Overview and Integration of Cellular Metabolism

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Week 04

Lecture 16: Galactose Metabolism and Associated Disorders

Hi, everyone welcome back to the lecture series on Overview and Integration of Cellular Metabolism. We have reached week 4 and we are continuing with Carbohydrate Metabolism. Today's class is on Galactose Metabolism and Associated Disorders and the concepts that we will be covering in today's class are the pathway of galactose metabolism, the biochemical abnormalities in galactosemia, the clinical manifestation of galactosemia, the diagnosis of galactosemia and management of galactosemia that is galactose metabolism and its associated disorders ok. So right of the bat you need to know I have already discussed glucose and galactose are monosaccharides during digestion absorption of carbohydrates. Now in that class you see the if you count the number of carbon atoms both of them have got 6 carbon atoms. So 1, 2, 3, 4, 5 and 6.

If you count the number of carbon atoms the formula is simple C6H12O6 we have all read in our from school days right this is the formula of glucose, but this is also the formula of galactose. So glucose and galactose are isomers right. Specifically glucose and galactose differ in the fourth carbon where the H and OH is actually reversed. If you have followed closely my H.

M. P.Shunt lecture 1 over there I told you the isomer in which the H OH is rotated in any carbon other than the penultimate carbons, other than the terminal carbons leaving apart 1 and 6. If in any 2, 3, 4 if in any of these carbons H and OH are rotated then the this type of isomerism is known as variable to answer epimers ok. So glucose and galactose are epimers epimers epimers ok.

So this information let us go forward. So again glucose is a monosaccharide and the major source of glucose is lactose major source of galactose sorry is lactose ok. So lactose is a disaccharide that is composed of glucose and galactose and the primary source is milk and milk products that is dairy products. So who breaks down this lactose into glucose that is lactase. Again during the class on digestion absorption of carbohydrate I told you the deficiency of lactase enzyme leads to a disease known as

lactose intolerance right.

So suppose we do not have lactose intolerance lactase is intact and now the glucose and galactose are being absorbed by the intestinal system right. So lactase hydrolyzing the lactase is hydrolyzing lactose into glucose and galactose and then they are absorbed. How galactose is produced in our system the absorption is about the oral food intake it is produced from lysosomal degradation of glycoproteins and glycolipids. It is one of the process by which galactose can be produced in the body, but the major source is from diet specially milk and dairy product. Where galactose is metabolized very important multiple MCQ question galactose metabolized almost exclusively by liver ok.

So much so that galactose tolerance test is one of the functional indicator of liver capacity right. Next fundamental ground thing that we need to know whenever we are we need galactose in any reaction ok galactose cannot directly participate. It prefers to be donated handheld by someone and who is the donor of glucose galactose during synthetic reaction that is UDP glucose uridine diphosphate. So galactose is bound to UDP it is in the form of UDP galactose where galactose is donated. This concept is not new to you have already seen it in previous lectures of glycogen synthesis right UDP glucose is donating glucose for glycogen synthesis.

Same way UDP galactose is donating galactose for any synthetic reaction. So considering now we have got galactose in our system the main problem why we need to study galactose metabolism is what happens to this galactose molecule how it is metabolized what are the reaction or changes or enzymes that are acting on galactose to produce the clinical features right. So the first reaction is actually galactokinase from your knowledge previously I am sure you have encountered this kinase group of enzymes hexokinase glucokinase phosphofructokinase all of them are doing what they are adding a phosphate molecule or phosphate group. So kinase adds a phosphate group and galactose is galactokinase is also not a exception. So upon action of galactokinase galactose is converted to galactose 1 phosphate right.

This is the first reaction and this is the cyclical form of galactose again I am telling you if you are having difficulty memorizing the structures be sure you just memorize the metabolic pathway by the name of substrates and products. So galactose is being converted to galactose 1 phosphate very important glucose by the action of hexokinase or glucokinase is being converted to glucose 6 phosphate galactokinase converts galactose to galactose 1 phosphate the phosphorylation occurs in the first carbon right. In the next step what happens the most important enzyme of galactose metabolism I told you galactose 1 phosphate uridyltransferase since there is UDP glucose UDP galactose that is donating galactose we need synthesis of UDP galactose. So how UDP galactose

will be synthesized? Remember I told you galactose cannot directly participate in any reaction if we need formation of suppose we need formation of lactose I am just giving you a very small example we need glucose and galactose. So galactose cannot simply go and bind to glucose simply like glycogen so we need galactose in UDP form.

So how this UDP galactose is formed? Again with the help of this enzyme galactose 1 phosphate uridyltransferase where galactose 1 phosphate and UDP glucose is combining to form UDP galactose ok this is the reaction. Galactose 1 phosphate and UDP glucose under the action of the enzyme galactose 1 phosphate uridyltransferase often abbreviated as GALT is getting converted to UDP glucose right UDP galactose sorry. So once UDP galactose is formed ok see galactose 1 phosphate reacts with UDP glucose to form UDP galactose and glucose 1 phosphate right. Galactose 1 phosphate mind it often this product or this thing is spelt wrongly ok glucose 1 phosphate in the presence of galactose 1 phosphate uridyltransferase. So what happens next? So up to this I hope it is clear.

So there are two things that you need to keep in mind UDP galactose is the active donor of galactose in any synthetic reaction. So what synthetic reaction UDP galactose is essential for the formation of compounds like lactose glycosaminoglycan glycoprotein cerebroside glycolipids etcetera. These are the compounds that needs galactose and galactose needs to be donated in the form of UDP galactose fine. In the next step what happens? UDP galactose can be converted back to UDP glucose ok. So when we need you galactose for synthesis UDP galactose can be formed and it can donate galactose as much as it wants to.

But when the requirement of galactose is gone the excess UDP galactose can be formed or converted back to UDP glucose by the enzyme. You tell me the what is the basic structural difference between UDP glucose and UDP galactose? UDP is same. Glucose and galactose is also same. Only glucose and galactose are different and glucose and galactose are itself epimers. So in the looking at the structure of whole UDP galactose if we just locate that fourth carbon and tweak the HOH it will become UDP glucose right and you are absolutely right in guessing UDP glucose and UDP galactose are epimers.

So the enzyme is galactose for epimers ok UDP galactose for epimers. So this enzyme then acts on UDP galactose and leads to formation of UDP glucose. So now what happens galactose is channeled to the metabolism of glucose so this galactose the these are optional see galactose 1 phosphate or see glucose 1 phosphate this one. What is the use of this glucose 1 phosphate? This glucose 1 phosphate can be converted to glucose 6 phosphate by the enzyme phospho glucomutase very important again a special class of enzymes that helps in transfer of molecule intramolecular transfer of functional group intramolecularly. So glucose 1 phosphate becomes glucose 6 phosphate.

So if we look at the structure of glucose the phosphate group is being shifted from first position to the sixth carbon. Why because now glucose 6 phosphate is essential for all other carbohydrate metabolism reaction. So glycolysis TCA cycle H-amplicient everything right. So galactose in this way can take part in glucose metabolism thus galactose can be channeled into you see. So this galactose molecule it is getting converted to two things UDP galactose and glucose 1 phosphate UDP galactose can be converted to UDP glucose and this can go to form glycogen part of carbohydrate again metabolism right.

Metabolism of glucose and it can be converted to glucose 1 phosphate which is eventually converted to glucose 6 phosphate and that can also go and take part in other metabolic pathways of glucose right. However you should know that galactose is not an essential why it is not essential because this enzyme UDP galactose for epimerase is a reversible enzyme it means even if there is no galactose to start with. So this galactose 1 phosphate is produced from galactokinase. So galactose upon being acted by galactokinase forms galactose 1 phosphate right and this by galactose on phosphate ureidyl transferase GALT is getting converted to UDP galactose. So if this whole pathway is absent how there is less galactose in diet suppose there is low low galactose will the body have no UDP galactose no it will have why because we can always get UDP galactose from UDP glucose the reverse pathway is very much feasible.

Therefore galactose is not an essential nutrient in diet right only and only what we need we need this in action of this enzyme the galactose for epimerase right and this requires NAD plus right. So galactose not essential in diet. So if you are facing an explain why type of question that galactose is not essential in diet this is the answer right and there can be multiple multiple multiple choice type question MCQs that can be formulated from this section right. There is an alternative pathway very minor. So let us deal with it now that after 4 to 5 years of age mind it these all enzymes are produced in utero while the baby is in uterus right.

The galactose metabolism starts because they are getting carbohydrate source from mother nutrition via placenta right. But so these all things can happen inside the uterus on at birth. So if these enzymes are deficient the baby will have problems will be discussing very soon but this alternate pathway happens after 4 to 5 years of age when the baby has grown up a little that is the galactose 1 phosphate pyrophosphorylase. This is one enzyme a very minor enzyme what will it do? It will directly produce UDP galactose which will convert which can be converted to UDP glucose right. Just know this for MCQ sake that galactose 1 phosphate pyrophosphorylase can directly produce UDP galactose ok on which it will act it will act on galactose 1 phosphate of course,

because whenever you are naming any enzyme it is named after the substrate.

So galactose 1 phosphate so when galactose is there galactose 1 phosphate pyrophosphorylase will directly produce UDP galactose and why it is important? It is because if the baby is having deficiency of the previous enzymes after he grows up to a certain age the symptoms will be lessened. Anyway this is a very minor reaction but you might find a question here and there but for all practical purposes even if you do not remember the action of this enzyme you are well and good you have to remember the action of other enzymes which if deficient produces a very important disease that is known as galactosemia right. So considering the disorders of galactose metabolism we move to the next part of the lecture which is regarding the disorders. This is galactosemia and the most important variety of galactosemia is classical galactosemia there may be many types of galactosemia that will also be touching very soon. This is an inbound error of metabolism as I told you the enzyme that is deficient is galactose 1 phosphate urinal transferase or GALT ok.

So if this enzyme is deficient what will happen and the incidence is 1 in around 35000 birth if this enzyme is deficient galactose cannot be metabolized and there will be many problems it is a rare congenital disease and it is inherited in autosomal recessive order. So the rate of expression is actually very low but still this is an inbound error of metabolism means the baby is born with a disorder where one metabolic enzyme is absent and it is leading to expression of a clinical disease with multiple symptoms right from the birth ok. So what will happen you can easily guess so galactose 1 phosphate will accumulate in the liver. Who acts on galactose 1 phosphate? Galactose 1 phosphate urinal transferase this enzyme GALT which is actually deficient we are talking about GALT deficiency. So if GALT cannot act on galactose 1 phosphate there will be accumulation of galactose 1 phosphate because the enzyme tryptokinase is also I mean galacto sorry galactokinase is not is one way ok.

So once galactose 1 phosphate is formed it cannot be converted back to galactose. After 4 to 5 years I discussed there is a minor enzyme galactose 1 phosphate pyrophosphorylase that can help in conversion of this to UDP galactose but till the baby grows up right from the day of birth to 4 to 5 years the action of GALT is extremely essential and if it is deficient there will be excess accumulation of galactose 1 phosphate and this enzyme will inhibit galactokinase as well as glycogen phosphorylase. You remember what is the role of glycogen phosphorylase? Glycogen phosphorylase is an enzyme of glycogen breakdown glycogenolysis right it helps in production of glucose from glycogen. So if glycogen phosphorylase is inhibited there will be less and less glucose and that will lead to hypoglycemia and since it is a disease of neonates a newborn baby it is leads to neonatal hypoglycemia and galactose cannot be converted to

glucose. Why we are relying on galactose to form glucose? The newborn babies are only and only dependent on mother's milk right there is no other source of glucose you and I can simply drink multiple energy sources and we are getting readymade glucose to start with the newborn babies do not only mother's milk that is lactose is getting converted to glucose and galactose and mainly whatever glucose is being converted and galactose it is also secret directive from milk.

Galactose is the primary source or food source in newborn babies ok and this galactose if it cannot be converted to glucose the amount of glucose that is produced from breakdown of lactose is insufficient. We need galactose as well to be converted to glucose I told you how it can be done it can be converted to UDP glucose it can be converted to glucose 1 phosphate then glucose 6 phosphate. We need glucose metabolism to happen so that the newborn babies get energy from mother's milk and if this does not happen galactose 1 phosphate is accumulated it is not only it is accumulating it is inhibiting the formation of glucose inside the body because all the substances that are present in the body from mother suppose what will happen? We will discuss this in regulation of blood glucose when we are starving ok when we do not have any food source that is diet our body actually synthesizes glucose by the process of neo glucogenesis. We are relying on that and if in between meals whenever the baby is having meal mother's milk it is getting converted from glucose from lactose to glucose some amount of glucose is going galactose is not being converted to glucose and in between meals it is relying on production of glucose from other sources that is known as glucogenolysis and neo glucogenesis. So stored glycogen will be broken down and other substances will be converted to glucose if glycogenolysis is hampered there will be hypoglycemia and since it happens in neonates it is neonatal hypoglycemia.

Remember again an explain why type of question if you see why there is neonatal hypoglycemia in galactosemia this is the answer galactose 1 phosphate accumulates and it inhibits glycogen phosphorylase there is inhibition of glycogenolysis and this leads to neonatal hypoglycemia. So increase galactose level increase during insulin secretion which lowers the blood glucose level. So what is this what is happening? So when galactose is increased right it leads to the liver I am sorry the pancreas the beta cells of pancreas senses a monosaccharide right it triggers release of insulin what is the role of insulin it lowers the blood glucose. It is not a problem in normal individual because in normal individual even if the blood glucose is low whenever we need we can produce glucose from various sources, but in this case not only is it preventing production of glucose from glycogen it is also reducing glucose by triggering insulin release. So everything is actually acting together to form neonatal hypoglycemia right.

What is the problem? This galactose will now remain in the circulation since galactose

1 phosphate is accumulated ultimately there will be no requirement of converting galactose to galactose 1 phosphate. So suppose some pathway A is getting converted to B it is converting to C I told you in feedback control so if something is blocked over here the whole reaction will be blocked right there will be no more requirement of B to be converted to C because this pathway is faulty this conversion pathway is faulty again this is now also not acting. So ultimately A will be accumulated some B will be accumulated right. So excess galactose if it is accumulated in the system it actually is exceeded in urine also see if we test blood there will be high galactose level that is known as galactose emia right. If there is excess galactose in urine this is known as galactoseuria right.

What happens bilirubin uptake is also less because the liver is at fault why because excess galactose 1 phosphate gets accumulated in the liver it leads to a condition that is known as hepatomegaly, megaly means growing of liver right. So hepatomegaly happens there is liver is at an assault so the cells are filled with galactose 1 phosphate and the liver cannot function properly and that is the reason why bilirubin uptake is less bilirubin conjugation is reduced and unconjugated bilirubin is increased in the system basically liver cells helps in conjugation of bilirubin if liver cells are not functioning properly again there will be jaundice in this case unconjugated hyperbilirubin emia. Why the liver cells are not functioning properly because of accumulation of excess galactose 1 phosphate why it is getting accumulated due to loss of action of galactose 1 phosphate uridyl transferase right. You get my point right so, enlargement of liver jaundice and severe mental retardation this is very important not only brain I mean liver there is also mental retardation because the food of for brain is glucose if the neonatal brain is subjected to hyperglycemia brain cannot develop properly right. So, there will be severe mental retardation and this is the reason why galactose 1 needs to be diagnosed early and it should be treated very early.

So, just to look at what are the features or acute symptoms which are mother a baby cannot complain because it is crying all the time. So, one of the reason of intractable crying of baby I told lactose intolerance is one this is one. So, swelling of the brain edema chill the since they cannot digest it the baby will refuse to feed. Rejection of breast milk one very important symptom of galactosemia right they will constant vomit jaundice I explained to you why jaundice is happening pressure around the brain our brain skull is in a bony cage. Suppose we have got trauma over a something hits over if it swells up there is no problem it can swell because the bone support is inside other outer side is free, but in case of brain the organ is inside if it swells up there will be pressure that is being exerted by the skull because it cannot expand that will that leads to increased CSF pressure right.

Again there will be kidney issues why again due to deposition of multiple by product there will be excess unconjugated bilirubin there will be problems of excretion of galactose why see kidney always try to reabsorb galactose, but if it is in too much excess it has to be filtered and that leads to galactosuria right. So, liver failure and this leads to a state of immuno I mean compromised immune deficient compromised immune scenario because the body is getting not getting enough nutrition right. And these are the chronic symptoms I will explain why there is cataract feeding deficiency and growth issues because of malnutrition I will very soon explain why there is cataract. Now this galactose is getting converted to its reduced form it is known as galactose is an aldehyde ok CHO it is getting converted to a compound known as galaxitol or dulcetol ok with the help of the enzyme aldose reductase. This dulcetol or galaxitol once formed it cannot escape the lens cell this whole thing is happening inside the lens ok.

Galaxitol is osmotically very active it attracts water molecules when water molecule come imbibes inside the cell there is change of refractive index and the lens becomes hazy ok. Moreover this galaxitol also contributes to the injury of lens protein. So this whole thing leads to an opacity in the lens in the form of cataract. Now this was the major deficiency or major concern in galactose metabolism that is the deficiency of galactose 1 phosphate uridyltransferase. However the disease can also happen if there are deficiency of other enzymes.

See for example, deficiency of galactokinase what will happen again excess galactose will accumulate it cannot be converted to galactose 1 phosphate galactose will be accumulated in the blood there will be extra urin, but cataract is rare galactose can be converted to galaxitol definitely right, but there is no galactose 1 phosphate. So galactose 1 phosphate is not deposited in the liver and kidney. So there will be absence of hepatic and renal complication cataract is also very rare, but still it can happen because of the aldose reductase enzyme. See aldose reductase is converting galactose to galaxitol or dulcetol. So considering the types of galactose or galactoseemia the main or the classical one is due to deficiency of galactose 1 phosphate uridyltransferase that is considered as type 1.

The symptoms more or less same it is most severe in case of type 1 or classical for the other case it is milder. So for galactokinase deficiency it is milder as I told you it can also happen if there is deficiency of galactose epimerase. So these are the genes GALK1 is galactokinase it codes for galactokinase this is galactose 1 phosphate uridyltransferase this is galactose epimerase this is galactose mutase which is actually triggering the conversion of alpha d galactose to beta d galactose. So those are milder variety, but main is GALT deficiency. So how we can diagnose diagnosis can be done in utero from drawing samples from the baby when even if he is not born those are known as chorionic

villus sampling CVS or amniotic fluid sample and gene mutation analysis is done specially the GALT gene.

If GALT gene is deficient we can easily predict that the baby is having is going to have galactosemia, but the treatment is actually very simple we need to replace mother's milk we need to remove galactose and lactose from diet because lactose will again lead to production of galactose and we use special formula diet for the baby. So the key points to remember from this lecture is major source of galactose is lactose that is obtained from milk and milk products UDP galactose is the active donor during any galactose synthetic reaction classical galactosemia occurs due to deficiency of enzyme galactose 1-phosphatidyltransferase it is one of the important causes of congenital catadact and it is done by clinical evaluation of GALT enzyme and GALT mutation analysis and treatment is done by removal of galactose and lactose from the diet. So these are the references for this class and I thank you for your kind attention.