Overview and Integration of Cellular Metabolism

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Lecture 07: Neoglucogenesis

Hello everyone welcome back. So, we are in the session of overview of integration, overview and integration of cellular metabolism. And here we will discuss Neo Glucogenesis or Gluconeogenesis, where the concepts covered will be the different sites where Neo Glucogenesis occurs definitely we will also discuss what is Neo Glucogenesis and where Neo Glucogenesis is happening inside the cell or in different organ. Then what are the different reactions and their respective enzymes, important enzymes or key enzymes related to Neo Glucogenesis and also different substrate which are utilized in the process. Now Neo Glucogenesis is basically formation of new sugar the term represents new sugar or new glucose. Now what happens as you can see in the say this picture that glucose 6 phosphate can be formed from different molecules.

So, this is Neo Glucogenesis which is formation of glucose molecule from non carbohydrate molecules. So, basically what happens as we have already discussed that that glucose is major fuel for few organs like brain, renal, medulla, then also RBCs they are they utilizes glucose as their most important fuel. Now glucose in the form of energy can be stored in glycogen, but what happens these stores are not always adequate. Suppose we are having prolonged fasting, starvation or in between meals where the gap is high in those cases these glycogen stores are depleted.

So, where from the energy will come. So, they will basically energy or the molecule glucose can be synthesized from different non carbohydrate molecules. So, this process is known as Neo Glucogenesis also we call it gluconeogenesis. So, what are the substrates which are utilized as the provider of glucose like non carbohydrate substrate. So, important one is lactate.

Lactate can form glucose via forming pyruvate. Different glucogenic amino acids they can enter in TCA cycle can replenish the intermediates different intermediates of TCA cycle and finally, can be can be directed towards formation of glucose. So, not the whole lipid molecule or fatty acid molecule, but triacylglycerol by forming glycerol can form

glucose by entering Neo Glucogenesis. Now CO 2 fixation mostly does not happen in mammals. These are this is the pathway which is occurring in plants.

So, in animals what are the substrates like lactate, glucogenic amino acid, glycerol and also propionyl coenzyme A. Now where Neo Glucogenesis occurs the most important organ as I already told in my previous class then that wherever you will see some important metabolic control you will find liver. So, here also the most important organ for Neo Glucogenesis is liver. And to lesser extent Neo Glucogenesis can happen in renal cortex and also the internal epithelial lining present in small intestine. Now Neo Glucogenesis sometimes is called just the reversal reaction of glycolysis where glucose is utilized to form pyruvate whereas, in case of Neo Glucogenesis pyruvate is converted to glucose.

But definitely if you remember in glycolysis there are 3 steps which are irreversible. Apart from that amongst the 10 steps of glycolysis apart from these 3 irreversible steps other 7 steps are reversible. So, basically if there is formation of glucose from pyruvate in Neo Glucogenesis all the reversal reaction can happen utilizing the same enzyme in the opposite direction. But for those irreversible steps there are bypass reaction. Let us see what happens.

So, in glycolysis these are our 3 irreversible steps that is formation of glucose 6 phosphate from glucose, then formation of fructose 1 6 bisphosphate from fructose 6 phosphate and finally, formation of pyruvate from phosphanol pyruvate. Now these 3 steps while forming glucose from pyruvate in Neo Glucogenesis should be bypassed with some other enzyme utilizing some other enzymes following the opposite reaction. So, these 3 enzymes hexokinase, phosphofluctokinase 1 and pyruvate kinase they are not present in Neo Glucogenesis whereas, other 7 steps the enzymes remain same. Now what are then what are the different enzymes for these 3 steps in Neo Glucogenesis? For formation of pyruvate from for formation of phosphanol pyruvate from pyruvate these 2 enzymes are utilized. One is pyruvate carboxylase another is phosphanol pyruvate carboxykinase.

So, basically formation of phosphanol pyruvate from pyruvate is a 2 step reaction. Then fructose 6 phosphate formation from fructose 1 6 bisphosphate their enzyme fructose 1 6 bisphosphatase is used. And finally, glucose 6 phosphate is converted to glucose with the enzyme glucose 6 phosphatase. So, these 4 are the key enzymes present in Neo Glucogenesis. So, basically you can see glycolysis is not a reversible reaction as it is.

Similarly, in Neo Glucogenesis also these 3 steps are not reversible. So, glycolysis and Neo Glucogenesis remember in these 3 steps of reactions they utilize different set of

enzyme. And for both of the pathway glycolysis and Neo Glucogenesis these are the steps which which are exorganic ok. So, let us see what happens while forming phosphanol pyruvate from pyruvate. So, there are 2 sets of enzyme used one is pyruvate carboxylase another is phosphanol pyruvate carboxykinase.

Now these are the 2 exorganic steps here because you can see while forming oxaloacetate from pyruvate there is formation of there is utilization of 1 ATP. And from oxaloacetate while forming phosphanol pyruvate there is utilization of 1 GTP. So, this is a 2 step reaction that is formation of phosphanol pyruvate from pyruvate via formation of oxaloacetate. And both of these steps are exorganic where 1 molecule of ATP here and 1 molecule of GTP here are utilized. Now formation of phosphanol pyruvate from pyruvate basically involves both cytosol and mitochondria.

So, you can see pyruvate it enters mitochondria inside mitochondria the first enzyme is present which is pyruvate carboxylase. Pyruvate carboxylase converts pyruvate to oxaloacetate. Now this oxaloacetate cannot directly go outside mitochondria because this is impermeable to the inner mitochondrial membrane. So, what happens oxaloacetate is reduced to form malate with the help of the enzyme malate dehydrogenase. This is the mitochondrial isoform of malate dehydrogenase present here and here 1 molecule of NADH is used and NAD is formed.

Next malate with the help of 1 specific transporter malate alpha ketoglutarate transporter which we will discuss in malate aspartate shuttle. So, the transporter is malate alpha ketoglutarate transporter. Via this transporter malate goes outside the outside mitochondrial matrix reaches cytosol. In cytosol it utilizes the cytosolic isoform of malate dehydrogenase to reform oxaloacetate and here again NAD is converted to NADH. Similarly oxaloacetate with the help of cytosolic isoform of phosphanol pyruvate carboxykinase it forms PEP.

So, here you can see that the formation of phosphanol pyruvate from pyruvate basically involves both cytosol and mitochondria. Now there is another set of reaction where pyruvate without forming malate can form phosphanol pyruvate. Now these 2 routes are important for different precursors. Another where there is formation of malate that is required when alanine or pyruvate itself is the source of neoglucogenesis or source of phosphanol pyruvate. Whereas, in case of lactate where lactate is the precursor for phosphanol pyruvate it does not involve formation of malate.

Rather what happens lactate with the help of the enzyme lactate dehydrogenase form pyruvate and with formation of 1 molecule of NADH. Then pyruvate enters mitochondria inside the mitochondria with pyruvate carboxylase enzyme it is converted

to oxaloacetate oxaloacetate with the help of phosphanol pyruvate carboxykinase which is the mitochondrial isoform. Here it was the cytosolic isoform and with the help of the mitochondrial isoform of PEP carboxykinase oxaloacetate is converted to phosphanol pyruvate which comes outside in the cytosol. Now, why these 2 types of routes are present? Now it is because in neoglucogenesis there is utilization of NADH. Now if you remember in glycolysis there is formation of NADH from NAD.

So, in the reversal reaction in neoglucogenesis there will be formation of NAD from NADH. Now while utilizing NADH in neoglucogenesis definitely there is depletion of cytosolic NADH and NADH concentration in mitochondria is very very high with respect to cytosol. So, basically this malate formation is actually the replenishment of NADH. What happens you can see that here with the utilization of mitochondrial NADH malate is formed with the utilization of mitochondrial NADH malate is formed whereas, these malate when it comes outside while forming oxaloacetate it provides NADH in the cytosol. So, basically this is an indirect transport of NADH from mitochondria to cytosol.

Now why it is not required in case of lactate? See you can see here while forming pyruvate form lactate already there is production of NADH. So, basically lactate itself is replenishing the concentration replenishing the amount of NADH in cytosol by forming pyruvate. So, in case of phosphoryl pyruvate formation from lactate malate formation is not required. So, this is the physiological modulation of the cell to replenish the concentration of NADH and to maintain the flux of neoglucogenesis. Now pyruvate carboxylase is the mitochondrial enzyme and as we discussed most of the carbo carboxylase utilizes the cofactor biotin.

Here for the allosteric regulation of carboxylase there is important role of acetyl coenzyme A. So, this is acetyl coenzyme A acts as the positive effector for activation of pyruvate carboxylase why? Remember when there is huge amount of acetyl coenzyme A. So, basically those those are formed from fatty acid oxidation which happens in neoglucogenesis. So, more amount of acetyl coenzyme A is formed from breakdown of fatty acid and that acetyl coenzyme A activates pyruvate carboxylase for production of glucose for supply of energy.

Now, this term is important. Neoglucogenesis is energetically expensive, but essential why? So, we told that there are 2 exergonic reaction while forming phosphanol pyruvate from pyruvate. Whereas, if you do remember that while forming pyruvate from phosphanol pyruvate there was only one ATP form. So, for formation of phosphanol pyruvate more amount of energy is invested, but it is essential why? To maintain the supply of energy in the cells, cells like brain, cells like RBCs which mostly depend on

the fuel glucose. So, neoglucogenesis is essential even if it is energetically expensive. So, we have already discussed this first 2 enzyme.

Now, formation of fructose 6 phosphate from fructose 1, 6 bisphosphate there is hydrolysis of one high energy bond and inorganic phosphate is released in the system. The enzyme used is fructose 1, 6 bisphosphatase. Similarly, for formation of glucose from glucose 6 phosphate again another phosphatase is used glucose 6 phosphatase with release of inorganic phosphate in system. So, these are the 3 steps of glycolysis which are irreversible in neoglucogenesis. For these 3 steps of reaction there are different sets of enzymes and these are the key enzymes where neoglucogenesis is basically regulated.

Now, we will discuss a few points about glucogenic amino acids. Now, most of the amino acids which are derived from protein they finally, catabolize to form either pyruvate or different other intermediates of TCA cycle. So, basically they can participate in formation of glucose and that is why these amino acids are called glucogenic amino acids. Now, glucogenic amino acids here are mentioned with their site of entry like isoleucine, methionine, threonine, valine. These amino acids they can form succinyl coenzyme A and intermediate of TCA cycle.

Similarly fumarate can be formed from phenylalanine and tyrosine. Oxaloacetate can be formed from asparagine and aspartame. Mostly the reactions are transamination or deaminations. Alpha ketoglutarate can be formed from arginine like glutamine, glutamate, histidine, proline. And finally, pyruvate can be formed from alanine, cysteine, glycine, serine, threonine these are the amino acids they can contribute in forming pyruvate.

Now these are the main amino acids alanine and glutamine which actually transport the amino group from extra hepatic tissue to liver with the reaction set of reaction transamination or sometimes deamination. Now basically majority of the amino acids majority of the neo glucogenic amino acid enter TCA cycle via formation of either pyruvate or alpha ketoglutarate. So, these are the major important glucogenic amino acids present in mammal. So, in this class we have discussed neo glucogenesis as it is the different reactions of neo glucogenesis. So, neo glucogenesis is basically a multi step process ubiquitous in nature present in all types of cell where glucose is produced from non carbohydrate substances like lactate, pyruvate, oxaloacetate or any other intermediate of TCA cycle.

In neo glucogenesis majority of the steps are the reversal of glycolysis, the reversible steps of glycolysis where same sets of enzymes are used, but there are 3 irreversible steps of glycolysis. So, in those cases those reactions are conducted by different sets of

enzyme the enzymes are pyruvate carboxylase and phosphanol pyruvate carboxykinase, then first fructose bis phosphatase and glucose 6 phosphatase. So, this is about neo glucogenesis. In the next class we will discuss how neo glucogenesis and glycolysis are regulated in coordination. So, basically those are how they are regulated reciprocally we will discuss .

Thank you very much see you in the next class.