Human Physiology
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Lecture - 03

Hello everyone, welcome to another new class on human physiology. In this class, we will discuss glial cells, different types of glial cells, and how they form the blood-brain barrier. So, we will see different forms of glial cells and their functions. So, this will be a very interesting class; please stay with it. So, what different types of concepts will be covered in this class? We will discuss what glial cells are, and then we will discuss different types of glial cells, for example, astrocytes, oligodendrocytes, Schwann cells, and microglia, and for each of those, we will look at a little bit of their structure and functions. So, what are glial cells basically if you remember, like we said, the primary cells of the CNS and PNS are the neurons, right? So, the primary cells are the neuronal cells, which are the primary cells of the CNS.

But there is one more form of cells that basically act as supportive cells to neurons, which is called glial cells. So, basically what we just said is that the primary cells of the CNS and PNS are called neurons. But there is another type of supportive cell that is also closely associated with neurons, and in terms of different types of functions and actions, it helps overall to maintain our central nervous system and peripheral nervous system. So, these helping or supportive cells are called glial cells.

And what they basically do is provide crucial support and protection for neurons. Unlike neurons, glial cells do not generate any action potentials. We have to remember that in the neuron, it generates action potentials to transmit different types of signals with the help of different types of neurotransmitters. But in terms of glial cell function, they do not generate any type of action potential. The term glia comes from a Greek word that is called glue.

So, it reflects their early perception of the role as simply holding the neuron together. Glial cells can also divide throughout adulthood, and unlike most neurons, they can proliferate or divide. This is highly important in terms of the repair mechanism after the injury. So, as we know, there are, of course, cases of neurons that are present in the PNS, and as we already discussed, they have a regeneration capability. But still, even though they have a regeneration capability, the new neuronal growth is not an easy thing.

But in the case of glial cells, they can easily divide and grow, and in that way, they have a very important role in terms of repair following an injury. And as we already said, there are different classes of glial cells. The first and foremost important glial cell is the astrocyte; after that, we will discuss oligodendrocytes, Schwann cells, ependymal cells, and microglia. So, let us see them one by one. So, to start with, the first and most versatile astroglial cell is called an astrocyte.

As you see, it looks like star-shaped cells with numerous processes. So, this looks like a star-shaped cell with numerous processes, and this has been most abundantly seen in cases of CNS. and it has astrocytes that have so many different functions to perform. Some of the crucial functions of astrocytes are to maintain the blood-brain barrier. So, it is a very essential component of the blood-brain barrier that we will discuss after this.

It also helps in terms of regulating the extracellular ion balance; for example, the potassium. It is highly kind of involved in terms of the neurotransmitter reuptake mechanism. It also provides general structural support. It also contributes to synapse formation and elimination. Finally, it can also provide different types of nutrients, specifically glucose, to the neuron.

So, as we said, the astrocyte is a highly important component of the blood-brain barrier. So, astrocytes, as you see, inside our brain—if you remember—there are a lot of blood vessels, right? There are a lot of blood vessels. As we all know, the brain is a very critical and delicate organ, right? And if we kind of see that not too many molecules or proteins can enter the brain through these blood vessels. Why is that? Because if any unwanted toxins, unwanted molecules, or even proteins enter the brain, it may significantly affect the neurotransmission signal. And if it affects these neurotransmission signals, all the responses, all the overall stimulation and inhibition, these processes will be hampered, which will be detrimental to us.

So, our blood vessels in the brain are structured and developed in a way that not all particles can eventually enter the brain. And these specific or specialized blood vessels that form the blood-brain barrier in the brain, astrocytes are one of the most important components of it. It basically restricts the proliferation of blood vessel-associated endothelial cells and narrows the tight junctions, reducing the penetration or infusion of different types of toxins and protein molecules. So, let us see what the structural formation of the blood-brain barrier is. So, if you can see in the blood-brain barrier, the primary thing we have is the endothelial cells.

So, this is the endothelial cell. And in between the two endothelial cells, there are a lot of structural proteins; for example, occludin, claudins, JAMs, and this type of protein basically forms tight junctions. So, what do they form? They basically form tight junctions between the endothelial cells. Just outside these blood vessels, we can see the astrocyte cells, and just below the astrocyte cells, we can also see the pericyte type of cells. There is one more layer you can see, like this bluish layer; this is called the basement membrane or basal lamina.

So, basically, the basal lamina is made of connective tissue. So, this blue color layer you can see here is called the basal lamina or basement membrane, which is basically made of connective tissue. So, this is the overall structure of the blood-brain barrier. So, one more time, we have blood capillaries where we have endothelial cells; you can see endothelial cells. In between endothelial cells, there are a lot of proteins that eventually form the tight junctions.

Just after this blood capillary, you can see that there is a connective tissue layer called the basal lamina, the basement membrane. Adjacent to the basal lamina, we can see the astrocyte cells, and just like close to the basal lamina and the astrocytes, we can also see another type of cells, which are the pericyte cells. So, each one of them has specific functions; let us discuss them one by one. So, for example, endothelial cells are like specialized brain microvascular cells, or these are also called BMECS, with very unique features because they contain tight junctions between them, and these endothelial cells in the blood-brain barrier have a lot of fenestrations. Fenestration means they may have some of the pore channels; they may have some of the porous channels in order to transport certain molecules.

We will discuss one by one what type of molecule it can transport and also, as we mentioned, what occurs between different endothelial cells. There is a protein molecule that forms tight junctions and different types of proteins like occludin, claudins, and ZO proteins that can eventually form these tight junctions. And basically, what they do is seal this porous endothelial

cell layer so that not all types of molecules can eventually diffuse inside, which can affect the neurons. In this way, it basically maintains the BBB integrity. And then we discussed the basement membrane, which is basically like the basal lamina, made of connective tissues that can contain collagen IV, laminin, and fibronectin, these types of proteins.

This basement membrane provides structural support and regulates endothelial cell behavior. Then we saw pericytes; basically, pericytes are the contractile cells embedded in the basement membrane of capillaries and venules. This ensures endothelial cells by regulating capillary blood flow, and it also contributes to the development, maintenance, support, and stability of the blood-brain barrier. Finally, the most important one, which is the glial cells or astrocytes, also provides structural support, but this has some crucial roles. Now, let us see what their role is.

So, before we discuss the specific role of astrocytes, let us first see what type of molecule can eventually diffuse inside. So, if I consider these blood vessels, we have several neurons on this side. So, what we do not want is basically different unwanted proteins or any type of toxins to go inside. Because if these unwanted proteins and toxins go inside, they will eventually either stimulate the neuron excessively or excessively inhibit the neuron, and this will basically hamper our regular neurotransmission process. So, what type of molecule will they basically allow? So, they will allow these BBB junctions to facilitate the exchange of gases, for example, oxygen and carbon dioxide, right? These endothelial cell receptors have a specific receptor called the GLUT4 receptor.

So, what do we have? We have GLUT4 receptors and what do they allow? Basically, it allows the entry of glucose because neurons need glucose. So, it will also allow the entry of glucose apart from that because, as you all know, the cell membrane layers are lipid bilayer membranes. So, any type of lipid-soluble molecules, any type of small lipid-soluble molecules, or drugs, some of the drugs can also penetrate the BBB. And finally, as we said, it has a lot of ion channels. So, for example, some of the crucial elements are sodium, chloride, calcium, and maybe phosphate.

So, different types of ions can also go. But mainly we have to remember that it prevents any type of unwanted large protein, any type of other large molecules like toxins, and different types of complex or larger drugs; they generally prevent the diffusion of this type of molecule. So, the point was how astrocytes play a role in maintaining the BBB integrity, right? So, you see these astrocytes, what astrocytes basically do is secrete different types of growth factors. It can be like a neuronal growth factor or another type of growth factor. Whenever they say that there are certain toxins present and circulated near these capillaries, they will secrete this growth factor.

And what will this growth factor do? Basically, as they secrete this growth factor. These growth factors will eventually stimulate the proliferation of the endothelial cells; along with that, it will also stimulate different types of proteins that are components of these tight junctions. So, two things it will do right: first, it will secrete different types of growth factors whenever it senses the presence of toxins or unwanted proteins. This growth factor will do a few things; first, it will stimulate the endothelial cell layer, and as you know, if there is proliferation of endothelial cells, what will happen is that more and more cells will basically form here, and eventually, it will kind of reduce the permeability of unwanted molecules. Apart from that, those growth factors will also stimulate these tight junctions.

So, basically, it will increase protein production, causing thicker tight junctions. So, basically, these tight junctions will become thicker. As it goes thicker, it will basically reduce the penetrability of different types of unwanted molecules; it will reduce the penetrability of unwanted molecules. So, in this way, by secreting these growth factors, astrocytes have a highly important role in maintaining the blood-brain barrier's integrity.

Hopefully, it is clear to you. Let us also see the different functions of astrocytes. So, we have already discussed this, for example, overall blood barrier functions and how different molecules can be diffused. So, as we said, glucose can enter or diffuse inside via GLUT1 receptors; amino acids can enter; different types of ions, like sodium, chloride, and calcium, can enter; oxygen and carbon dioxide can diffuse; different types of lipid-soluble substances can diffuse; and some drugs can also enter. And specifically, they can kind of diffuse via either the lipid bilayer membrane or through different types of active or passive transport. But we also discussed what type of molecule it will prevent from diffusing, which includes various toxins and different types of unwanted proteins.

Now, let us see another important and interesting function of astrocytes, which acts as a potassium buffer. So, you remember the neurons we discussed during the depolarization; it kind of has a lot of sodium ion channels. So, basically, a lot of sodium ions come inside, but again we discussed this later on the downside of the neuron when there is this repolarizing wave. When there is a repolarizing wave, a lot of potassium comes out of the cell. And just imagine that continuously, depolarization and repolarization are happening, and a significant amount of potassium ions is eventually coming out of the cells.

And what it will cause is that it will basically reduce the potassium level inside the cell; it will significantly reduce the potassium level inside the cell and also increase the potassium level outside of these neuron cells. And basically, what will it cause? It will cause the irregularity of the potassium ion gradient because ideally, potassium should be higher inside and lower outside of the cell. And in this way, they can only maintain a normal ion channel-gated or voltage channel-gated potassium diffusion. But in case the concentration gradient gets reversed, for example, potassium becomes low inside and potassium goes high outside of the cell due to repeated rounds of repolarization. This can be detrimental, and it can cause inhibition or an overall reduction in the neurotransmission process.

What astrocytes do is similar to what happens whenever there is a high amount of potassium ions building up outside of the cells; they also have potassium receptors. So, basically they will uptake this excess potassium inside themselves. And the most beautiful and interesting thing is that astrocytes, like each astrocyte, have a definitive capacity or volume for potassium ions. So, for example, let us think like this: the first astrocyte can only take up to 5 potassium ions. So, once they can uptake 5 potassium ions, they are already full.

cannot take any further right, but there is another interesting thing that astrocytes are generally attached to other astrocytes by processes of gap junctions. And these gap junctions, you can see, are made of different types of connexin, like the CX43 protein. And whenever they are full, they can also remove some of the potassium and send it to the surrounding astrocytes. So, in this way, one astrocyte can send some additional potassium to the surrounding astrocytes; again, the potassium concentration will deplete in these cases of astrocytes; further, they will help in terms of taking up those extra potassium that is being generated by the repolarizing wave. So, in this way, astrocytes can act as a potassium buffer, and they can maintain the

potassium ion level properly, as well as the potassium concentration gradient inside and outside the cell.

Another very crucial function that astrocytes have is that they can help in terms of neurotransmitter uptake. So, let us see this very quickly; for example, we have one like a stimulator or the neurotransmitter, which is glutamate, right? So, let us see how this glutamate neurotransmitter, after the calcium bridging, causes the vehicle to become infused with the axonal terminal membrane, which leads to the exocytosis or release of this neurotransmitter, and what are these neurotransmitters? I told you these are glutamate. And now some of this glutamate will basically be taken up by the next neuron, right? So, this was like the postsynaptic neuron. So, this is the postsynaptic neuron, this is the presynaptic neuron, this is the presynaptic neuron. So, the presynaptic neuron will secrete some of this glutamate neurotransmitter, which will be taken up by the postsynaptic neuron, and eventually, it will also send its stimulation signal to the next neuron; in this way, it will work.

But just imagine there are hundreds of glutamate molecules; initially, all these vehicles were secreted from the presynaptic neuron. To stimulate the next postsynaptic neuron, we do not need 100; maybe glutamate, maybe we just need like 10 molecules of glutamate. So, what will we end up with? We will still have about 90 excess glutamate, right? We will still have 90 excess glutamate, and we do not need this excess glutamate to stay in this, like in neurosynaptic junctions. Because if this glutamate is continuously present in the synaptic junctions, it will keep on stimulating the next postsynaptic neuron. So, in this way, the neuron will be continuously under the stimulation phase, and it will not be able to undergo the next inhibition phase, right? So, will be continue continuously in an excitatory condition.

So, in this way, the majority of the glutamate, for example, the neuron or the terminal area of the neuron, also has a glutamate reuptake protein. So, it has glutamate. Re-uptake proteins and the excess majority of this excess glutamate can be re-uptaken, and once they can be re-uptaken again, they form vesicles with the leftover glutamate, and further, by the movement of the dynein protein, they eventually go to the cell body where lysosomal degradation occurs. But let us consider this glutamate reuptake protein, which is present on the surface near the axonal terminal area; it can only reuptake 70 molecules, right? So, a total of 90 excess glutamate molecules are present; unfortunately, this glutamate reuptake protein can only remove about 70 excess glutamate molecules from this synaptic junction. So, what will we be left with? We are left with another 20 excess glutamates, right? So, we left with another 20 excess glutamate, and now how this will eventually get reuptaken, and if they are not reuptaken by the neuron, then there will be continuous stimulation, as we said, will be in a continuous excitatory phase.

Here, astrocytes help, basically. So, astrocytes also have glutamate uptake protein. So, some of this excess glutamate protein will eventually first go to the astrocytes. So, these are astrocytes, as you can see. So, this excess 20 glutamate will initially be taken up by the astrocytes, and through an enzymatic activity, which is the glutamate synthase, this excess 20 glutamate will be converted to glutamine. So, what is happening is that we said some of the excess glutamate will be re-uptaken by the glutamate re-uptake protein in the presynaptic neuron, but it will still leave with maybe around 20 glutamate molecules.

This glutamate will be taken up by the surrounding astrocytes and inside the astrocytes by the enzymatic activity of glutamate synthase; this glutamate will be converted to glutamine. Now, this glutamine will come out from the astrocytes, and very interestingly, the cell membrane or the axonal terminal area, although the glutamate reuptake protein has been saturated, still has

some glutamine reuptake protein. So, is it not interesting that the cell with the glutamate reuptake protein, which initially got saturated, also has some glutamine reuptake protein? So, in this way, all this glutamine will eventually be able to come inside the cell, those excess 20 converted glutamines. Now, they cannot stay as glutamine inside the neuronal cell, right? So, this glutamine is acted upon by the enzyme glutaminase. So, this glutamine, by the action of the glutaminase enzyme, will again be converted to glutamate.

And whenever they convert to glutamate, the glutamate will finally form vesicles, and eventually these vesicles that contain the glutamate will be transported for lysosomal degradation by a protein called dynein. So, this is the overall mechanism, and as you can see, astrocytes are crucial for basically uptaking excess glutamate, converting glutamate to glutamine, and eventually transporting that glutamine back to the neuron. Isn't it interesting? So, quickly now we will go through some of the other glial cells. For example, there are another important type of glial cells that are present in the CNS called oligodendrocytes. And these oligodendrocytes are mostly responsible for the myelination in the CNS.

And as you all know, you already discussed what the most important function of myelation is. It basically improves or increases the speed of the transmission signal. So, basically, it increases the action potential propagation speed because this myelin sheath contains a lot of insulator-related fat. So, they basically act as insulators and contain a lot of fat. So, basically, as they act like insulators when the action potential starts, they can jump from one node of Ranvier to another node of Ranvier; in this way, they can increase the speed of the action potential.

So, basically what it does is increase the speed of the action potential. The next one is the Schwann cells; these are found in the PNS. So, basically, oligodendrocytes, which are a type of glial cell, are found in the CNS and are part of forming the myelination or the myelin sheath. In the case of the PNS, it has been observed that the Schwann cells are the glial cells responsible for forming the myelination. In the same way as we said, the primary role of these cells is forming the myelin sheath that helps increase the speed of the transmission signals.

Apart from that, very interestingly, Schwann cells also have a crucial role in the action of regeneration. Remember in the last few classes, we discussed nerve injury and repair, and in that class, we thoroughly discussed how nerve injury happens and how peripheral nerves can regenerate by the function of the Schwann cells. So, hopefully you remember that briefly swan cells can initially differentiate, and after differentiation and degeneration, they can further proliferate and secrete different types of growth factors that can promote axonal rigor. So, basically, Schwann cells and oligodendrocytes are the two important components for glial cells. Now, what are the basic differences between the oligodendrocytes and Schwann cells? As we said, oligodendrocytes are the type of glial cells that are responsible for myelination, but where in the CNS, like cranial nerve 2? In cases of schwann cells, they are mostly responsible for myelination in the peripheral nervous system and cranial nerves 3 to 12.

One oligodendrocyte cell can myelinate multiple axons. For example, one oligodendrocyte cell can multiply 30 to 60 times. So, this is very crucial to know that one oligodendrocyte cell can myelinate 30 to 60 axons. But in cases of small cells, it can only myelinate one PNA action. So, in the case of Schwann cells, one Schwann cell can myelinate only one axon. Oligodendrocytes don't have any regenerative ability, and that's why, as in cases of the CNS, it is very difficult, almost impossible, to regenerate the CNS nerves.

But in cases of swan cells, they have regenerative abilities, as we already discussed during our nerve repair class, and that's why in cases of the PNS, it has a highly regenerating capability. In cases of oligodendrocytes, demyelination leads to conditions like multiple sclerosis; it can also resemble amyotrophic lateral sclerosis or other types similar to multiple sclerosis. In cases of swan cell demyelination, it can lead to conditions like Guillain-Barré syndrome. So, these are some types of diseases that can also occur in cases of demyelination.

Then another important type of glial cell is the ependymal cell. These you can see are ependymal cells, which mostly line the ventricles of the brain and the central canal of the spinal cord, resembling an epithelial layer, although they have this type of ciliated or antenna-like projections. The main function is to produce cerebrospinal fluid, or CSF, which selectively transports water and solutes from the blood. It also helps to circulate the CSF; it also helps to form the blood-CSF barrier, regulating the exchange of substances between the blood and CSF. Ependymal cells are joined together by tight junctions, forming a barrier that regulates the movement of substances between the CSF and the brain tissue. This also helps in terms of joining the blood-brain barrier to control molecular movement, but the primary role is to produce and secrete the CSF.

CSF is very important because it can carry a lot of nutrients, a lot of immune cells, a lot of essential solutes, and water. Lastly, the type of glial cells that are the smallest glial cells, although they constitute almost 12 percent of the brain, are called microglia cells. And these microglia cells can either be under resting conditions or under active conditions. Basically, these microglial cells form from monocytes, and they are called resident immune cells of the brain. They really stay, as we said, either in a resting condition—in cases of a resting condition, you can see that it has a small cell body—but when it gets activated, it either becomes amoeboid or can be in a secretory condition.

In cases of amoeboid condition, there has been seen a large, enlarged cell body with retracted processes, and it has a high capability of phagocytosis. In cases of secretory microglia, it can secrete a lot of different pro-inflammatory or anti-inflammatory cytokines and other factors, and it can contribute to the polarization or depolarization of macrophages to M1 or M2, and it has highly specific functions. So, let us see what the different functions of microglia are, particularly in cases of any pathogen attack on the brain. What microglia do is essentially convert from a resting state to an amoeboid condition, and amoeboid microglia have a phagocytosis role. So, basically, it will either directly phagocyte the bacteria or destroy the bacteria.

It can also present the bacteria via the major histocompatibility complex and, in this way, it can activate the surrounding T cells and also contribute to phagocytosis. In cases of secretory type microglia, it can get activated either in response to different toxins or different viruses. So, whenever there is a toxin attack or virus attack, what happens is that there are a lot of pro-inflammatory cytokines that get secreted, or the pro-inflammatory type of molecules or signal molecules that get secreted. For example, like IFN-gamma, LPS, and GM-CSF. So, whenever microglia send this type of pro-inflammatory molecules or cytokines, they convert into M1 pro-inflammatory microglia.

And when they convert into M1 pro-inflammatory microglia, they secrete a lot of different pro-inflammatory cytokines; you can see these names, and it contributes to the degeneration of the neuron. So, if there is any viral infection in the neuron and if it persists, it will not only hamper that particular neuron, but the viral infection can also spread to a surrounding neuron.

So, basically, microglia in this way perform their immune functions to destroy the damaged neuron. But in cases of certain injuries, for example, when any injury occurs, the body tries to repair that injury by secreting different types of anti-inflammatory cytokines. For example, IL-10, IL-4, and whenever this type of microglia senses the presence of different kinds of anti-inflammatory cytokines in the brain, they basically convert to the M2 anti-inflammatory microglia.

And whenever they convert into M2, like anti-inflammatory microglia, they secrete a lot of anti-inflammatory cytokines like IL-10 and TGF-beta, and eventually, they contribute to repairing the injured area and also to maintaining the health of the neurons. Importantly, the M1 pro-inflammatory microglia and the M2 anti-inflammatory microglia can have an alternative activation mechanism, and they can basically interchange or exchange with each other, forming the other type. So, if you like the microglia and you saw that microglia have a very specific role to play, specifically, these are the immune cells of the brain, the immune cells of the CNS. So, these are very important.

Also, glial cells maintain brain plasticity as well. For example, glial cells are involved in synaptic plasticity. Astrocytes also modulate synaptic transmissions and can have an important influence on long-term potentiation and long-term depression processes. Microglia have a very important role in terms of synaptic pruning. It eliminates weak or inactive synapses. So, hopefully, you liked the overall glial cell class, and glial cells have different roles in terms of different neurodegenerative diseases; also, you can go through the slides.

Do you know that the alteration in glial cell function has been implicated in various mental health-related disorders, including depression, schizophrenia, and bipolar disorder? Do you know if glial cells divide or not? So, please try to answer if you have further questions; please contact us during the live sessions. Hopefully, you are enjoying the human physiology classes. So, we are almost in our last week where we are discussing different types of glial cells. So, finally, we will see different types of disorders related to our brain and spinal cord.

Very soon we will meet with you with another new class of human physiology. Thank you again.