Overview and Integration of Cellular Metabolism

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Lecture 55: Integration of Metabolism II (Starve feed cycle)

Hello everyone. We are back to the lecture series of overview and integration of cellular metabolism. In the last class, we have started integration of metabolism where we have discussed the metabolic integration in cellular as well as tissue level and also the varied metabolic profiles of different organs. Now, here we are going to discuss about the star feed cycle or star fast feed cycle, but before that I want to remind you this is the time when you must revise or rather complete your revision of all the overview of metabolism, metabolism of carbohydrate, protein, fat, nucleotides everything because now in this class I am going to discuss all of these and I am going to bring all the references from the previous topics and if you revise it will be easy for you to understand. So, in this class the concepts which will be covered are the metabolic profiles under well fed condition and then what are the metabolic adaptations which occur during fasting or starvation. Now, star feed cycle here we are talking about starvation.

Now, what is starvation? Starvation is basically deprivation of exogenous supply of food. So, energy is not provided to meet the demands of body to maintain the basic functions or basal metabolism. So, that is deprivation of food, but remember this deprivation of exogenous supply of energy or rather the starvation occurs immediately when the absorbed meal digestion or their absorption is completed. So, basically starvation starts at the post absorption phase.

Now is starvation just a deprivation of food or scarcity of food? No remember there is biochemical starvation as well. So, meta medical conditions which are posing the cell to such an environment where energy is not supplied energy is not available like trauma, surgery, uncontrolled diabetes mellitus, cancers, different types of infection or malabsorption. In all these disease scenario cells actually they are not getting adequate energy to maintain the basic functions of for survival. So, that is also biochemical starvation. So, the cells undergoes just the similar phase which occurs actually when we do not get food.

So, then when there is starvation definitely body depends on the stored food or stored energy which are stored in the form of glycogen stored in liver muscle fat in adipose tissue and proteins everywhere most importantly muscle. Now the most important thing whenever there is starvation we talk about glycogen, but surprisingly the store of glycogen is very less in comparison to protein or fats in our body. So, here you can see glycogen in liver is just the storage form is just 70 grams which account for 280 kilo calories of energy. Glycogen in muscle is around 120 grams which is equivalent the energy equivalence is around 480 kilo calorie. So, very fluid glucose are very low in amount what is important most huge amount of energy is present in adipose tissue in the form of fat.

So, you can see it is around 15000s of 15000 grams of adipose tissue which generates energy equivalence like 1,35,000 kilo calories and also muscle proteins around 6000 grams in weight provides 24000 kilo calories of energy. So, in the energy reserve in a 70 kgs men the important or the major storage is fat followed by protein followed by glycogen in terms of amount, but during utilization glycogen is the first one which is getting utilized when there is glucose deprivation. So, let us start with the physiological condition physiological stir fit cycle where we are talking about after taking meal there is a break. The commonest thing is overnight fasting because after dinner or after evening meal we mostly give a food intake break for around 10 to 12 hours. So, this nightly stir fit cycle has three stages first one is the definitely the well fed condition or well fed state the postprandial state after that there is post absorptive phase when early fasting starts.

Now this can be continued this phase can be continued till 12 hours and finally, the this phase is reversed by refed state when we take meal after dinner when in the morning we take break fast. So, this is the physiological stir fit cycle our body every day goes through this cycle. Now what happens here? Now what happens here in the stir fit cycle the purpose of our body is to maintain the constant amount of energy mostly in the form of glucose. Now remember this stir fit cycle is switched on by the hormonal interplay the important hormones here are most important is insulin and the counter regulatory hormone glucagon. Now insulin signals for the condition where there is raised blood glucose level.

So, definitely insulin signals for glucose uptake from blood to the cells and then those glucose are redistributed to different organs for either utilization or for storage. Whereas, when this blood glucose level falls glucagon is activated glucagon signals for because in blood there is no scarcity of glucose. So, glucagon signals for production of glucose from different sources like glycogen like neo glucagonases or beta oxidation or oxidation of fatty acids. So, that the blood glucose level or the energy supply can be maintained.

Now what happens in the well fed condition the hormone for well fed condition is insulin.

So, here is insulin which is secreted when there is rise of blood glucose level. Suppose we are we take a meal then there is circulatory blood glucose level is raised. So, that is that that is sensed by beta cell of pancreas with secrets insulin. Now insulin is important for clearing of glucose from the circulation and its proper utilization. So, what happens insulin enhances glycolysis in liver.

So, the first remember as I told liver is the metabolic hub of all the metabolism. So, all the nutrients first enters liver. So, similarly glucose amino acids they also enters liver or on entering liver glucose is converted to glucose 6 phosphate and that glucose 6 phosphate once again dephosphorylated in liver produces glucose that glucose comes in the circulation and is redistributed to the important organs like brain which utilizes glucose for its energy production. So, glucose is the first or preferred substrate for brain. Next these glucose goes to skeletal muscle which skeletal muscle remember skeletal muscle in resting state utilizes fatty acid whereas, moderately or extensively exercising skeletal muscles they take glucose as their fuel.

Otherwise also the glucose circulating glucose in skeletal muscle can be stored in the form of glycogen means the synthesized glycogen can be further utilized on requirement. Then glucose undergo glucose is going to triacylglycerol as well for storage as triacylglycerol. Apart from that the liver glucose once again can be can in glycolysis forms pyruvate pyruvate forms acetyl coenzyme. Now, acetyl coenzyme as I have already discussed can form triacylglycerol and that triacylglycerol is circulated to different tissues for storage the most important one is adipose tissue. Now dietary amino acids the majority is utilized for synthesis of protein like protein which has been depleted during the glucose alanine cycle.

So, that replenishment in skeletal muscle protein is done from the absorbed amino acid and the amino acid which is excess in amount it undergoes deamination and is excreted as urea. So, this is the fate of this is the condition we the metabolic condition after well fed condition, but what is actually influencing is the hormone insulin. Now how insulin enhances or rather controls this well fed state. So, if you remember once again this is the time once again you go to your previous metabolism sessions where you can see that insulin enhances the expression of glucose transporter GLUT4 which causes increase glucose uptake in muscle and adipose tissue not in liver. Remember liver the glucose transporter is GLUT2 whereas, the glucose transporter GLUT4 is insulin sensitive, but then also insulin in enhances the uptake of glucose in liver also how? By enhancing the activity of glucokinase remember more glucose is converted to glucose 6 phosphate via

glucokinase more influx of glucose inside liver occurs.

Similarly it enhances the glycogen synthesis via enhancing glycogen synthase enzyme then glycogen breakdown is prevented because glycogen phosphorylase is depressed. Then phosphofluctokinase activity phosphofluctokinase 1 and 2 both are enhanced pyruvate dehydrogenase complex enhanced acetyl coenzyme a carboxylase enhance. So, basically biosynthetic part biosynthetic biosynthesis of different molecules they are enhanced like fatty acid synthesis triacylglycerol synthesis or say cholesterol synthesis as well all are enhanced by insulin. So, this is the time when you go through the regulation how insulin regulate this enzyme activities. Then we are moving on to the fasting phase.

So, the early fasting phase occurs at post absorptive state when the absorption of the nutrients from gut is complete. Now after meal within 1 hour remember blood glucose level is normalized begins to fall and by 2 hour it returns to the fasting range 70 to 100 milligram per dl that is the basal range we talk about the fasting blood glucose level. So, the basal level is obtained of glucose is obtained after 2 hours. So, this is the time when actually cell is cell is changing is phase from well fed to fasting phase and this fasting early fasting phase starts I mean it remains for around 4 to 16 hours and how at this phase blood glucose level is maintained definitely by the hormone glucagon and how glucagon maintain this blood glucose level the major the initial phase is actually hepatic glycogenolysis. So, the stored glycogen in liver is actually broken down to form glucose 6 phosphate which finally, provides glucose to organs like brain, RBC, neurons, kidney those are the organs which are dependent on the glucose supply constant glucose supply they prefer that their preferred substrate is glucose.

Then neoglucogenesis when the glycogen stores starts to replace remember the liver glycogen store takes around 8 to 12 hours and it can provide energy for 8 to 12 hours, but even before the total depletion of glycogen neoglucogenesis starts. So, neoglucogenesis starts from lactate glycerol and also the glucogenic amino acids. Then there is fat breakdown lipolysis. So, adipose tissue provides their triacylglycerols to beta oxidation sorry the triacylglycerols are broken down by hormone sensitive lipase to form fatty acid and glycerol. Now, this fatty acid undergoes beta oxidation to provide ATP and that can form ketone bodies as well remember ketone body is the second preferred substrate for brain in fasting condition.

And another thing is very important that whatever glucose are available after this hepatic lipogenesis neoglucogenesis or lipolysis whatever glucose is available in circulation they are actually not utilized by skeletal muscle or adipose tissue. So, these organs actually spares glucose for those organs like brain RBC so that they can survive. So, the metabolic events in early fasting phase is actually controlled by glucagon and

here are the mechanism how glucagon actually controls the fasting phase. So, what happens when the blood glucose level falls neoglucogenesis is increased how glucagon actually activate this cyclic AMP dependent protein kinase which activates the phosphofructose bisphosphatase 2 and it decreases the fructose 2 6 bisphosphate level. Similarly it also inactivates the phosphofructokinase 2 so, the glycolysis is also inhibited.

So, again pyruvate kinase level is also here you can see by phosphorylation actually pyruvate kinase is inactivated and this phosphorylation is done by glucagon. So, once again pyruvate kinase is also inactivated means glycolysis is inactivated. So, these are the enzymes which are regulated by glucagon. So, you can see glycogen breakdown is increased to provide supply neoglucogenesis is increased then fatty acid mobilization breaking down of triacylglycerol is increased ketogenesis is increased and these are the enzymes which are actually regulated by glucagon. Once again go through the previous metabolic discussions metabolic classes of the respective metabolism.

Then refate state so, it occurs when in the morning we wake up we take the breakfast. So, what happens there is replenishment of the depleted storage as well as provision of the energy. Now fat is processed in the same way as the normal fed state, but for glucose remember glucose it enters liver, but liver does not absorb glucose liver does not utilize glucose for its own biosynthetic for its own energy supply. Then after the refate state starts even we take meal in the morning liver remains in neoglucogenetic phase for around 2 to 3 hours. So, for replenishment of glycogen liver still depends on the neoglucogenetic materials like amino acids like fatty acid the glycerol lactate liver depends on this not the dietary glucose.

And finally, when the blood glucose level is normalized or it is rather spiked up and the liver glycogen store is normalized then liver started to synthesize fatty acids from glucose or like that. So, in refate state liver maintains neoglucogenetic phase for around 2 to 3 hours. So, here you can see these are the relative changes during starvation that when the starvation starts the first thing which starts to fall is glucose definitely. Initially there is utilization of glycogen, but when the glycogen store is depleted fatty acid is starts to utilize which comes down and finally, starts ketone body synthesis. Similarly, if you see the storage level.

So, you can see carbohydrate level it is completely depleted then starts fat breakdown which which when decreases starts the protein breakdown the amino acids supply the energy to the cell. So, this is the normal physiological stir fit cycle. Now if instead of the refate cycle body prolonged is starvation which occurs during fasting for 2 to 3 days 4 days like that or more. So, if starvation prolonged for longer than 24 hours starvation starts and that is the exaggerated form of early fasting phase. Now let us see what are

the different changes which occurs in starvation which differs from the early fasting phase.

So, these are the metabolic adaptation which occurs during starvation here protein is degraded and the supply is glucogenic amino acids. Now when amino acids are transaminated or deaminated these amino acids actually supply for the intermediates in TCA cycle. So, it replenishes the TCA cycle product by forming oxaloacetate and these oxaloacetate are actually utilized to form glucose 6 phosphate via phosphanol pyruvate finally, forms glucose. Now these glucose actually exported to those organs which are completely dependent on glucose like brain one very important thing. Now what happens because you can see this TCA cycles intermediates are actually siphoned off out of TCA cycle to form glucose TCA cycle cannot be completed the balance of TCA cycle is hampered.

So, even if there is fatty acids forming acetyl coenzyme A via beta oxidation those acetyl coenzyme A cannot enter TCA cycle because for accepting the acetyl coenzyme A to form citrate oxaloacetate is not available oxaloacetate is utilized that. So, what happens acetyl coenzyme A because it is getting accumulated acetyl coenzyme A it is now diverted to another pathway that is ketone body formation and ketone body is one very important fuel for brain in fasting condition. So, these are the gradual adaptation in starvation in the first phase there is glycogenolysis which occurs for initial 18 hours and even before the glycogen stores are depleted there is neoglucogenesis amino acids are utilized up. So, alanine is one such important amino acid which comes from muscle protein breakdown also the branch and amino acids liberated from by protein catabolism are utilized by muscle for energy provision. Then in the third stage there is lipolysis triacylglycerols are broken down forming fatty acids to provide energy in beta oxidation ketone bodies are formed.

Similarly ketone bodies are actually taking over causing ketosis rather ketoacidosis and at the last stage this exaggerated metabolic acidosis as well as dehydration excess protein breakdown also finally, leading to death. So, these are the stage phasic adaptation in the starvation phase where you can see that basically glucagon takes over and induces lipolysis and neoglucogenesis. So, what we are getting acetyl coenzyme and that acetyl coenzyme inhibits glycolysis also citrate level is increased from triacylglycerol breakdown and this citrate also gives product inhibition over glycolysis. But the problem is as I told you acetyl coenzyme cannot be utilized in TCA cycle because the TCA cycle intermediate oxalacetate is depleted. Then glucose the uptake of glucose in muscle is also decreased because I told you muscles spares glucose for the for brains availability.

Now what happens muscles mostly depend on the fatty acids and this beta oxidation of fatty acids actually provides acetyl coenzyme. Now once again beta oxidation of fatty acid it is also regulated or rather inhibited because acetyl coenzyme is stimulate phosphorylation of the pyruvate dehydrogenase complex. So, beta oxidation itself also gives one inhibitory action over TCA cycle. So, the main initial metabolic adaptation occurs via neoglucogenesis and also the glycerol which is derived from the triacylglycerol acts as a precursor here. Then there is proteolysis the carbon skeleton of amino acid of different organs are actually now providing glucose.

The initial source of this proteolysis remember the labile proteins the enzymes present in GI tract they are initially broken down. Remember labile proteins are those which when broken down the basic function of the in the starvation the basic function of organs are not hampered. After that there is muscle protein breakdown. So, alanine glutamine they are broken down and definitely alanine comes to liver via chor recycle. Then the rapidly dividing cells they even in fasting state requires glutamine.

Remember for synthesis they are glutamine is the nitrogen donor for purine nucleotide synthesis or for rapidly dividing cells glutamine is required, but once again this is also diminished. So, depletion of body proteins occurs and when there is around 30 to 50 percent of body proteins are lost it ensures death. Now this proteolysis mostly occurs in 3 phases first there is a rapid depletion, then there is a gradual slowdown of this proteolysis finally, at the end once again there is rapid degradation of protein. So, here you can see there is rapid break initial phase there is rapid breakdown of protein. Now why this rapid breakdown is slowed down in the second phase for provision of ketone bodies.

So, remember the acetyl coenzyme A which was actually provided by beta oxidation of fatty acid that pool of acetyl coenzyme A is now getting accumulated because it cannot enter TCA cycle rather it is diverted to form ketone bodies like acetoacetate, beta hydroxy butyrate and these ketone bodies are used up by brain for their energy provision. So, remember even this ketone bodies are actually entering brain in brain it is forming reforming acetyl coenzyme A for the energy provision. At this phase around 3 days of starvation brain actually the fuel requirement of brain is actually shifting towards ketone body. So, a quarter of energy of brain is now made by ketone bodies as well as these ketone bodies are utilized by heart also. Then after several weeks of starvation ketone bodies become the major fuel of brain and even after that brain still needs glucose why for synthesis of different neurotransmitter.

Now, if you remember in the for the previous class I mentioned around 120 grams of glucose daily is required by brain. So, initially in the initial phase of starvation body

tries to maintain that 120 gram glucose supply to brain, but now that is also been reduced now brain actually accommodate in around just 40 grams of glucose. Similarly muscles are also the muscle proteins degradation now because ketone body has take so has taken over. So, muscle protein breakdown has been decreased. So, 75 grams of protein initially has been degraded now in after several weeks of starvation it is 20 grams around.

So, also the proteolysis has decreased. Then when there is proteolysis definitely when there is deamination the ammonia is excreted via urea formation. Now because there is because there is a decreased in proteolysis definitely the deamination is also decreased. So, the urea excretion is also decreased. So, urea you here you can see that nitrogen excretion is decreased from 12 to 15 grams per day to 3 to 4 grams per day. So, this is the metabolic adaptation after several weeks of starvation.

Now body can maintain this thing for around 45 days to 3 months after that definitely the body proteins are depleted around 40 to 60 percent which causes death. Now these are the different organs which choose we choose their fuels based on the availability of their based on the metabolic phase of body. Now brain after post mill or even in the early fasting phase it prefers glucose. So, brain needs glucose only when there is starvation prolonged starvation brain starts to utilize ketone bodies. Next skeletal muscle the preferred substrate for resting skeletal muscle is fatty acid.

The exercising skeletal muscle or moderately or during massive exercise it only then takes glucose as its fuel. But fasting condition once again the fuel is shifted to fatty acids and at the later stage ketone bodies are branch in amino acids they are utilized. Cardiac muscle in cardiac muscle glucose is the preferred fuel, but in fasting it shifts to fatty acids and in prolonged fasting ketone bodies can be utilized. Now adipose tissue adipose tissue remember mostly depend on fatty acid and in fasting also it takes fatty acid is always pairs as much as possible its pairs glucose for the utilization of the preferred organ. In prolonged fasting also it depends on fatty acids and then shifts to ketone body remember ketone body is the last preferred substrate for prolonged substrate for prolonged starvation.

Now these are the list of enzyme which are changed or their levels are influenced by the hormones or different activators like glucokinase, phosphofructokinase, fructose 1, 6 bisphosphatase, pyruvate carboxylase, phosphanol pyruvate carboxykinase. So, these are the enzymes which are regulating the glycolysis and neoglucogenesis influenced by insulin glucagon and here are the activators or inhibitors. So, you can coroborate this with the previous classes. Next glycosine synthesis or breakdown the glycosine metabolism the most important two enzymes are glycogen phosphorylase and glycogen

synthase and if you remember glycogen phosphorylase is activated by glucagon or and inhibited by insulin. Similarly, glycogen synthase is just the opposite one is the activities enhanced by insulin whereas, inhibited by glucagon.

So, accordingly in the well fed state when there is insulin level high rather I will give arrow to this insulin level is high enzymes behave like influenced by insulin. Similarly, in the fasting or starvation stage enzymes behave when they are in like when they are influenced by glucagon. So, these are the list of enzymes you should go through. Now for skeletal muscles for skeletal muscles as I told you the preferred substrate is always free fatty acids only case of exercise it takes glucose. In cardiac muscle preferred one is free fatty acid, but remember cardiac muscle takes ketone bodies and lactate as well and differ during the time of exercise or rather high energy requirement it takes fatty acids.

So, we have come to the end of our session these are the key points once again the key points are also important please remember that the purpose of this star fit cycle is to maintain the flow of energy or fuel to the organs. The circulating blood glucose concentration are tried to be maintained at 17 milligram per dl even during the initial phase of starvation and keeps and body keeps to tries to maintain it even in prolonged starvation. Now the carbohydrate reserve glycogen is depleted at 8 to 12 hours of starvation the initial priority during the starvation is to provide glucose to brain and RBC or kidney those organs which mostly depend on the glucose. Neo glucogenesis is the preferred mechanism in early fasting phase and prolonged fasting phase where the substrate are amino acids from skeletal muscle protein breakdown. The second priority of the starvation is to preserve the body protein.

So, it utilizes fatty acids for fuel then glucose utilization is in brain is decreased during the prolonged starvation when brain actually shifts to ketone body majority of the organs their choice of fuel now shifts to ketone body there is excess synthesis of protein ketone body in prolonged starvation which causes production of huge amount of ketone body and that causes ketosis. And also the we talked about protein degradation occurring in a phasic variety in the phase of starvation. So, here are my references I thank you and see you in the next class. Thank you.