Overview and Integration of Cellular Metabolism

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Lecture 43: Metabolism of Serine, Threonine and Alanine

Hello everyone, welcome to your lecture series on Overview and Integration of Cellular Metabolism. We are in lecture number 43 and we will be covering the metabolism of amino acids serine, threonine and alanine. The concepts that we will be covering are the chemistry of these amino acids, the amino acid metabolism, how serine participates in the one carbon metabolism, we will be also looking similarly into threonine and alanine, we will look how all these metabolisms are interrelated and how these amino acids are tied in a common metabolic fate alright. So, let us first start with serine. Serine is a non-essential and glucogenic amino acids. By now you already know these concepts that whenever an amino acid is non-essential means we need to consume it in diet, we do not need to consume it in that and it is actually synthesized in the body.

Whenever the amino acid is essential we need to consume it in diet. So, serine will be synthesized in body from sources right and glucogenic means ultimately the metabolic fate is entry into the carbohydrate metabolism. Very important statement over here serine and glycine are interconvertible, if we have one we can have the others. Not only that serine is also synthesized from intermediates of glycolysis.

So right away we know two sources, one is glycine and another is the intermediates of glycolysis. Let us look into the overview of serine metabolism. As always I say it may look daunting to start with, but when we are done with discussion of serine we would have covered all of these pathways that look like a spider right. So the enzyme serine hydroxy methyl transferase, we already know about this. How we have read this in glycine synthesis that is serine was being synthesized I mean serine was used in synthesis of glycine.

The reverse and I told you the enzyme is reversible the enzyme requires pyridoxal phosphate that is vitamin B6. So, the same enzyme is now actually acting as a source of serine, how the source is actually glycine and from glycine serine is produced. Of course, the methylene tetrahydrofolate will be converted to tetrahydrofolate if the

reaction goes in this way alright. So there is an involvement of an one carbon over here. So this is the reaction by which glycine and serine are interconvertible if the body needs more glycine, serine will be converted to glycine if the body needs more serine, glycine will be converted to serine and there will be an exchange of a one carbon moiety in the form of methylene group 2 tetrahydrofolate.

Very important for MCQ remember the coenzyme is pyridoxal phosphate or active form of vitamin B6. Next synthesis from intermediates of glycolysis. Now we already are familiar with what are the intermediates of glycolysis right. So, you can see 3 phosphoglycerate is an intermediate of glycolysis. Now there have been found in animals and few plants and lower animals that the production of serine can happen from both varieties that is a pathway in which the intermediates are non phosphorylated that means from 3 phosphoglycerate just at the beginning an inorganic phosphate is removed by the enzyme phosphatase right.

And thereafter by dehydrogenation and transamination glycine can be formed. Similarly from the phosphatid or phosphorylated intermediate even serine can be formed by the action of these enzymes 4, 5 and 6. So, first dehydrogenase acts on it, second transaminase acts on it and again ultimately the phosphate group is removed by phosphatase. So, in this pathway phosphate is removed first, in this pathway phosphate is removed later, but the core mechanism remains the same dehydrogenation followed by transamination. OG stands for oxoglutarate which is nothing, but alpha ketoglutarate 2 oxoglutarate is alpha ketoglutarate.

So, this is occurring inside in the cytoplasm and this is occurring in the chloroplasts in plants right. So, needless to say this are this is the very important source of serine production and rare diseases which are very actually not very common of serine deficiency results from deficiency of these enzymes either these hydrogenases or phosphatase or transaminases. Deficiency of any one of these three enzymes or two or more of these three enzymes can result in serine deficiency alright. It is uncommon, but it is possible mind it phosphatase dehydrogenase and transaminase. We next move on to the conversion of serine to pyruvate.

Mind it this reaction is also familiar, how we discussed how glycine leads to formation of pyruvate the glucosinic fate of glycine is covered through serine. So, glycine was being converted to serine by the enzyme serine hydroxy methyl transfer HMT, the same figure has been coated here. So, serine by the action of a dehydratase is first converted to an amino acid which loses ammonia to form pyruvate. And we already know pyruvate is an entry portal into the carbohydrate metabolism and it can lead to production of glucose via gluconeogenesis. Not only that pyruvate can be transaminated to form alanine.

So, in this slide we can see how serine has got fate by which it can convert into alanine another amino acid and this reaction also reversible mind it alanine can also be converted to pyruvate. So, serine to pyruvate, pyruvate to glucose and pyruvate to alanine ok. So, serine to alanine is possible and serine to glucose is also possible alright. So, next we move on to choline synthesis a very important product that is synthesized from serine. How serine is first decarboxylated, decarboxylase enzyme needs again vitamin B6 that is pyridoxal phosphate as a cofactor.

What happens? Ethanolamine is produced. Ethanolamine is actually a precursor for choline synthesis. Have you heard the names choline, ethanolamine anywhere? Of course, you have heard when we are discussing synthesis of sphingolipids that chapter alright. If you have forgotten I am not sure you have it is very important that you give that chapter a recall alright. You can pause this video, you can go back watch it and then come back right here to catch up where we left in that chapter right, but I am sure you have must have revised your lessons.

So, choline then is converted to acetylcholine which is an important neurotransmitter. So, let us see how it happens from choline actually 3 1 carbon methyl group can be removed. So, let us see what is happening. Serine is first decarboxylated to form ethanolamine ok. It loses one carbon dioxide by the help of serine decarboxylase which requires a PLP or pyridoxal phosphate.

Then there is methyl transfer reaction not 1 not 2, but 3 times methyl group are transferred to ethanolamine which leads to the formation of trimethylmethanolamine or choline. We will be seeing this reaction again in detail. Once choline is formed you can see there are 3 methyl group and that can actually readily donate these methyl groups into the reaction whenever it is required and that donation of methyl group is known as 1 carbon metabolism which will be seeing very soon. Now this choline once it is formed it can actually combine with acetyl coenzyme A. The enzyme is choline acetyltransferase to form acetylcholine which is a very important neurotransmitter alright.

And of course, coenzyme A is also generated in this reaction. So, acetyl coenzyme acetyl group goes there and coenzyme A is formed. So, as I was discussing this is the entire reaction how serine and glycine participates in the 1 carbon metabolism. You see glycine to serine conversion by serine hydroxy methyltransferase SHMT SHMT alright. Next serine by decarboxylation from ethanolamine and methyl groups are being added I already told you who is the methyl group donor S adenosyl methionine.

Remember SAM is the most common activated methyl is the most common methyl

donor. So, 3 times methyl group can be donated to ethanolamine. So, first it forms methyl, second it forms dimethyl, second it is form trimethyl, thirdly which is nothing but choline. Now this choline actually can be oxidized you see CH2H is an alcohol group whenever it is oxidized it forms trimethyl glycine whose common name is betaine very important this is an oxidation reaction this is an oxidation reaction alright. Now this betaine can actually lose or donate 1 carbon or methyl group into the reaction that needs 1 carbon moiety.

So, thus betaine can participate in 1 carbon reaction as well. So, when betaine loses methyl group say first it becomes dimethyl glycine, then it becomes methyl glycine which is also known as sarcosine and again another 1 carbon atom 1 carbon is lost and then it forms glycine and the whole cycle is completed. Mind it this is not the only reaction where 1 carbon metabolism is taking place I will be showing you more, but this is a very important portal by which both serine and glycine takes part in the 1 carbon metabolism and this is also known as glycine serine choline cycle often it is also termed as glycine or choline betaine cycle whatever it is mind it 1 carbon metabolism are being exchanged in every steps. Next you have already read this because metabolism of sulphur containing amino acids have been done.

So, cysteine synthesis. So, the entire molecule of serine is actually absorbed in I mean utilized in synthesis of cysteine except the sulphur molecule which comes from homocysteine alright. So, very important mind it and you already know serine is also used in synthesis of cysteine right. I am not discussing the enzymes because you are supposed to answer by now. A very important deviation you can see serine and cysteine just differs by a sulphur in serine is a hydroxyl group containing amino acid OH cysteine contains sulphur the sulphur comes from homocysteine. A very closely related is selenocysteine where this oxen is replaced by selenium.

Selenocysteine is actually a the 21st amino acid I told you there are 20 amino acids selenocysteine and pyrolysine are 21st and 22nd amino acid they have been discovered much later in the field right. So, for multiple choice question purposes you should know name of these following enzymes where selenocysteine participates in their active site. The name of these enzymes are thioredoxin reductase glutathione peroxidase diiodinase and selenoprotein P. The role you are not supposed to know this the roles of each and every enzyme right now, but you will need it eventually. So, I suggest that you can give it a read from your text book of choice what these enzyme does, but this enzyme has already been discussed when we are discussing about tyrosine metallism and thyroid hormone synthesis right and glutathione peroxidase you already know free radical scavenging.

So, what happens in if selenium is deficient the concentration of these enzymes fall and the role they are playing will be hampered as simple as that for you you only need to know serine is utilized in synthesis of selenocysteine in a similar way how it synthesizes cysteine all right. So, here is a broader view of the one carbon metabolism cycle. You can actually pause this slide you can take a screenshot or you can make your hand drawn notes, but it is very important that you are able to join the bits together by now. One part is still unexplored you can see purine synthesis and thymidylate synthesis we will be discussing all of them in nucleotide metabolism, but other than that the rest you already know you all by now you have seen that folic acid in the form of tetrahydrofolate, methyl tetrahydrofolate, methyl tetrhydrofolate are constantly exchanging one carbon from each other and they have been acting as a cofactin multiple important enzyme. In our case we have seen in serine hydroxy methyl transfer which converts glycine to serine all right and that where a methyl group is being transferred we already know that the most common methyl donor is methionine to homocysteine or whenever there is an acceptance of methyl group homocysteine is converted to methionine.

So, this way we can see choline gives rise to butane, butane loses a methyl group that methyl group is accepted by homocysteine to form methionine and in turn methionine as acyl adenosyl methionine is donating a methyl group to glycine to form sarcosine methyl transferase again. So, this whole thing goes on and on and moreover we already know from sulfur containing amino acid metabolism classes that homocysteine also forms cystathionine which ultimately leads to formation of cysteine right and how from cysteine compounds like glutathione and torine are synthesized all right. So, if you get a question of one carbon metabolism any long question you should touch the metabolism of serine, glycine, choline as well as purine metabolism as well as folic acid in the answer ok. So, that being said we now move on to the next part of the lecture which is a minor deviation because we have discussed about the molecule sarcosine. What is sarcosine? Sarcosine is nothing, but methyl glycine right.

So, this can actually lose the methyl group and can form glycine. So, sarcosine actually is a good source of glycine whenever required and in this figure we can see how the forms of glycine first it gets converted to serine, ethylene, choline, betaine that we already know from our previous diagram and this glycine is being used in synthesis of multiple compound that you already read in the previous class right. So, creatine is one of them you know the most important thing to know is you may get question about sarcosinemia. It is an autosomal recessive disorder which is produced by deficiency of the enzyme sarcosine dehydrogenase in the gene which is located in the 9 q 33 to q 34 ok gene locus very important and it causes build up of sarcosine in blood and cysteine sarcosines system is I mean the system sarcosine level is remains high and it is excreted in urine right. A very familiar slide I will not be going into the details because I have

already discussed that serine how by various steps it was leading to the formation of sphingosine and sphingomyelin ceramides.

If you want to know the details you can go back to the class on sphingolipid metabolism not only this, this slide is also very common where serine was participate this is phosphatidic acid and serine was participating leading to the formation of phosphatidyl serine ok. So, basically what happens the hydroxyl group of serine serves as a carrier of phosphate which is involved in regulation of many enzyme activities right. So, what is the role of serine in serine component in protein right, protein serine is a very important part of protein. So, what happens it is used to esterify phosphate groups in multiple protein for example, case C very important serine helps in phosphorylation right. We already know by the regulation of enzyme activity you have read that certain enzymes are activated in phosphorylated form, certain enzymes are activated in dephosphorylated form.

The anabolic enzymes are activated in dephosphorylated the catabolic enzymes are activated in phosphorylation. So, this phosphorylation and dephosphorylation that is the covalent mechanism we have read in the very second class is actually important mechanism of regulation of enzyme activity right and whenever phosphorylation happens it helps it is done by the various kinases enzyme and protein kinases are actually serine and threonine kinase both enzyme amino acids will be discussing in today's class. So, what happens the carbohydrate groups are usually attached to the hydroxyl group of serine and threonine residues of protein in whenever glycoprotein is from that is a combination of carbohydrate and protein it is known as glycoprotein and those carbohydrate residues prefer to get attached to the hydroxyl residues of these amino acids serine and threonine. Not only that it is found in numerous enzyme serine for example, serine protease that breaks down protein for example, trypsin coagulation factors serine is present as an active protein in their catalytic residue alright. So, whenever you look into the active site serine is found.

So, we look into the overview of serine metabolism and now we can see all the things have been covered how serine plays a role in protein, how it forms glucose by pyruvate, how it forms glycine, alanine, cysteine already discussed, how it plays a role in one carbon metabolism, how it from singamiline, phosphatidyl serine, selenocysteine, ethanolamine and choline right. So, all pieces of the puzzle have been covered. So, we move on to our next amino acid that is threonine. Now this is the structure of threonine you already notice the structure of serine there was an OH group in threonine also there is presence of an OH group. Threonine is an essential amino acid alright it is glucogenic right, but it does not participate in transamination very important MCQ question.

Threonine is also carrier of a phosphate group in protein structure we just discussed the same thing in the earlier slide. Just like serine the OH group of threonine residue in the protein serves as a site for phosphorylation. Whenever the there is serine and threonine those sites will be selectively phosphorylated. And this OH group also serves as a combining or anchoring area for carbohydrates whenever glycoprotein is being formed similarly like serine. So, looking at threonine what happens what are the metabolic reaction which threonine participates? Threonine is acted upon by dehydrogenase it can be acted upon by dehydrogenase to form alpha keto butyrate alright.

And this alpha keto butyrate can be acted upon by another dehydrogenase to form propionyl coenzyme. Where have you read propionyl coenzyme? Oxidation beta oxidation of odd chain fatty acids right very important. What is the fate of propionyl coA? You should know by now that propionyl coA this is again a revision what was taught in fatty acid oxidation class. Propionyl coA is acted upon by a carboxylase enzyme whose cofactor is biotin it forms D-methylmanilin coA it undergoes racemization to form L-methylmanilin coA by racemase enzyme L-methylmanilin coA undergoes an intramolecular adjustment by the enzyme methylmalonyl coA mutase and it forms succinyl coA. Succinyl coA is an intermediate of TCA cycle which can now enter into the carbohydrate metabolism.

So, thus threonine is converted to succinyl coenzyme A. Have you heard of methylmalonic aciduria? If you do not know this, this is caused due to deficiency of this enzyme methylmalonyl coA mutase, but you must have heard because it has been taught in beta oxidation of fatty acid that was discussed that methylmalonyl coA deficiency leads to methylmalonyl aciduria leads to the presence of excess amount of methylmalonic acid and ketone bodies in urine symptoms are mental retardation, ketosis, hypotonia all right. How we can treat it? We can give excess amount of vitamin B12 because this enzyme acts I mean needs vitamin B12 as a coenzyme. So, thus methylmalonic aciduria can be treated. This is the fate of propionyl coA which is common in the metabolism of many amino acids ok of which now we are discussing threonine or chain fatty acids have already been discussed methylene has been discussed we will be discussing valine and isoleucine in future class.

Next familiar reaction again in the synthesis of glycine we have already read that threonine by the action of threonine aldolase is converted to glycine and acetaldehyde it cleaves threonine. So, this is how threonine is converted to glycine all right a 4 carbon is cleaved into two 2 carbon compounds. Now very important threonine to acetyl coenzyme A. In the previous reaction we saw how threonine was being acted upon by a dehydratase. Here it is first acted upon by a dehydrogenase NAD dependent dehydrogenase by which it forms 2 amino 3 keto butyrate is different from the previous

one alpha keto butyrate here it is 2 amino 3 keto butyrate this 2 amino 3 keto butyrate by the action of a ligase enzyme is converted to glycine all right.

Now coenzyme A enters and acetyl coenzyme A is produced all right. So, this is very important because this acetyl coenzyme A served as a precursor for production of ketone bodies ok. So, thus threonine actually help is plays a role in ketogenicity ok. We already know how it becomes glucose by propionyl CoA to succinyl CoA right. So, there is a minor pathway in which that 3 2 amino 3 keto butyrate can actually undergo spontaneous decarboxylation to amino acetone that amino acetone can be acted upon by an enzyme monoamine oxidase or MAO which leads to formation of methylglyoxal ok very unique compound right.

This methylglyoxal you see spontaneous decarboxylation of 2 amino 3 keto butyrate is a deviation from the thing that is happening in humans in human is does not happen. This methylglyoxal has got its own pathway from which basically pyruvate lactate etcetera can be formed. Mind it there is no ATP production in this pathway and it is an alternate pathway of glycolysis you can see from fructose 1 6 bisphosphate both glycerol dehydrate 3 phosphate and dihydroxy acetone phosphate are formed. Normally glycerol dehydrate 3 phosphate can undergo glycolysis to form pyruvate. But whenever there is an excess phosphate in the system it triggers this pathway where it is the methylglyoxal pathway takes off and it converts the methylglyoxal or this intermediate of glycolysis to pyruvate without the production of ATP all right.

Why it happens? It has been hypothesized it happens to save inorganic phosphate all right whenever there is phosphate the need of phosphate this pathway is triggered. There have been experiment by which the scientists have been able to trigger this pathway by adding phosphate to the media, but this is still experimental stage and it happens in lower animals prokaryotes for humans this is not relevant, but still you should know it as an alternative pathway of glycolysis in prokaryotes. So, this is the overview of threonine metabolism. Threonine is converted to protein it can be converted to alpha keto butyrate and then succinyl coA it can be converted to acetyl coenzyme A it can be converted to serine and then pyruvate it can be converted to glycine all right and it can also be converted to aminoacetone in prokaryotes and all these intermediates like methylglyoxal pyruvate and lactate right. Lastly we are left with this simple very simple aminoacy that is alanine right.

So, glycine this carbon skeleton is only H alanine one additional methyl group. So, alanine is a non-essential glucogenic amino acid you already know by now how we can get alanine in the body it can be synthesized by transamination of pyruvate right. So, thus it is glucogenic. So, alanine can also form pyruvate right the reverse reaction can

also happen this is the enzyme alanine transaminase or ALT we already know that from our previous class of transamination this is the reaction this is actually reversible reaction that can go in both way and the cofactor is pyridoxal phosphate. There is an applied clinical importance I told you that it is raised in liver diseases ok.

Now, we also know about glucose alanine cycle we have extensively discussed it in ammonia metabolism that how alanine is the most important amino acid that takes part in nitrogen transport in peripheral tissue along with glutamine alright. Another condition like starvation this becomes very significant right. So, this diagram that was discussed in ammonia metabolism is also relevant in alanine metabolism. Now there is a variant of alanine there is a beta alanine where the amino group is attached to the beta carbon. It is important in metabolism of pyrimidine and synthesis of coenzyme A, but still we are discussing it we are mentioning it now because we are discussing alanine.

So, this is the variant of alanine you can see this is the structure of L-alanine normally and here where the amino group is attached to the alpha carbon here it is attached to the beta carbon ok. So, now let us discuss the interrelationship of amino acids how amino acids are interrelated you can see serine ok this diagram might be might appear too much to start with. So, let us break it down. So, we have already seen how threonine is converted to alpha keto butyrate then by the action of lysosome it is converted to glycine and then glycine by the action of SHMT is converted to serine. There is an one carbon metabolism going on over here which also acts as a acceptor and donor of electron in the glycine cleavage system mind it H protein, L protein and T protein very important.

So, this is how these three are related. Going down not only serine cysteine can be converted to pyruvate already discussed in metabolism of sulphur content amino acid and you know tryptophan can be converted to alanine and alanine can also be converted to pyruvate by a transamination. So, these three amino acid metabolism are very interestingly interrelated right not only that we can see this is another diagram how amino acids that have been discussed till now are forming succinyl coenzyme. So, methionine we already know via homocysteine is converted to alpha keto butyrate we already discussed in the first reaction the theionine is also converted to alpha keto butyrate by losing water and ammonia by the action of a dehydratase enzyme that also needs pyroxyl phosphate as a cofactor ok. So, once alpha keto butyrate is formed again by the action of dehydrogenase we already discussed it from stropionyl coenzyme A and then same pathway that was discussed in lipid metabolism propionyl coenzyme A to methylmalonyl CoA methylmalonyl CoA mutase to succinyl CoA.

Alright. So, this is the whole picture how methionine and theionine are connected and they give rise to succinyl CoA. More players will be added when we discuss more

amino acids in the next class alright. So, this is how our today's players that is the amino acid are located we discussed alanine how it converts to pyruvate we discussed serine how by the same pathway it can be converted to pyruvate we discussed theionine how it can be converted to succinyl CoA and we also discussed theionine over here that can be converted to acetyl coenzyme A. So, I told you this is the final common metabolic pathway of all carbon skeleton how the amino acids are converted and goes into the either glucogenic or ketogenic pathway. So, to conclude the lecture has covered the chemistry of serine the overview of serine metabolism how it plays a role in one carbon metabolism we have also discussed the overview of alanine and theionine metabolism how all the amino acids are related via integrated reaction and what is their common metabolic fate either glucogenic or ketogenic these are my references and I thank you all for your patient attention.