Overview and Integration of Cellular Metabolism

Prof. Arindam Ghosh

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

Indian Institute of Technology Kharagpur

Week 04

Lecture 17: Fructose Metabolism and Associated Disorders

Hello everyone, welcome back to late another lecture series in overview and integration of cellular metabolism. Today's class is on fructose metabolism and its associated disorders. We will be covering the following concepts, we will be covering the pathway of fructose metabolism, we will be covering facts about polyol or sorbitol pathway, we will see how fructose metabolism can lead to hyperlipidemia, how fructose plays a role in fertility or infertility, what is essential fructoseuria and what is hereditary fructose intolerance, all these concepts will be covered one by one. Now, considering fructose it is a ketohexose. So, glucose in the last class I showed you where how glucose and galactose are epimers. In this case the structure of glucose and fructose again if you count the number of carbon atoms they are same C 6 H 12 O 6.

How it varies? There is an aldehyde group in glucose, but there is a keto group in the second carbon of fructose right. So, this is how fructose differentiate from glucose just to have the fundamental concept. Now, regarding so this is a ketohexose right 1 2 3 4 5 and 6 6 carbon atoms, this is an aldohexose to the present of aldehyde group glucose and this is the ketohexose right. So, ketohexose where it is present mainly in fruit juices and honey right all the sweet products they contain fructose, but the chief dietary sources the sugar that you that we are taking everywhere with the tea with any bread toast or any food right sugar.

Shucrose is hydrolyzed by the intestine with the enzyme shukrase ok. And fructose is absorbed by facilitated transport and this taken up by portal blood to the liver where it is mainly converted to glucose. So, these are few facts which I think you already know by now because we have covered it in the class of glucose I mean carbohydrate transport right. And fructose is easily metabolized and it is a very good source of energy. These are few facts let us discuss about fructose and then we will be going delving deep into the once that needs explanation.

So, it is easily metabolized and is a good source of energy we will see how it is easily

metabolized much easier than glucose. Seminal fluid is rich in fructose and sperms uses fructose as a source of energy right. In diabetics fructose metabolism through sorbitol pathway may lead to the formation of cataract do not worry I will be explaining everything just keep these things in mind. So, first thing first the phosphorylation of fructose this is the first step in fructose metabolism. So, fructose can be phosphorylated in two ways in the last class you learnt about the enzyme galactokinase that was converting galactose to you must be knowing I would not answer it is for you to answer.

Fructokinase is an enzyme that converts or phosphorylates fructose in the first position to convert it to fructose 1 phosphate. Remember hexokinase is an enzyme that can also act on all hexoses of fructose glucose galactose hexokinase can act on all hexoses and it generally preferentially phosphorylates in the sixth position right. But the affinity for hexokinase to fructose is very low we will be discussing it again. So, fructose always prefers to be phosphorylated by fructokinase as compared to hexokinase. So, fructokinase where this enzyme is mainly present liver, kidney, muscle and small intestine very important fructokinase is not dependent on insulin, but hexokinase is dependent this is a fundamental difference and affinity of hexokinase enzyme for fructose is very low.

So, this reaction where fructose is getting converted to fructose 6 phosphate. So, if till now till if I ask you or if you are being asked about how fructose can go into carbohydrate metabolism. You can easily use your knowledge from previous classes that hexokinase can act on fructose to form fructose 6 phosphate and fructose 6 phosphate is a product of glycolysis right. So, glucose 6 phosphate to fructose 6 phosphate by phospho hexo isomerase and this is basically M pathway M den mera pathway is glycolysis right, but this does not happen often why because hexokinase never or almost does not want to act on fructose. So, what act on fructose fructokinase acts ok.

So, fructokinase acts on fructose to form fructose 1 phosphate. So, phosphorylation has happened in the first position ok if you look at the structure as I told you it is easier to understand, but you may choose to ignore the structure. It is the next enzyme that is extremely important. So, what it is doing remember in glycolysis there was an enzyme aldolase A or aldolase that was breaking down a 6 carbon into 2 3 carbon compounds. It was breaking fructose 1 6 bis phosphate to glyceraldehyde 3 phosphate and dihydroxyacetone phosphate.

If you are finding difficulty in remembering go back to as early as week 2 then you can tackle the lecture on glycolysis over there you will be able to see able to see right week 1 fourth lecture of the glycolysis right. So, in glycolysis we discussed the aldolase A enzyme over here aldolase B it is an isoenzyme right an enzyme that is present in

different part of the body, but exerting a similar function on as isoenzyme. So, what aldolase B is doing aldolase B is breaking down a 6 carbon compound fructose 6 C to 2 3 carbon compounds they are glyceraldehyde ok it is glyceraldehyde and dihydroxyacetone phosphate right glyceraldehyde and dihydroxyacetone phosphate. So, this phosphate group is with this one dihydroxyacetone phosphate and this from here it is getting cleaved in the form of glyceraldehyde ok. This glyceraldehyde can be phosphorylated by a kinase enzyme since it is a tri carbon or 3 carbon carbide it is a triose just like glucose is a hexose a etherose is a I mean 4 carbon compound right pseudoheptulose is a 7 carbon compound.

So, this is a triose ok it is getting converted by triose kinase to glyceraldehyde 3 phosphate. Glyceraldehyde 3 phosphate dihydroxyacetone phosphate you already know what are their fates they all continue to glycolysis right or even they can go in the reverse phase in the when depending on the need if we need to store glucose they can also be utilized in the formation of I mean they can also be utilized by other pathways to form glucose whether by glycolysis or by gluconeogenesis. When energy is required they are diverting into glycolysis when we need glucose they are diverted into the gluconeogenic pathway we will be looking into that, but the important message over here is the enzyme aldolase B is converting the fructose 1 phosphate to glyceraldehyde and dihydroxyacetone phosphate and this glyceraldehyde is converted to its phosphate form by the enzyme triose kinase. So, if we look at this thing in an over nutshell you see fructokinase it is converting fructose to fructose 1 phosphate and it is getting converted by aldolase B to glyceraldehyde and dihydroxyacetone phosphate and this dihydroxyacetone phosphate and glyceraldehyde 3 phosphate can actually go in this direction whenever you see pyruvate and lactate it is glycolysis right glycolysis or they can be acted upon by other enzymes where the 2, 3 carbons these are 3 carbons they are getting converted to 6 carbon and ultimately the reversal of glycolysis is happening and this is neoglucogenesis or gluconeogenesis ok neoglucogenesis right. So, fructose can be I mean the fructose can enter carbohydrate metabolism and they can be diverted into glycolysis or gluconeogenesis depending on the requirement.

You should also note we will be also be discussing that dihydroxyacetone phosphate can be diverted to glycerol pathway and ultimately it is still the production of lipids we will be discussing that right. But one fate is TCA cycle and glycolysis into the formation of energy and another is formation of glucose. This is the direct pathway of fructose metabolism. So, remember 2 important and 3 important enzymes rather fructokinase aldolase B and this is basically trioskinase anywhere glycerol dihydrofuse the source it can be converted to phosphate by trioskinase. So, this is the most important enzyme aldolase B this is also important why we will see very soon.

So, now let us deal with sorbitol or polyol pathway. So, what is sorbitol or polyol pathway? This pathway deals with production of fructose from glucose that is transformation of fructose to fructose via sorbitol. Is do you know any situation where the body has excess glucose of course, in the disease diabetes mellitus we will be discussing very soon. So, what happens in though that disease there is excess amount of glucose in uncontrolled diabetes mellitus and that leads to our excess activity of the end these enzymes that is aldose reductase and sorbitol dehydrogenase. Mind it glucose the in the previous lecture I told you aldose reductase enzyme actually converts galactose to its alcohol dulcetol or galactetol.

The alcohol form of glucose is actually sorbitol the alcohol form of fructose is also sorbitol ok. So, in presence of NADPH derived from HMP shunt aldose reductase reduces glucose to sorbitol. What is the fate of sorbitol? This sorbitol ultimately is acted upon by sorbitol dehydrogenase to form fructose ok. Just know this in diabetes glucose can be converted to fructose by the sorbitol or polyol pathway right. So, what is the problem? You see in uncontrolled diabetes significant quantities of glucose can infiltrate the cells that are insulin independent right.

This leads to a problem where the intracellular glucose levels increase right and in specific organs that can lead to a huge problem because specifically the organs like lens, retina, nerve cells, kidney. Mind it these are the organs that faces the maximum brunt of the disease that is diabetes mellitus. These four organs the eye, the lens, the nerves and the kidney. Eye is actually in the lens is actually in the eye only right. So, they have got high aldose reductase activity and adequate NADPH.

So, what happens all these glucose are converted to sorbitol, but these once it is converted to sorbitol in diabetes these cells sorbitol dehydrogenase is either inactive or absent right. Because if there is a finite amount by which sorbitol dehydrogenase can convert sorbitol to fructose, but in excess and excess amount of sorbitol is being produced this enzyme will not be able to cope up right. And it has been seen there is down regulation of sorbitol dehydrogenase in these cells specially in lens, retina, nerve cell and kidney. All other cells do have adequate amount of sorbitol dehydrogenase activity. So, they can actually tackle excess sorbitol and they can convert into fructose and then fructose can be utilized for energy.

But in these cells fructose cannot be converted I mean fructose cannot be produced because sorbitol dehydrogenase is low. So, what happens excess amount of sorbitol will be deposited and just like the mechanism by which cataract was being produced in galactosemia this sorbitol is hydrophilic in nature it will imbibe water molecules and all those cells of those organs will swell up. So, be it nerve, be it kidney, be it eye, be it

retina everything will have the same problem of osmotic swelling and that will lead to hell lot of complications. So, there will be retinopathy, eye damage, there will be cerebral edema, there will be nephropathy, there will be neuropathy, there will be diabetic food. There will be the multiple paradigm or the plethora of symptoms is due to this one culprit that is excess sorbitol accumulation in these cells in uncontrolled diabetes because of the hamper of the polyol pathways.

Normally in polyol pathway glucose can be converted to fructose it is good for our body. If this enzyme is deficient there will be excess amount of sorbitol and sorbitol will lead to all these problems right. Now there is a dictum that is or often the question is found that fructose is more harmful than glucose why because fructose actually bypasses the rate limiting steps of glycolysis. So, what is the rate limiting step? Mind it our body can control what is the amount of metabolic steps that are needed it has already been discussed. So, the process of glycolysis is done by the first two steps either hexokinase step and most importantly by the phosphofructokinase step those two are irreversible reactions.

You can see fructose actually bypasses those two important steps and it directly enters glycolysis in the form of glyceraldehyde 3 phosphate and dihydroxyacetone phosphate alright. So, this first step of hexokinase and the second step of phosphofructokinase they are bypassed. So, if the body tries to regulate or if my body now does not need any glycolysis we do not need any anabolism from glucose we need glucose for other storage functions. So, what is happening fructose if you are taking excess in form of raw sugar this whole step is bypassed and we are adding needless calories to our body and ultimately this will lead to excess production of acetyl coenzyme A via TCA cycle and that acetyl coenzyme A will be used in fatty acid synthesis right also synthesis of cholesterol and all other culprit. As I told you the minor pathway in which fructose is entering into the glycolysis by bypassing the hexokinase pathway by greatly forming glucose 6 phosphate usually does not happen right.

Even if it happens it is still bypassing the one regulating step that is hexokinase, but if it does not does not consider this step because it is very very very rare why I told you hexokinase has got very low affinity for fructose it is mainly acted upon by the enzyme fructokinase this is a fructokinase enzyme and fructose directly enters into the glycolytic pathway and it is being it is contributing to the excess unwanted calories of the body. Next excess fructose over everywhere we see raw sugar every dietician will prescribe you or every doctor any anybody who knows about diet and now you will also know that raw sugar is harmful for our body why these are the reasons because it will lead to excess calorie and now it is also lead to an alteration lipid profile. Let us see how fructose consumption leads to insulin independent action of several important lipogenic enzymes.

It means what those lipogenic enzymes means that are helping in synthesis of various lipid particles that are being up regulated. So, there will be more and more synthesis of lipids it has been seen that diets in high fructose are leading to hypertriglyceridemia Tg in population these are all population based studies and it has been seen that a diet that is high in fructose or raw sugar sucrose again it is getting converted to fructose those cases of those subjects are do have high Tg on measuring in lipid profile and that is again very harmful and leads to a lot of cardiovascular disorder.

If you want to know the biochemical pathway it is right here right in front of you where dihydroxyacetone phosphate and glycerol dehyde is actually diverted to formation of glycerol 3 phosphate and as already told you excess fructose is leading to the formation of acetyl CoA and it is leading to the formation of fatty acid. So, we all know fatty acid and glycerol is the key component or unit by which a lipid is produced. So, triglyceride very low delcid lipoprotein Tg all are formed in excess only and only due to high fructose in diet right. Mind it for production of fat we need both fatty acid and glycerol excess fatty acid why it is produced it is because of excess glycolytic activity excess glycolytic activity excess TCA cycle excess acetyl coenzyme A. So, that acetyl coenzyme A will be diverted to synthesis of fatty acid.

We will learn in detail how fatty acid is synthesized in the upcoming lectures when you are dealing with lipid metabolism. For now you know that it is leading to excess production of fatty acid that is acetyl coenzyme A it is also increased and glycerol production is also increased because of increased glycerol 3 phosphate by the enzyme glycerol kinase right and dihydroxyl glycerol 3 phosphate dehydrogenase. These two enzyme actually act on glycerol dehyde and DHAP to form glycerol 3 phosphate glycerol 3 phosphate along with fatty acid they esterify together and ultimately leads to the formation of triglyceride and that is a culprit why excess fructose in diet leads to hypertriglyceridemia. This will also help you to answer the justify type of question. Now, something regarding fructose and infertility or fertility.

See seminal fluid actually have got large concentration of fructose because it is important for survival of sperm ok, it is rhemino physical discharge fructose. So, what happens if there is some disease that is azuspermia ok. Azuspermia is a disease in which there is a dead sperm or quality of sperm is hampered it is a disorder of males and which is a major cause of infertility right. So, during azuspermia we do a test for any anatomical defect anatomical defect is defect in any duct or any pipeline for that matter. So, what happens over there you see seminal vesicle.

So, what if there is a block and seminal vesicles sperms are not being delivered there is no sperm right. So, what happens since we know seminal vesicle secretes fructose ok.

So, with that with one simple test we can have an idea whether the block if suppose there is a kink or block in the pipeline then sperms cannot reach right. So, if the azuspermia is caused by duct obstruction right fructose concentration I mean the semen fructose content is estimated ok. So, how we can get an idea whether the block is present above or below.

See if fructose is present the block is located above. So, if there is block above the seminal vesicle the fructose is actually coming from seminal vesicle right. So, if there might be no sperm in semen, but there will be excess quantity of fructose right, but what if the block is in here it means the sperms are reaching, but they are not getting out. So, the block is located after seminal vesicle if the block is located after the seminal vesicle fructose will not be found because over here fructose cannot reach the semen you get my point again a very easy illustration suppose you are getting a black water black colored water from this pipeline ok. And when and ultimately we are getting gray colored water because white color is coming from here black color is coming from here gray color is coming from here right.

What if the block is above if the block is over here then what will happen black water will be coming from here and ultimately we will be getting gray colored water. What if the block is below it means there will be no black colored water right mind it there multiple other ducts by which other contents of semen are secreted into the ejaculatory tract, but this simple test can tell us whether the block is above the seminal vesicle in which there will be fructose which is secreted from seminal vesicle or there is no fructose if the block is below the seminal vesicle. This is for just multiple choice question you just remember if block is located after seminal vesicle the fructose will be absent if the block is located above seminal vesicle will contain fructose in cases of azus permeae right. But needless to say we need fructose for healthy sperm for healthy sperms ok and that will treat infertility that is one major cause of infertility. Anyway now coming to fructose metabolism, fructose metabolism defect leads to inborn errors.

So, let us see what are the errors the major error with which we should be concerned is actually hereditary fructose intolerance or HFI ok and this is due to deficiency of aldolase B the incidence is 1 in 1 and 20,000 to 30,000. So, what again what is the problem just like the concept of galactosemia over here since aldolase B is deficient fructose 1 phosphate is accumulated it will inhibit glycolysis and gluconeogenesis it will get accumulated in multiple cell and that will lead to all the symptoms ok. Just relate with if you have understood galactosemia you will easily understand hereditary fructose intolerance. So, fructose 1 phosphate accumulation inhibits glycogen phosphorylase and glycogenolysis is inhibited. This results in glycogen accumulation in the liver just like galactosemia ok.

So, glycogen if it cannot be broken down glycogen is accumulated in the liver and it accumulates and lead to the formation of hypoglycemia as well as hepatomegaly. The children the baby with hereditary fructose intolerance cannot thrive ok. So, there is vomiting loss of appetite hepatomegaly and joint diseases the reasons are same as galactosemia ok. The if so this is the beauty of metabolism if you understand one topic one concept the next concept will very clear. And since again due to excess accumulation of glycogen and fructose 1 phosphate the swell swell up due to osmotic imbalance the liver cell since fructose metabolism preliminary happens in liver, liver cells are again at a dysfunction and that if it is in severe grade it will also lead to cirrhosis and death that is permanent damage of the liver.

Now, you see galactosemia since it is coming from mother's milk it exhibits it right at birth right, but generally fructose since the main dietary sources sucrose it expresses when weaning or artificial feeding is started to the baby which generally occurs at 6 months of age. So, what is the treatment? The treatment is elimination of all sources of fructose from diet we need to eliminate raw sugar and then there will be no problem ok. So, fructose is excreted in urine and since I told you excess fructose will get accumulated because fructose 1 phosphate is excessively formed and after some time there will be no need of conversion of fructose to fructose 1 phosphate. So, there will be fructose in urine that is fructose suria and this fructose is a reducing ketohexo. So, this will be positive benedict test which is a test for reducing substances that will give positive celly one of test which is a test for ketos keto monosaccharides right monosaccharides, but keto sugar.

Now, this is all about hereditary fructose intolerance what do we need to know about essential fructose suria it is a minor disease where fructokinase enzyme is deficient fructose cannot be converted to fructose 1 phosphate excretion of fructose. So, since fructose is excess it will be excreted in urine right that is the only problem mind it fructose will not be accumulated just like galactosemia fructose hereditary fructose intolerance also leads to cataract right. So, in this case there will be no treatment is not indicated. However, since there is fructose suria there will be positive benedict and say one of test. So, hereditary fructose intolerance as well as galactosemia both are reason for congenital cataracts mind it congenital cataract same reason aldose reductase excess orbital excess accumulation in the lens and all the problems right.

So, to summarize you see essential fructose suria is formed due to deficiency of fructose enzyme hereditary fructose intolerance is due to deficiency of aldolase B fructose can bypass the rate limiting stress of glycolysis and it can be converted to dihydroxyacetone phosphate and glycerol dehyde 3 phosphate and can enter into the glycolysis and TCA

cycle or it can be used in gluconeogenesis. So, these are the concepts that have been covered this is basically a summary slide of concepts covered and these are the references and I thank you for your attention that will be it for today. Thank you.