Overview and Integration of Cellular Metabolism

Prof. Aritri Bir

Dr. B.C. Roy Multi-Speciality Medical Research Centre

Indian Institute of Technology Kharagpur

Week 08

Lecture 40: Tryptophan Metabolism

Welcome back to the lecture series of Overview and Integration of Cellular Metabolism. We are at week 8 lecture 40. We are going to discuss Tryptophan metabolism in this class. So, the concepts here covered are metabolic fate of tryptophan, different metabolic roles imparted by tryptophan, then there are different specialist products which are synthesized from tryptophan their roles and the associated clinical conditions with defective tryptophan metabolism. Tryptophan is one aromatic amino acid essential amino acid because it cannot be synthesized in our body then it is a glucocitogenic amino acid glucogenic amino acid because alanine is produced from it and ketogenic because acet acetate is produced from it. Then there are different important biomolecules which are formed from tryptophan like serotonin which is a neurotransmitter, niacin is a vitamin and melatonin is a hormone.

Remember this is not melanin melanin is a pigment whereas, melatonin is a hormone please concentrate on this ok. Now, we are moving on to catabolism of tryptophan. Now, remember catabolism of tryptophan the whole pathway might not be that much important, but the product kynurenine is important here you can see kynurenine. Now, kynurenine more than 95 percent of tryptophan are actually metabolized rather catabolized to form kynurenine and in this regard the enzyme pyrolyze is important.

Now, pyrolyze can be indolamine 2, 3 dioxygenase which is present in immune system and brain or can be the variety of tryptophan 2, 3 dioxygenase which is present in liver. Both of them based on the tissue specificity present in different tissue differential expression in different tissues this is the most important enzyme for breakdown of tryptophan. Now, tryptophan it forms N-formyl kynurenine with pyrolyze then forms formylase where you can see formic , format is , format is released for and kynurenine is formed. Then kynurenine undergo steps of reaction series of reaction forming hydroxy kynurenine via the enzyme hydroxylase then it undergoes kynurenines where 3 hydroxy anthranilate is formed. Now, these step of reaction is basically a , where the aromatic ring is actually opened up here you can see the aromatic ring is opened up while forming

3 hydroxy anthranilate and what is released is alanine that is the reason we say this is one , glucogenic amino acids.

And this kynurenines enzyme is vitamin B 6 dependent enzyme. Now, , here you can see , 3 hydroxy anthranilate via the enzyme oxidase undergo opening of the ring forming acrylyl aminofumarate. So, remember , kynurenine undergoes ring opening via the enzyme kynurenines and oxidase where , molecular oxygen is also required. Now, it finally, this acrylyl aminofumarate finally, following different series of reactions form acetoacetate which is the ketogenic form of a ketogenic product of tryptophan. So, , regarding the kynurenine which is one very important metabolite of tryptophan it has few , correlations with different diseases like , cognitive deficits in schizophrenia it is associated with the disorder in kynurenine degrading enzyme.

Similarly, the levels of kynurenine is found to be decreased in bipolar disorder or the production of kynurenine is increased in case of Alzheimer's disease or cardiovascular disease also kynurenine is associated with different movement disorders or ticks. So, these are the association of kynurenine with different diseases . Metabolic role of kynurenine tryptophan the important products are NAD nicotinamide adenine dinucleotide from which NADP nicotinamide adenine dinucleotide phosphate is also formed. So, along with NAD there is NADP also then serotonin as well as melatonin these are the important products formed from tryptophan. Now, , to remember indycan is one such , metabolite or biomolecule which is formed from tryptophan during its catabolism and is excreted in urine.

So, when there is excess tryptophan catabolism indycan level in urine will be high. Next I am coming to the synthesis of NAD and NADP. So, basically , from tryptophan we have seen how kynurenine is formed how, how hydroxykinurenine is formed and finally, 3 hydroxy anthranlylic acid is formed. Now, from 3 hydroxy anthranlylic acid there are multiple steps following which quinolate is formed. Now, this quinolate undergoes phosphoribosylation.

So, this phosphoribosyl group is actually from PRPP phosphoribosyl pyrophosphate PRPP is donating the phosphoribosyl group to , quinolate. So, here you can see formation of nicotinate mononucleotide due to transfer of phosphoribosyl group by the enzyme phosphoribosyl transferase. Now AMP is donated from ATP. So, here you can see there is one adenosyl group , sorry there is one phosphoribosyl group as well as there is another phosphoribosyl adenine group present forming desamidonecotinamide dinucleotide. These undergo transamination.

So, glutamine donates the amine group to it. So, here we are getting one , ribosyl

phosphate adeno adenylated ribosyl phosphate along with that other ribosyl phosphate. So, that is why it is known as nicotinamide dinucleotide. So, NAD is formed here along with that adenine that NADP can be formed from NAD via phosphorylation. So, here you can see these 2 phosphate groups where they are already.

Now, another phosphate group phosphorylation occurs , in NAD to form NADP nicotinamide adenine dinucleotide phosphate. So, this is how NAD and NADP are formed from tryptophan. Then we are moving on to serotonin synthesis. Serotonin is a neurotransmitter , and that is formed from tryptophan via hydroxylation and decarboxylation. Now, tryptophan on hydroxylation form hydroxytryptophan that is 5 hydroxytryptophan.

The enzyme is tryptophan hydroxylase and like all the hydroxylases there is tetrahydrobiopterin which forms hydroxy tetrahydrobiopterin. So, we are getting 5 hydroxytryptophan 5 hydroxytryptophan undergoes decarboxylation with the enzyme decarboxylase like all the decarboxylase the cofactor is PLP or pyridoxal phosphate. So, on decarboxylation there is formation of 5 hydroxytryptamine and that 5 hydroxytryptamine is basically known as serotonin. So, this is how serotonin is formed from tryptophan via by 1 hydroxylation then 1 decarboxylation reaction. Now, the formed serotonin is degraded via the enzyme monoamine oxidase and the product is 5 hydroxy indole acetic acid which is excreted in urine.

So, this is how serotonin is formed and broken down. Now, we are moving on to melatonin synthesis once again to remind melatonin is a hormone whereas, melatonin is a pigment we are talking about melatonin the hormone. So, melatonin hormone is basically related to our circadian rhythm sleep awake sleep cycle pattern is regulated by the secretion of melatonin. Now, melatonin is synthesized in pinealocytes and the major part of melatonin synthesis occurs in the dark phase of the day. So, while it is exposed to the light there is basically proteosomal degradation which causes the melatonin which halt the melatonin synthesis.

Now, for melatonin synthesis the important enzyme is serotonin N acetyltransferase. So, from serotonin which is 5 hydroxy tryptamine the enzyme serotonin N acetyltransferase forms acetyl serotonin which undergoes methylation to form melatonin. So, this is the formation of melatonin hormone. Now, remember mela this is melatonin synthesis melatonin is degraded or catabolized by forming 6 hydroxy melatonin which is conjugated and rather solubilized by sulfation that is adding sulfate group it is solubilized and then it is excreted in urine. So, this is how melatonin is synthesized and degraded or catabolized.

So, here we are to discuss the defective tryptophan metabolism related disorders. These are the disorders I am going to discuss Hartnap's disease, pellagra and carcinoid syndrome. Now, remember pellagra is basically dietary niacin deficiency, but because tryptophan is important precursor for niacin synthesis that is why tryptophan deficiency is the tryptophan deficiency is manifested as pellagra like manifestations. Then Hartnap's disease, Hartnap's disease we already have mentioned this in the the absorption and digestion of protein metabolism the first the very first class of protein metabolism let us discuss a bit in details. So, Hartnap's disease is basically one autosomal recessive variety of disease is an inborn error or inherited disease.

This occurs due to mutation in the gene SLC 6A19 which encodes for the protein B081 which is also known as BOT protein. Now, BOT 1 protein is basically a sodium dependent co transporter which is present in lumens of gut small intestine also in kidney. So, where those proteins are located specifically those are in the apical surface of small intestine as well as the lining of renal tubular cells. So, those are the transporters for whom neutral amino acids. So, what will happen? Neutral the transporter for neutral amino acid is not working in small intestine.

So, absorption of those neutral amino acid will not occur. So, what will happen to those which are present in the diet they will be excluded in stool faces. Then also neutral amino acids which are actually filtered through glomerulus they cannot be reabsorbed in kidney because once again the transporter is absent in renal tubular cells the site for reabsorption. So, what will happen once again? Urinary excretion of those neutral amino acids will be there. Now, amongst the neutral amino acid there is tryptophan.

Now, remember once again tryptophan is the precursor for niacin that is why niacin deficiency will be there and will be manifested as the symptoms of pellagra like skin eruptions as well as neurological symptoms dermatitis ataxia these are the manifestation which are due to niacin deficiency basically. Then because there is urinary excretion of the neutral amino acid a generalized amino acid urea will be present. So, there is excretion of neutral amino acid amino acid in urine also the neutral amino acid in gut they will be excreted through colon. Now, there is colonic bacteria which will act upon those compounds will convert those in endoly compounds which will be conjugated in liver and will be excreted in urine as indican remember the metabolite indican that is excreted in urine in during tryptophan catabolization catabolism. So, indican will be excreted in urine.

So, how this will be diagnosed the commonest diagnosis is a generalized amino acid urea where the amino acids neutral amino acids can be detected via chromatography in urine. Now, proline has a different proline though it is a neutral amino acid it has a

different amino acid transporter. So, basically in the generalized neutral amino acid urea proline will not be there who are will be there valine, serine, phenylalanine, histidine, glutamine, leucine, asparagine all these amino acids along with tryptophan will be detected in urine also indicans will be also present in urine. So, what will be the basic line of treatment because there is neutral amino acid deficiency that should be supplemented as much as possible in diet via providing high protein diet as well as because there is manifestation of niacin deficiency because tryptophan is not there. So, niacin should be supplemented in diet.

So, these are the line of treatment when there is heart naps disease. Now, we are moving on to carcinoid syndrome. Now, carcinoid syndrome is a type of paraneoplastic syndrome. Now, remember what is paraneoplastic syndrome? Paraneoplastic syndrome is the manifestation of malignancies, but majority of the not majority, but mostly the manifestation of malignancies are coming from the malignant cells mass actions or different other functions, but paraneoplastic syndrome those malignant cells secret some biomolecules which exerts their chemical function or endocrine function over body. So, those functions those biomolecular biomolecules related functions which are generating from malignancy they are known as paraneoplastic syndrome.

So, carcinoid syndrome is one such paraneoplastic syndrome and the malignancy here is neuroendocrine tumor mostly argentephenoma tumors of argentephen cells and that malignancy is mostly located in gut. Gut common regions are appendix, stomach, rectum, colon, pancreas as well as apart from gut those are also can be located those tumors occurs in lungs as well. Now, what are the manifestations? Because, excess vasoactive mediators are released apart from serotonin, histamine, collicrenes these are released there are excess gut secretion also excess secretion in bronchioles in the lung variety. So, what happen the manifestations are diarrhea, hot flushes, asthma, wheezing, pain abdomen. So, these are the manifestation due to release of vasoactive mediators like serotonin, histamine, collicrenes like that.

Apart from that once again there is pellagra like symptoms why? Normally tryptophan around 1 percent of the tryptophan are actually converted to serotonin, but here in carcinoid syndrome around 50 to 60 percent tryptophan are actually utilized to form serotonin. So, basically the production of niacin will be decreased causing this pellagra like symptoms. The diagnostic mode is basically imaging via which the tumors to be detected and also in urine 5 hydroxy indole acetic acid can be detected. So, these are the different biologically important substances we have discussed regarding tryptophan metabolism like alanine and acetyl coenzyme acetacetyl coenzyme A these are the catabolism related products. Also formyl group as released as formate which can be utilized as a 1 carbon unit in different metabolism then niacin and nicotinamide adenine

dinucleotides as well as NADP are also important.

Then serotonin melatonin those are also formed and as excretory product of product hydroxy indole acetic acid and indicans these are the important products from tryptophan. So, the key points are tryptophan is a non essential amino acid. So, basically synthesis in body is not there whereas, catabolism is there the main product is kinurine which has relation to different diseases and also other metabolites like serotonin melatonin niacin NAD or NADP these are the different derivatives from tryptophan. These are my references and see you all in the next class. Thank you.