



University of Jordan
Faculty of Medicine



Medical Committee
The University of Jordan

Biochemistry

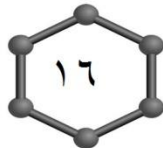


Sheet



Slides

Lecture #:



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Title: Beta-Carbon Oxidation.....

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Last time we talked about the mobilization of fat from adipose tissue to the peripheral tissues, liver, muscle for oxidation. Fatty acids are good source of energy; they produce almost twice as much as the energy produced by carbohydrates.

Slide 15

Fatty acids are Stored as the form of triacylglycerol, fat or oil.

Triacylglycerol “Fat” is stored in the adipose tissue where it gets transported and exported as fatty acids when they are needed as a source of energy in response for hormonal signal... once they reach the cells to be oxidized to produce energy, the oxidation happens at Beta carbon “Carbon number 3 of the fatty acids”. The first step in the oxidation involves linking the fatty acid with co enzyme A with thioester high energy bond.

This activation step requires equivalent of 2 ATP, then through 3 reactions the beta carbon is oxidized. Oxidation usually involves loss of hydrogen and/or gain of oxygen so the oxidation here converts CH₂ into ketone group which results in Beta fatty acid “beta acyl coA”, and the last step involves cleavage of carbon 1 and 2 in the form of Acetyl coA that can be used as a source of energy in the citric acid cycle. The resulted fatty acid now is similar to the one we started with, except that the number of carbon atoms is 2 carbon less so it’s ready to start another cycle, cycle after cycle, the fatty acid is completely oxidized to acetyl coA... this is what’s called beta oxidation. Now we’ll explain its steps with more details.

Slide 21

In the slide, alpha and beta carbons are colored in red.

The first step involves dehydrogenation, removal of 2 hydrogens from carbon alpha and carbon beta, this removal from 2 adjacent carbons is called oxidation reduction reaction, usually the acceptor of the electrons when the 2 hydrogens are joined to 2 adjacent carbons is FAD that is converted to FADH₂ and the bond between carbon alpha and carbon beta is now a double bond. Double bond might be cis or trans... usually when fatty acids have natural double bond it’s a “cis” configuration bond but in this case the configuration of the double bond is trans.

The next step involves addition of water “remember that the addition of water to an alkene gives an alcohol”... HOH is added to the alpha and beta carbon, regardless to Markownikoff’s rule, the OH group is added to carbon beta because this is an enzyme catalyzed reaction, which means that the product is specific and doesn’t follow a chemical rule. So H is added to carbon alpha and OH is added to carbon Beta.

Then, another oxidation reduction reaction occurs where the H is removed from OH and the Beta carbon. This is to convert the beta carbon into ketone group so the compound’s name now is ketoacyl “when acid attaches to ester the result is acyl, for example palmitic acid becomes palmitoyl, acetic acid becomes acetyl” so here we get fatty acyl coA because it’s attached to the derivative of coenzyme A by

thioester bond.

Enoyl: En means alkene so this is an alkene derivative of the fatty acid "Enoyl coA". this is a 3 hydroxy acyl coA or another name for it is beta hydroxyl acyl coA so if we know how to name an acyl coA we can name its derivatives, in this way the beta carbon is oxidized from CH₂ into a ketone group.

This sequence reminds us of a similar sequence in the citric acid cycle where succinate was first converted to fumarate by succinyl dehydrogenase then to malate by the addition of water then oxidation gives as oxaloacetate "a ketone". So the last 3 steps in the citric acid cycle are similar to the sequence of reactions where the beta carbon is converted from CH₂ into the ketone group. We also have similarities in the cofactors "FAD, FADH₂", in the addition of water and so on.

We should be able to name the enzymes... The first enzyme's name is fatty acyl coA dehydrogenase : fatty acyl coA because fatty acyl CoA is the substrate .

The second enzyme does a hydration reaction ""not hydrolysis reaction be careful" so the enzyme should be named as hydratase.

The third one → 3-hydroxyacyl CoA dehydrogenase.

So by knowing the reactions we can name the enzymes responsible for them easily ☺

Slide 23

After that we get this reaction: cleavage of the bond connecting alpha carbon to the beta carbon... it is cleaved by the addition of acetyl coA.

let's imagine this, if we added water "HOH" instead of acetyl coA, we will get acetyl coA + fatty acid, but here the cleavage occurred by HS coA where the H is added to alpha carbon and the coA is added to the fatty acid which gives us a fatty acid product that is already activated and ready for the next step so we don't need an activation step that consumes 2 ATP as the one needed if the cleavage occurred by the addition of HOH.

Note: if the cleavage occurred by water we call the reaction hydrolysis while in this case when the cleavage happens by coA "sulfur containing compound" that forms a thioester, the reaction is called thiolysis.

Note: Phosphorylysis → cleavage by phosphorylation "like in glycogen"

So the enzyme suitable for the cleavage step is named Thiolase because this is a thiolytic cleavage.

All this happens in the mitochondria in the liver cells, in the muscle, in the peripheral tissues that use fatty acids as a source of energy.

Slide 25

Now we are in the position to calculate the energy of fatty acid oxidation.

Notes:

1. Calculation of energy will give us an idea that the number of ATP produced is very high so fats are a much better energy source than carbohydrates.
2. If we are able to calculate the energy yield then this means that we understand the pathway.

So now let's take this example in slide 25... this is palmitic acid already in the activated form for simplicity, how many Beta oxidation cycles will be required to cleave a fatty acid with 16 carbons into 8 fragments acetyl coA ? 7 times to get 8 fragments "like a normal long thread, it needs to be cut 7 times in order to get 8 segments of it". So this fatty acid can undergo fatty acid oxidation cycle, after 6 cycles of beta oxidation cycles we'll get 6 FADH₂ "one for each cycle", 6 NADH, and 6 Acetyl coA. The product is a 4 carbon compound "butyryl coA"... with the last cycle this butyryl CoA gives 2 Acetyl CoA, 1 FADH₂ and 1 NADH. So TOTALLY we have 7 FADH₂ produced, 7 NADH & 8 Acetyl coA.

Now let's convert this into ATP:

for simplicity we'll consider that the reoxidation of FADH₂ gives us 2 ATP while the reoxidation of NADH gives us 3 ATP.

7 FADH₂ → will give us 14 ATP "7*2"

7 NADH → 21 ATP (7*3)

8 Acetyl coA → 96 ATP

"every Acetyl coA will give 12 ATP from the citric acid cycle"

The Total is 131 ATP but the activation of the acyl consumes at the beginning 2 ATP "notice that we only need one activation step not 7", so Net total is 129 ATP per one mole of C16 fatty acid! A very large number!

HW: calculate how many ATP are produced from oxidation of Stearic acid "18 carbon fatty acid" and compare it with 3 moles of glucose "that gives 36 to 38 ATP mols" to prove that the oxidation of fatty acids produce much more ATP than carbohydrates. And then calculate the number of ATP produced per 1 gram of fatty acid or per one gram of glucose.

Slide 27

We said before that the entrance of fatty acids "fatty acyl coA" into the mitochondria requires transport shuttle "Carnitine shuttle"

Carnitine is a carboxylic acid that contains a quaternary amine and a hydroxyl group "the doctor said that it's important to be able to identify it from its structure".

It carries the acyl group across the inner mitochondrial membrane "IMM".

Its source:

2. It can be obtained from dietary sources "when we eat tissues, muscles by eating meat (lamb or beef meat since they use fatty acids to get energy in the same machinery)".

3. By synthesis in our kidneys, we can make it ourselves.

Functions:

1. Helps in Oxidation of fatty acids by carrying it across the IMM.
2. Export of branched chain acyl groups from mitochondria.
3. Excretion of acyl groups that cannot be metabolized in the body by urinary excretion.

Carnitine deficiency: we have secondary and congenital.

Congenital deficiency → “present at birth, as a result of heredity” caused by a decrease in the synthesis of enzymes that are involved in the carnitine shuttle or by a decrease in the uptake “it’s taken but not absorbed properly into the cells” or by decrease tubular reabsorption “in the kidney”. So there are many reasons that lead to the deficiency of carnitine.

Secondary deficiency → “not a result of heredity but instead can be developed due to liver disease since the synthesis occurs in the liver. It can also be caused from malnutrition (not eating meat) and increasing requirements of carnitine”

A deficiency in Carnitine affects the person this way: the person will suffer from a decrease in the ability of using fatty acids as a fuel, so if he has to run his legs’ muscles will suffer from weakness and fatigue, and thus, he will use glucose as a source of energy instead of fatty acids → which causes lowering of glucose levels in the blood → hypoglycemia. The deficiency will cause accumulation of fatty acids and branched acyl groups in cells as well.

Some athletes might take carnitine in order to increase their ability to use fatty acids as a source of energy. Carnitine is sold in pharmacies. “The doctor said that he doesn’t know the exact effect of carnitine that can be got from pharmacies on normal people (not athletes)”

Slide 29

Now, we’re done with the oxidation of saturated fatty acids. We’ll move to the oxidation of unsaturated fatty acids:

unsaturated fatty acids might contain one double bond “like oleic acid”, 2 double bonds “linoleic acid”, 3 or 4 double bonds.

We said that the configuration of naturally occurring double bonds is “cis”

1 double bond → monounsaturated fatty acid
2 or more → polyunsaturated fatty acid.

We don't expect to have a totally different pathway, only some modification of the saturated fatty acid oxidation pathway is enough to oxidize unsaturated fatty acids.

Note: the way we write the fatty acid is not necessarily written the way it is in the slides we can write it in a short hand way, example: 18:cis Δ 9 means that this is a fatty acid with 18 carbons that has a double bond at carbon 9 and the configuration on the double bond in cis. "Note: counting of the carbons begins from the side of the carboxyl".

Let's look at the fatty acid in the slides. From carbon 1 to carbon 9 it's like any saturated fatty acid so we can use 3 rounds of beta oxidation. The product after 3 rounds would be a fatty acid with 12 carbons length "18 - 6 = 12". And since 6 carbons were removed by the 3 rounds of beta oxidation then now it's Δ 3 instead of Δ 9. So now it's 12:cis Δ 3.

Now if this fatty acid will continue beta oxidation as usual, the next step would be to introduce a double bond between alpha and beta carbon "between carbon 2 and 3", but we already have a double bond in the fatty acid in there so this step won't be possible ! So we need to shift the double bond from its location to another one by using an enzyme that does so and that also converts the fatty acid's configuration from cis into trans... so we use an additional enzyme "Isomerase" that converts the double bond from carbon "3 to 4" to "2 to 3" and converts cis configuration to trans as well. So as a result, we get a fatty acid that is like a saturated fatty acid and that the dehydrogenase works on normally, so this is as if we are oxidizing saturated fatty acid of 12 carbons.

Note: 12:cis Δ 3 and 12:trans Δ 2 are isomers, so the enzyme used in here is called isomerase. So all what we need is isomerase, and the oxidation of fatty acid with double bond at carbon number 9 proceeds as usual.

Now oxidation of another unsaturated fatty acid "linoleic acid", it contains 18 carbons with 2 double bonds, at carbon 9 and carbon 12. After 3 rounds of beta oxidation we'll get 12: Δ 3,6.

isomerase changes the location of the double bond from carbon 3 to 2.

Then an acetyl CoA is gone, the double bond is now located on carbon 4, we're not going to shift it like this, a new double bond will be introduced by dehydrogenase that will produce a fatty acid with 2 double bonds between carbon "2 and 3" and "4 and 5" → a conjugated double bond. This will be the substrate for another enzyme called "Reductase" that will reduce these 2 double bonds into one double bond by adding hydrogen at carbon 2 and hydrogen at carbon 3, the 2 double bonds will be reduced to one double bond located in between "between carbon 2 and 3". The next step now is isomerase.

We may need isomerase alone → location of the double bond at carbon 3

we may need isomerase and reductase → if the location of the double bond is at carbon number 4

Slide 31

Oxidation of FA with odd number of carbons:

usually more than 90% of the fatty acids that we consume in our diet are even numbered, 10% contains odd number "13 or 15 or 17.. etc carbons"

but the fatty acids that are stored in our body are even number fatty acids.

Now let's take the example in the slides, how many carbon atoms are present in this fatty acid? 15 carbon fatty acid → same mechanism, after 6 cycles of beta oxidation → fatty acid with 3 carbons that's named as propionic acid so we have what so called Propionyl CoA. So oxidation of odd number fatty acid will produce acetyl coA and the very last cycle will produce Propionyl CoA.

Slide 32

The fate of Propionyl CoA:

the first step for its metabolism is addition of CO₂, notice that it's added to the alpha carbon → this results in methyl malonyl coA. The enzyme responsible for the step is propionyl CoA carboxylase "carboxylase = addition of CO₂". This reaction needs ATP since we're adding a carboxyl group and it requires Biotin cofactor.

Why do we need ATP for such reaction?

Always the decarboxylation reactions are exergonic reactions → irreversible "like pyruvate dehydrogenase for example. So how do we convert irreversible reaction and make it proceed in the reverse direction? We need energy input and that's why ATP is required for carboxylation reactions while the decarboxylation reactions are exergonic, release energy.

So anyway now we have D-methylmalonyl CoA, "notice that the malonic acid is like the succinic acid but it has 3 carbons and we have a methyl group on the carbon in the middle" → so this very important intermediate is called methylmalonyl coA. Now we do a shift for the carboxyl group to the carbon adjacent to it which results in succinyl coA "check the slides to understand this point completely". But firstly D- methylmalonyl coA is converted to L- methylmalonyl coA which is not very important step to know.

Then L- methylmalonyl CoA is converted to succinyl coA by an enzyme called mutase "note: this enzyme also converts phosphate group from carbon 1 to 6 or from 2 to 3 and so one". This reaction requires co-enzyme from vitamin B12, and in the body there are only 2 reactions that require vitamin B12 and this is one of them.

So having vitamin B12 deficiency → leads to the accumulation of methylmalonyl coA or methylmalonic acid.

In the past measuring Vitamin B12 in the body wasn't as simple as it is today, so vitamin B12 deficiency was assessed by measuring methylmalonic acid in the urine since it causes methylmalonyl urea. When methylmalonic acid accumulates in the blood it will be secreted in the urine and this was an indication for vitamin B12 deficiency.

Now getting back to our product succinyl coA, notice that it's an intermediate in the citric acid cycle, so

this part of the fatty acid can be converted into glucose while acetyl coA cannot be converted into glucose because converting pyruvate to acetyl coA is an irreversible step so we cannot get pyruvate back from acetyl coA, so we can't convert carbohydrate into fat and fortunately we cannot convert fatty acids into carbohydrate, an exception is those 3 carbons but they are not significant because odd chain fatty acids are only 10 percent of our diet

So this is how odd numbered fatty acids can be oxidized.

GOOD LUCK :D

