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 18: Regulation of Blood Glucose

Hi everyone, welcome to the lecture series on Overview and Integration of Solar Metabolism. Today is fourth week and lecture number eighteen we have almost done, we are almost done with carbohydrate metabolism, but the very important concept of regulation of blood glucose is left. So, in this class we will be covering these important concept, we will be understanding what is the normal level of glucose, what are the symptoms of hypo and hyperglycemia, what are the factors that regulate blood glucose level, we will be discussing how this glucose level is maintained. So, glucose homeostasis, we will discuss how liver plays an important role and we will also be discussing what hormone plays role in maintaining this blood glucose level. So, first things first for this class you should know that the fasting levels of blood glucose, that is normal level of blood glucose in fasting is 70 to 100 mg per dl and for postprandial that is after food 2 hours after meal the normal blood glucose level is up to 140 to it is generally 70 to 140 unit is milligram per dl. Mind it in many text books you might find it is up to 110 milligram per dl, we always quote ADA criteria that is American Diabetes Association criteria and it says up to 90 to 99 or 70 to 100 is normal level right.

Over that we go into pre diabetic state and we will be discussing that in the next lecture on diabetes mellitus. So, this normal blood glucose level can be maintained by two factors number one the rate suppose there is a jar of water ok and there is a tap and we are constantly filling the jar from above. So, in order to maintain the water level what to be the factors the two factor definitely by which the rate of entry into the bowl and the rate of exit. So, if these two rates are same then the glucose and the level of water will be same the same analogy can be expressed in terms of glucose concentration.

So, rate of entrance of glucose into the blood circulation rate of removal of glucose from the blood stream will determine whether the level of blood glucose can or cannot be maintained in the circulation right. So, here are few quick references quick values that are very important for MCQ point of very important for MCQ point of view multiple choice. So, 70 to 100 is the normal level that is shown in green if the blood glucose level

for fasting goes above 126 all according to American Diabetes Association criteria. We declared the patient to be diabetic and if the blood glucose level goes above 200 for postprandial we again declared the individual to be diabetic. So, anything above 100 to 126 for fasting and 140 to 199 for postprandial is actually a prediabetic state.

Anyway one very important thing over here is mentioned that is renal threshold what is renal threshold? Renal threshold means generally glucose is not excreted in urine up to a certain level right, but if the blood glucose level goes above 180 glucose will start coming out in urine and that is known as glycosuria right. So, our goal is to check whether the blood glucose level should be below 180 in that case will not be getting glucose in urine. If glucose is found positive in urine it will give rise to test for reducing sugar that will be positive those tests are Benedict's test or or Fehling's test. These tests will be positive for reducing substances because glucose is a reducing sugar. Going into the lower end hypoglycemia.

So, when the when something is high we refer to as hyper when something is low we refer to it as hypo less ok. So, when it is hypoglycemia when do we consider hypoglycemia the symptoms it will happen when the glucose level goes below 40 right. So, even if the glucose level is between 70 to 100 the body will always try to maintain. So, that the patient does not go into a hypoglycemic state or the renal threshold is not crossed ok. So, this is the working range of multiple factors that regulates glucose homeostasis homeostasis means maintaining the normal level.

So, if you are going any further let us learn what are the symptoms of these two extremes. So, what will happen how will we understand if the patient is having or if I am having hypoglycemia. Suppose I skipped my morning meal and I was supposed to take lunch and I was supposed to deliver this lecture to you for example, but somehow due to a pre scheduled meeting I miss the lunch also. Now, as I am giving the lecture I am talking to you right I am spending so much energy. So, the glucose level will ultimately go down and I might face this sort of problems.

So, what are these these are tiredness I will face fatigue, confusion, dizziness, headache, mood swings, muscle weakness, tremor like a sweating very important when blood glucose level is low a patient sweats ok. And if this goes unchecked if blood glucose level continues to fall down ultimately I will become unconscious because there will be irreversible brain damage and I will go into coma ok. Any that is why it is very important to diagnose case of hypoglycemia and that is a dictum when any unconscious case comes in a hospital emergency we always first tends the capillary blood glucose level just to rule out this very treatable cause of unconsciousness. Because a patient may be unconscious for many reason, but if hypoglycemia is detected if we just infuse some

glucose the patient will magically sit up ok. So, that is the beauty of hypoglycemia.

We also need to know the symptoms of hyperglycemia. So, what happens if excess blood glucose is there right in case of diabetes mellitus right. So, there will be excessive thirst, excessive hunger, excessive fatigue, excessive urination in the long run there will be excess weight loss diabetes lead to cataract I told you in the last class. So, it will lead to loss of vision, blurring, retinopathy and there will be the there will be nerve problem, neural problem and ultimately the immunity power of the body will go down and to lead to infection. But mind it these symptoms are slow a patient or an individual might not be aware that we are having hyperglycemia.

But he will definitely be aware if he is having hyperglycemia because he will start to sweat and he will start to feel confused and he will lose consciousness. So, hyperglycemia can be easily diagnosed easily treated. Hyperglycemia generally may go unnoticed unless a individual is very self conscious they are doing routine blood check otherwise a patient or individual may land up in a clinic appearing to be fine, but he may have very high level of blood glucose right. So, let us see what are the factors that are increasing the blood glucose level ok normally. So, we have a pool of blood glucose.

So, what are the inputs to this pool who is increasing? Number one absorption from intestine glucose main source is diet right. Next when diet is not there hepatic glycogenolysis next storage form of glucose will be broken down. So, this is glycogenolysis. When all the glycogen is depleted then what happens gluconeogenesis happen that is obtained from other sources. For example, a me glucogenic amino acid the ketone body there are multiple sources from that can act as substrate by which it can be converted back to glucose ok.

And very minor portion can be by internal isomerization from fructose and galactose because glucose, galactose, mannose they are all isomers ok, but they are very minor the main most important source is diet followed by glycogenolysis followed by gluconeogenesis. And what are the factors by which glucose is utilized from the body? So, these are the factors that are decreasing glucose level. Number one glucose is entering into the glycogenolysis and TCA cycle. So, it is utilized the moment glucose is being converted glucose 6 phosphate glucose level is has gone down right. Next hepatic glycogenesis this glucose 6 phosphate can be used to form glycogen that leads to decrease of glucose level glycogen formation in both liver and muscle contributes to the decrease in glucose level.

Next carbohydrates can be converted to fat. So, glucose it forms acetyl coenzyme a by TCA cycle it gets converted to fats ok lipogenesis we will be discussing it very soon. So,

one mechanism by which glucose can be reduced from a high pool of glucose is by formation of fatty acid. Again glucose can be converted to fructose polyol pathway and it is essential in seminal fluid glucose can be converted with galactose to form lactose it is essential for milk secretion memory grant as well as via HMP shunt glucose can be converted to pentoses ok ribose sugars and for synthesis of DNA. So, these are all the mechanism by which glucose is actually continuously pulled from the system and then balance between the input and output creates a harmony between maintenance of glucose level.

So, what will happen if the blood glucose level is certainly low suddenly the blood glucose level is low what happen the low blood glucose level signals the pancreas to secrete glucagon right glucagon is a hormone that increases the level of glucose. So, how glucagon will increase it will stimulate the liver to up regulate two processes remember from the very second class of enzyme regulation glucagon promotes catabolic enzyme by phosphorylation by the action of cAMP. So, glucagon so we need glucose glucose production is basically catabolism right we need glucose from glycogen. So, a big storage glycogen will be broken down to simpler form. So, glycogen will promote the catabolic pathways of gluconeogenesis and glycogenolysis and thus glucose level will be increased in blood right.

So, once the blood glucose level rises to normal level the glucagon brain will sense or the pancreas will sense ok we have adequate amount of glucose we do not need any more glucagon. So, this will stop. So, this is what happens if the glucose level is low just ignore the upper part for now. So, when the glucose level is low alpha cells of pancreas are stimulated to secret glucagon, glucagon will promote breakdown of glycogen and synthesis of glucose in the liver glycogenolysis and nucleogenesis and that will ultimately increase the blood glucose level. So, this is the way how glucose amiostasis happens when the blood glucose level is low.

What will happen when the blood glucose level is high? When blood glucose level is high there are two separate signaling event. The first signal is that blood glucose level is very high it is given to the pancreas. What pancreas does? Beta cells of pancreas, beta cells of islets of Langerhans of pancreas islets of Langerhans. Beta cells of islets of Langerhans of pancreas secrete insulin and the second signal is actually from insulin to the target cells. Insulin promotes anabolism now there is high amount of glucose.

So, glucose will be utilized to form complex products glycogen ok. So, glucos insulin will now help in anabolism mind it you may be thinking about ok glucose is insulin is helping glycogenesis it is fine. It is also helping glycolysis in glycolysis glucose is ultimately finally, broken down to pyruvate right. But remember in glycolysis there is

this pyruvate can be utilized to synthesis of many other compounds. So, in a way since glycolysis actually behaves has got a both anabolic and catabolic role.

When we are considering the metabolism generally the regulation of glycolysis occurs in an anabolic way. This is an of the thing I mean this is not a part of this lecture, but I thought that this question might prop up anywhere. So, even if you are having difficulty understand we can address it in the life classes ok. Do not worry about that anyway for this discussion just note that insulin will give a signal to target cell and that will increase all the anabolic pathway. So, glucose will now be utilized anabolic pathway utilizes glucose.

So, what are the processes that utilize glucose number on glycogenesis glucose is converted to glycogen, glycolysis glucose is be converted to pyruvate. So, all the pathways that utilizes glucose are converting to lowering of blood glucose effectively ok. So, this is what happens in case of high blood glucose level. So, insulin is secreted the first signal is to pancreas and the second signal is insulin that gives target signals for target organs that is whether it is liver or it is cells. So, glucokinase or hexokinase whatever the target is mind it glucokinase is not inducible by insulin.

Liver the signal is to utilize more and more glucose to convert it into glycogen. The signal to the muscle cell is also to convert it glycogen right and thus the glucose pool is depleted and the high blood glucose is now normalized ok. So, this is the overall pathway by which the glucose level is maintained in the system. Now, let us learn about the stages of blood glucose homeostasis. So, by the stages I mean a scenario where the we are having adequate diet right.

So, when adequate diet is there the absorptive phase of glucose starts and it last to 3 to 4 hours after the meal ok. So, this dietary glucose the enters into our system it reaches the liver and most of the tissue glucose is the fuel for most of the tissue right and excess amount of glucose is stored by glycogen in liver there is no problem when you are adequate in diet. So, main if the adequate level of diet is there it means glucose level is high and then insulin level will be acting. So, this is actually when this is we are in absorptive phase ok you can consider this right. What if now we are done with the meal now we are not eating right.

So, there is something in the post absorptive phase. So, we are now after the meal this there is a changes in metabolic pathway. So, what happens after 16 to 18 hours after the absorptive phase that is absorptive phase last for 3 to 4 hours we are considering after 16 to 18 hours the main activity is actually since there is no more diet right. So, the body or the brain most important needs glucose. So, what will be the sources of glucose liver will

be the most important organ that will supply glucose how by glycogenolysis.

So, glycogenolysis becomes the main source of glucose and muscle also utilizes. So, we when we are having doing exercise we are normally walking after skipping breakfast do we fall down never ok there is a buffer system and these are the phases that we are discussing. So, normal blood glucose level is actually maintained very beautifully how by the process of first by the process of glycogenolysis. After the glycogen sources are depleted then what happened gluconeogenesis starts, but it only starts after 24 hours ok. For the first 24 hours the dietary the continued absorption of dietary glucose as well as the breakdown of glycogen from liver and muscle maintain the blood glucose level ok.

And generally after 24 to 30 hours the glycogen sources are actually depleted and generally they start to decline ok. So, from 3 to 4 hours till the next 16 to 18 hours the liver will continue to supply blood glucose from its glycogen. So, what happens after 16 to 18 hours is done and there is still no food source mind it this is from the absorptive phase that is after 4 hours till 16 to 18 hours this is the phase of starvation right. There is still no food someone trapped in earthquake it might so happen right under the debris there is no food source. So, at 1 and 1 and half day of like I mean after 1 and half day of starvation glyconeogenesis is the main source of blood glucose.

The goal is to maintain blood glucose level for the brain to function otherwise there will be coma and death right. If the still starvation continues glyconeogenesis will be there who what are the substrates from glyconeogenesis multiple fatty acid, glucogenic amino acids anyone. So, fatty acids are mobilized from anti-post tissue and become an alternative fuel for energy for most sources as well as lactate and glycerol are reutilized for gluconeogenesis why? See after the entire carbohydrate source is done with body will try to search for alternative sources of energy and by this time the fats of the body they start to get utilized right. And the glycerol and lactate that are produced from this for hypolysis are reused as substrate for gluconeogenesis right. Now there will be fat the fatty acids will be broken down by the process of beta oxidation, alpha oxidation, omega oxidation again a topic of interest that will be discussing later in our lecture series.

So, fatty acid oxidation will lead to the production of ATP that ATP will be utilized by the liver for gluconeogenesis and other body function because we also need ATP to continue simple very simple reaction that we discussed in the very first class of thermodynamic coupling right. And what happens high rate of hepatic gluconeogenesis continues for few days in early starvation. So, when we are in the first few days right hepatic gluconeogenesis very high. So, somehow liver tries to catch hold of any substrate that can be converted to glucose and it converts into glucose to maintain the glucose homeostasis of the blood level of glucose. Next what happens even if there is starvation

after 2 to 3 days then the hepatic gluconeogenesis start to decrease and renal gluconeogenesis happens ok kidneys are also equipped to undergo gluconeogenesis ok.

But by that point we need more and more substrates for gluconeogenesis right. So, who are the substrates for gluconeogenesis those are amino acid or glucogenic amino acid those amino acid that can be converted to glucose and where from we will get those amino acids mind it amino acids are the building block by which proteins are made right peptide bonds. So, proteins that is the muscles of the body will be broken down and they will act as a substrate for gluconeogenesis. So, if we are continuing with this starvation phase ultimately what will happen all the sources of lipid sources of the body will be depleted all the amino acid those that is the substrate for gluconeogenesis that will also be depleted mind it we need to produce glucose why because ultimately this glucose will go into the TCA cycle glycolysis and they will produce energy right glucose is utilized for production of ATP that is why it is the fuel of the body. But in later stages that will be discussing in our subsequent class of lipid metabolism when we are completely bodies completely depleted of carbohydrates the only way we can achieve nutrition is by formation of ketone bodies.

So, then ketone bodies are acidic in nature there is keto acidosis water is lost from the body and ultimately death occurs. So, there is a point beyond which homeostasis cannot happen right. So, at this point during a prolonged starvation the patient or the affected individual needs to be fed with dietary glucose and all this will reverse the phenomena first glucose will be utilized to fuel the brain all the important enzymes of the body ATP will be provided and ultimately excess glucose will be then stored to deplete the I mean replete the body glycogen stores and all the phases will be reversed right. So, from starvation to once feeding start this whole thing is actually reversed right. So, what is the role of liver and extra hepatic tissue in maintaining the blood glucose level? During glucose transport I mentioned to you that GLUT2 is a transporter that is present that is in non insulin dependent is present in the hepatic site where glucose from blood is being delivered to the liver.

And this is a freely permeable to glucose and it is the main hepatic glucose transporter by which liver up takes the glucose from periphery. Whereas in case of other muscles and fat cells adipose tissue what happens there is presence of GLUT4 which is actually insulin dependent right. So, you see whenever body or the pancreas needs to send a signal to the extra hepatic tissues it can do it via GLUT4. So, insulin can tell the muscle the adipose tissue to uptake excess amount of glucose as you want right. And insulin can also tell them to stop when it is needed, but it cannot tell the liver.

So, in liver the uptake is independent of insulin right. This is a very important

mechanism by which the peripheral cells can actually spare glucose in order to divert the available glucose for the brain to have in case of hypoglycemia right. Now, how does the liver actually acts as a or plays a role in glucosomeostasis is beautifully governed by two enzyme that is hexokinase and glucokinase. You see hexokinase is actually present in the peripheral cells. In peripheral cells what does hexokinase do we all know by now it converts glucose to glucose 6 phosphate.

In peripheral cells how glucose is entering the cells by the action of insulin. When insulin tells glucose enters into the peripheral cell and hexokinase can easily utilize the peripheral glucose in the peripheral cells and it get then gets convert to glucose 6 phosphate and all the important processes are continued. But in liver it can utilize glucose with the help of the enzyme glucokinase right. Mind it liver has both hexokinase and glucokinase. So, when liver needs to synthesize glucose 6 phosphate it can do it right, but when it does not it do not have to because it is insulin independent.

So, liver has it has got its own control. Let us understand together what it happens. So, hexokinase is actually saturable means if you give excess amount of glucose inside the cell hexokinase would not be able to act right. There is a finite amount by which hexokinase can convert glucose to glucose 6 phosphate. Unlimited uptake at the cellular level is not possible. So, if glucose level is very high excess glucose cannot be taken up by the cells and stored, but liver can do that.

How it is because glucokinase is non saturable it has got high came for glucose and it is not product inhibited very important glucose is getting converted to glucose 6 phosphate there is a hexokinase. I discussed in the feedback inhibition once glucose 6 phosphate is formed it will inhibit hexokinase to convert further glucose to glucose 6 phosphate. This inhibition is not present in case of glucokinase all right. Therefore, liver can continue to have high uptake of glucose and thus it is acts as a storehouse of glucose. Whereas extrahepatic tissues even if insulin is present it will the glucose uptake will be inhibited right.

So, this all leads to one summary that at high blood glucose concentration, liver has a net uptake of glucose, but the beauty is when imagine the glucose concentration is low. Now, the brain and peripheral centers all need glucose and now the insulin can actually the control of insulin is gone and we need glucose to be converted to glucose 6 phosphate right. However, since the Km or the Km is actually inverse related to the affinity since glucokinase has high Km, liver do not need excess glucose when the glucose condition is low. Liver will surrender it will say whatever glucose I have I give it to you glucose is handed over to the periphery so that the peripheral tissues like muscle and brain can utilize glucose. So, glucokinase and hexokinase by working in tandem,

liver can utilize glucose in presence in high when the glucose is very high and liver can actually let go of glucose when the glucose level is very low right.

So, thus now in the next few slides we will summarize the action of hormones by which the blood glucose level is altered ok. There is only one hormone that will decrease the blood glucose level, but there are multiple hormones that will increase the blood glucose level. So, glucagon epinephrine, cortisol and glucocorticoid they will all help in increasing blood glucose. This is the summary when blood glucose is high insulin level glows up insulin what it does it helps in internalization of glucose and thus the blood glucose goes down and insulin is lowered insulin signaling is lowered.

This slide I already discussed during the metabolism. So, now you can relate more and more. So, what are the processes these are the process that lowers blood glucose and these are up regulated by insulin and down regulated by glucagon. These are the processes that helps in up regulation of blood glucose. So, they are lowered by insulin and they are actually enhanced by glucagon. So, this is these are the for the next two slides these are the whole table by which you can easily know what are the functions each and every hormone is doing.

It is not essential to know the individual function of all hormone with respect to carbohydrate metabolism only, but the only take home message over here is that insulin lower the blood glucose level whereas, somatostatin, glucagon, epinephrine, cortisol, ACTH, growth hormone, thyroxine all acts in tandem to raise the blood glucose level. You can easily pause these two slides and take a note of what hormone action are being exerted by each and every hormone or not when it comes to the action on glucose everyone is trying to raise the blood glucose. Can you tell me why because hypoglycemia is dangerous patient will immediately die. So, hypoglycemia needs some more players to tackle. So, these are the players that have been allotted to raise blood glucose whereas, insulin it is the only player which lowers blood glucose and if there is insulin deficiency that will lead to diabetic somatitis.

So, the key home take take home as and the key points where we learn what are the normal level of blood glucose, we learn what are the symptoms of hypo and hyperglycemia, we learn what are the factors that regulated blood glucose level, we learn what are the stages of glucose homeostasis, how liver and hormones regulate blood glucose level. So, these are the references for my lecture today. I thank you for your patient hearing and I will see you in the next class which will be regarding diabetes mellitus.