Human Physiology
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Lecture – 58
Physiology of Glucocorticoids - Part 1

Yes it has. We have been trying to understand yet another very extremely important endocrine gland and what did we identify it as? Cortex, adrenal cortex. You remember we talked about adrenal cortex and then we focused on an important hormone that is aldosterone and we classified it as what kind of, what kind of hormone was it? It is a mineralocorticoid and its main function was to conserve, to conserve what? Sodium and also to get rid of the potassium ions that was and what was the main dominant factor that regulates the release of aldosterone? Angiotensin 2. Angiotensin 2, you are right. What was it? Angiotensin 2. And for that again we go back to the kidney and that entire system of, we have done that.

Now we will go to the yet another equally important second hormone by the name which is, we will take it as an example that is glucocorticoid. Now please remember these two words are used interchangeably. One is corticosteroid or corticoid, same thing. I mean that word has come so often that people do not even just say corticoid or glucocorticoid or mineralocorticoid or corticosteroid or whatever.

In chemistry they are steroid hormones and so we will talk about this interesting. So this is being secreted by, remember there were three layers. Gondomerulosa, outermost, fasciculata. So the fasciculata, the cells of the fasciculata, those cells which are arranged in a radial strands of cells, those cells are source for cortisol. So cortisol comes from where? The zona fasciculata, zona fasciculata which is the second layer in the adrenal cortex is the main source of this hormone which we call as cortisol, cortisol, great, great.

And what is the peculiarity of this hormone? It is a glucocorticoid, it is a, in long term it increases the blood glucose level, it acts on the, but one of the very characteristic features of this hormone is that it is a great promoter of gluconeogenesis. Means what? Formation of glucose from? Non-carbohydrate. Non-carbohydrate source which means fats and, fats and what? Fats. Fats, yeah fats and proteins and fats. So let us see, if you take a slightly global view, you will find that what does insulin do? There is suddenly lot of glucose in the blood after food intake, then you conserve it because there is plenty of is there.

How do you conserve it? Well, you first take it to the liver, convert it to glycogen, you take it to the adipose tissue, convert it to fats and store, I mean you are in an energy rich condition. And then as the time passes and now you are starving for a while, you have not had food for another 2 hours, then the glucagon comes into role, you have done glucagon

also and glucagon will do something opposite. So whatever has been stored has been, has to be. But if you starve for a longer time, now starvation for a longer time is almost unheard of in since our civilization. But as for an animal in the wild, for an animal in the wild, starvation for a very long time is a very common phenomenon.

So, if a carnivore like a tiger or a panther has had good food today, what is the guarantee that it will get next? And there is easily a period of 7 or 10 days when the food is just not available. And there is no, there is absolutely, till again there is feast, there is a feast, so fasting and feasting. So during that period, you cannot completely depend on the stored carbohydrates either in the form of glycogen or in the form of adipose tissues. Under those conditions, utilizing the sources from the non-carbohydrate, non-carbohydrate sources means what? Proteins. And again when I mean by proteins, what do you mean by skeletal proteins? That is a great source.

I mean it is an expensive source but it is a great source because the animal has already invested a lot in making of the molecules in actin, myosin and a range of other proteins that bring about the mechanical, the mechanical part, the muscle part. But that is a great source when you have been fasting for a very long time. And that can be mobilized by cortisol. So what does cortisol do? It will mobilize proteins which are stored in the form of muscles, number 1. Number 2, the long term storage in the form of fats, adipose tissue, the triglycerides, you bring them down to fatty acids and glycerol and then use it as energy.

So we call it, so this is a main hormone, main hormone which helps us to cope up with a starvation for a very long time by continuously, look, look. As long as life is there for a human being, blood sugar level cannot go below 80 mg per 100 ml, period. Got the message? Got the message? Laud it, that is it. You cannot, you are a human being, you have to, as long as, that is the limit. And you do not get food for 7 days and 10 days, okay, then what do you do? You keep on, you keep on, you keep on digesting your muscles under the influence of cortisol.

What is the aim? You take those amino acids, okay, break down the muscles and to amino acids, take those amino acids to the liver, in the liver the amino acids will convert them into glucose, send them into the blood, make sure that the blood sugar level remains at 80 mg per 100 ml. Got the message? Laud it here. So, so whether you eat or you do not eat, okay, you are now actually eating your own muscles. Who is doing it? The cortisol is doing it. How? Digest the muscles, into amino acids, take them to the liver, deaminate them, convert them into glucose molecule, one aim, keep because, because you can, you can spare all your muscles but you cannot spare your brain by reducing the level of blood glucose supply to the brain which has to be at the level of how much? 80, 80 what? mg.

mg what? 100 mg. 100 mg, that is the level, I mean you see as far as brain is concerned the amount of oxygen that is there in the blood and the amount of glucose that is in the blood is non-negotiable, it has to be so much. Okay and for that you can draw from anywhere, anywhere in the body you can draw. So let us, let us look at this, this very interesting molecule which we call as, which we look, we call as cortisol. Okay, we have done this yesterday but yesterday our hero was aldosterone, today our hero is different, it is cortisol.

But the story is more or less same, what are we doing it? So we have the cortex there, from the cortex now I will take a cell, now this cell is from the zona fasciculata, one single cell and then I have this, I have this single cell plasma membrane of the cell and then as we saw yesterday the LDL, what does LDL stand for? Low Density Lipoprotein. Low Density Lipoprotein and it is, it comes along with the blood and it is internalized by the plasma membrane by a receptor mechanism. So there is a protein there, there is a protein there in the plasma membrane of all the steroid secreting cells, all steroid secreting cells will have that protein. Whether you are in the adrenal cortex or whether you are in the ovaries or you are in the testes, they are all steroid. If I just ask you, tell me three different sources, steroid secreting sources, you will of course name what and what and what and what? Adrenal cortex number one and then testes in the male and ovaries in the case of female, these are the main sources for the secretion of steroid hormones.

In the plasma membrane you will have a receptor, that receptor will mediate the influx of, it just does not flow, okay. It is mediated, then it comes and then the cholesterol comes in. You know the cholesterol is a molecule which is extremely labile, it can actually go anywhere. But if the cell wants to store it for future use, how do you store it? The answer is there. You will convert cholesterol into what? Into an ester, okay.

The cell will do it in ester and then it can be made into a vesicle and then it can stay. Yeah. It is a lipocutaminate, so it is basically covered in lipid. Why does it have a receptor to it internally? Which one? You mean this one? Oh, it is a very large system.

It is a large system. No, no, it cannot go. It cannot go. It cannot go. It cannot go. It is a lipoprotein system.

Okay, so it is not just a lipid molecule that can go. It is a much larger system. Okay, then so it goes in and then here is an interesting connotation that author wants to give that you can store the cholesterol in the form of what? Cholesterol ester. Okay. So, when it is in the form of an accessory, it can be released and then when it can be released, then okay, then comes a very interesting molecule that we have already spoken about it.

This is a protein that is sitting on the mitochondria called as what? Star. Star, what is the full form? Steroid. Acute regulatory.

Acute regulatory. Okay. So, this star will take it in the mitochondria. In the mitochondria, it will be acted upon by what enzyme? Same enzyme, what is it? Cytochrome. Yeah, cytochrome C450.

SCC. Side chain cleavage. Side chain cleavage. So that cholesterol is converted into a smaller molecule, pregnant alone. So again same, we are just repeating yesterday's story. Pregnant alone, then it goes into the endoplasmic reticulum and then it again goes by and then cortisol is finally synthesized at the level of the mitochondria and then the cortisol is ready for the release. And this is all under the control of the, I will talk about it again later, it is again under the control of the hormone ACTH.

What did I say? ACTH. Say that again. ACTH.

ACTH. Say that again. ACTH. Adrenocorticotrophic hormone. What did I say? Adreno. Adreno, you have to, you just have to know it.

Adrenocorticotrophic. Adreno. Adreno. Corticotrophic.

Corticotrophic. Harmon. Okay. Its adrenal is adrenal. Corticoid adrenocortics. So, trophic is what to grow or to promote the growth. Adrenocorticotrophic hormone. That hormone is coming from where? Pituitary gland.

Which part of the piturgal anterior posterior? Antirepitular. So anterior piturgal, okay. Tell me the name of the anterior pituitary gland hormone that we have studied in some details.

TSH. Growth hormone. Number one. What did we do? And then second TSH. Number one was what? Growth hormone. And number two was what? TSH. And the third one I am talking about is now what? SCC.

SCC. Okay. Got it? Got it. This is the third hormone that is coming from anterior pituitary gland. ACTH. And this and all these biochemical steps are being, all the enzymes involved in this will be upregulated under ACTH. We will talk about it ACTH a little later.

So yeah. Where is the lipid of the diastolic light? You mean here you mean? Once it is converted into acetone. Okay. Okay.

Oh it is vacuoles. Endoplasmic reticulum. Separate compartments made of endoplasmic by lipid of layer. Vacuoles, some vacuole. Some vacuole. Some vacuole we will store it as and in the ester form it can be stored for quite some long time, quite long time. And then when ACTH comes, as and when required when ACTH comes, okay, then those enzymes will convert as cholesterol, ester back into cholesterol, then it can diffuse out and then it can.

Okay. So here we have the cortisol. Okay, okay, okay, okay. So we are looking at the cortisol and it acts on its receptor. Now you can ask a simple question where does on what kind of cells cortisol ask. I have already told you.

It asks on all skeletal muscles. It acts on all adipose tissues. It has, it has abundant action on the brain everywhere. Cortisol has profound action all over. I mean you will, it is difficult to say that this particular place is smooth muscles have relatively low but it is almost all other tissues are under immune system, immune system, sites, huge number of receptors for cortisol. What am I talking? We are discussing as to what are the sites in the body where cholesterol is likely to exert its effect.

What is the answer? Proformed effect on liver, profound effect on all skeletal muscles, profound effect on entire immune system, profound effect on the adipose tissue. Some of the, some of the main organs on which the cholesterol will have the effect. How does it work? Okay. So this is a cortisol, steroid molecule, no problem. So, it will just go inside the plasma membrane in the once it is in the, in the cytoplasm it is coming across its receptor.

What does GR stand for? Yesterday MR stood for what? So today GR will stand for what? Leukocorticoid receptor. So there are two proteins, the dimer. They are not a dimer yet. Two separate proteins, identical proteins.

When the cortisol combines with these two. But but but but these are attached to a cheperon protein called as HSP. What does HSP stand for? Everybody should know this word. HSP word will come very often. HSP stands for what? Heat shock protein, heat HSP 30, HSP 50, HSP 50, there is a whole family of proteins. And the receptor is bound to the HSP molecule and it is inactive to form.

When the cholesterol comes, cholesterol will combine and then HSP will move away and now the two protein molecules will come together and you have a dimer. Now once it is dimerized then it can enter into the nucleus. It will find out its suitable response element,

DNA, whatever it is. And then it will give rise to, this is glucocorticoid respond element, the segment of DNA molecule where it will combine and it will give rise to mRNA and then you will have de-response, de-response. What do I mean by response? Let us presume that this is skeletal muscle cell.

And then you have been starving, no food for 24 hours, 48 hours, 36 hours. In that particular scenario then this will give rise to, this mRNA will give rise to huge number of proteins which will start breaking down the large protein molecules in the skeletal muscle cell. Did you get the message? Start breaking down and converting those proteins into what? Amino acids. Okay. And we have already seen those amino acids will go into the blood.

From the blood where will they go? Into the liver. And they will be de-aminated and amino acids are converted into carbohydrates and this process will call as what? Gluconeogenesis. Gluconeogenesis. Okay. And what are the, this is, this we have already spoken, let us see.

So cortisol can act on the muscles. Look at the top arrow, protein degradation will go up, protein synthesis will go down. Okay so in a cell, so as if the entire enzyme machinery will shift in such a way that the proteins will broken down. Glucose utilization goes down, sensitivity to insulin goes down and then the amino acids will be taken to the liver. From the liver, liver will give rise to glucose and it will, cortisol will also act on what is this tissue please, adipose tissue.

This will have huge flat fat globules. It will be converted into glycerol. Glycerol will go and again glycerol will also be converted into glucose and you will have you will have the homeostasis with reference to glucose in the, this is more specifically the fat, adipose tissue, fat under the influence of cortisol, fatty acids, glucose, amino acids, proteins being broken down into amino acids and being brought into circulation. Okay. Now whereas, this is interesting, whereas the cortisol has profound influence on all the tissues, now there is an exception is coming. What is the effect? What is the effect? Bring down the breakdown of proteins.

Trigger all the enzymes and we took a classical example of a skeletal muscle tissue. Okay so far? Similar effect on adipose tissue, on immune system. The exception to the rule is liver. Means what? Does cortisol bring about the digestion of proteins in the liver? No, no, no, no. What does it do? It actually promotes the synthesis of a large number of new enzymes and proteins in the liver cells which play a critical role in deaminating, in converting the amino acids into carbohydrates and fats into carbohydrates.

So the protein concentration in the liver cell actually goes up. So you can exactly divide the action of cortisol into two categories. One is extra, extra hepatic. What do you mean by

extra hepatic? Liver, everywhere other than liver. And that is what we have seen just now. What is extra hepatic? Break down the proteins, convert them into amino acids and in the liver it is exactly opposite.

Okay, what do you do with the amino acids? Of course you convert them into carbohydrates but then you have far more number of proteins synthesized. What are they? Because they are the enzymes, you need them for doing the function of the liver. And what is the function of the liver? Gluconeogenesis which converts the non-carbohydrates into carbohydrates. So we need to clearly divide the action of the, the effect of cholesterol into these two categories.

Okay. Same with reference to the effect of cortisol on the fats. Increases the concentration of free fatty acids in the plasma which also increases utilization of the, cortisol also seems to have different effect. Okay. We know very well that in the case of prematurely born babies, one of the major problems is the occurrence of or not the, or the absence of what surfactants in the lungs as a result of that the lungs have a problem in, in the alveoli have a problem in fully opening because of the surface tension. You remember what I talked about? Okay. Cortisol, cortisol being made available to the fetus at the stage of about 25, 26, 27 weeks of gestation is responsible for the formation and release of secretion that is surfactant from the type 2 alveolar cell.

Means for the type 2 alveolar cells to become fully functional in the, in the lungs.

Okay. The lungs. Okay. Who is, who, who plays a key role? Cortisol. Cortisol plays a key role. Do you get the importance? So in the, in the development this is the, oh this, let us try to understand what I have highlighted in the blue font. Can you, can somebody interpret for me? Mice with homozygous disruptions in corticotropin releasing hormone. Now let me explain to you what is corticotropin releasing hormone.

ACTH comes from where? Very good. Comes from where? Very good. ACTH comes from anterior pituitary gland. Good. ACTH itself is under the control of a hormone from the hypothalamus because we have already seen that pituitary is under the control of a triggering factor from the hypothalamus. That hypothalamic factor is called as, is called as, is called as, what is it called as loudly? Corticotropin releasing factor.

Corticot, say that again. Corticotropin releasing factor. Now what is this corticotropin releasing factor? It is again a small peptide. It is a 41 amino acid peptide that is being synthesized by certain neurons. Okay so far. As the name indicates corticotropin releasing peptide or a factor, it comes from certain neurons. Now can you tell me the, can you tell me

the way it travels, it is released by the neurons at the level of, at the level of median eminence, at the level of median eminence.

In the median eminence it will get into dash dash dash hypo, portal system.

Hypothalamo. Hypofacial. Hypofacial. Portal. Portal. System. System and it will take the peptide, the tiny peptide from the, from the hypothalamic neurons to the anterior pituitary gland and in the anterior pituitary gland it will act on the, what kind of cells? ACTH cells. What kind of cells? ACTH cells. So answer my question, in the ACTH cells will you get receptor for CRH? You will. Okay you will, you have them. Okay so under the influence, okay now, now in the background of what we discussed shortly in last couple of minutes, can you interpret for me what is the meaning of that experiment? Mice with what? Mice with homozygous disruption of corticotropin releasing hormone gene, means what is it? Both, both, both, you see there are two copies, are you with me? Yes or no? Homozygous, both the copies are what? So that this particular, in that particular mouse, both the copies of what gene? C-R-A.

No, no, no. C-R-A gene. C-R-A gene, okay is non-functional. As a result of that, that mouse is not able to generate CRH, as a result of that it is not able to stimulate what? ACTH. ACTH, as a result of that it is not able to release what? Cortisol. Cortisol, as a result of that what effect are you getting? Can you interpret for me the latter part of the sentence? There are no, which means die at birth due to what, pulmonary? Which means what? There are not. There are not, have you followed the entire story? Means this, on what basis we are saying that cortisol does not rely on the basis of such experiments, okay. We come to the conclusion that cortisol has an important role in the maturity or maturing, maturation of the alveoli of the, second yet another very important role that is played by cortisol.

You see it is, cortisol is often called as a stress hormone. Remember this, okay. Is a stress hormone. Okay, now what is this stress hormone? Well, stress is a part of normal life, okay. Can we imagine life without stress? Hello? It would be great, wouldn't it? But no, that does not work, okay. So actually people say that little amount of stress is also good, keeps us fit, you know.

So let us forget about humans, okay. Let us talk about the animal world. So what are the different kinds, I have made, the author has given us a list. Trauma of almost any type, wound, injury, whatever, whatever, accident, infection, intense heat or cold, just go through the injection of epinephrine, surgery, injection of necrotizing substances like an acid, restraining the animal, okay, even if you put a mouse in the, in a cage, tiny cage, so that the guy does not have enough room to move around. Imagine if I put you in a cage like that, how will you or I feel, okay. That is a stress. What is it? What are we doing right now? What are we doing? We are just trying to enlist the different factors which can cause stress, okay.

And if I were to extend this list to the humans, okay, I can add to that a psychological stress, okay. Examination can be a stress, not getting success in the stress, failure in the stress, rejection, I mean they are all different forms of stress through which we all at some stage in life we have gone through and we will go through. So these are all the, any debility, it has been found that in all these cases, stress of any kind, stress of any kind, the cortisol goes up. And this was discovered by, he was a Canadian scientist. And very early, I think almost 1935 and 40, he made a very interesting observation that in the animal, in the mouse that was subjected to any kind of stress, different kind, in the previous one that is why I gave a list of different kind.

You see, no matter what kind of stress, he found, very interesting observation, he found that in the adrenal cortex of that animal was always overgrown. Do you appreciate his observation? I am talking very old thing, I mean his observation is of 1935, 40 or so. And he found that adrenal always, no matter what stress you give, we had a long list in the previous one, adrenal was always large and then he found that there is a involution of the thymus, thymus was always low and the mass of the lymphoid tissue, you know lymph glands, you know we talked of lymph system and lymph glands and that was always suppressed. What are we talking about? He is talking about general observation, general observation that whenever there is a stress, no matter what is the reason behind the stress, you consistently get some changes. And what were the changes, number one, adrenal cortex was always large as compared to the normal or the unstressed animal, thymus was always reduced in size and the lymphoid tissue was always also reduced.

Got it? This he called as a stress response and later on it was discovered, much later we discovered a whole range of changes which I will talk about shortly including this slide.