**Overview and Integration of Cellular Metabolism**

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**Lecture 37: Tyrosine Metabolism - I**

Hello everyone, welcome back to the lecture series, Overview and Integration of the Cellular Metabolism. So, we we are in the discussions of amino acid metabolisms. Today we are going to discuss metabolism of tyrosine. Now, in this class we will discuss a brief of tyrosine, what are the characteristics of this amino acid, what are the metabolic fate of tyrosine metabolic roles, different metabolic roles of tyrosine. And there are different specialized products which are formed from tyrosine those metabolites, what are their importance, how they are formed and finally, the different disorders related to tyrosine metabolism. So, let us move on to the basic briefs of the amino acid tyrosine.

Now, as you have already gone through the phenylalanine. So, if you remember this is the structure of phenylalanine. So, here we are having a benzene group. Now, in this benzene group there is additional hydroxyl group added at the para position of this benzene ring.

So, phenylalanine when hydroxylated at the para position it forms tyrosine. So, if you remember from your previous classes of phenylalanine metabolism you remember phenylalanine is actually forming tyrosine by a hydroxylation. So, this is the hydroxyl group added to form tyrosine. Now, about tyrosine, tyrosine is one of the aromatic amino acids and also a non essential amino acid because it can be synthesized from phenylalanine. So, it is not essential amino acids.

Then the degradation of tyrosine occurs in liver the end products of the degradation is fumarate and acetoacetate. So, you can see tyrosine can be both glucogenic as well as ketogenic. Glucogenic why because it forms fumarate, fumarate can enter the TCA cycle ketogenic why because it forms acetoacetate, acetoacetate is a ketone body. Now, phenylalanine as also basically is degraded or rather catabolized via forming tyrosine which when catabolized is actually the complete catabolism of both phenylalanine and tyrosine. Now, there are different biologically important compounds or bio metabolites rather which are formed from tyrosine like different catecholamines.

Catecholamines are epinephrine norepinephrine, dopamine which acts as a neurotransmitter, hormones thyroid hormones, then also a pigment melanin these are the important metabolites of tyrosine we are going to discuss about them. So, if you remember this pathway. So, this is the formation of tyrosine from phenylalanine and the further this pathway if proceeds further we will see how tyrosine is catabolized. So, you remember that from phenylalanine tyrosine is formed via hydroxylation the enzyme is phenylalanine hydroxylase and which is a biopterin dependent enzyme. So, you remember this that tetrydrobiopterin is forming dihydrobiopterin whereas, phenylalanine hydroxylase by hydroxylation forms tyrosine.

Now, these tyrosine undergoes transamination with a enzyme tyrosine aminotransference or transaminase. Now, like all the transaminases in our body these transaminase tyrosine transaminase is also pyridoxal phosphate dependent enzyme and can be induced by steroids. So, these path is induced by steroid. Now, because it is a transamination reaction what happens you can see this amine group is basically transferred to alpha ketoglutarate and glutamate is formed. Now, this step if inhibited inhibited why if there is tyrosine transaminase deficiency that causes tyrosinemia type 2 then.

So, after transamination what we are getting is para hydroxy phenylpyruvate. Now, this para hydroxy phenylpyruvate forms Homogentisate with the enzyme para hydroxy phenylpyruvate dioxygenase. Now, dioxygenase or oxidase is a copper containing enzyme. So, the cofactor is copper here. Now, you can see there is decarboxylation.

So, basically this is a type of oxidative decarboxylation as well as hydroxylation which is occurring in the phenyl ring. So, here you can see previously there was one hydroxyl group now here are two hydroxyl group added and in this step vitamin C as well as B 12 they act as cofactor. Now, when this dioxygenase enzyme is absent or defective it causes another type of tyrosinemia tyrosinemia type 3. Then from homogentisate there is formation of mallel acetoacetate. Now, you can see till Homogentisate there is benzene ring, but after this step that ring is opened.

So, this is this step is important because there is cleavage of the aromatic benzene ring and the enzyme here is another dioxygenase Homogentisate 1 2 dioxygenase and this is one iron containing protein iron metalloprotein and here to open up this aromatic ring what is utilized molecular oxygen. For this step the specific one specific inhibitor which inhibits the dioxygenase enzyme is dipyridyl dipyridyl inhibits dioxygenase or Homogentisate oxidase enzyme. Remember this enzyme also known as Homogentisate oxidase and when there is Homogentisate oxidase deficiency there is a specific disorder

which is known as Alcaptonuria fine. We will be discussing these diseases later in this class. Then mallel acetoacetate undergoes isomerization forming fumaryl acetoacetate with the help of one isomerase enzyme.

Then fumaryl acetoacetate finally, undergoes hydrolysis via fumaryl acetoacetate hydrolase or acetoacetase fumaryl acetoacetase. So, it generates the glucogenic part fumarate and the ketogenic part acetoacetate and this acetoacetate with the ketoacyl coenzyme A transferase can form acetoacetyl coenzyme A where succinyl coenzyme A is the coenzyme group donor and it forms succinate after donating the coenzyme group. So, the fate is formation of fumarate which is glucogenic and also acetoacetate which is ketogenic. So, this is the complete catabolic pathway of both phenylalanine as well as tyrosine where phenylalanine via phenylalanine hydroxylase forms tyrosine. Then this tyrosine undergoes transamination via transaminase to form para hydroxy phenyl pyruvate.

Then para hydroxy phenyl pyruvate form Homogentisate oxidase Homogentisate with the enzyme Homogentisate sorry with the help of the enzyme dioxygenase. Then Homogentisate forms malyl acetoacetate with the help of the enzyme dioxygenase which is also known as Homogentisate oxidase. Then malyl acetoacetate undergoes isomerization to form fumaryl acetoacetate and finally, fumaryl acetoacetate is cleaved or rather hydrolyzed to form fumarate and acetoacetate fine. So, remember once again which one is the ring opening reaction here or cleavage of aromatic ring remember formation of malyl acetoacetate from Homogentisate is the cleavage of aromatic ring, aromatic amino aromatic benzene ring is basically open to the linear structure. So, let us discuss about the different disorders of tyrosine metabolism.

So, we have already told there is tyrosine type 1 when there is enzyme deficiency fumaryl acetoacetase. So, this is basically the last enzyme remember from fumaryl acetoacetate via hydrolysis there is formation of fumarate and acetoacetate. When this enzyme is deficient the hydrolase or fumaryl acetoacetase when this is deficient it causes the type 1 tyrosinemia. Now remember when the tyrosine degradation pathway is hampered at any stage what is the fate there is accumulation of tyrosine. So, these group of disorders are known as tyrosinemia and now at which label the inhibition is based on that the names are given type 1, type 2 like that.

So, the type 1 is the last reaction remember type 1 the first type of tyrosinemia is basically the last reaction of its catabolism. Now remember all these tyrosinemias are basically inborn error of metabolism. So, these are basically genetic defects where the enzymes are somehow defective due to different types of mutation or complete absence or partial absence of the enzyme. Now though these disorders are rare type 1 is the

commonest of all types of tyrosinemia. Now what happens what is the manifestation basically manifestation can be either acute or chronic.

Now in case of acute manifestation there is hepatic and renal failure which finally, leads to very early date within around 1 year. Whereas in chronic manifestation there is diarrhea, vomiting, cabbage like odour this cabbage like odour coming from the body because of production of different types of organic acids like phenyl lactate, lactate phenyl acetate like that. Because remember tyrosine is accumulated similarly in the back reaction phenylalanine will also be accumulated and just like phenyl ketoneuria those accumulated phenylalanine can form other keto acids. So, those organic acids accumulation gives gives the cabbage like odour. Now also there is vitamin D resistant rickets now why there is vitamin D resistant rickets because the renal tubules are affected and that is when the renal function is affected remember phosphate excretion is affected.

So, these vitamin D is basically because of hypophosphatemic rickets and when treated with vitamin D they these type of rickets do not resolve. So, that is that is why it is called vitamin D resistant rickets which is manifested in tyrosinemia type 1. Now apart from that you remember the enzyme delta alla synthase which was required for which is required for heme synthesis this enzyme is delta alla dehydratase enzyme is sorry the enzyme is delta alla dehydratase. So, delta alla dehydratase enzyme is basically inhibited in tyrosinemia type 1. Now what happens fumaryl acetoacetate it forms succinyl acetoacetate.

So, you can see fumaryl acetoacetate as well as maloyl acetoacetate they form succinyl acetate. Now succinyl acetate forms the lactone succinyl lactone. Now the succinyl lactone is one inhibitor of that delta alla dehydratase. So, finally, delta amino levulinic acid is accumulated and heme synthesis is hampered in tyrosinemia type 1. Now how this can be diagnosed succinyl lactone is accumulated.

So, this accumulation of succinyl lactone is a diagnostic metabolite rather for tyrosinemia type 1. Then tyrosine level is either very slightly elevated or sometimes remain normal because it is bypassed to some other products. Then there is methionine level which is also high delta amino levulinic acid is high alpha-fetoprotein level is also high as I told they are doing there is liver failure. So, this alpha-fetoprotein is a marker of hepatocellular carcinoma. So, this alpha-fetoprotein level is also high in tyrosinemia type 1.

Then we are coming to tyrosinemia type 2. Now remember type 1 is the last reaction whereas, type 2 is the first reaction where tyrosine is trans transamination is there. So, that enzyme transaminase or amino transferase when inhibited it causes tyrosinemia type

2. Now this disease is also known as oculocutaneous tyrosinemia also Rickner-Hanhart syndrome. So, remember tyrosinemia type 2 the other names are oculocutaneous tyrosinemia or Rickner-Hanhart syndrome.

So, once again the tyrosine degradation pathway is hampered accumulation of tyrosine is there that is why it is tyrosinemia. Now this disease is specifically characterized by some skin lesions like hyperkeratosis of palm, soles, eye lesions in eye there is painful cornea lesions in eye, mental retardation these are the manifestation of tyrosinemia type 2. You can see there is so, these are the hyperkeratosis see thickening of skin also hyper sorry cornea lesions you can see the cornea lesions are there. So, these are the manifestation of tyrosinemia type 2. Then we are moving on to tyrosinemia type 3 where the dioxygenase is absent.

So, homogenity cannot be formed from para hydroxy phenyl pyruvate. Now because this enzyme is dependent on vitamin C it is sometimes responsive to vitamin C treatment or ascorbic acid vitamin C is known as ascorbic acid as well. Then we are coming to one very important disease alkylurea. Now alkylurea remember the enzyme is homogenity set oxidase deficiency or that enzyme is also known as homogenity set 1, 2 dioxygenase the common common is homogenity set oxidase. So, basically homogenity set cannot be degraded.

Now, it was first described by Leucitnus autosomal recessive disorder 1 in 25 5000 birds it is detected. Now what happens because there is homogenity set accumulation it is accumulated in different tissues levels are very high in blood and also excluded in urine. Now what happens the commonest manifestation is that urine is becoming black if for if it is kept for long time. So, because you know this is one inborn disease babies are affected. So, the commonest complaint from the mothers come that the diaper or the inner garments are are I mean they are coloured black because when they are stained with urine those urine are turning to black or coke in colour.

So, you can see this urine while it is kept for long time it has turned to black because homogenity set why this blackening because homogenity set it cannot be degraded it is accumulated and it is I mean diverted to some other pathway what that pathway is it forms different types of quinones. So, here you can see benzoquinone acetate is formed by a polyphenol oxidase and these benzoquinone acid acetates undergoes oxidations and form compounds which converts which gives a blackish or brownish colour. Now via chromatography the presence of homogenity set in urine can be detected it can be detected in blood as well for the clinical manifestation remember alcaptonuria is detect at early stage it remains mostly benign it is not a fatal condition, but on long standing condition for long time what happens this quinone derivatives benzoquinone acetates

they undergo polymerization to form a pigment which is which known as alcapton bodies and these alcapton bodies are accumulated in different tissues connective tissues bones different organs and forms and the condition is known as ochronosis. So, you can see this is the vertebral column and here these blackish stains are basically ochronosis or accumulation of alcapton body also this can be accumulated in different types of joints as well causing arthritis. The treatment is just the phenylalanine restricted diet give low phenylalanine to control it is catabolism and formation of homogenity set.

So, here you can see this is ochronosis this is also ochronosis and also the urine colour is converted to black. So, these are these are all for our today's session. So, what we have learned is about a brief discussion of tyrosine where tyrosine is glucogenic as well as ketogenic because on catabolism tyrosine forms sorry tyrosine forms fumarate which is glucogenic then also forms acetoacetate which is ketogenic then different tyrosinemias type 1, type 2 and type 3 tyrosinemias we have discussed where there is inborn defects in the degradation related enzymes of tyrosine. Then we discussed about alcaptonuria alcaptonuria related to the defective homogenity set enzyme causing accumulation of homogenity set which is finally, forming alcaptone bodies also known as black urine disease and and also we have discussed the diagnosis and basic therapeutics of alcaptoneuria. So, these are all for today these are my references. Thank you and see you in the next class.