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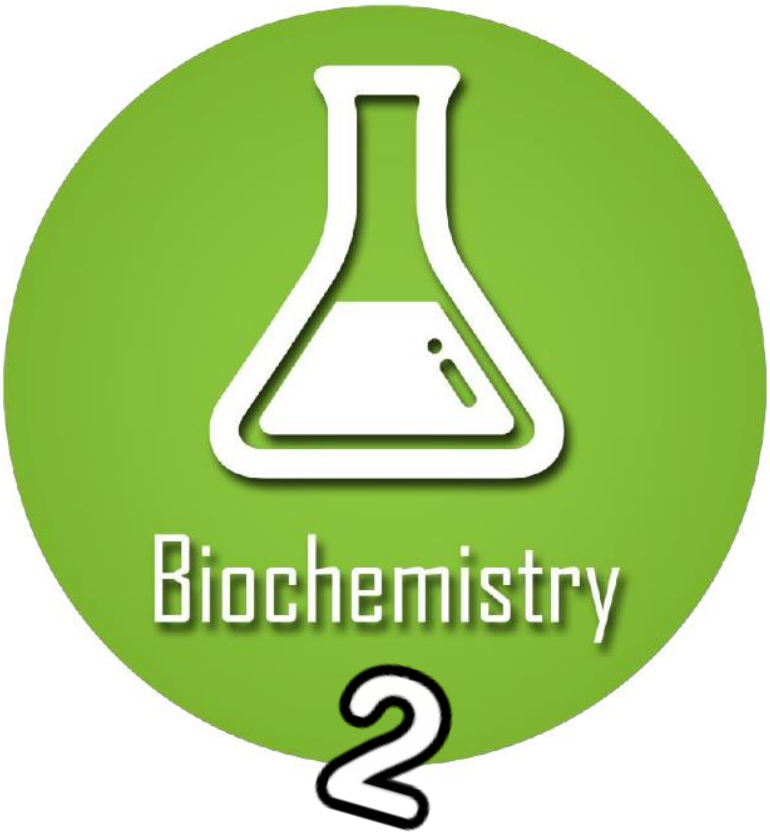

◉Sheet ○Slides

Number: 14

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Subject: Ketone Bodies

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β – Oxidation in the peroxisome:

- Very long chain fatty acids (which contain more than 22 carbons).
- Found in some lipid constituents especially myelin in the myelin sheath.
- Usually they are not found in significant amounts in the diet or as source of energy.
- The oxidation pathway of them is similar to β oxidation of other FAs except the place where the pathway occurs.
- This pathway occurs in the peroxisome.
- These FAs cannot be oxidized (or transported) in the mitochondria.
- The first step is oxidation by an enzyme “Fad containing oxidase” which convert FAD to FADH2.
- The “FAD” is a cofactor here not an electron acceptor.
- It is called “oxidase” because it uses Oxygen as an electron acceptor, (notice that if an enzyme uses NAD+ or FAD or NADP+ as electron acceptor it is called then a “dehydrogenase”).
- FADH2 produced doesn’t re-oxidize in the electron transport chain, because the rxn is not in the mitochondria.
- FADH2 produced re-oxidize by transferring electrons to oxygen by certain enzymes, so FAD work as an intermediate in transferring the electrons toward the oxygen, which is then converted to H2O2.
- The rxn continues until the FA becomes suitable for β-oxidation so that it can be transported and oxidized in the mitochondria.

α – Oxidation of fatty acids:

- The oxidation occurs at carbon α.
- Branched-chain fatty acids that have several methyl groups (every fifth carbon) (the first methyl group on carbon β).
- This kind of FAs associated with chlorophyll. (So it is present in our diets in vegetables but in minor amounts).
- α carbon is hydroxylated (by oxidative hydroxylases).
- Then it is undergo oxidative decarboxylation; in which the carboxyl group leaves as CO2, and the hydroxyl group is oxidized into carboxyl group, after that β carbon becomes free and the oxidation occur as usual.
- It is a minor pathway but it has a clinical significant, in a rare disease in which one of the enzymes is missing resulting in accumulation of these FAs in some cells leading to neurological disorders.

Ketone bodies:

- As we know, the end product of β oxidation is acetyl CoA, which can be oxidized completely by TCA (Krebs's cycle) or it can be converted into ketone bodies.

What are ketone bodies?

They're 3 compounds; notice that the first structure (acetoacetate) is a derivative of butyric acid. The left half of the compound (CH3CO-) is acetic acid, and the right half is acetate, acetic group and acetic group linked together, so it's named acetoacetate,

- It's one of the ketone bodies it may undergoes spontaneous decarboxylation (the carboxyl group to the right is lost as CO2) to give a ketone (acetone).
- It also can be reduced by NADH so a hydroxyl group is added to give 3- Hydroxybutyrate.

These ketone bodies (acetoacetate,acetone, 3-Hydroxybutyrate) are synthesized in the liver starting from acetyl CoA (the precursor) which is produced by β oxidation of fatty acids, the synthesis occurs all the time at low rates but during fasting and uncontrolled diabetes mellitus it will be synthesized in high rates.

We will study the high rate condition because it has a clinical significance.

The pathway of the synthesis has 3 steps:

The first step is a condensation of 2 acetyl CoA molecules which produces acetoacetyl CoA, by an enzyme called thiolase.

- Notice that his product is the last intermediate in β oxidation, the last step in β oxidation is the cleavage of acetoacetyl CoA to 2 acetyl CoA. Therefore, high amounts of acetyl CoA whether it's coming from β oxidation or from any other source will increase the rate of the reaction (condensation).

The second step is a condensation reaction; a third acetyl CoA condenses with acetoacetyl CoA to give a product with the name HMG CoA.

- So named because if you look at its structure you'll notice a 5-carbon chain with 2 carboxyl groups at each end, it's similar to glutaric acid which is a 5-carbon dicarboxylic acid,

so HMG CoA is derivative of glutaric acid, notice that it has methyl and hydroxyl groups at the third carbon, so the name becomes 3-hydroxy-3-methylglutaryl CoA (abbreviated HMG CoA.)

The enzyme responsible for this step is HMG CoA synthase, notice not synthetase because there is no ATP involved in the reaction.
The third and last step is cleavage of HMG CoA by HMG CoA lyase, acetyl CoA is removed (not the one added in step 2) and what remains is acetoacetate.

What is the net of this pathway?
Any intermediate in the pathway is cancelled from the net reaction (intermediate is any compound that is used in one
Step and produced or removed in another step), such as acetyl CoA (the third one) and HMG CoA which are intermediates
So they're not mentioned. Therefore the net reaction is:

2 Acetyl CoA → Acetoacetate + 2 CoA

- From the net you can tell the purpose of the pathway for these ketone bodies. The aim is to produce (regenerate) **CoA** which is important in the liver.
- Acetoacetate is also produced in the net but for the liver it's considered as a waste product.
- Acetoacetate in other tissues may be used but in the liver it's not used.

Palmitic acid as example (16-carbon fatty acid) is oxidized by β oxidation to give 8 acetyl CoA, and this acetyl CoA groups are used to **completely degrade** to give CO2, NADH, $FADH_2$, and **coenzyme A is regenerated** and released in the first reaction.

- As you know, citric acid cycle uses intermediates, and for oxaloacetate there's no net production or consumption, it's required in catalytic amounts (it's needed with no net).
- It's used in the first reaction and produced in the last one so it does not increase or decrease during the pathway but without it the **cycle cannot run**, so catalytic amounts (small amounts) of oxaloacetate are required.

The liver during fasting uses oxaloacetate to produce glucose (gluconeogenesis), as a result the level of oxaloacetate decreases as it's being converted into glucose, therefore the cycle cannot continue and it runs at very slow rate, so this is the purpose of β oxidation (β oxidation gives us energy even if acetyl CoA is not completely degraded).

- Notice that β oxidation requires 8 CoA for palmitic acid, and the end product is 8 acetyl CoA, that means that CoA is locked or trapped as acetyl CoA. In the citric acid cycle.

So to sum up CoA is regenerated as it's explained above (in the first step of the cycle), but here CoA is regenerated by ketone bodies synthesis. Ketone bodies synthesis allows acetyl CoA to Be converted to ketone bodies to regenerate CoA that will be used in β oxidation.

- So the aim for ketone bodies synthesis is not to produce ketone bodies for the liver, but to allow CoA to be available for β oxidation to go on.
- Ketone bodies cannot be used for energy production in the liver but they can be used by other tissues.

- During fasting, rate of ketone bodies production is high As well as gluconeogenesis.

Because during prolonged fasting FA oxidation becomes the main source of energy but as gluconeogenesis consuming oxaloacetate to produce glucose so we need a mechanism that regenerate CoA instead of Krebs cycle which in our case ketone bodies synthesis.

- Therefore during fasting the level of fatty acid mobilization is high too.

- Notice that FAs in this case is not completely oxidized to CO_2 only beta oxidation occurs (citric acid cycle is not functioning).

In uncontrolled diabetic patients, blood glucose is very high (maybe 3 or 4 times the level normal glucose) so the liver is expected to
Lower the production of glucose, however the liver is actively making glucose even the blood glucose level is high.

- That because the liver does not sense the level of glucose in blood, it senses hormones; insulin and glucagon. Insulin is low, glucagon is high, and they tell the liver to do gluconeogenesis.
- Liver continues to do gluconeogenesis even though the blood glucose is high because it responds to insulin and glucagon but not the glucose level in blood. (So the liver acting like it senses a starvation).

Active gluconeogenesis in diabetes, active lipolysis, free fatty acids in the plasma are high, liver's output of ketone bodies is high, and this all results in ketoacidosis.

- Acidosis means drop in the pH.
- Ketone bodies like acetoacetate or β-Hydroxybutyrate are acids; therefore they lose their protons and that leads to an increase in proton concentrations (H^+ concentrations) which is acidosis, and this acidosis which results from ketone bodies production is known as ketoacidosis.

In uncontrolled diabetes, ketoacidosis occurs, and ketoacidosis results in increase excretion of ketone bodies in urine (the level of acetoacetate and β-Hydroxybutyrate is very high in the plasma so they will be excreted in the urine, they are anions, negatively charged, so they are excreted as sodium salts, and loss of sodium ions results in loss of water As a result dehydration occurs.

- So the diabetic ketoacidosis is very common in uncontrolled diabetes (DKA), and it is an emergency case.
- DKA occurs mainly in type 1 diabetic patients (complete loss of insulin).
- If it continues it leads to loss of consciousness and coma and if persist it may lead to death.
- Before the using of insulin for diabetic patients, death occurred in many diabetic patients who had acidosis, but nowadays the rate of deaths by ketoacidosis in diabetic patients is low due to the use of insulin.

- During prolonged fasting, the ketone bodies produced, are released to the plasma and taken up by other tissues, like muscle tissue.
- There Hydroxybutyrate can be oxidized to acetoacetate, then acetoacetate can be consumed but it requires CoA, it should be linked to CoA to produce acetoacetyl CoA.
- Succinyl CoA is the donor of CoA, it's an intermediate in TCA that provides CoA for acetoacetate to be converted into acetoacetyl CoA which can be cleaved into 2 acetyl CoA to be used in the citric acid cycle in the muscles. (So the muscle uses these acetyl CoA as source of energy because the amount of oxaloacetate is adequate (no gluconeogenesis in the muscle).

- So ketone bodies are used as a source of energy in skeletal and cardiac muscles.
- Even the brain during prolonged fasting can use ketone bodies as a source of energy.
- Normally brain completely depends on glucose, fatty acids are not a source of energy for the brain.
- Except during prolonged fasting in which the brain starts to utilize ketone bodies (they are small/soluble molecules so this an advantage for them).
- Without the utilizing of ketone bodies and during prolonged fasting If the brain continues to use glucose at the same level/rate, then protein degradation will occur at high rate and protein mass will be used.
- So this is the purpose that the brain can use ketone bodies, brain saves glucose that is coming from protein degradation and as a result saving proteins.

What happens during starvation?

- Concentration of fatty acids in the second or third day increases almost 3 times, fatty acids in high concentrations in the circulation.
- Notice the level of ketone bodies, it increases 10-20 times, so they're available and can be used as a source of energy.
- Glucose is maintained at 80% by gluconeogenesis.

Fuel metabolism in starvation:

- Glucose used by the brain is 100 grams/day after 3 days whereas 40g/day after 40 days of starvation.
- Glucose consumption is reduced from almost to the half (60%).
- For ketone bodies the consumption was 50 to 100 g/day by the brain alone.
- Fat mobilization is the same (180g/day).
- Muscle protein degradation from 75 to 20 g/day (notice how much muscle-protein we have saved by using ketone bodies as a source of energy; an important adaptation during starvation).