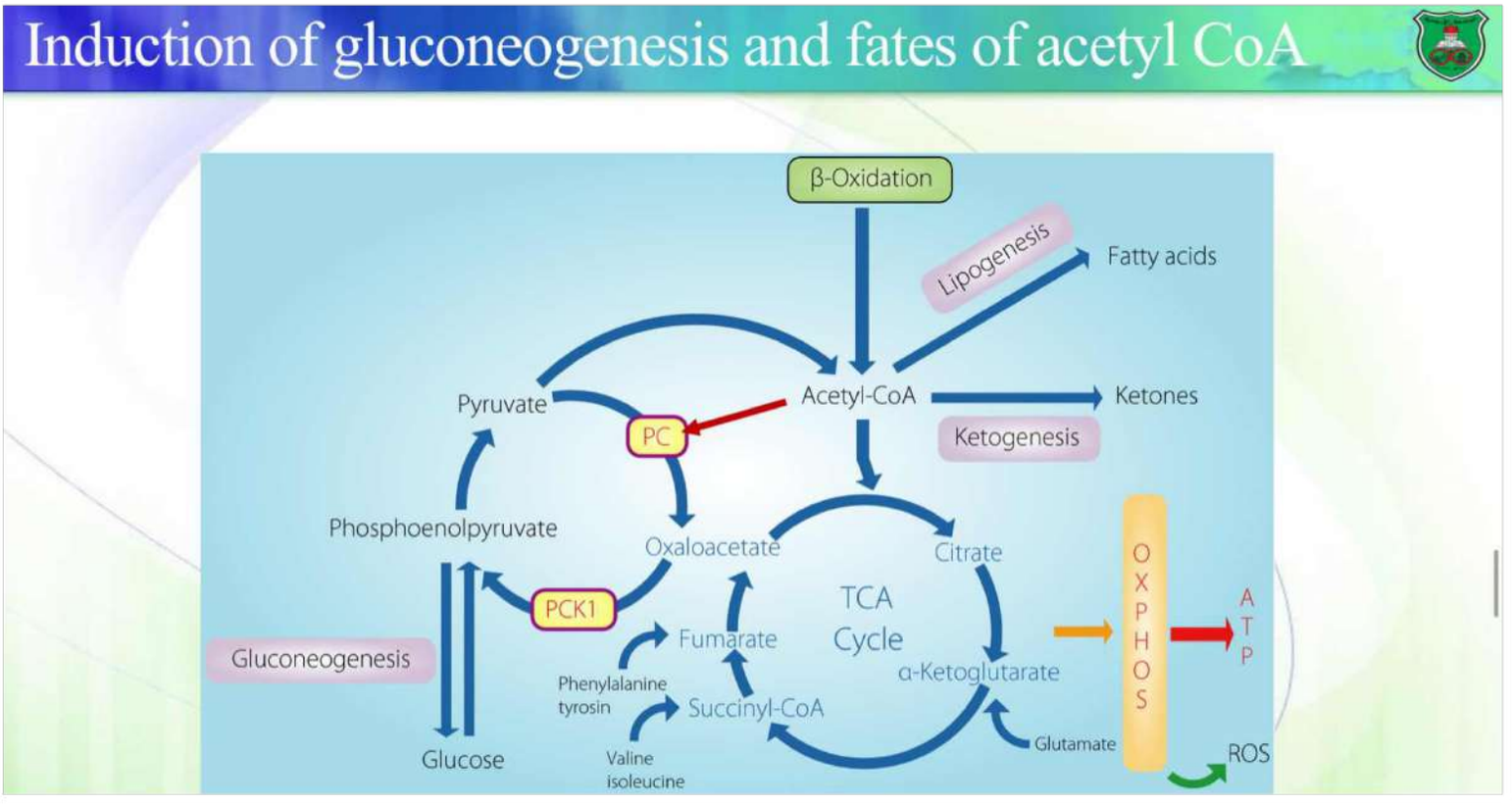
Beta oxidation is linked to gluconeogenesis.

We have the production of Acetyl CoA, Acetyl CoA is regulator for pyruvate carboxylase, so you have the production of oxaloacetate OA which will be converted to phosphoenolpyruvate PEP and you have gluconeogenesis that takes place in liver cells.

Acetyl CoA has different fates:

1. It can enter Kreb's cycle.

2. It can be used in ketogenesis (the production of keton bodies (in following lectures)



There are differences between the degradation and synthesis of fatty acids and this table shows some of these differences:

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

Inhibition of CPT I = inhibiting the transport of fatty acids into the mitochondrial matrix.

Dehydrogenation = oxidation

Pay attention to the donor of carbons in synthesis, it is malonyl CoA, while in elongation after synthesis is Acetyl CoA.

The End