Overview and Integration of Cellular Metabolism

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Lecture 10: Hexose Monophosphate Shunt : Steps and Phases

Hi, everyone. Welcome to yet another lecture series on Overview on Integration of Cellular Metabolism. We are discussing carbohydrate metabolism and today's lecture is on hexose monophosphate shunt. We will be learning about the steps and phases of hexose monophosphate shunt. Specifically, we will be covering the concept how you can classify the hexose monophosphate shunt path into the oxidative and non oxidative phases. We can we will show how the regulation of HMP shunt is done and what is the metabolic and clinical significance of HMP shunt pathway.

So, hexose monophosphate shunt the short form being HMP is known by many names. It can be denoted as PPP which stands for pentose phosphate pathway named after discoverer Warburg Dickens pathway. It may be known as phospho gluconate pathway after a very important intermediate that is produced in the HMP shunt. So, mind it if you see any one of these in any question be it multiple choice question or be it any explanation downwards in the lectures session, mind it we are referring to this one in the same thing of HMP shunt.

So, what is HMP shunt? We have already learned about glycolysis and tricarboxylic acid cycle that does oxidation of glucose. Well, this is an alternative pathway to glycolysis and TCA cycle for oxidation of glucose. Mind it the keywords alternative and oxidation of glucose. HMP shunt is anabolic in nature again an important keyword because it will help you to understand the regulation of HMP shunt. And no direct ATP is produced or utilized in HMP shunt.

This is also another important thing that we need to remember when we are discussing about HMP shunt. So, without proceeding further from your lecture from the lecture on enzyme regulation will you be able to tell me since it is anabolic who or what will help in the uplifting the HMP shunt or who will help in down regulation of HMP shunt. If you can very good write it down and we will see later whether your answer matches the explanation it means you have paid attention to the earlier classes right. So, the

importance of hexose monophosphate shunt is why do we need hexose monophosphate shunt? If you need to answer in one sentence it is production of two very important compound NADPH and pentose specifically pentose sugars ok. So, NADPH pentose is the resultant of the HMP shunt pathway.

Again another MCQ thing what is the total amount of glucose that enters this pathway per day roughly 10 percent of daily glucose. Where does the other glucose enter? Of course, through the other pathway that is via glycolase and TCA cycle the main path 90 percent goes there here 10 percent. Next RBCN liver they metabolize more than everyone 30 percent of glucose by this pathway ok. So, these are few facts that you need to remember and this may prop up here and there as multiple choice questions. So, be mindful.

Location regarding location of HMP shunt a hexose monophosphate shunt I may abbreviate as HMP it is located in cytosol means the enzymes for HMP shunt are present in the cytoplasm and what are the tissues that are rich or that utilizes HMP shunt. Liver fat cell adipose tissue supranal gland adrenal gland RBC testis lactating memory gland they are highly active in HMP shunt. How this information will help you number you need to remember what where these HMP shunt is happening preferentially to other carbohydrate or glucose utilization pathway and this can also be framed as an all except type of question. So, HMP shunt is highly active in all except. So, might be these tissues are given and brain is a third option or fourth option you need to select that one.

So, be very careful. So, these are the tissues in which HMP shunt is happening best right. So, why why it is important in these tissues because most of these tissues are involved in fatty acid biosynthesis a topic that will be again covered later when we are dealing with lipid metabolism. It helps in production of fatty acid and steroid biosynthesis of fatty acid and steroid which is dependent on the supply of NADPH and I told you whenever we need NADPH we need HMP shunt. Mind it the major contributor of NADPH that is almost 95 percent of NADPH of the body is from HMP shunt.

So, where is the rest of the body 95 percent just for MCQ mind it it is malic enzyme a very minor amount of NADPH is provided via malic enzyme, but that is close to negligible because 95 percent more than 95 percent is formed from HMP shunt ok. So, this is the whole pathway where it starts with glucose 6 phosphate where NADPH is produced there are enzymes like 6 glucose 6 phosphate dehydrogenase epimerase ketoisomerase transketolase transaldolase transaldolase and ultimately it lands in lands into glucose 6 phosphate and I just confused you like yes it is a hell lot of intimidating if you just look at the overall pathway. So, this is not the right way to look at it right yes this picture or this diagram is present in all text books ok and it will get simpler as we go

along right. So, right way we can divide the whole thing into phases ok considering the first three steps these are the these are known as the oxidative phase of HMP shunt. So, step 1 step 2 and step 3.

So, let us see what is happening see this is glucose 6 phosphate this is a cyclical structure of glucose which is acted upon by the enzyme G 6 p d or glucose 6 phosphate dehydrogenase this is the short form ok. It utilizes NADP plus with the help of magnesium minus a cofactor converts NADP plus to NADPH plus H plus or reduced NADP or NADPH ok. Very important and this is the rate limiting step or key regulating step by which the whole HMP shunt can be controlled right and it leads to the formation of the product is 6 phosphor gluconolactone ok. Minded I told you gluconolactone pathway due to production of this ok this is one very important intermediate after which the whole pathway can be named. In the next step what happens there is addition of one water molecule ok.

So, one water molecule is added. So, simply H OH is added over here OH is incorporated and here and H is incorporated and over here we can see this is the carboxyl group has been added. So, when a compound ends with C double O it becomes an acid. So, this is 6 phosphor gluconic acid. Let me pause here if you are having difficulty in memorizing the structures it is purely allowed you can simply answer any question without knowing the structure ok and that is well and good if you can memorize it correctly, but if you are more interested just by looking at the structure the reactions can be better understood or it may appear more complicated.

So, suit yourself you can simply cover the structures and you can simply read out glucose 6 phosphate is converted to 6 phosphor gluconic is converted to gluconic acid like that ok well and good. So, next what happens a dehydrogenase enzyme acts on 6 phosphor gluconic acid. One molecule of carbon dioxide is lost a NADP plus is reduced to NADPH plus H plus and ultimately since one carbon atom is lost this 6 carbons you can see 1 1 2 1 2 3 4 5 6. So, glucose is 6 carbon compound is the ok and it gets converted to a 5 carbon compound the hexose is getting converted to a pentose. So, ibulose 5 phosphate is an example of a pentose sugar ok.

So, NADPH and pentose both we have got. So, there is no need of studying the other part of course, there is because the cycle or the step does not end here, but here ends the oxidative phase why oxidation because there is loss of hydrogen where hydrogen is donated hydrogen is accepted by NADPH. So, NADP plus is getting reduced right and the whole thing is getting oxidated. So, as and when NADP plus is getting converted to NADPH plus dehydrogenation actually means oxidation. So, this is an oxidative phase.

So, 2 dehydrogenases with an inter in hydrolase phase. So, once this is formed this is the ribulose 5 phosphate this ribulose 5 phosphate gets inter converted to various isomers ok. So, via isomerase enzyme this keto group ribulose 5 phosphate COO is a keto sugar it is a pentose ok. Ketopentose it gets converted to a CHO simple the formula is same if you count the number of carbon hydrogen oxygen phosphorus they are absolutely same just an aldose I mean the keto group has been changed to a CHO aldehyde group. So, it is ribose 5 phosphate extremely essential for synthesis of DNA and RNA again a pentose or it can be altered in some other way where the terminal groups are not altered, but the intermittent groups are altered you can see in this carbon it has been the HOH has been altered mind it any form of or any change where the HOH in the inter in carbon is getting altered is in carbon is getting altered is known as epimerization and these two isomers are known as epimer ok.

So, ribulose 5 phosphate and xylulose 5 phosphate are epimers because HOH is changing in an intermediate carbon other than the end carbons and the enzyme is epimerase basically it is a special type of isomerase where there is an intramolecular shifting of bonds right. So, next step is isomerization. So, after isomerization what happens very important this ribulose and xylulose right. So, both are 5 carbon this ribulose and xylulose are 5 carbon. So, with the help of trans ketolase enzyme what is happening a 2 carbon is getting shifted from the 2 carbon to the 2 carbon from ribulose to xylulose ok and it is getting converted to sedoheptulose and this is converted to glyceraldehyde 3 phosphate.

So, the end product both are 10 carbons. So, 5 plus 5 there is a 2 carbon shift and leading to the formation of a 7 carbon compound that is sedoheptulose 7 phosphate and a 3 carbon compound glyceraldehyde 3 phosphate ok clear. So, next next what happens again there is a shifting of carbon unit a 3 carbon unit from sedoheptulose 7 phosphate just for the sake of is I have excluded the structural layout you can see 3 carbon unit is getting transferred from. So, this is the trans ketolase reaction which I just explain in the last slide ok. So, trans aldolase reaction a 3 carbon is getting shifted from sedoheptulose to glyceraldehyde.

So, now, 7 plus 3 becomes 4 plus 6. So, 3 from here is getting added to this 3 it becomes 6 and 3 is removed from 7 it becomes 4. So, what are the resultant compounds they are fructose 6 phosphate and erythrose 4 phosphate. So, this is fructose 6 phosphate and erythrose 4 phosphate fine. You can again follow along very slowly watch it again rewind it is up to you ok, but if you are clear up to here next we can learn the second trans ketolase reaction very important thing did you notice what was the cofactor in trans ketolase reaction it is thiamine pyrophosphate abbreviated as TPP you have read in pyruvate dehydrogenous complex reaction it is a form of vitamin B 1 or thiamine ok.

So, thiamine pyrophosphate TPP is a cofactor of trans ketolase reaction. So, again a trans ketolase reaction happens where a 2 carbon unit is transferred. So, 2 carbon unit is transferred from xylulose to erythrose leading to the formation of fructose 6 phosphate and glyceraldehyde 3 phosphate. So, 5 plus 4 ok. So, 2 gets converted added here it becomes 6 and 5 it becomes 3 carbon compound.

So, ultimately glyceraldehyde 3 phosphate and fructose 6 phosphate these 2 are produced at the end of the second trans ketolase reaction ok. So, you may ask where from the xylulose 5 phosphate is coming well xylulose 5 phosphate is coming from here ok it is an earlier product which was which is now reacting which is the utilized in this second trans ketolase reaction. So, if you are getting confused on how a single carbon atom can or a single glucose molecule can actually lead to formation of ribulose and xylulose and how the 2 intermediates are acting among themselves well you are actually on the right track because in order to fully understand the HMP shunt we need to consider it as a whole system where multiple carbon atoms are going into the HMP shunt and multiple products are coming out ok. So, finally, in the regeneration phase what happens 2 molecule of glyceraldehyde 3 phosphate that are formed in the earlier step this one is getting converted or condensed. So, 2 glyceraldehyde molecule they condense to form fructose 6 phosphate and then converted to glucose 6 phosphate.

So, 2 3 carbon is condensed to form 6 carbon compound ok. So, fructose 6 phosphate can be converted to glucose 6 phosphate just by the enzyme phosphates isomerase and this fructose 6 phosphate is not only formed at the end it was formed in earlier steps also in trans aldolase and the second trans ketolase also fructose 6 phosphate are formed they also get converted to glucose 6 phosphate by the action of phosphohexoisomerase. Why it is written half because considering glucose glyceraldehyde 3 phosphate as a 3 carbon compound it can only lead to half fructose, but in reality 2 molecule of glyceraldehyde 3 phosphate condense to form 1 molecule of fructose 6 phosphate and eventually 1 molecule of glucose 6 phosphate. So, what is the summary of the pathway? Considering 6 molecule of glucose ok that are 36 carbons because hexose 1 glucose molecule has got 6 carbon atoms. So, the first 5 carbon atoms are lost as CO 2 in the oxidative phase itself.

So, 36 carbon atoms that is 6 molecule of glucose will get 6 molecules of carbon dioxide 12 NADPH are produced ok and how many pentose are produced? It is very easy arithmetic if you can subtract the total amount the 5 carbon pentoses are interchanged in such a way. So, mind it pentoses are produced in between ok here pentoses are produced it is useful in synthesis of DNA and RNA, but pentoses are not the end product the reaction does not end after a pentose is produced it has to proceed in such a way. So, that again glucose 6 phosphate is regenerated right. So, considering 6

molecule 5 molecules are lost as CO 2 5 pentose are formed and if they are not utilized in formation of DNA and RNA they will be readjusted in such a way sorry 6 pentoses because 30 carbons that ultimately 5 molecules of glucose are regenerated or glucose 6 phosphate is regenerated. So, if we look at the bigger picture then you will be able to understand that 6 molecules went in 5 molecules came out and then one entire molecule of glucose has been as if one entire molecule of glucose has been burnt out to form carbon dioxide ok and 12 NADPH have been generated, but this is actually not the case.

So, if you just consider one molecule of glucose or glucose 6 phosphate if you think that it is getting completely converted to series molecule of CO 2 it is actually working hand in hand with 5 other molecule of glucose 6 phosphate that are also entering together, but are regenerated at the end of the reaction ok. So, this is the total picture. So, in the oxidative phase itself 12 molecules of NADPH are generated 6 molecules of CO 2 are eliminated and the entire non oxidative phase and also pentoses are generated right and the entire non oxidative phase in which multiple pentoses are generated are actually to regenerate the reactant that is other 5 molecules of glucose 6 phosphate that are regenerated at the end of HMP shunt. Mind it when we are considering fructose 6 phosphate to glucose 6 phosphate is actually going in the reverse direction of glycolysis which have already been taught to in gluconeogenesis right reversal of glycolysis in gluconeogenesis. So, you already know that how fructose 6 phosphate can be converted to glucose 6 phosphate it is a reversible enzyme phosphates isomerase ok.

So, to conclude the lecture has elaborately covered the oxidative and non oxidative phases of HMP shunt pathway. In the next lecture will be looking at the regulation as well as physiological and clinical significance of HMP shunt. So, that is it for today please note the importance of the products of HMP shunt that is NADPH and pentoses which are highly essential for all biological systems. So, these are my references for the lecture. Thank you for your attention.