Overview and Integration of Cellular Metabolism

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Lecture 42: Metabolism of Glycine and its disorders

Hello everyone, we are in our lecture series of overview and integration of cellular metabolism, we are continuing with individual amino acid metabolism and their disorders. And in today's class we will be discussing metabolism of glycine, very important we will be covering the chemistry of glycine, we will be discussing the overview of glycine metabolism, how glycine is synthesized, how it is degraded, what are the specialized products from glycine and the various disorders of glycine metabolism. So, it is a huge daunting task. So buckle up, gather your own notebooks and we will try to cover the entire topic in this class, alright. So glycine as you all know it is a very simple amino acid with only hydrogen in place in place of the carbon skeleton. It is a non-essential amino acid means it can be synthesized in our body, metabolically it is glucogenic amino acid ultimately it will enter into the TCA cycle by any means possible, right.

It is involved in one carbon metabolism, it is present in interior of many structural protein for example, collagen every third amino acid is glycine MCQ question and multiple specialized products are produced from glycine such as hemes, purines, creatinine etcetera will be discussing it all. So this is the overview of glycine metabolism which might seem very daunting to start with because there are so many things, right. But as we progress we will again revisit the slide at the end of this class and where we will see we will pick off every possibility that has been shown over here. Now first starting with the synthesis of glycine it is done from four sources, alright.

Serine, threonine, carbon dioxide and ammonia directly by capturing of carbon dioxide one carbon and glyoxylate. So let us see. From serine it is converted to glycine by the enzyme serine hydroxy methyl transferase. Serine is another amino acid, it acts as a source to produce glycine. Now what happens? The beta carbon is removed, alright, this CH2H is removed and it is donated to this tetrahydrofolic acid and this enters the one carbon pool.

So thus by this step glycine is actually participating in one carbon metabolism. Mind this reaction is also reversible, ok. It goes both ways. So glycine can also be converted to serine. So exchange of one carbon thus happens and by doing so the alpha carbon of serine becomes the alpha carbon of glycine, alright.

Next source is production from threonine. Threonine is also another amino acid, it is cleaved by the enzyme threonine aldolase and it gives rise to glycine and acetaldehyde, alright, threonine aldolase, very important MCQ. Third source that is production from carbon dioxide and ammonia, right and another one carbon unit. So how it is done? It is done through the one carbon unit, again it is donated by N5N10, methylene tetrahydrofolic acid, it is converted to tetrahydrofolic acid. The whole enzyme system is actually glycine synthase complex, alright and it directly converts carbon dioxide and ammonia to glycine, alright.

This is NADH dependent. So NADH plus H plus is converted to NAD plus, it is a multi enzyme complex. This is also reversible and the reverse is no process is known as glycine cleavage system which we will be discussing very soon, alright. So this is the third source of glycine production and the fourth source is from glyoxalate. How it is produced from glyoxalate? By the simple process of transaminations.

So glyoxalate along with alanine is acted upon by a transaminase enzyme or amino transferase enzyme to produce pyruvate and glycine. However this reaction strongly favours synthesis of glycine. It means whenever glyoxalate is present in body, it tends to form glycine. You need to remember this step and also the previous steps because how glycine is synthesized and degraded because any problem in this will lead to diseases, right. So now we have discussed the synthesis of glycine from all the four ingredients that is serine, threonine, carbon dioxide, ammonia as well as glyoxalate.

Now we will be discussing the degradation of glycine. How glycine is degraded and the main mechanism of glycine degradation is known as glycine cleavage system which is a very complex thing as it appears because there is so much thing written in the slide. It consists of four proteins as a part of the multi enzyme complex, P protein, T protein, L protein and H protein and it actually looks like this. This is the major route of glycine breakdown for animals. So let us it is actually very easy.

So let us follow along. The P protein is actually glycine decarboxylase which again has got pyroxyl phosphate as a cofactor which catalyzes removal of carbon dioxide from glycine. So this is the P protein with PLP. It removes carbon dioxide from glycine decarboxylation, right. The T protein, this is basically a transfer of amino methyl group.

T protein containing lipoamide, this actually releases ammonia. So amino methyl transferase, if you look at the T protein, it is transferring the amino methyl group. So here the amino methyl transferase is occurring and ammonia is being released. Next L protein, L protein is basically a dehydrogenase. It is similar to dihydrolypol dehydrogenase of PDH complex, ok.

This regenerates lipoamide. So this is an FED containing coenzyme. It actually regenerates lipoamide and in controlling all of them, in connection to all of them is basically the H protein. Basically it is a protein that is modified with lipoic acid which interacts with all the other components of the cycle which includes reductive methyl amination catalyzed by P protein, methyl amine transfer as well as electron transfer that is reduction. So all of this occurs in conjunction to break down glycine.

Now if we are looking to 3D structure, it might seem very daunting, but we can actually express them in a much simpler way. So this is how it happens. So first glycine decarboxylase acts, CO2 is given out and ultimately all the other cofactors etridrofolate, lipoamide, NAD, FED, they are PLP, they are all acting to regenerate the intermediate so that this cyclical reaction can take place. Basically what we are dealing, we are reversing the glycine synthase complex. So it means glycine is broken down into carbon dioxide, ammonia and one carbon metabolism is happening, I mean more carbon exchange is happening.

So this is the most important route of glycine breakdown alright. Next we are discussing about the fate of glycine when it enter, how it can enter the glucogenic pathway. So how it can enter the glucogenic pathway? See glycine as we already discussed can be converted to serine by the action of serine hydroxy methyl transferase SHMT right. Thereafter serine is acting as a precursor for glucose, how serine is acted upon by dehydratase enzyme one water molecule breaks I mean goes out, it forms an amino acid and ultimately one water molecule is again entering and ammonia is being removed. So by deamination of the amino acid it is forming pyruvate.

So glycine is being ultimately via serine it is converted to pyruvate right. So now we are dealing with the specialized product from glycine ok. So specialized products from glycine are many and we will also be discussing the role of glycine along with them right. So they are creatinine, creatinine, creatinine, phosphate and creatinine, heme, purine nucleotides, glutathione, how glycine is acting at a conjugating agent, role of glycine in protein, neurotransmitters. So let us discuss it one by one ok.

So first the biosynthesis of creatinine. Creatinine synthesis starts from synthesis of creatinine ok. So creatinine is basically a high energy compound that is synthesized and

it is present in the muscle and it is synthesized from three amino acid glycine, arginine and methionine very important. So this is an MCQ. So any other amino acid if it is mentioned it can be a question.

So all of this are come I mean constituent of creatinine except so be mindful. So let us see how it happens. The first step occurs in mitochondria of kidney and pancreas. It involves transfer of guanidino group from arginine to glycine catalyzed by an amidotransferase enzyme to produce guanidino acetate. So this is what is happening in the first step.

This group is being shifted to glycine and ultimately guanidino acetate is formed ok. This is the first step. Amidotransferase, amido group is being transferred right. The next step what happens? This guanidino acetate will be methylated. Who is the most common methyl donor in all metabolic reaction that is activated methionine in the form of S adenosyl methionine ok.

S adenosyl methionine ultimately methylates this guanidino acetate to form creatinine and this methylation occurs in liver. So there is a simple methylation. So addition of one methyl group that is happening over here ok. We got creatinine. Now in the next step what happens? This creatinine is phosphorylated.

Whenever we need phosphorylation kinase enzyme will work. So creatinine kinase is the enzyme that phosphorylates this creatinine to produce creatinine phosphate or phosphocreatine. This phosphocreatine is actually a ready energy source for muscle. So let us deviate a bit that this is the step 3 creatinine kinase alright. So what happens? This creatinine phosphate we need creatinine phosphate to go ahead to form creatinine right, but this creatinine phosphate when required can actually be broken down to creatinine.

You see creatinine is requiring an ATP to form creatinine phosphate. So this is a high energy compound. So whenever the muscle needs ready ATP creatinine phosphate is broken down alright. So this reaction is actually known as Lohmann's reaction and this actually serves as an immediate store of energy in the muscle. Whenever we require sudden energy therefore, creatinine is a very important nutritional supplement for those who are trying to build body and muscle gains right.

So we are coming back to synthesis of creatinine. So what happens? We have got creatinine phosphate which is actually spontaneously and non enzymatically converted or broken down to creatinine and this creatinine is excreted in urine. So this reaction is pretty spontaneous and non enzymatically is automatically converted to creatinine and an inorganic phosphate is let go from the creatinine phosphate molecule. So this is the

highlight of the total synthesis of creatinine. Mind it these are the enzymes and these are the location where these enzymes are acting.

So all of them are again multiple choice question. The first step is in kidney, second step is in liver and the third and fourth step are happening in the muscle cells. So what is the clinical implication of creatinine? The normal serum level ok normal serum level is 0.

7 to 1.4 in males. In females it is a bit less 0.6 to 1.3 milligram per deciliter. Generally we measure creatinine level. Creatinine level is not measured generally even if it is measured the normal level is 0.

2 to 0.4 mg per dl. Similarly in case of urine creatinine as it is excreted in urine it is the normal excretory product so 1 to 2 gram per day mind it is gram whereas the value of creatinine is 0 to 50 mg per day it is almost negligible compared to creatinine excretion right. So all these levels are important and MCQ answers right. So what is the clinical implication of creatinine? It is a very important indicator of renal function and the amount of creatinine actually parallels with the disease severity. The more damage the kidney the more the higher will be the creatinine level in the serum blood right. It is an indicator of so glomerular filtration rate.

Similarly the 24 hour creatinine clearance creatinine excretion is very important indicator of it reflects renal function. However even if from a single value of creatinine we can estimate the GFR roughly by using calculator. One such example is MDRD calculator. There are online softwares you can simply put your age, sex, race and the creatinine value and it will give you a rough idea about the estimated GFR near renal condition you may like to try it right. Next this value is increased in muscular dystrophies alright both blood urinary creatinine and creatinine are raised.

It is also raised in renal failure fever and starvation where there are in remember in starvation there is muscle degradation in fever due to shivering again there is a micro injury to muscle. Now this enzyme creatine kinase is also very interesting and it is a diagnostic enzyme because this enzyme the level of creatine kinase since it is present in inside cells whenever there are destruction of the cells this enzyme comes out and its level is also an indicator of certain diseases. It is raised in myocardial infarction muscular dystrophy etcetera and specifically you should briefly know because this is not an enzyme ology class but still you should know in this connection that there are three isoforms of this enzyme. The main isoenzyme that is increased in muscular dystrophy is CKMM variety and when in case of hardy's that is myocardial infarction CKMB variety is raised and hence it is an important marker of it is an important cardiac marker very

early marker of and specific marker of heart disease right. Moving forward this creatinine production is actually very spontaneous there is no fluctuation and it actually is depends on muscle mass therefore, creatine excretion is absolutely constant for a particular person it will not vary right.

So generally how the 24 hour creatinine is expressed is generally expressed as a amount of per gram I told you per gram and this creatinine is actually it is so constant it is also expressed or it is used to normalize other parameters for example albumin they are expressed in MG per gram concentration of creatinine. So it is also used to normalize the excretion of multiple other exterior products like albumin. So albumin creatinine ratio is a very important indicator of renal function. So as you have understood by now creatine synthesis demands the major supply of glycine arginine and methionine told you MCQ. So these 3 amino acids are very essential and where there is a error in creatine synthesis or this pathway it has been found that those children are presenting with multiple neurological symptoms.

Hence it has been hypothesized that creatinine plays a critical role in brain development and brain function ok. It is still research phases, but mind it creatinine synthesis difficulty or problem leads to neurological symptoms in babies. So next we moved on to another important product that is heme synthesis. You all know heme is required for hemoglobin that is present in our blood red blood cell and this succinyl coenzyme A combines with glycine by the action of the enzyme delta aminolevulonic acid synthase it forms delta aminolevulonic acid which is also known as ALA.

And this is the first step in production of heme. We will be discussing heme metabolism in across multiple classes in details for how what are the steps what are the diseases. So for now you just need to know glycine is a important is an important precursor for heme synthesis alright. Next purine synthesis very important interesting glycine the whole molecule of glycine is utilized for synthesis of purine specifically if we number the purine ring we can see the fourth fifth carbon and the seventh nitrogen are actually contributed by glycine. Again we will be discussing synthesis of purine and nucleotide metabolism in detail in future classes. So for now you should know that glycine is also acting as a precursor in production of purine nucleotides right.

Next we move on to synthesis of glutathione. Glutathione is a tripeptide it contains glutamic acid cysteine and glycine. We have discussed glutathione when we were discussing about HMP shunt we have discussed in detail how the reduced form of glutathione helps to fight various free radicals and how it helps in maintaining RBC members integrity and this glutathione needs glycine to be synthesized alright. So there it happens in multiple steps where first glutamate and glycine or glutamic acid and

glycine forms gamma glutamyl with the help of the enzyme gamma glutamyl cysteine synthetase from gamma glutamyl cysteine and then with the help of glutathione synthetase since both are require ATP those are synthetase enzymes it forms glutathione which is also known as gamma glutamyl cysteine glycine. This whole phenomena will also be touched upon again during absorption and digestion of protein in Meister cycle so be mindful right you have already read. Next conjugation reactions in conjugation reaction glycine is an important conjugating agent for two things we will be discussing over here number one is bile acid.

In cholesterol metabolism you have been taught how cholesterol with the help of several steps several intermediate steps they are converted to primary bile acids like colic acid and kinodioxy colic acid. They conjugate with amino acid like torin and glycine in this case since it is a glycine class we are discussing glycine conjugation so they are conjugated with glycine to form glyco colic acid and glyco kinodioxy colic acid. They can then form sodium react with alkalis like sodium and potassium in the system or cations to form sodium glyco colate so that is how it forms bile salt and thus glycine actually helps in synthesis of bile salts. So this is conjugation of bile acid and formation of bile salt. Next conjugation with benzoyl coenzyme A we have already read this we already are already familiar with this diagram when we discussed about ammonia metabolism right ammonia metabolism treatment.

So over there we discussed how this benzoyl coe is actually conjugating with glycine to form hepuric acid and thus it is excreted in ureter soluble right. Benzoic acid is actually a preservative input so what is the benefit of this? This is actually removing glycine from the system and since glycine is an amino acid which is to be synthesized in our system subsequent synthesis of glycine removes excess ammonia from the system. So this is a example of ammonia clearance with the conjugation that has already been detail discussed in detail in ammonia metabolism alright. So how glycine acts as a neurotransmitter? You see glycine is actually present the amino acid is actually present in brain stem and spinal cord and it opens up specific chloride channel again an MCQ multiple ion may be given, where glycine opens up chloride channel and it in moderate level inhibits it acts as an inhibit in udol transmitter, but in high level it can cause over excitation. So this is a very careful balance of glycine that needs to be maintained in the tissue level specifically at the central nervous system.

And how glycine acts as a constituent of protein? Generally glycine is present where polypeptide chain bends or turns that is when we look at the secondary structure we have seen that whenever beta bends or loops are present glycine is there because it helps in easy bending of the protein primary structure. I already told you it is a very important structural protein of collagen and in collagen every third amino acid is glycine again an

MCQ alright. Another amino acid is of collagen is proline hydroxyproline lysine hydroxyl lysine, but the glycine is most common alright. So what are the metabolic disorders of glycine? So I told you remember the slides because that will be required when we were discussing disorder. So glycine cleavage system we were glycine was being broken and is the most common breakdown pathway of glycine.

So if it is defective what happens? Non ketotic hyperglycinemia simple glycine level will be extremely raised it will lead to severe mental retardation and seizure and there is no effective management. So high level of glycine blood urine and CSF glycine cleavage system problem. There is another disorder glycineuria which is basically rare disorder and in this what happens serum level of glycine concentration may be normal or decreased, but a very high amount is present in urine because normally glycine is reabsorbed, but here glycine is not reabsorbed due to some problem in renal reabsorption and hence it is characterized by excess glycine urine which is glycineuria and then these patients have got an increased tendency to form oxalate renal stones ok. We also remember this slide where I told you this reaction where glycine is formed from glyoxalate strongly favors synthesis of glycine, but if there is some problem there will be no formation of glycine and glyoxalate will be accumulated in excess right and this is leading to a disease that is primary hyperoxaluria excess amount of oxalic acid is excreted urine and it is leading to the formation of oxalate stone. So what happens basically is a protein targeting disorder where the enzyme that is normally present it is supposed to be present in peroxisome due to a protein targeting defect the enzyme is present in mitochondria.

So basically it is inactive in patients. So if it is enzyme is inactive this enzyme aminotransferase. So what happens X this reaction cannot occur. So glycine in glyoxalate cannot be converted to glycine right. Moreover in animals some glycine is actually oxidized spontaneously to glyoxalate. So all of this leads to conversion of this glyoxalate to oxalate by the enzyme glyoxalate oxidase.

G O stands for glyoxalate oxidase or glycolate oxidase same thing. So this leads to formation of excess oxalate and thus excess amount of oxalic acid or oxalate are excreted in urine right. There is another variety that is known as so what happens so let us discuss first. So parts of oxalic acid they could be directly oxidized to oxalic acid by glyoxalate oxidase this is what I was discussing all right. So ultimately it leads to nephrolithiasis that is formation of renal stones renal colic because once it is stone that will lead to excess pain that is also known as renal colic pain and blood in urine that will also known as hematuria right.

It so much so because all the organs are affected oxalate crystal may be seen in heart

blood vessel and bones very serious disorder. There is a milder variety that is known as type II primary hyperoxaludia over what happens the enzymes that is glyoxalate reductase or hydroxy pyruvate reductase are deficient. Those are also those are enzymes because the glyoxalate normally one it is formed in peroxisome or it is normally channeled between the organelle and the cytoplasm. So if the enzyme in peroxisome is fine mainly I told you the reaction favors glycine synthesis though the oxalate will be pulled from here, but even if some amount of glyoxalate is remaining in the cytoplasm the normal pathway by which it was degraded because it normally it is reduced to form glycolate then it is all these things are basically hampered. So what happens this leads to production of oxalate, but I told you if this is only the reason it is very mild right.

So hydroxy pyruvate deficiency what happens it leads to excess formation of glycolate and then glyoxalate to oxalate right. So this is a very milder condition and only leads to urolithiasis the condition leads to production of stones only inside the kidneys not external lithiasis. The primary one leads to production of stones in heart blood vessel and bone in this case it is present stones are only present inside the kidneys. So what is the treatment of this hyperoxaluria? For example, we need to excrete oxalate by excess water intake we need to take more and more water so that it is dissolved in water and excreted in urine dietary supplementation of calcium it forms calcium oxalate crystals and this will also help in chelation of the oxalate crystal and excreted in urine and dietary restriction of excess leafy vegetable like tea, beetroot because they are also they are a very important source of oxalic acid normally. So if there is already oxaluria we should keep in mind that these compounds which are a precursor of oxalic acid are restricted in diet.

So finally, we come to the slide where we are revisiting our original slides we have discussed production from serine, threonine as well as one carbon right proteins are broken down to form glycine by multiple proteolytic enzyme that we all know and finally, how glycine is utilized from also that is important glyoxalate glyoxalate also forms glycine right. So glycine cleavage system we have discussed serine production of pyruvate to glucose we have discussed glyoxalic acid to oxalic we have discussed we have discussed in detail creatine phosphate we will discuss in detail production of purine ring we are discussing purine metabolism we will be discussing we have touched on, but we will still discuss heme synthesis in heme metabolism we have discussed production of glutathione we have discussed how it is conjugated in bile salt and conjugation of hyphuric acid. So this is the final metabolic fate that I always tell you this is shown at the end of every amino acid metabolism class with a goal that our final amino acid be it glucogenic and ketogenic we are expressing the fate of carbon skeletal of amino acids our player glycine lies here it is converted to pyruvate and it being a glucogenic amino acid. So to conclude this lecture has covered the chemistry of glycine how glycine is

synthesized we have discussed how glycine is degraded we have discussed what are the important products from glycine and we have discussed what are the disorders of glycine metabolism. So this is the these are my few references for this slide and I thank you all for your patient listening and I see in the next class take care.