Overview and Integration of Cellular Metabolism

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Lecture 41: Metabolism of Sulphur containing Amino acids (Methionine and Cysteine)

Hello everyone, we are in the lecture series of Overview and Integration of Cellular Metabolism in NPTEL platform. We have started the metabolism of amino acids. In today's class we are going to discuss few sulphur containing amino acids, methionine and cysteine metabolism. So, the concept which will be covered in today's session are related to methionine metabolism where we will discuss how methionine is activated, how that activated methionine takes part in different types of metabolic activities, then the catabolism of methionine and finally, few clinical disorder related to methionine metabolism. Then we will move on to cysteine, how cysteine is synthesized in our body and how it is degraded, then the metabolic roles of cysteine and finally, few clinical conditions related to defective cysteine metabolism. So, let us move on to methionine metabolism.

So, methionine the amino acid is represented as met or M, this is the code how amino acids are represented. Now, methionine is one essential amino acids and remember all the essential amino acids the characteristics is that essential amino acids are not synthesized in our body, those are basically obtained through diet. So, again methionine is not synthesized in our body, it is a sulphur containing amino acid and also glucogenic amino acids. So, glucogenic amino acids somehow contribute to form intermediates which finally, gives rise to glucose on requirement.

Then the major function of methionine is that it acts as methyl group donor in different types of reactions in our body. So, here you can see the structure of methionine. So, this is our sulphur containing amino acid here. Now, how the activated methionine is formed? So, the activated methionine is SAM S adenosyl methionine. So, by the name it is evident that there will be addition of one adenosine molecule to the methionine and where that aden where from that adenosyl group comes it is from ATP.

So, ATP here is the adenosine group adenosyl group donor which with the help of

adenosyl methionine adenosyl transferase forms S adenosyl methionine or SAM. And also here you can see the pyrophosphate as well as the inorganic phosphate is released. Now remember S adenosyl methionine here we are getting one high energy methyl group containing molecule SAM. That is why SAM can donate this methyl group to various reaction where methyl group is required with the help of the enzyme methyl transferase. So, once the methyl group is donated from SAM it forms S adenosyl homocysteine.

S adenosyl homocysteine then undergoes hydrolysis where adenosine is released. So, what we are getting is homocysteine. Now, homocysteine either it can undergo catabolism or it can reform the methionine. Now how the methionine is reformed from homocysteine via methionine synthase. The enzyme here is methionine synthase and with the help of the molecule methyl tetra hydrofolate.

So, basically methyl tetra hydrofolate here transfer its methyl group to homocysteine. So, we are getting methionine whereas, methyl tetra hydrofolate is converted to tetra hydrofolate and these reaction is vitamin B 12 dependent reaction. So, here you can see methionine while forming methionine the methyl group donor is methyl tetra hydrofolate, but the active form of methionine that is S adenosyl methionine is another methyl group donor which is the activated methionine again. So, here you can see that homocysteine can be reutilized to form methionine or it can undergo catabolism, catabolism to form propionyl coenzyme A. So, the end product of methionine catabolism is propionyl coenzyme A and you know the fate of propionyl coenzyme A via methyl malonyl coenzyme A formation it forms succinyl coenzyme A and the succinyl coenzyme A can enter TCA cycle.

So, that is why methionine is called glucogenic amino acid. Now, how this propionyl coenzyme A is formed? So, from methionine we have seen there is formation of homocysteine. Now, homocysteine forms homoserine and cysteine via reacting with serine another amino acid. So, here you can see homocysteine and serine reacts to form cystathione with the help of the enzyme cystathione beta synthase. Then cystathionase basically hydrolyze this cystathione molecule to form cysteine and homoserine.

So, here you can see cysteine the amino acid cysteine is actually formed from during the catabolism of methionine. Then homoserine undergoes deamination to form alpha ketobutyrate here you can see alpha ketobutyrate. Then alpha ketobutyrate undergoes oxidative decarboxylation with the help of the enzyme dehydrogenase releasing one molecule of carbon dioxide forming propionyl coenzyme A. So, this is how propionyl coenzyme A is formed from methionine and during the process we also get cysteine the other sulfur containing amino acid. So, this is the process from methionine we are getting S adenosyl methionine S adenosyl methionine donates is its methyl group in via

methyl transferase enzyme.

What it forms is S adenosyl homocysteine which on hydrolysis releasing the adenosine group it forms the homocysteine homocysteine with react when reacts with serine it forms cystathionine cystathionine then form cysteine and homoserine homoserine undergoes deamination and oxidative decarboxylation to form propionyl coenzyme A and this propionyl coenzyme A takes part in neo glucogenesis. So, what are the different role of methionine? So, definitely methionine is one glucogenic amino acid as well as the source of cysteine we already have discussed. Apart from that the major important role of methionine is as a methyl group donor to different types of reaction here I have mentioned few important one like formation of epinephrine. So, catecholamines are formed from methionine one catecholamine epinephrine is formed from methionine. So, here you can see from norepinephrine with the help of the enzyme methyl transferase and definitely the active methionine that is S adenosyl methionine is the methyl group donor.

So, with the help of the methyl transferase there is formation of epinephrine then creatine is also formed from with the help of methionine. So, creatine is one nitrogen based compound which is adequately present in the skeletal muscles and that is formed from the amino acid glycine and arginine. The detail will be discussed in the respective glycine metabolism, but here you can see from glycine and arginine guanido acetic acid is formed. Guanido acetic acid takes methyl group once again from S adenosyl methionine with the help of the enzyme methyl transferase to form creatine. Then choline is also formed from methionine here the methyl group is donated thrice.

So, from the amino acid serine there is formation of ethanolamine by decarboxylation. Now, this ethanolamine undergoes methylation for 3 times. So, this is one methylation methyl group donor is same. So, here you are getting methyl ethanolamine another methyl group is added forming dimethyl ethanolamine then the third methyl group is added to form trimethyl ethanolamine which is also known as choline. So, choline is also formed with the help of methionine.

Finally, melatonin is formed from serotonin via taking the methyl group from SAM. So, the detailed of melatonin formation will be discussed in tryptophan metabolism because melatonin is a derivative of tryptophan. So, here in short you can see from tryptophan there is formation of 5 hydroxy tryptophan then there is formation of serotonin which is also known as 5 hydroxy tryptamine. So, this is one amine. Now, 5 hydroxy tryptamine forms undergoes acetylation to form n acetyl 5 hydroxy tryptamine sometimes we call it n acetyl serotonin then n acetyl serotonin undergoes methylation to form melatonin.

Now, different polyamines are also formed from via methylation with the help of methionine. Now, this polyamines are important because these are the positively charged compound and those positively charged compound basically binds with negatively charged compound like DNA like the amphipathic membrane lipids phospholipids and they alter their function or the modify or modulate their function. So, these polyamines are also synthesized from with the help of methionine. So, here is the list of different types of trans methylation reaction here you can see formation of creatine n methyl nicotinamide catecholamines like epinephrine metanephrine nor metanephrine then choline anserine melatonin methyl histidine methyl lysine and as well as methylated tRNA are also formed from with the here the methylation reaction occurs where the methyl group donor is S adenosyl methionine. Then few disorders related to methionine metabolism now one such important disease is homocysteine urea.

Now, homocysteine urea can be genetic or can be acquired the genetic or the disorders which are rising from mutations are basically of autosomal recessive conditions. Now, there are different types of homocysteine urea the four types here we have I have presented via the diagram. So, here you can see homocysteine is basically formed from cystathionine with the help of the enzyme cystathionine synthase. Now, this enzyme if defective it causes type 1 homocysteine urea. Next homocysteine forms methionine with the help of the enzyme methionine synthase where the methyl group donor is basically methyl cobalamin or vitamin B 12.

Now, this vitamin B 12 comes from dietary sources. So, if there is dietary deficiency that is type 4. Now, remember type 4 homocysteine urea is not the genetic variant rather the acquired pattern where vitamin B 12 deficiency occurs from dietary deficiency. Now, this vitamin B 12 forms methyl cobalamin with the help of the enzyme cobalamin methyl transferase when this enzyme is defective it causes type 3 homocysteine urea and where lies the type 2. So, you can see the methyl group donor to form methyl cobalamin is methyl tetra hydrofolate.

After donating the methyl group to the cobalamin B 12 it forms tetra hydrofolate and from tetra hydrofolate methyl tetra hydrofolate is formed with the help of one reductase enzyme. When this reductase is deficient it causes type 2 homocysteine urea. So, once again to the different types of homocysteine urea type 1 is due to the deficiency of cystathionine synthase which is directly related to the formation of homocysteine. The other variants of homocysteine urea are basically where methionine synthesis from homocysteine is defective. The type 1 is due to the deficiency of the reductase enzyme which is forming methyl tetra hydrofolate.

Type 3 is defect in formation of methyl cobalamin where the defect lies in the enzyme

cobalamin methyl transferase and finally, the type 4 pattern that is the acquired homocysteine urea which is due to dietary deficiency of vitamin B 12. Now, for all the homocysteine ureas the normal homocysteine level is 5 to 15 micro mole per liter. The autosomal recessive pattern the increase is around 50 to 100 times whereas, in case of the acquired pattern or the dietary deficiency the defect the homocysteine level is not much raised. Now what are the manifestation of homocysteine urea? Mostly the initial years like initial 1 to 2 years the babies remain asymptomatic till around 3 to 5 years where there is adequate or enough accumulation of homocysteine or rather enough deficiency of methionine manifestation of homocysteine urea occurs. The initial or the very first detected manifestation of homocysteine urea is abnormality in vision due to ectopia lentis.

Now what is ectopia lentis? It is basically the displacement of eye lens to the posterior chamber of eye for that there is disorder in vision. Then there is mental retardation bones are weak due to osteoporosis and also there is chances of thromboembolism due to coronary artery disease or cerebral strokes. Now why there is increased risk of thromboembolism due to homocysteine urea we will discuss in further slides. So, what are the basic abnormalities in homocysteine urea? So, as we are talking about homocysteine urea it is evident that there will be excretion of homocysteine in urine as well as what we will get in blood accumulation of homocysteine also methionine can be increased in blood. Then we are going to discuss the screening and diagnosis of homocysteine urea screening is done by cyanide nitroprusside test.

So, what is the function of cyanide here? One when treated with cyanide it basically reduces the disulfide bond present in homocysteine to produce homocysteine. Remember the sulphur containing amino acid cysteine or cysteine here it contains the sulphide will group free sulphide will group. Now the free sulphide will group has the tendency to get oxidized. So, basically what happens when oxidized it forms the 2 molecules of cysteine are actually joined to form cysteine. So, here please notice the spelling it is t e i n e whereas, cysteine is only t i n e.

So, basically cysteine is the di amino acid whereas, homocysteine is the single amino acid we are talking here. So, once the disulfide bond is reduced homocysteine is also forming homocysteine. Now the cysteine reacts with the nitroprusside and forms a red colour. Now the problem is if there is cysteine itself only cysteine not homocysteine only cysteine is present in urine that can be misleading because homocysteine as well as cysteine they both will react with nitroprusside. So, how to differentiate with the help of the test silver nitroprusside test here we have talked about cyanide nitroprusside test and this is silver nitroprusside test where there is no cyanide.

So, basically in silver nitroprusside the sulfhydryl group will not be reduced whereas, cysteines will form red colour. So, what will happen homocysteine will not react to the silver nitroprusside or will not give rise to red colour while treated by silver nitroprusside. So, how to discriminate cysteineuria and homocysteineuria by doing both the test both cyanide nitroprusside test as well as silver nitroprusside test. So, what will be the effect there will be positive cyanide nitroprusside test, but negative silver nitroprusside test in case of homocysteineuria, but remember this is only screening test what is the confirmatory test? Why by first detecting the homocysteine level in plasma and also measuring the activity of cystathionine synthase enzyme. So, these are the confirmatory or diagnostic test for homocysteineuria.

So, the defect in congenital or autosomal recessive patterns are related to the different enzyme deficiencies whereas, acquired homocystinemia's or the increased level of homocysteine in blood are mostly due to either nutritional deficiency like cobalamin folic acid pyridoxine which were needed for synthesis of homocysteine or to methionine formation. Then there can be metabolic defects like chronic renal disease or hypothyroidism and also few drugs like folate antagonist or vitamin B 12 antagonist or pyridoxine antagonist . They actually produce a scenario like folate or vitamin B 12 or pyridoxine deficiencies. Then estrogen antagonist also causes hyper homocystinemia, nitric acid antagonist they also causes hyper homocystinemia. So, all these vitamins remember cobalamin folic acids or pyridoxine they were required if you remember from homocysteine to methionine formation all these vitamins were required and their deficiency will hampered the methionine synthesis for from homocysteine which will gives rise to increase homocysteine level in blood causing hyper homocystinemia.

Now remember hyper homocystinemia of maternal pattern can gives rise to neural tube defects in fetus. So, very high dose of folic acid is advised in pregnancy. So, this is one important question why high dose of folic acid is advised in pregnancy because maternal hyper homocystinemia can affect fetus causing neural tube defects. Now why hyper homocystinemia or increased homocysteine is a risk factor for coronary artery disease because homocysteines are considered as prothromboembolic molecules. Now how the coronary artery disease is propagated via homocysteine by defective collagen synthesis.

Now how this collagen synthesis is affected by homocysteine. So, I am not going much in detail with the collagen synthesis, but I want to highlight one very important enzyme that is lysyl oxidase enzyme which is required for cross linking and maturation of collagen. So, this lysyl oxidase enzyme required for formation of hydroxyl lysine and that hydroxyl lysine is important for collagen cross linking. Now copper here acts as a cofactor for the proper action of lysyl oxidase. Now this lysyl oxidase enzymatic activity is basically hampered by homocysteine.

How the copper ion forms a complex with homocysteine and that copper ion is not now available for the action of lysyl oxidase. So, basically what is hampered collagen cross linking. Similarly homocysteine and homocysteine both react with lysyl semi aldehyde. So, lysyl semi aldehyde is a product of lysine via oxidative de deamination. This semi aldehyde is also important for formation of collagen fiber cross linking via formation of sheafs base.

So, in both the cases collagen cross linking as well as collagen maturation is affected. So, what is actually affected the vascular walls formation of vascular walls as well as remodeling that predisposes to thromboembolic risks. Apart from this homocysteine thiolactone a free radical generated from homocysteine also acts as pro thrombotic molecule. Basically what it does this thiolactone thiolates the LDL particle. Now this thiolated or modified LDLs have the tendency to aggregate and block the vessels causing coronary artery disease.

Next we will move on to cysteine metabolism. Once again cysteine is another sulfur containing amino acid which is also glucogenic, but remember cysteine is a non essential amino acid. So, basically cysteine can be formed in our body and we have already discussed that cysteine is actually formed from methionine. Now as I have told you already that cysteine is the di amino acid form of cysteine once again concentrate on the spelling t e i n e is the single amino acid that is single amino acid whereas, cysteine is the di amino acid. So, here you can see cysteine this is one molecule of cysteine and this is another molecule of cysteine they both form together cysteine the di amino acid. So, once treated with the reductase enzyme the sulfhydryl groups are actually reduced to form the cysteine from cysteine.

So, basically we have already discussed that cysteine is actually formed from methionine, methionine via formation of s adenosyl methionine the methyl group donated form is homocysteine. Then homocysteine forms the cystathion during the catabolism to form cysteine. Now there is one effect which called cysteine sparing effect cysteine imparts one sparing action on methionine. Now what is that there is a requirement of total sulfur containing amino acid in our body which consist of both cysteine requirement as well as methionine requirement. Now if dietary supply of cysteine is high it will basically cut down the requirement of methionine the minimum obligatory methionine requirement is reduced.

So, that is called the cysteine sparing effect on methionine. So, we are coming to the metabolic role of cysteine. So, as we have already discussed glucogenic amino acid it is. So, here you can see this is the very common chart we have continuously discussed

throughout the session of amino acid metabolism that methionine and cysteine can contribute to TCA cycle. Methionine contribute to TCA cycle via formation of succinyl coenzyme A whereas, cysteine forms pyruvate during its catabolism.

Pyruvate can be formed from cysteine via two different reaction type series of reaction. So, here you can see in this pathway there is transamination to form 3 mercapto pyruvate which finally, forms pyruvate via donating the sulfur as H 2 S. The other variety which involves the enzyme dioxygenase is the major variety. So, here you can see there is formation of cysteine sulfenate that forms sulfino pyruvate finally, pyruvate is formed.

So, this is how pyruvate is formed from cysteine. So, once again remember methionine and cysteine both the sulfur containing amino acid can contribute to TCA cycle that is why they are glucogenic amino acid. Cysteine forms pyruvate whereas, methionine forms succinyl coenzyme A. Then moving to the next very important function cysteine is required for formation of glutathione we already have discussed that glutathione is a tri the glutathione is a molecule which contains 3 amino acids. Now, this synthesis will be discussed in the glycine metabolism, but remember the 3 amino acid is glutamine I already have told you again I am reminding that the 3 amino acids are glutamic acid then glycine and our very cysteine. Now, this glutathione is important with regard to multiple functions the detail function once again will be discussed in glycine metabolism, but to remember glutathione is required for amino acid absorption I have already discussed the Meister cycle in digestion and absorption of protein.

Then glutathione is important for various reduction related reaction and via these reduction based reaction there are various enzymes which remains in active reduced state. Then the integrity of RBC membrane is also maintained with the reducing property of glutathione also this reducing property is important for formation of hemoglobin from methylated hemoglobin or meth hemoglobin. Then detoxification reaction where glutathione is important for conjugation with the help of the enzyme glutathione S transferase. So, via detoxification glutathione from soluble products for clearing of this toxins from our body. Next another important product is taurine which is formed from cysteine remember taurine was important with formation of bile acids taurocolic acids or taurokenno deoxycolic acids both are formed from taurine.

Now, this taurine is formed from cysteine here you can see cysteine from cystite acid which undergoes decarboxylation to form taurine. Then there are various enzyme catalysts catalysts basically enzymes which contains sulfide groups they are mostly based on cysteine and their sulfide groups remains in reduced form with the help of the cysteine molecule. Then we are going to discuss few disorders related to cysteine metabolism one is cystathione urea remember that is cystathione urea not cysteine urea

this is cystathione urea. So, here we are talking about cystathione excretion in urine. So, once again to remind cystathione is formed from homocysteine with the enzyme cystathione synthase.

Now, cystathione synthase if defective that causes homocysteine urea because cystathione is not formed. So, what is accumulated is homocysteine whereas, cystathione urea is related to cystathione in accumulation and that is because cystathione cannot be degraded to homoserine due to the defect in in the enzyme cystathionase. So, cystathione urea is related to cystathionase enzyme deficiency once again it is a recessive pattern inheritance manifested as severe mental retardation what you will get is increased concentration of cystathionine in urine and blood. So, what you need to do? Methionine containing diet should be restricted and alternatively what should be supplemented cysteine because these degradation is hampered.

So, there will be cysteine deficiency as well. So, cysteine will be should be supplemented then pyridoxine as well as folic acid these vitamins should be supplemented in diet. Then we are coming to cysteine urea. So, here cysteine will be released or excreted in urine and the defect is in different transporters of amino acids. Remember these type of transporters these amino acid transporters they transport cysteine as well as few other amino acids like lysine ornithine or also arginine. So, commonly this condition is known as cysteine lysine urea both cysteine and lysine can be detected in urine.

So, that is known as cysteine urea is also known as cysteine lysine urea it is also of autosomal recessive pattern what you will get because the cysteine lysines are excreted in urine cysteine crystals will be deposited in kidney forms calculus as well as crystals will be excreted in urine and in severe cases this crystals when deposited will cause renal insufficiency. Once again the screening is cyanide nitroprusside test if you remember that nitroprusside used to form red color in presence of cysteine, but the specific amino acid urea what specific amino acid is present in urine whether that is cysteine or lysine or ornithine or arginine can be detected by chromatography. So, what is the treatment once again fluid should be taken adequately. So, that the urinary excretion can be increased where the excretion of the cysteine as well as the small calculi as well as the small crystal can be increased then alkalinization of urine it causes the it basically solubilizes the crystal and also the penicillamine forms complexes and causes enhances the release of the crystals of cysteine. Then cysteinosis this is of autosomal recessive variety of disease and also familial disorder.

So, in a family these genetic type of disease can be seen in the related members. So, cysteinosis is basically accumulation of cysteine crystals in different tissues mostly what

is affected is lysosome because the lysosomal transporter the membrane transporter of lysosome is defective and which organs are affected livers, spleen, bone marrow they are affected. So, cysteine crystals are accumulated in livers, spleen, bone marrow as well as this crystals can be detected in white blood cells. What will happen a generalized amino acid urea can be seen and those when deposited in kidney can cause renal failure. Once again the treatment is to increase the urinary output via adequate fluid intake and also alkalinization of urine causing solubilization of the crystal and also administration of deep penicillamine.

So, what are the key points from this session we have discussed methionine metabolism. In methionine metabolism what you need to remember is the active form F adenosyl methionine which acts as the major methyl group donor. Then cysteine is formed from methionine and also cysteine is the diamine acid cysteine is the single amino acid here it acts as a sulphur donor rather sulphide will group here. Then glutathione and torine are the two important product which are formed from cysteine and we also have discussed few disorders like homocysteine urea, cysteine urea and cysteinosis. These are my references. Thank you all see you in the next class.