Overview and Integration of Cellular Metabolism

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Week 06

Lecture 26: Fatty acid catabolism (Oxidation of Fatty acids) - III

Hello everyone, welcome back to the lecture series session of over time analysis. In this lecture we will discuss the overview and integration of cellular metabolism. So, we were in the discussion of fatty acid catabolism mainly the oxidations of fatty acids. So, the topics which we already have covered are the different types of fatty in the different types of fatty oxidation we have vividly discussed beta oxidation of fatty acids. The process of beta oxidation starting from activation to transport of fatty acid inside mitochondria then the different reactionary steps of all the different types of fatty acids like oat chain, eventually fatty acids then saturated unsaturated fatty acids. Then we have discussed the energetics of beta oxidation regulation and also the related disorders.

Now in this class we are going to discuss other types of fatty acid oxidations like alpha oxidation, omega oxidation and peroxisomal oxidation of oxidation of fatty acids. Now if you remember from the previous classes that alpha oxidations and omega oxidations are based on the numbers of carbons in fatty acid. So, if you remember that omega carbon is the distant most carbon from the carboxylic group in fatty acid. Whereas, the the carbons which are attached to fatty carboxylic group of fatty acids the first one is known as alpha the second one is known as beta based on that these the carbons are named as well as those when those specific carbons like alpha carbons, beta carbons or omega carbons are oxidized that type of fatty acid oxidation is named accordingly.

Now peroxisomal oxidation is named based on where the oxidation of fatty acid is occurring. So, as we have discussed that beta oxidation of fatty acid the organ the organelle for beta oxidation is mitochondria whereas, peroxisomal oxidation occurs in peroxisome. Now peroxisome is one membrane bound organelle present in both plants and animals and these organelle is very much known for the presence of the enzyme catalase. It is a this peroxisome is a catalase rich organelle and also it is dealing with see there are different type of oxidations like amino acid oxidation, fatty acid oxidation those are occurring in peroxisome from which free radicals are generated and those free radicals are rather neutralized with the help of the enzyme catalase. So, peroxisome is

one such very known organelle for handling different free radicals.

Now peroxisomal oxidation the target fatty acids are mostly either very long chain fatty acid or branch chain fatty acids and those fatty acids are mostly obtained from dairy products fats of ruminant animals meat fish these are the origin of very long chain or branch chain fatty acids. Now peroxisomal oxidation is more or less similar with the beta oxidation which occurs in mitochondria and it generally peroxisomal oxidation also consists that same 4 steps that is dehydrogenation, then hydration or addition of water, then finally, oxidation and then thiolitic cleavage. Now then where is the difference? The difference lies in two specific conditions one is and that those conditions are related to the first step only. Now the first step the enzyme is a flaboprotein dependent oxidase here in peroxisomal oxidation and that flaboprotein dependent acyl coenzyme oxidase is transferring the electron directly to hydrogen peroxide. Now in case of beta oxidation this is our beta oxidation shown here.

So, if you remember the electron through the flaboproteins in beta oxidation is transferred to electron transferring flaboprotein which carries the electron to mitochondria electron transport chain. But in case of peroxisomal oxidation these electron does not enter does not enter ETC because definitely this is peroxisome. So, what happens to those electron they are directly transferred to H 2 O 2 and these H 2 O 2 actually they are directly transferred to molecular oxygen forming H 2 O 2 and these H 2 O 2 is broken down with the help of the enzyme catalase. So, basically here no ATP is formed. So, no ATP at from this stage rather the energy released is basically dissipated as heat.

So, in the first step there is the even if there is electron transferred through flaboprotein those electron does not enter ETC rather it forms H 2 O 2 which is which is which is degraded with the help of the enzyme catalase and the energy is released as heat. Next the specificity of this acyl coenzyme A oxidase also differs they prefer the these enzymes prefer very long chain fatty acids like hexacozanoic acid that is a 26 carbon fatty acid and also branch chain fatty acids like phytanic acid or pristanic acid. So, the specificity of this enzyme the enzyme designated for the first step that is fatty acyl coenzyme A oxidase its specificity as well as the way of transferring electron differ with the beta oxidation of fatty acid. So, this is paroxysomal oxidation of fatty acid. Now, remember paroxysomal fatty acid the oxidation occurs in paroxysm where there is no TCA cycle.

Now, when there is excess brum chain or very long chain fatty acid ingestion there is high concentration of this type of fat in our diet what it does it it has some effect over paroxysmal beta oxidation located in liver. So, the enzymes related to paroxysmal beta oxidations are basically increased. Now, what happens this a paroxysm does not contain

TCA cycle. So, what will be the fate of those fatty acids broken down? So, basically in liver they form shorter chain fatty fatty acid products like hexanoyl coenzyme A and those shorter chain fatty acid comes out of paroxysmal enters in mitochondria to follow the complete degradation or complete oxidation through beta oxidation to form acetyl coenzyme A and carbon dioxide. So, this is paroxysmal oxidation, paroxysmal oxidation takes help of mitochondrial beta oxidation as well for the complete oxidation of the long chain or brum chain fatty acids.

Now, we are going to discuss few disorders related to paroxysmal oxidation. Now, one such disorder is Zellweger syndrome. Now, Zellweger syndrome is related to absence or reduced paroxysm in cell. So, either there is paroxysmal content is reduced or there is complete absence of paroxysm. Now, what happens there are few genes PECS genes basically.

So, PECS genes are synthesizing a specific protein which causes organization of paroxysm. Now, because of the deficiency of that specific protein which is also known as paroxysm this paroxysm protein deficiency causes disorganized or formation of paroxysm sometimes paroxysm is completely absent. Now, what will be the effect all the metabolic pathways which happens in paroxysm they will be absent. So, including paroxysmal fatty oxygen paroxysmal fatty acid oxidation it will also be hampered. Then there is another disease adrenoleukodystrophy sometimes we call it x linked adrenoleukodystrophy because the defect the or the mutation is related to the x chromosome.

Now, the defect lies in a paroxysmal membrane transporter those membrane transporter proteins located in paroxysm is mostly carrying the branched or long chain fatty acids. So, the tissues which are mostly affected are central nervous system where those long chain or branched chain fatty acids are synthesizing the myelin sheath. So, basically myelin sheath formation is affected then adrenal cortex affected ladic cells of testes also affected. So, basically what is the faith that the long chain fatty acids accumulated those long chain fatty acid causes damage to the myelin sheaths. Now, x ALD or x linked adrenoleukodystrophy they affects young boys and the manifestation mostly occurs before 10 years of age there are different types of neuronal neural neuronal manifestation loss of vision behavioral disturbances and finally, they can lead to death as well.

So, in both of these diseases basically there is paroxysmal beta paroxysmal fatty acid oxidation is affected leading to accumulation of very long chain fatty acids in the circulation and their detection in blood can be a can be a screening for diagnosing these diseases. Next we will move on to alpha oxidation. So, alpha oxidation here we are

talking about oxidation of the alpha carbon of fatty acid. So, mostly this alpha oxidation is related to branch and fatty acid where the single carbon is removed from carboxyl and the just adjacent carbon to the carboxyl carbon is removed via oxidation. Now, again the steps in this alpha oxidation important one is hydroxylation of the alpha carbon then that is finally, oxidized to alpha keto acid.

Again the alpha oxidation occurs mostly in paroxysm and the important organ here is brain then keto acid follows decarboxylation releasing one molecule of carbon dioxide which forms a new fatty acid which is one carbon less . Now, why why this alpha oxidation is there why branch and fatty acids mostly undergo alpha oxidation because there are few dietary branch and fatty acids which have methyl group in the beta carbon. So, basically those beta carbon cannot undergo beta oxidation because that cannot be oxidized. So, what we need is to remove this hydroxyl group from alpha carbon. Now, one such important dietary methylated fatty acid is phytonic acid.

So, here we will discuss the alpha oxidation with the example of phytonic acid. So, here you can see that the alpha in the beta carbon there is hydroxyl group present. So, with the help of the enzyme phytonoyl synthetase we get the activated fatty acid that is phytonoyl coenzyme A then comes the important enzyme that is phytonoyl coenzyme A hydroxylase. Now, with this hydroxylase enzyme what happens here you can see there is decarboxylation. So, one one new fatty acyl coenzyme A is formed which is one carbon less then we are getting hydroxy phytonoyl coenzyme A.

So, this alpha carbon here you can see is hydroxylated. So, with the help of the hydroxylase enzyme there is decarboxylation as well as hydroxylation of the alpha carbon. Next with the help of the enzyme lyase formyl coenzyme A is released forming pristinic acid or pristinal this is the aldehyde form pristinal. Now, this pristinic acid further can undergo beta oxidation via forming pristinic acid this pristinic acid then can enter the proper beta oxidation. So, once again in alpha oxidation what happens the problem is there is a methyl group in beta carbon position for which beta carbon beta oxidation cannot occur.

So, what is done is once the first thing is alpha carbon is hydroxylated as well as there is decarboxylation then this part is removed as formyl coenzyme A forming pristinal pristinal is forming pristinic acid. Now, pristinic acid is basically derived from the phytanic acid only and then pristinic acid undergoes the normal beta oxidation after entering in mitochondria. So, the product the end product which is generated from the oxidation of pristinic acid is propionyl coenzyme A form and this part which is trimethyljecanoyl coenzyme A. So, this is alpha oxidation. Now, there are few one defect related to alpha oxidation one important one is refsomes disease.

Now, refsomes disease is related to that specific enzyme which is exclusive in alpha oxidation that is alpha hydroxylase enzyme that is the phytanic acid oxidase enzyme. Now, what happens definitely the phytanic acid oxidation is hampered leading to phytanic acid accumulation and this phytanic acid affects the central nervous system as well as peripheral nervous system. So, what we can see there is polyneuropathy, retinitis pigmentosa, nerve stiffness as well as cerebellar ataxia. Now, phytanic acid mostly is not endogenously derived acid. So, basically that is the phytanic acid is obtained from diet.

So, as therapeutic regimen what should be done is to restrict phytanic acid containing food and phytanic acid mostly present in the fish, milk, fats from ruminant animals, tuna, cords this type of fish they contain phytanic acid. So, these diet should be avoided along with that accumulated phytanic acid can be cleared from circulation via plasma phoresis. So, this is refsomes disease, but the other variant of refsomes disease is infantile refsomes disease. Now, infantile refsomes disease is a condition where children are affected at the very early age and their manifestations are mostly like Zellweger syndrome where basically the peroxisome synthesis or peroxisome formation is hampered leading to alpha oxidation defect. Then we are coming to omega oxidation now once again omega carbon is the distant most carbon from the carboxyl group in the fatty acid.

So, it is just opposite direction of beta oxidation or alpha oxidation where the omega oxidation is occurring in the carbon chain. Now, omega oxidation is located in endoplasmic reticulum and this occurs mostly in liver as well as kidney. Now, the preferred substrates are the fatty acids with at least 10 to 12 carbon chains . Then omega oxidation remember omega oxidation is the minor pathway and in normal persons there is omega oxidation along with the major fatty acid oxidation pathway that is beta oxidation. But omega oxidation the manifestation or the omega oxidation process is exaggerated when the beta oxidation is defective and what is the fate there is dicarboxylic aciduria.

So, how this dicarboxylic aciduria occurs when there is beta oxidation defective we will discuss via the enzymatic reactions of omega oxidation. So, here you can see the fatty acids this is our omega carbon which is distant most from the carboxylic group in the fatty acid in the fatty acid molecule. Now, the most important enzyme in omega oxidation is the hydroxylase enzyme that is a mixed function oxidase. Now, with the help of this mixed function oxidase and NADPH there is formation of an alcohol. So, this methyl carbon is converted to methyl alcohol with the help of mixed function oxidase.

Then there are few dehydrogenases that is alcohol dehydrogenase which convert this alcohol group to aldehyde then aldehyde dehydrogenase which convert this aldehyde group to acid group rather carboxylic acid group. So, here after this mixed function oxidase and subsequent dehydrogenase treatment what we are getting a carboxyl group formation in the omega carbon as well as the previously or the inherent carboxyl group which was there in the fatty axis. So, basically we are getting a dicarboxylic acid. Now, these dicarboxylic acid can be activated from the both side. So, this carboxyl groups on the both side can be activated forming coenzyme A or acyl derivative of fatty acid and this enters mitochondria for further beta oxidation.

So, remember omega oxidation occurs in the omega carbon only for single time forming a dicarboxylic acid then that dicarboxylic acid actually enters mitochondria for further beta oxidation. Now, just assume the situation where beta oxidation is defective. So, what will be the fate of these fatty acids? They will form dicarboxylic acid, but there will be no beta oxidation. So, these dicarboxylic acids will be excreted in urine that is why in defective beta oxidation there is dicarboxylic acid urea. So, what is the fate of the beta oxidation of this dicarboxylic acids? There is formation of succinate the end products and adipic acid.

So, these are the two end products of beta oxidation of those dicarboxylic fatty acids which were originated in the process of omega oxidation remember that is one very important question. So, again if there is beta oxidation defects in the enzymes dehydrogenases or thiolases or lyases in ketone body formation in those cases there is dicarboxylic acid urea as well as non ketotic hypoglycemia and also fatty liver. So, these are the key points of today's class that we have discussed alpha oxidation alpha oxidation is specific for the branch and amino acid where there is a methyl group in beta carbon in our dietary the fatty acid which we get from diet is phytanic acid which is a branch and methylated fatty acid for which there is alpha oxidation and also the alpha oxidation defect. Refsum disease or infantile refsum disease we have discussed then we have discussed peroxisomal oxidation which is specific for either very long chain fatty acids or branch and fatty acids. The peroxisomal oxidation is similar to the mitochondrial oxidation, but the difference is in the first oxidation step where the transfer of electron occurs directly to the molecular oxygen forming H 2 O 2 which is degraded dissipating the energy as heat.

Then we discussed omega oxidation which occurs in endoplasmic reticulum and there is formation of dicarboxylic fatty acid and that intermediate remember the once again that the product of omega oxidation is a dicarboxylic fatty acid which enters mitochondria for further break down through beta oxidation. So, these are my references and see you in the next class. Thank you.