Overview and Integration of Cellular Metabolism

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Lecture 13: Glycogen Metabolism (II)

Hello everyone. So, we are back with our lecture series of Overview and Integration of Cellular Metabolism. We were discussing Glycogen Metabolism since the last class. We have discussed how glycogen is synthesized the mechanism glycogenesis and also how glycogen is broken with the mechanism glycogenolysis. In this class the concepts covered will be the regulation. Regulation of glycogenolysis and glycogenesis with how they these regulation occurs with the help of different hormones by covalent modifications and allosteric regulation.

In this class we will most mainly discuss glycogenolysis or glycogen breakdown. So, if you remember the most important enzyme as we have discussed in the last class the most important enzyme of glycogenolysis is glycogen phosphorylase. So, the regulation is mainly over this enzyme how this glycogen phosphorylase is regulated is the regulatory mechanism of glycogenolysis. Now before starting the discussion I would like to highlight some points about glycogen phosphorylase.

Now glycogen phosphorylase is one very important enzyme with respect to history. Now glycogen phosphorylase remember this is the first enzyme where allosteric activity is explained. So, this is the first allosteric enzyme discussed. This is the first enzyme where covalent modification by phosphorylation and dephosphorylation is discussed. And also this is the first allosteric enzyme which has been whose structure whose actives and inactive structures are illustratively demonstrated with x-ray crystallography.

So, glycogen phosphorylase is one very important enzyme. And then another very important thing that glycogen phosphorylase it remains in two different form and that has been discovered by Carl Corey and Gertie Corey the two those two important scientist those they actually where ever did Nobel prize in the stream of medicine and physiology for this for demonstration of glycogen phosphorylase and its activity. So, they demonstrated that glycogen phosphorylase remains in two form one is phosphorylase A and another is phosphorylase B. Now remember glycogen

phosphorylase as this is the first phosphorylase even which has been discovered. So, to honor this discovery it is named as it is known as phosphorylase whenever we say phosphorylase it means we are talking about glycogen phosphorylase.

So, glycogen phosphorylase remains in two form one is like phosphorylase A another is phosphorylase B. Now phosphorylase A is the active form of the enzyme whereas, phosphorylase B is the inactive form what is the difference phosphorylase A is the phosphorylated form and phosphorylase B is the dephosphorylated form. Now how this activated form is formed definitely by phosphorylation with some enzyme enzyme which is having phosphorylation function. So, the enzyme is some kinase what that kinase is that is phosphorylase kinase A. So, phosphorylase kinase A is actually phosphorylating the phosphorylase B to form the active phosphorylase.

So, these terms are quite jargons here, but to remember that phosphorylase A is the active form and that activation is done by phosphorylation with the help of a kinase again that kinase has active and inactive form. So, the active form is kinase A inactive form is kinase B and again the active form is the phosphorylated form. So, basically there is activation of the kinase with phosphorylation and on activation this kinase activates phosphorylase. Now how this activation occurs by some hormones hormones like epinephrine glucagon they actually activate this kinase by some enzyme cascade reaction. So, there are series of reaction which causes activation of this phosphorylase kinase with the help of epinephrine.

Now epinephrine what that enzyme cascade is actually epinephrine epinephrine forms cyclic AMP with the help of the enzyme adenyl cyclase. This cyclic AMP activates cyclic AMP dependent protein kinase kinase is related to phosphorylation. So, this protein kinase cyclic AMP dependent protein kinase actually phosphorylates this phosphorylase kinase. So, basically there is activation of phosphorylase kinase by cyclic AMP dependent protein kinase. If there is a kinase there is a phosphatase as well which actually deactivates this enzyme by dephosphorylation.

So, dephosphorylation occurs by protein phosphatase 1. Now this protein phosphatases sorry this protein phosphatases actually inactivates all this phosphorylase as well as phosphorylase kinase. Now there is one inhibitor substrate inhibitor 1. Now this inhibitor 1 is also present in active and inactive form and definitely the active form is once again phosphorylated form. Again this phosphorylation is done by cyclic AMP dependent protein kinase.

So, cyclic AMP dependent protein kinase activates the inhibitor 1 on activation this inhibitor 1 inhibits protein phosphatase. So, basically cyclic AMP dependent protein

kinase not only activates the phosphorylase kinase which helps to form the active form of phosphorylase also cyclic AMP dependent protein kinase helps to inhibit this degradation of the active forms with the help of inhibitor 1. So, if these pathway is inhibited if these pathway is inhibited what will happen? There the active form will remain as inactive there will be no formation there will be any form inhibition of the formation of inactive form. So, once again there will be activated phosphorylase present in the system which will finally, lead to glycogen breakdown. Then there is role of calcium along with this covalent modification.

So, this is a sort of this is an example of covalent modification in enzyme activity regulating enzyme activity. Along with this covalent modification there is some there is role of some allosteric activators and inhibitors also. So, in skeletal muscle 2 important allosteric molecules one is calcium. So, this calcium basically activate calmodulin part of phosphorylase kinase phosphorylase kinase which have domain similar to calmodulin is induced by calcium. So, calcium also helps to form the activated form of kinase.

Similarly another allosteric activator is AMP. Now, AMP if you remember from the previous classes AMP signals for energy demand. So, if there is energy demand means there is less amount of ATP present now this molecule activates those pathways which can provide energy. So, basically glycogen breakdown can provide energy breaking down of glycogen we will get glucose which will enters for 2 which will actually like glucose will be providing ATP. So, AMP is a signal molecule here it acts as allosteric activator of phosphorylase kinase in skeletal muscle.

Now, another important molecule is glucose 6 phosphate. Now, glucose 6 phosphate acts as allosteric inhibitor it inhibits phosphorylase kinase. Glucose 6 phosphate remember inhibits phosphorylase kinase glucose 6 phosphate comes from glycolysis. If there is huge amount of glucose which is forming glucose 6 phosphate means we do not need breakdown of glycogen. So, this is a signal that there is enough amount of adequate amount of energy present this is an allosteric inhibitor here which inhibits phosphorylase kinase.

And these glucose 6 phosphate formation if you remember it is reduced with the help of the hormone insulin. So, this is regulation of glycogen phosphorylase by covalent modification phosphorylation and dephosphorylation activated by epinephrine following a cascade of enzyme activation as well as there are few allosteric activators and inhibitors. To jot down once again phosphorylase enzyme is regulated in liver and muscle, but in some different mechanisms. So, we have discussed the cyclic AMP dependent regulation, but then this calcium induced activation it happens differently in liver and muscle. Now, remember as I told calcium induces calmodulin part of the

protein kinase see calmodulin part of the protein kinase.

Now, this phosphorylase kinase this enzyme has 4 subunits alpha beta gamma and delta. This alpha and beta subunits they have residues which can be phosphorylated. So, covalent modification or phosphorylation occurs in this alpha and beta subunits. Delta subunit the subunit which is similar with calmodulin. So, calcium here binds with this delta subunit induces some conformational change that conformational change induces this gamma subunit which is having the actual catalytic activity.

Now, this calcium induced activation occurs inside skeletal muscle whereas, in liver calcium induced activation is cyclic AMP dependent independent and it is activated by epinephrine nor epinephrine with activation or induction of alpha 1 adrenergic receptors. So, this is one in liver calcium induced activation of phosphorylase kinase is basically a cyclic AMP independent mechanism where with the trigger with after getting signal from epinephrine nor epinephrine there is extensive release of calcium from sarcoplasmic reticulum that calcium enters inside the hepatocytes inside hepatocytes it activates the phosphorylase kinase. Then there is allosteric activation which is also different in case of skeletal muscle and liver. In both the organs active phosphorylase activation of phosphorylase occurs inhibition occurs with the help of ATP and glucose 6 phosphate these are common for liver and skeletal muscle. In skeletal muscle I have already told that 5 prime AMP or AMP is an allosteric activator in liver and 5 prime cyclic AMP is not an activator in liver whereas, in liver free glucose is one molecule which inhibit which inhibits the phosphorylase enzyme.

Now, let us see how this occurs. So, basically when there is glycogen breakdown that means, there is low blood glucose level and that low blood glucose level and that has been sensed by glucagon, glucagon activates glycogen phosphorylase glycogen phosphorylase starts to break down break break the glycogen molecules. So, there is formation of glucose those glucose released in circulation. Now, when there is in circulation when there is raising of blood glucose level that glucose enters inside hepatocytes in hepatocytes it binds to some to the allosteric sites of phosphorylase A. So, phosphorylase activated phosphorylase actually have some allosteric site where glucose can bind.

Now, you can see this phosphorylated residues are inside are buried inside the molecule when glucose binds in this allosteric site this glucose induces some conformational change which actually exposes this phosphorylated residues they are exposed to whom to the phosphatase and this phosphatase actually causes the dephosphorylation and inactivation of phosphorylase B. So, basically glucose here free glucose the circulating glucose circulating free glucose enters hepatocytes and by allosteric modification it

causes dephosphorylation of phosphorylase B and causes inactivation and this happens in case of liver. So, this is how actually liver phosphorylase acts as a sensor of blood glucose level. So, in this session we have discussed the regulation of glycogen breakdown the regulation of glycogen phosphorylase which is activated in response to the hormones glucagon or epinephrine. Glucagon and epinephrine they starts and series cascades of reaction which ultimately raises the concentration of cyclic AMP.

Cyclic AMP activates cyclic AMP dependent protein kinase A, protein kinase A phosphorylase and activates the phosphorylase kinase phosphorylase kinase activated phosphorylase kinase actually activates glycogen phosphorylase forms the glycogen phosphorylase B and this causes breakdown of glycogen molecule. Similarly, the enzyme phosphoprotein phosphatase 1 reverses this phosphorylation in glycogen phosphorylase and inactivates it. Now, glucose it binds to liver isoenzyme favoring its dephosphorylation and inactivation by this glucose can act as allosteric in activator or inhibitor in liver. In liver glucagon stimulates the glycogen breakdown and these breakdown spares the glucose from export to other brain tissues. So, basically on those tissues which are actually dependent on glucose for the provision of energy they get glucose via glycogen breakdown and that is solely controlled by the action of liver glycogenolysis.

Whereas, in muscle epinephrine stimulates glycogenolysis and that glycogen breakdown is to form glucose 6 phosphate which finally, provides ATP to support the contraction. So, this is about the regulation of glycogenolysis or glycogen breakdown these are my references. In the next class we will discuss about the regulation of glycogen synthesis and also how reciprocally these 2 pathways that is synthesis of glycogen and breakdown of glycogen they are coordinated. Thank you all see you soon in the next class.