Human Physiology
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Lecture – 49
Secretory functions of Pancreas and liver

I keep on forgetting, yesterday we spoke of two hormones being released by the stomach, you remember names? One was gastrin, right? And what was it doing? It was communicating with something, what was it communicating? I am forgetting. Parietal cell. Parietal cell. What is the name of the HCL secreting cell again I am forgetting? Parietal cell.

Parietal cell, good. And what was the other hormone? Ghrelin, that sounds familiar. And that ghrelin is released by the cells - that is right, you are right.

Ghrelin communicates with what? It is a hormone, it is come from, it comes from the cells in the stomach and it talks to what? Brain. What does it talk to? Hypothalamus and what is the message that is encoded by this peptidergic hormone called Ghrelin? Hunger. Good, very good, very good, okay. And then hunger in triggered. The information that is issued by the hypothalamus will now translate into motivating what kind of behaviour? Search for food intake. Food intake, search for food intake, okay, good, good, good, good.

Now we will move on. So the food is there in the stomach, it has received plenty of acid and the, and the pepsinogen and the pepsin and the different proteins have been digested or at least large molecules have been broken into small, small molecules - and then after say about half an hour or one hour of digestion in the stomach, the pyloric valve, hello, pyloric valve which is guarding the opening from the stomach into the duodenum, okay, which is closed, okay, closed because of the latch formation, it stays closed. After the process has gone ahead the valve will gently open, it does not open and keep open, it gently opens and closes, opens and closes, opens and closes and as the stomach gives a peristaltic, strong peristaltic action - the valve opens and the food is actually ejected from the stomach into the duodenum. Now duodenum has to be very careful because it is receiving strong acid, okay and duodenum is not as much equipped as the stomach to deal with so much of acidity. Therefore the nature has provided the duodenum – duodenum will have a rich secretion of bicarbonate, okay. Now the beauty here - let us take a look at this cell, what is this cell? Pancreas, pancreas have lots of acini, let us say exocrine pancreas - let us forget about endocrine pancreas. In the exocrine pancreas, the cells, acini cells - are actually responsible for the secretion of pancreatic enzymes, they have those zymogen granules. Those zymogen granules are actually vesicles, in the vesicles you have all the enzymes - which are responsible for digestion of fats and proteins and carbohydrates. That is one of the richest source, okay and then you have enzymes like trypsin and chymotrypsin and carboxypolypeptide. All sorts of enzymes are there in the pancreas and here we have, the author has given us what one pancreatic cell is actually very much similar to that in the salivary gland. There are acini and there is a duct and there are hundreds of them, okay and then ducts all are connected, okay and then finally there is common pancreatic duct and then

as the pancreatic duct opens into the duodenum, it is joined by the bile duct. Hello, are you with me? Okay and the entire system is stimulated when the food arrives in the duodenum - and the duodenum will be flushed with bile proper and the pancreatic juice. So we are talking of a single cell of the pancreas which is there to secrete zymogen granule. It is going to have different kinds of enzymes which are secreted by the exocrine pancreas, good.

On the basal side we are having different signaling molecule and its receptors which will excite the cells. When it is excited it will release the zymogen granules and its contents, are you okay so far? So look at this image system and tell me what are the three very important secretagogues, what word am I giving you? Secretagogue, say that again, very funny word, okay, almost sounds obnoxious but there is nothing obnoxious about it. Secretagogue, okay. So I will just frame a sentence, you will immediately get the meaning. These are the three secretagogues which will act, they are only hormones, they will act via their receptors, the receptors are sitting on the pancreatic cell, okay. So what are the three secretagogues, one is secretin, now very secretin, secretin is again yet another peptide hormone, yet another what? It is secreted by what? It is secreted by the cells in the duodenum, okay. Or I will say that just as we had two hormones in the stomach, ghrelin and gastrin, I am drawing your attention to the two hormones that are released by the duodenum. So is duodenum an endocrine gland, yeah. Duodenum is also an endocrine gland and what are the two hormones, they are again peptides. One of them is called as secretin, what do you call it as? Secretin, so in the wall of the mucosa of the duodenum there are some cells - some people also like to call them as secretin cells. Does the name Starling mean something to you? Hello, you remember Frank Starling, okay, yes, yes good. You remember that name, a great scientist, great physiologist, in the year 1905, just see how old, okay, he for the first time demonstrated the presence of and physiological significance of secretin. I am just opening in front of you an interesting page from the history of physiology, what is the name of the hormone? Secretin, okay, what he did was cut all the nerves, okay cut all the nerves to the duodenum and in the case of a dog and even in the dog when the food arrived from the stomach into the duodenum, the physiology kept on working as if nothing has happened, in spite of cutting away all the nerves. And the things are still happening - there must be some communication, okay and then eventually they proved that this hormone, and that hormone eventually happened to be what? Secretin, okay and he is the one to coin the term hormone. So here we have the acidic food - arrived from the stomach into the duodenum, so the secretin, secretin cells which are there, they first experience sudden arrival of acidity, they get excited, so who is exciting the secretin, secretin cells, are you getting my language? The cells which are there, they are sensitive to pH and when the pH is low, they start secretin, so again G protein coupled system, ATP, cyclic AMP, intracellular signaling cascade and release. That hormone has profound action on the duct, hello, duct, so there is an acinus okay, a few hundred cells, they will secrete the pancreatic juice and then there is a duct, are you with me? And there are hundreds of ducts and they all join, join, join, join, finally common pancreatic duct which will open into the duodenum. I am talking about the lining of that duct, okay, and that the lining of the duct, they have receptors and they have receptors for secretin and they play a profound role in the synthesis of bicarbonate. What you did there in the stomach, okay, now you have to do something opposite, okay, so you have acidified, now you need to what?

Neutralize, okay, so whereas these cells of the proper pancreas, they secrete the enzymes which are present in the zymogen granules, the ducts do not have zymogen granules, they do not secrete the enzymes proper but then they secrete a large amount of water, okay and a large amount of bicarbonate ions. I am just saying that bicarbonate ions. But more interesting is it has to secrete as much bicarbonate ions, so as to neutralize the amount of acid. So that you ultimately end up with the pH of around 7.2 or something like that which is characteristic of duodenum, not too high, not too low. So there is titration happening, okay. We have already done it yesterday, I will tell you once again, there is yet another kind of cell, okay and that cell is responsible for the secretion of CCK. Now tell me the full form of CCK, so it is coming from where? Cells in the duodenum, there is a CCK cell, there is a secretin cell, okay and whereas the secretin cells are more sensitive to the pH, CCK cells in the duodenum, they are more sensitive to the amount of fats that is coming and amount of amino acids that is coming, okay.

They are sensitive and the CCK cells will secrete CCK, the CCK will act on the 7 transmembrane G- protein coupled system. It will release calcium ions and that those calcium ions are responsible for what? Calcium ions are responsible, what do you think it will be doing? Calcium ions, what do you think they will be doing? Trafficking of the vesicles, what is it? Trafficking you mobilize, okay, there will be cytoskeletal proteins, they will be mobilized and the zymogen granule will now merge with the plasma membrane, it will release its content, it will go into the primary duct, okay and it will start moving along the duct. As you go along the duct, let us see what happens - so what do we have here? So we have the 100s and 100s of acini, they will have the duct, here is the larger duct here and if you take the lining of a duct - we are looking at a single cell, single cell of what? The duct and the moment you see a duct, we immediately should ask one thing which is the basal side, which is the apical side. On the basal side you must have the enzyme system, what do you call it as? Sodium potassium ATPase. Sodium potassium ATPase, so do you see a sodium potassium ATPase here? So this is the capillary, this is the basal side, that is the lumen, okay. On the basal side you have this, you have the pump and the pump keeps on pumping the sodium to the outside as a result of you have too much sodium, as a result of you have this another system which is the antiport system - and what is that antiport system – it is driving the H+ ions away from the lumen and towards the blood. Do exactly what you did opposite to, opposite to what you did in the stomach. In the stomach you were driving the bicarbonate ion towards the capillary and H+ ions towards the lumen, now you will do the opposite, what would you do? You would drive the H+ ions here and the bicarbonate, bicarbonate ions are coming from where - the carbon dioxide will combine with water, carbonic anhydrase, bicarbonate ions, bicarbonate ions are going there with the help of an antiport system which is exchanging chloride ions to bicarbonate ions. So you need to re-circulate the chloride ions repeatedly because it is only the antiport system so the chloride ions keep on circulating and they facilitate the transfer of bicarbonate ions into the lumen. The system is so efficient that the bicarbonate ions in the lumen are about 5 times more than in the blood, are you understanding? You see if you, one way to look at the biology is that biological systems are capable of continuously partitioning things, are you with me? Partition, so in this case what is being partitioned? Bicarbonate ions are being partitioned, they are being driven where?

Into the lumen, what is the purpose? You have to neutralize, neutralize what acid that is coming from the stomach- Stomach, good good.

So you have the, are we okay with this diagram or not? Is this, yeah go ahead. How do you get, how do you get the CO2 enough to go into the liquid? The problem is, the problem is CO2 flows from anywhere to anywhere because of extremely high solubility. CO2 can go anywhere to anywhere and in every cell. We have no dearth of, even if you say that this particular cell may not generate enough, it will flow, the partial pressure of carbon dioxide - it is not stopped anywhere. For carbon dioxide there is no compartment.

Yes. Then it takes the solution and it is not able to transfer? No, it does not cause, it does not cause, does it really change the pH? That is your question. The pH does not really change, there are enough buffers in the blood to absorb those ions. There is very slight change but there is no major change because the blood has enough buffers. Okay, now come see, I mentioned a particular term which did not click but I will reuse the term. And I will give its meaning because it is very interesting, I will tell you what. The chloride ion channels, what did I say? Chloride ion channels. Chloride ion channels - means what, means what? It is a system of proteins, where does it sit in the plasma membrane.

You can, it is closed, okay but if you have sufficient amount of voltage difference across the plasma membrane, it can open, therefore I will call it as voltage gated chloride ion channels. We have done it 100 times, chloride gated, okay. Now there are different families, chloride ion channels are again dozens of them. Here we are talking of one particular type of chloride ion channel, so what is this? What is this? This is the same image as we have seen in the previous, same image, little difference I will tell you. So what are we talking about? We are talking about the lumen of the duodenum - on the basal side, there is a capillary somewhere, where is the pump? The pump is somewhere here, there is water, there is carbon dioxide, carbonic anhydrase - and then antiport system, bicarbonate goes here, chloride goes and chloride keeps on circulating. Now comes a problem.

There is a human genetic disorder in which this particular chloride ion channel, okay, which allows the chloride ion to circulate – the circulation is necessary so that this antiport system can work. Every time it goes through a cycle, it does not use energy, it does not use directly, it is not a pump, but it allows what to go? It allows the bicarbonate ions to go in this direction and the chloride ions to go in another direction. But the chloride, you need the supply of chloride so that the cycle can continue and for providing that you have this channel. This channel is a protein, that protein comes from mRNA and gene. In humans that gene is known to have mutation, okay, and the persons who have that mutation are known to suffer from a disease called as cystic fibrosis.

What is the disease called as? Cystic fibrosis, say that again. In the cystic fibrosis what happens because the system does not work, they have lot of accumulation of mucus, okay. So this system also works in our lungs and in the pancreas. In both the places there is

accumulation of mucus and that can give rise to many serious problems, okay. Therefore this channel is called as, this is called as cystic fibrosis, I want you to read here cystic fibrosis transmembrane conductance regulator, very funny name, abbreviated as what? CFTR.

CFTR, what does CFTR stand for? So what is CFTR? CFTR. Most of us are healthy, we are healthy because there is no mutation and we are doing fine. We are fine because the chloride ions are just going through this channel. It is permitting chloride ions to continuously leak out. Now I am talking about patient, what is the problem there? There is a mutation in the gene, as a result of that the protein is defective. It does not allow the chloride ions to go out. Are you with me now? So the whole system is now screwed up, are you okay so far? And then the patient suffers from CFTR. Is every chloride channel CFTR? No - there are several of them, only one family is chloride channel, okay.

So now we are talking about - we look at that image. Very nice image, this histological image – immunohistological image in which you have used antibodies against which peptide? Secretin, okay. It is about 27, 28 amino acids, small peptide. Can you see this brown dot here, here, here, here, what does each brown dot represent? Secretin, secreting cell, okay, alright, good. So let us understand this image, this is very interesting image. The food has been delivered in the form of chyme from the stomach in the duodenum and look at this arrow - enroute, it stimulates the same thing, it stimulates what and what? CCK and secretin cells. Now whereas the secretin goes and stimulates the cells of the duct so that they release what? Bicarbonate and water and the CCK will stimulate the pancreatic acini cell. Therefore the cells will start discharging more and more of enzyme. So there are two components, two components, pancreas has lot of synthesized enzymes from the zymogen granules, okay, okay so far. And then in the duct you have to give bicarbonate ions, okay and that is promoted by the CCK, good, good. And please read this and this will give you the basic information as to how the signaling happens in the, a very interesting graph.

We are looking at the duodenal pH on the X axis. Okay so far and this is what strong acid, hello, are you with me? And little weak acid, little weak acid and a weak acid. So we are monitoring the pH of the duodenum, number 1 and at the same time we are trying to correlate it with the pancreatic bicarbonate output. How much of it is given and what is the correlation? Very high, how much is the bicarbonate concentration? So much, as you make it less and less and less acidic which means your pH is going from 4 to 5, what happens to the bicarbonate? A very beautiful correlation, okay the more the acidity the more the bicarbonate, I mean that is common sense, okay. And but that is been scientifically proved here by establishing the correlation. I will stop now about the importance of description of pancreas, you will read more about it in the slides, I will move on to yet another interesting organ that is liver. And I am going to talk another 10 minutes, I am going to talk about liver.

Yes, liver is a very interesting organ, it is very large, more than 1 kilo. One of the largest organs, one of the most important organs although there is nothing endocrine about it. But it is a laboratory, hundreds of hundreds of things, it is a storehouse for glycogen, it is storehouse for lipids, it is an organ for the synthesis of a large number of proteins, the

proteins which are responsible for the coagulation of blood and number of proteins are being actually synthesized - it is huge. So let us see what is this liver. Now focus on what we are talking - about liver. I am sure you can see the liver there, I am sure you can see the gallbladder there, hello, are you okay? Can you see the gallbladder there? Okay, then course you can see the rest of the structures. Now follow this, be with me, this is interesting. Blood is drawn to the liver through two independent sources.

How many? Two independent sources. One is very simple. One is very simple - one is dorsal aorta - heart, aortic arch, dorsal aorta gives branches, one is one of them is called celiac artery, again branches and one of them becomes hepatic artery. What does it do? It takes blood to the heart, I am sorry, it is carrying, so the oxygen supply to the liver is happening via, via this supply, hepatic artery done. Everybody you are good so far? Good.

Can you see this is - we have removed lot of alimentary canal but lot of is still there. So you have, this is the intestine and this is the ascending colon, horizontal colon that is descending colon. The blood which has been, the blood, the arterial blood which has been taken to the alimentary canal, follow this. It has given away oxygen to the intestine, are you okay? Then that blood has again got together in the venous system, okay, does it, does it have oxygen? No, it is deoxygenated, very low, whatever, it is low. Now that should normally go directly to the heart, it is deoxygenated blood.

It is deoxygenated, so arteries went to the intestine, they gave away their oxygen, that blood got into the venous system, it should go to the heart, it does not. So the bluish vessel here which indicate the veins which are bringing the deoxygenated blood from the entire intestine, it goes to the liver. So this is what, this is the second blood supply to the liver. Are you with me? I said how many blood, liver receives blood supply from two sources, one was hepatic artery, this blood supply is called as hepatic portal system. What do you call it as? Hepatic, say that again, do not confuse.

So whereas the liver will get its supply of oxygen through the hepatic artery, the liver will get all its food which is not that liver needs it, no, liver needs to process it, okay. And for processing that food the nature has provided with the portal system which does not take oxygen to the liver but which takes all the digested food material from the intestine. Now there is again additional twist in the tail. Let us go to the intestine. What it has absorbed? Okay, it has absorbed the proteins that you have taken, they have been broken down, broken down, finally amino acids, the carbohydrate, let us presume they are reduced to fructose, glucose, galactose, etc.

and fats are there, fats are also digested. So three forms, digested fats, proteins, carbohydrates. Whereas fats get into the lacteal system, we talked about it, okay. And then it is taken away. The broken down and digested carbohydrates and proteins which is amino acids, okay, they are taken by the system to the liver. Are you with me? So it is not, I cannot totally say that everything that is absorbed goes to the liver, no, no the digested

carbohydrates, means glucose, etc. small small monomers, okay and then the amino acids, they will go where? Absorbed at the level of intestine, they will go to, they will be taken where? Liver, how? How? Hepatic, say that loudly, hepatic portal system, okay.

Now remember this in the villi of course there is a lacteal system and the lacteal system will carry the fats, we have a different system for that. So liver actually, we have seen this in the slide, liver actually is made up of what you call as tiny lobules. Now what is this lobule, I will tell you what. This is a, okay you take a cylinder, okay the diameter of a cylinder is less than 1 mm, 0.8 mm or okay, it is not a perfect circle but it has angles, angle something like this, maybe 5 or 6 angles are there, maybe like a structure of benzene, 6, it is a cylinder like this.

Is it really a cylinder? No, I am still calling it a cylinder. Are you with me? Is it a circle there if I take a transverse section? Yes or no? Is that a, okay I will take you to the next slide that will clear the answer. Is that a circle? Not in strict sense, something like this, okay. Now but it is like this and then as you, this is lengthy maybe about 4, 5, 6 mm but then it tapers. So what am I doing? I am giving you a rough idea of what a lobule is and there are thousands of such lobules in the liver, okay.

Now we have to understand the structure of a lobule, okay which is a unit, okay lobule one unit and there are thousands of them. If you have understood the structure of one lobule, you have understood the structure of all the lobules but understanding the structure of one lobule is very important and that is what I am going to do. So what I am going to do is I am going to talk to you about a single single lobule. I talked about this and I am going to talk it. So we are looking at a single lobule here.

So can you see there are about there is 1, 2, 3, above there are almost 6, 6 faces are there and 6 angles are there, yes or no? Good. Now at every corner there are 1, 2, 3, 4, 5, 6, how many corners are there? Six corners. If I take a transverse section of a lobule right in the middle, I am going to get 6 corners, 6 angles. At each angle I am going to get how many tubes, can you count for me how many tubes are there at each corner? Three of them, people also call them as a triad.

Okay so far? Very good, very clear. Now out of the 3 tubes there is one red here, red means it must be it is for blood, it must be carrying what kind of blood? It must be branch of what? Hepatic artery, it also has a celiac artery, and a branch here and then thousands and thousands and thousands and so one is here, one is here, one is here, one can you see red here, red here, red here. So the ultimate branch of that goes at all the 6 corners, one of the 3, are you done? The second one is the blue one here, the blue one here, at the corners, do not go to the middle yet, I am not ready for that. There is a blue one there, now the blue one is coming from where? Hepatic portal system. So the hepatic portal system now is the blue one here is a part of the hepatic portal one. Now at the centre of each lobule there is an opening and that is called a central vein, what do you call it as? What do you call it as? Central vein.

Now just as in a bicycle you know we have a central hub and spokes in the similar manner in the oh I am sorry I am exceeding my limits, we will stop now. Thank you.