**Overview and Integration of Cellular Metabolism**

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**Week 05**

**Lecture 25: Fatty acid catabolism (Oxidation of Fatty acids) - II**

Welcome back to the lecture series of overview and integration of cellular metabolism. We are in lecture 25 which is the continuation of fatty acid catabolism. In the previous class we have discussed the mobilization of stored fat and production of free fatty acid and different steps of beta oxidation how activation trans and transport occurs and finally, the more important steps or cyclical steps of beta oxidation to produce the product which is acetyl quenzyme A. Now, we have this we have already told that fatty acid oxidation is important because it produces energy when there is energy deficiency in our body there is breaking down of fat and provision of energy via beta oxidation. Now, let us see where these energies are formed where these ATP's are formed. So, when we discussed about palmitic acid beta oxidation remember from the previous class we told that there are 7 cycles of beta oxidation and the products are 8 acetyl quenzyme A.

Now, remember beta oxidation of fatty acid occurs inside mitochondria. Inside mitochondria there is from beta oxidation there is production of FADH2 NADH and also acetyl quenzyme A. All these 3 are important for ATP production how remember acetyl quenzyme A enters TCA cycle which is located in mitochondria. So, beta oxidation occurs in mitochondria the product acetyl quenzyme A directly can enter a cycle TCA cycle which is in mitochondria.

Similarly, inside mitochondria only there is electron transfer chain. So, FADH2 and NADH they also are formed inside mitochondria and can enter mitochondrial electron transport chain. So, this is a when beta oxidation occurs fatty acid can completely oxidize via formation of acetyl quenzyme A NADH, FADH2 they enter either TCA cycle and via TCA cycle they enter electron transport chain. So, there is complete oxidation of fatty acid during beta oxidation. So, in each in each cycle of beta oxidation of fermitic acid there is one molecule of FADH2 form and one molecule of NADH form and these are entering electron transport chain.

Now, let us see if you remember from the TCA cycle this is a time to revise that how

acetyl quenzyme A is giving rise to each acetyl quenzyme is giving rise to 10 ATPs we have discussed in TCA cycle. Now, here we are getting 8 acetyl quenzyme A which is finally, producing 80 ATPs. Similarly, 7 FADH2 they are forming 10.5 ATPs, 7 NADH per molecule of NADH forms 2.5 equivalent ATP.

So, here is production of total 17.5 ATPs. So, grossly there is 108 ATPs are formed when fermitic acid is oxidized, but remember for activation of fatty acid there have been utilization of one ATP molecule and there was breaking down of two high energy phosphate bond. So, basically we will consider there is breakdown of two ATPs. So, finally, the the net production is 108 minus 2 that is 106 ATPs.

So, remember on a complete oxidation of fermitic acid the net production of ATP is 106 ATPs and the efficiency of these beta oxidation is around 33 percent. So, this is the energetics of beta oxidation remember this is one very high energy forming pathway beta oxidation around 106 ATPs from one fatty acid complete oxidation of one fermitic acid is produced. Now, fermitic acid is one even chain fatty acid 16 carbon compound, but what happens when there is odd chain fatty acid. So, odd chain fatty acids follows the same pathway that is there is dehydrogenation, there is hydration again energy dependent dehydrogenation and thiolytic cleavage this is same till and there is continuously there is formation of 2 carbon less fatty acyl coenzyme a production. Now, when that 2 carbon less fatty acyl coenzyme a is a 5 carbon fatty acid.

So, 5 cannot be divided in 2 plus 2. So, there will be 2 plus 3 2 plus 3. So, that 2 is acetyl coenzyme a what is that 3 carbon compound that is propionyl coenzyme a and propionyl coenzyme a cannot further enters beta oxidation. So, propionyl coenzyme a metabolized via different pathway involving different other enzymes. So, what are those enzymes carboxylase epimerase and mutase.

So, these are 3 important enzymes required for propionyl coenzyme a metabolism. Now, propionyl coenzyme a first is treated by one carboxylase propionyl coenzyme a carboxylase which is one biotin dependent enzyme. Remember majority of the carboxylase are having a cofactor biotin and there is formation of D methylmalonyl coenzyme a D is D stereo isomer and this D stereo isomer is treated by epimerase. So, there is epimerization forming L isomer. So, you can see L methylmalonyl coenzyme a formation.

Now, this L methylmalonyl coenzyme a undergoes molecular rearrangement to form succinyl coenzyme a with the help of the enzyme methylmalonyl coenzyme a mutase and that is one coenzyme B 12 dependent enzyme. So, this is one vitamin B 12 dependent pathway and remember whenever there is B 2 vitamin B 12 deficiency there

is disturbed or hampered propionyl coenzyme a metabolism. And now you can see succinyl coenzyme a now can easily enter TCA cycle and converted to oxaloacetate. So, this is a substrate for so, propionyl coenzyme a via oxaloacetate can enter TCA cycle. So, this is a substrate for neo glucogenesis.

So, remember in fatty acid what is glucogenic only propionyl coenzyme a. So, oth chain fatty acids when broken down the propionyl coenzyme a part is the neo glucogenetic or glucogenic molecule. So, I have told you in neo glucogenesis class one substrate for neo glucogenesis is propionyl coenzyme a. So, this is how propionyl coenzyme a takes part in neo glucogenesis. Now what we have discussed that is palmitic acid or others are saturated fatty acid, but most of the fatty acid which are generated from triacylglycerol or phospholipids they are unsaturated having double bonds and those double bonds are in cis configuration.

And remember in case of beta oxidation what we have discussed that hydratase is specific for trans double bond trans double bond. So, cis double bond present in the naturally occur in unsaturated fatty acids they cannot be treated upon by hydratase. So, what we need is two different auxiliary enzymes in case of unsaturated fatty acid one is isomerase another is reductase. So, these are the two important enzyme remember that is one important point for m c q's what are the two different enzymes which required for unsaturated fatty acid beta oxidation that is isomerase and reductase. Now when these enzymes are required.

So, let us discuss with respect to oleate or oleic acid that is one 18 carbon based monounsaturated fatty acid. So, there is one single double bond I mean one double bond and that double bond is in cis configuration present between C 9 and this is our C 10. Now for the first three cycle here you can see beta oxidation can occur. So, there are three cycles of beta oxidation after activation of oleic acid olel coenzyme A formed and three cycles of beta oxidation occur till there is formation of this product that is cis delta 3 dodecenol coenzyme A. What is the problem here? Here is the cis double bond which needs to be converted to trans 1 how with the help of the enzyme isomerase.

So, that is delta 3 delta 2 enol coenzyme A isomerase what it does what this enzyme is important because it converts the cis double bond to trans double bond. Now once there is formation of trans delta 2 dodecenol coenzyme A it can be treated by the hydrates and follow further beta oxidation steps. So, this product dodecenol coenzyme A can undergoes 5 cycles of beta oxidation producing 6 acetyl coenzyme A. So, this is the beta oxidation of olel coenzyme A when where there is one cis double bond which is treated by isomerase to form trans double bond others are just same like beta oxidation of fatty acid I mean saturated fatty acid. Now this is about mono unsaturated fatty acid what

happens to the poly unsaturated fatty acid? So, there we need another auxiliary enzyme apart from isomerase that is reductase.

Now again one such poly unsaturated fatty acid is linoleic acid. Linoleic is the 18 carbon long fatty acid where there are 2 double bonds one between 9 10 another between carbon 12 and 3. So, there is delta 9 delta 12 configuration in linoleic. So, there are 2 double bond both of them are in cis configuration. Again linoleic acid undergoes 3 cycles of beta oxidation releasing sorry 3 acetyl coenzyme A.

Now what is formed is this molecule. So, you can see there is a 12 carbon unsaturated fatty acyl coenzyme A when there are 2 double bonds both of the double bonds are in cis configuration. Moreover you can see beta carbon is not free here the beta carbon is not free in beta carbon position the double bond is present. So, what we need to do we need to convert the cis to trans as well as we need to shift this double bond. So, there are 2 enzymes the first one is reductase.

So, you can see reductase is actually shifting the double bond. So, from delta 3 the double bond is shifted to delta 2 as well as the double bond is converted from cis to trans. So, now, it is ready to be treated by hydratase and it can undergo the following 4 steps of reaction in beta oxidation cycle. So, this is the total beta oxidation of linoleic acid finally, can be treated by after getting by treated by reductase and isomerase it forms 5 acetyl coenzyme A. Next is regulation of beta oxidation.

Now remember beta oxidation is required when there is deficiency of energy. Now when there is mobilization of fat or entry of fat in cytosol that long chain fatty or fatty acyl coenzyme A they can either undergo beta oxidation for breaking down or can undergo biosynthetic steps forming different membrane lipids triacyl glycerol phospholipids like that. So, either it can undergo catabolic pathway or it can undergo anabolic pathway now that is a decisive factor. So, provision of long chain fatty acyl coenzyme A in cytosol or in mitochondria is the rate limiting step. So, what is important is the carnitine shuttle or the first reaction of carnitine shuttle that is carnitine acyl transfer is one enzyme.

So, once the fatty acyl coenzyme A from cytosol enters mitochondria it is dedicated or committed for beta oxidation or oxidation of fatty acid. So, this carnitine shuttle is the decisive step for beta oxidation whether beta oxidation will occur or not. Now how this regulatory signals are transmitted definitely via different hormones, hormones like insulin, glucagon, epinephrine like that. Now remember all the enzymes as we have already discussed for multiple times that all the enzymes are regulated all the metabolic pathways are regulated either by short term regulation where enzymes either deactivated

or activated or long term regulation where enzyme synthesis is controlled. So, there is either more synthesis of enzymes or reduced synthesis of enzyme.

So, that is long term regulation is related to the numbers of enzyme. Now, in case of short term regulation what happens in case of beta oxidation or beta oxidation is basically important with relation to the levels of I mean the provision of energy in body. So, when there is adequate energy supply fatty acid breakdown is not needed it is needed when there is deficiency of energy. So, deficiency of energy is indicated by low blood glucose level and that low blood glucose level is sensed by glucagon hormone. Now this is one very important enzyme ACC which stands for Acetyl Coenzyme Carboxylase and that acetyl coenzyme a carboxylase is required or important regulatory enzyme for fatty acid synthesis which we will discuss in the next classes.

Now when there is activation of acetyl coenzyme a carboxylase it means there is adequate energy. So, fatty acid synthesis can be done because why fatty acid synthesis can be done? Remember when there is adequate flow of glucose in cell that glucose enters glycolysis forms acetyl coenzyme there is adequate provision of acetyl coenzyme and that acetyl coenzyme can enter fatty acid synthesis. So, that is a storage form. Now when acetyl coenzyme a carboxylase is activated it means that is a phosphorylated state. So, glucagon once again through cyclic AMP dependent activation of protein kinase A there is phosphorylation of ACC or acetyl coenzyme a carboxylase.

So, once there is activation of acetyl coenzyme a carboxylase acetyl coenzyme a is converted to malonyl coenzyme a. Malonyl coenzyme a is one regulatory biomolecule for beta oxidation. Now when there is excess production of malonyl coenzyme a it inhibits the carnitine shuttle carnitine acyl transferase 1. So, basically there is adequate energy adequate acetyl coenzyme a. So, acetyl coenzyme a is forming fatty acid in the storage form.

So, no more breakdown is needed and how it is signal via the intermediate of fatty acid synthesis that is malonyl coenzyme a and malonyl coenzyme a is inhibiting what of beta oxidation carnitine acyl transferase 1, one important question. Now, first apart from that there are two other signals that is NADH NAD ratio. Now remember whenever there is excess amount of NADH, NADH produced in glycolysis and TCA cycle it indicates there is adequate amount of energy. So, NAD high NADH or high NADH NAD ratio is a signal that no more beta oxidation is required. Similarly adequate amount of acetyl coenzyme a which is coming from circulatory glucose to TCA cycle it is also one signal that there is adequate amount of energy.

So, how they are this NADH NAD ratio or acetyl coenzyme a they are imparting the

inhibitory signals via inhibition of two important enzyme. So, high NADH NAD ratio is actually inhibiting the enzyme beta hydroxyl coenzyme a dehydrogenase and increased acetyl coenzyme a it inhibits the thiolitic cleavage related enzyme thiolase. Now, apart from that glucagon mediated phosphorylation there is also AMPK dependent phosphorylation. Now AMPK is the kinase enzyme AMP dependent kinase enzyme it is activated by AMP. Now, remember AMP when AMP is produced in our body when there is ATP breakdown means when there is excess exercise when there is starvation when there is I mean energy utilization high energy utilization in our body there is ATP breakdown and formation of AMP.

Now AMP signals or rather activates AMP dependent protein kinase AMPK AMPK causes phosphorylation of acetyl coenzyme a carboxylase and acetyl coenzyme a carboxylase is activated. Now, these are the short term regulation what happens to the long term regulation? Long term regulation is signal by different transcription factors one such important transcription factor is PPAR that is peroxisome proliferator activated receptor. This is a nuclear receptor transcription factor which activates different which when activated actually activates different beta oxidation related enzymes like the translocase or dehydrogenases they are activated by PPAR mainly the isoform is PPAR alpha which is abundantly present in skeletal muscles, liver adipose tissue as well. Apart from that glucagon also activate another transcription factor cyclic AMP dependent transcription factor which is known as CREB. So, these are the transcription factor through which long term regulation of different beta oxidation related enzymes occur.

Now, we will discuss different diseases related to beta oxidation. Now, beta oxidation related defects are either in transport of fatty acid inside mitochondria or defect lies in different I mean the enzymes. Now, whenever there is defect in beta oxidation there is hypoglycemia. Hypoglycemia when fasting hypoglycemia or when there is excessive exercise there is hypoglycemia, but that hypoglycemia remember that hypoglycemia is hypoketotic or non-ketotic hypoglycemia. So, there is very less production of ketone body in case of defective beta oxidation.

Along with that there is hyperammonia high ammonia is produced then skeletal muscle weakness definitely there is when the exercise beta oxidation provides energy. So, beta oxidation defects skeletal muscle does not get adequate energy supply. So, there is skeletal muscle weakness and also liver disorders because liver is one important site for beta oxidation. Now, as I told you beta oxidation defect can be in in relation to the transport of fatty acid and for fatty acid transport the molecule is carnitine. So, carnitine can be deficient primarily means in born carnitine synthesis or supply defect and those manifestations occur very early in life like infancy early childhood most prevalent or most predominant in preterm babies where there is inadequate I mean high energy

requirement is there.

So, they suffer episodes of hypoglycemia apart from that the metabolism of brain is hampered. So, there is severe encephalopathy, heart metabolism is hampered, cardiomyopathy, then confusion, vomiting and of course, muscle weakness I told you, but this severity depends in between individuals and the episodes or episodes are triggered by either fasting or some illnesses like viral infections. So, this is about primary carnitine deficiency. Now, what happens when there is primary carnitine deficiency remember I am talking about the molecule carnitine molecule is deficient, but even if there is the carnitine shuttle is hampered when the enzymes are also deficient. So, that is transporter defect now that can be carnitine permittile transfer is one carnitine permittile transfer is two or translocase enzyme deficiency.

Now, remember the manifestation is in long chain fatty acid metabolism because short chain and medium chain they can be transported easily via the membrane. What happens once again muscle weakness manifested as muscle cramps during fasting exercise or high fat diet. Now, inherited carnitine acyl transfer is one deficiency it is mostly it mostly affects the liver whereas, CAT 2 initially affects the skeletal muscle in severe condition it affects the liver. These are the primary deficiency, but apart from that few acquired conditions are there which inhibits the transporters like sulfonylurea drugs which are anti diabetic drugs like glibanclamide, tholbutamide these enzymes it inhibits carnitine permittile transfer is one enzyme. Now, this carnitine permittile transfer is one inhibition causes defect in beta oxidation.

Next we are going to discuss organic acid ureas. Organic acid ureas are the manifestation of beta oxidation enzyme related defects and it can be related to metabolism of fatty acid sometimes branched chain and aromatic amino acids as well and also defects of TCA cycle. So, once we will discuss the integration of all the metabolism protein, carbohydrate and fat you will see how this organic acid urea is connected. Now, what happens there is accumulation of organic acids and those organic acids are excreted via urine. So, that is the diagnostic landmark that organic acids are present in urine and is detected by chromatography. Now, how that can be restricted? The substrates which when oxidized produces organic acid those substrate should be removed or should be restricted in diet along with that few cofactor deficiency defect the enzymes of beta oxidation their cofactor can be deficient.

So, those cofactor can be supplemented in diet that can be helpful for management of organic acid ureas. Now, what are those organic acid ureas? So, the organic acid urea can be related to propionate propionyl coenzyme or propionate metabolism. Now, the first enzyme if you remember in case of metabolism of propionyl coenzyme was propionyl

coenzyme carboxylase and that primary condition is autosomal recessive. So, propionyl coenzyme a carboxylase deficiency is one autosomal recessive condition and mostly the breakdown or metabolism of amino acids valine, methionine, isoleucine and phionine they are hampered. When you will you will attend the classes of amino acid metabolism you will see how these amino acids are forming propionyl coenzyme A.

Now, because this enzyme is deficient what will happen? The methyl malonyl coenzyme A will not be formed. So, what will be accumulated? Propionyl coenzyme A will be accumulated and that will follow one other pathway and it will form propionic acid which will cause propionic acidemia, ketoacidosis as well as manifest it will be manifest as developmental anomalies. Next disorder is in conversion of methyl malonyl coenzyme A to succinyl coenzyme A and because there is defect in convert this conversion what will be accumulated? Methyl malonyl coenzyme A will be accumulated and it will be excreted via urine in the form of methyl malonic aciduria. Now, where is the deficiency? The deficiency is in the function of mutase. Now, there can be a primary mutase deficiency or can be the cofactor deficiency that is coenzyme B 12.

So, manifestation can be due to B 12 deficiency or can be due to primary deficiency of the enzyme. Now, when the I mean the when the manifestation can be reversed by dietary supplementation of B 12 it means there is B 12 deficiency, but if the dietary supplement of B 12 is not reversing the manifestation it means there is primary deficiency. So, what will happen there will be accumulation of methyl malonic acid and finally, it is causing mental retardation the brain development will be hampered. So, these are the lists of organic acid urea, methyl malonic acid urea, propionic acidemia we already have discussed apart from that acyl coenzyme A dehydrogenases we have discussed there are different types of acyl coenzyme A dehydrogenases based on the chain length of fatty acid there is short chain acyl coenzyme A dehydrogenase based on that the deficiency will be manifested. Similarly, medium chain acyl coenzyme A dehydrogenase deficiency, MCAT deficiency or LCAT deficiency that is long chain acyl coenzyme A dehydrogenase deficiency.

Now, remember the commonest one is MCAT deficiency. This is the commonest beta oxidation defect. So, this is one very important MCTO the commonest beta oxidation defect is MCAT deficiency which is manifested as hypoglycemia remember that is non ketotic or hypoketotic hypoglycemia, fatty liver acidosis, hyperammonemia these are the manifestations in case of organic acid ureas. So, these are the list of organic acid ureas related to beta oxidation defect. Now, apart from that there is another disease Jamaican vermitin sickness which is very interesting with respect to beta oxidation defect. Now, this disease is also known as toxic hypoglycemic syndrome.

What happens is the manifestation is due to digestion of unripe achy fruit. Now, unripe achy fruit it contains one toxin known as hypoglycine hypoglycine A and hypoglycine B both are toxic and these hypoglycines they inhibit medium and short chain acyl coenzyme dehydrogenases. So, definitely there is beta oxidation defect. Now, how this manifestation occurs after ingestion of achy fruit within 2 to 6 hours there is abdominal discomfort which is followed by vomiting a sudden onset vomiting and that if it continues in or it proceeds to severe condition it is manifested as profound dehydration finally, there is convulsion coma event death may occur. So, these are the defects of beta oxidation and the related diseases.

So, what we have discussed is the bioenergetics of palmitic acid on complete oxidation there is 106 ATPs which are produced. The end product for event chain fatty acid is all acetyl coenzyme A, but in case of odd chain fatty acid the end product is all acetyl coenzyme A and one propionyl coenzyme A. Then oxidation of unsaturated fatty acid we have discussed where two additional important enzymes are required one is isomers another is reductase and finally, we have discussed different metabolic disorders related to beta oxidation defects. So, these are all about oxidation of fatty acids different types of oxidation of fatty acids will be discussed in the next class apart from beta oxidation these are my references. Thank you all see you in the next class.