>> So it is March 14, 2016. This is lecture 10 in Physiology. Let's back up-- Let's review just the last concept that we left you with on Wednesday. It was all about something called action potential propagation. Propagation means to recreate an action potential at each of these sites known to you as nodes or nodes of Ranvier. To recapitulate, there's a certain threshold voltage that has to be applied that causes the opening of sodium channels, sodium rushes in that brings to the interior positive charge which quickly moves to the adjacent node where it depolarizes that node and sets up a new action potential there. So, meanwhile, the sodium potassium exchange pump is working to maintain these independent equilibrium potentials by putting out sodium and reclaiming or moving back in some of the lost potassium. So, that was called saltatory action potential propagation. And we left you with two benefits. It makes the speed of conduction quicker and it also uses less ATP than would otherwise be necessary. That being said, at the bottom of the page, we have this topic or definition, something called the refractory period. To be refractory means to be insensitive. You see, we showed the influx of sodium which is part of the depolarizing process. And we said that these charges would move toward any area of negativity and is the node here in a negative state of course. But will these charges also move in the opposite direction? The answer is yes. But those charges will be ineffective on the previous node because the previous node has a condition known as a refractory state. A refractory period is the time during which the membrane is depolarized and or even hyperpolarized and therefore is insensitive to stimulation. Why is the previous node insensitive? Because it hasn't recovered yet, it is still in a depolarized or maybe hyperpolarized state. So, what? Essentially, the refractory period has two important consequences. First, it tends to limit or determine maximum AP frequency. That's easy enough to memorize but what does it mean? Here's an action potential quickly illustrated. Remember, it includes the what? D word, depolarization followed by R word, repolarization, and a brief moment of what's called hyperpolarization. So essentially, the action potential starts right here and returns to a normal resting potential right about there. So, during this period of time, the nerve is basically engaging in, that means producing an action potential and you can't stimulate it during this time because it hasn't finished with what it's doing so to speak. It hasn't recovered. So, let's say by definition, the refractory period begins as the nerve depolarizes and ends when the nerve is completely repolarized. So, this would be the refractory period, let's say. And so stimulating a nerve during this time will or will not be effective? Will not be effective. Some nodes incidentally might have a slightly longer RP. What's RP? Refractory period. So, what if the refractory period were a little longer, would that allow the nerve to produce action potentials more frequently or less frequently? Less frequently. And why does that even matter? It turns out as we'll see today that the frequency of action potentials is really what delivers information that can be quantified or interpreted so the greater the frequency that a nerve can produce, the more information it can convey either to the central nervous system or even out to muscles. The second benefit of the refractory period is that it assures, that means guarantees, unidirectional AP what? So, in other words, can action potentials ever back up and go where they have come from? No, because as this voltage moves backwards, it will find the previous node in a refractory period. So, as we finish this topic, the refractory period is just this period of time where the nerve is insensitive to any stimulation and this will help to set or at least limit what's called maximum AP frequency. It also prevents action potentials from backing up or working in reverse. So now, at this point, we've introduced and explained what an action potential is. We explained how they're generated and more recently, we've explained how they're propagated. But sooner or later, the action potential will arrive at the end of the axon where an abrupt termination will occur. In other words, the end of the nerve will create this unit of communication called a synapse. So now, today, a new concept which is simply is synaptic transmission. To transmit means to convey these signals across this physical gap which you know from anatomy is known as a synaptic cleft. How does that actually occur if these two membranes don't actually touch? And that's worth remembering and reminding you that in the nervous system, the fibers that we speak of actually don't physically touch. There is a space that separates them known as the synaptic cleft. So what are the events that occur across synapses to bring about synaptic transmission? Here's a diagram of what we're talking about. This represents the end of the presynaptic neuron forming what's called a synaptic bulb and here is the postsynaptic membrane which may or may not respond to the activities that were about to describe. On the presynaptic side, we have these containers, these membrane-bound bubbles which you know are now called synaptic vesicles and they contain a precise, exact amount of a so-called neurotransmitter. And these bubbles will merge with and essentially rapture at the surface of the presynaptic neuron and through the process of exocytosis, they will spray or release the neurotransmitter into this gap called the synaptic cleft. So those are basically the physical events that take place but how does this electrically amount to synaptic transmission? What we're going to do is put these events in a timeline, chronological order, and explain the whole process step by step. So imagine if you will, action potentials arriving as they will through saltatory propagation. Can these voltages just leap across this gap? Not at all. So these voltages arrived and their first effect is to allow or cause the influx Ca, what's that? Calcium ions, through calcium channels which are seen here and are voltage gated, that means they open in

response to this voltage. So, step A, arrival of action potentials which cause the influx of calcium ions into this presynaptic area of the neuron. This will set in motion physically a precise number of these bubbles, what are they called? Synaptic vesicles and they will release their contents through exocytosis. And the number of vesicles and the amount of transmitter that's released would be, you think, proportional to what? What would determine the number of vesicles that are released? Would it be the size of the action potential or the frequency of the action potentials? It's the frequency. So the more frequent they arrive, the greater the influx?

>> Calcium.

>> And therefore the greater number of synaptic vesicles which will be released. So, the exocytosis is basically proportional to the arriving AP frequency. So, the transmitter is literally diffusing now across the synaptic cleft and it will act on, that is attached to, sites on the postsynaptic membrane. This is the postsynaptic membrane which is designed to react with, respond to, these molecules. And if our goal is to cause depolarization on the postsynaptic side, and it very often is, what do we want to happen? Remember, this postsynaptic neuron is maintaining a resting potential. And although it's not numerically stated here, notice that the inside is negative and the outside is currently positive. So, what is the standard or resting potential for the postsynaptic membrane? Negative 70 millivolts. And if we want to trigger it, we have to depolarize it or hyperpolarize it? Depolarize it and that would call for the influx of what ion?

>> Sodium.

>> Sodium. So you're quite ahead of me here. The attachment of these neurotransmitters, at least in many cases, will bring about a change in postsynaptic ion permeability specifically in the scenario we're discussing, will cause an influx of sodium ions. In other words, the sodium gates are opened, sodium will come in and that will effectively depolarize the postsynaptic membrane. Which is fine and good but what should follow depolarization if we want to repeat this process in rapid succession? Is depolarization enough? No, we have to what? Repolarize and have that achieved based on what you know from Wednesday. We've got to somehow allow the efflux of potassium. So, the influx of sodium is followed by what's called postsynaptic depolarization but what has to happen now is the R word, what?

>> Repolarization.

>> Repolarization. Now that's contingent on the opening of potassium gates which is not going to happen as long as this neurotransmitter remains in a effect because what is the neurotransmitter doing? It's causing an influx of sodium. And as long as that transmitter lingers in the synaptic cleft, the influx of sodium will continue. So clearly, what has to be done here is a means to neutralize this transmitter. In other word, render its effects canceled. Luckily, and in every synapse, there are enzymes in the synaptic cleft which are hydrolytic, that is their job is to break down the neurotransmitter and therefore nullify, cancel, the effect that it's having on the postsynaptic neuron. And therefore allow what? Once we've enzymatically hydrolyzed the transmitter, now efflux of potassium will occur and repolarization is achieved. This repolarization is a result of the breakdown of the neurotransmitter and or it's what? It's presynaptic reabsorption. Though some of these transmitter molecules just wander away through diffusion and whether they're broken down or whether they simply wander away, notice in the sketch that they are brought back in to the presynaptic neuron. And what do you imagine, what would you hope or assume will happen to these molecules once they reenter the presynaptic neuron? They're going to be repackaged. You're absolutely right, into these synaptic vesicles which maintains a kind of constant supply for these vesicles and the neurotransmitters that they contain. Now we really have to emphasize the importance of this step, this enzymatic hydrolysis. Because what if these enzymes were inhibited by any means, then would achieve influx of sodium. We would achieve postsynaptic depolarization but we'd be unable to, R word? And therefore how many action potentials would successfully be transmitted? One, any more? No. So that would shut down this synapse and prevent the T word, the what? Transmission of action potentials. If this is happening at a sensory synapse, that means no further sensory information would reach the brain and if this is happening at a motor synapse, that would mean no further motor action potentials would reach their destination and what is the destination of a motor action potential? Muscle. So either way it's bad news because it would lead to anesthesia on the sensory side and P word on the motor side? Paralysis. This is not just a hypothetical situation because there are very powerful nerve agents which act at synapsis and block this very process of repolarization. And they kill people by preventing the passage of motor nerve action potentials. How does that kill people? You can't breathe because the diaphragm is dependent on a constant stream of motor action potentials for inhalation and exhalation. So, these events occur in this

order and lead to depolarization followed by repolarization and this depolarization will spread to the first node of the postsynaptic cell where it triggers and causes another sequence of APs to be, what's the P word? Propagated. So, let's be clear. Propagation brings the action potentials to this location then the T word, what's that? And then the P word again, propagation, transmission, propagation. It's incredible to think that this happens in, you know, less than the wink of an eye in a merely second or less and it's happening over and over and over again every moment of your life. This then is the basic operation of any so-called chemical synapse. Let's go over it one more time. Action potentials arrive, what gates are open? Calcium. Calcium flows in down the concentration gradient. The influx of calcium physically brings into motion these containers, what are they? Which release their contains in proportion to the frequency of arriving action potentials. The transmitter diffuses across the cleft, attaches to postsynaptic sites and often causes an influx of? Which brings about depolarization. What happens to the neurotransmitter, one of two things? It will either be diffused back or taken back into the presynaptic neuron or it would be enzymatically, H word? Hydrolyzed which nullifies its effect and therefore makes possible, the R word, repolarization. This then will be propagated, that is this event will be recreated into action potentials propagated down the postsynaptic cell. So this sounds and is fundamentally a sequence of events. But here's the important news, not all synapsis promote depolarization. If every synapse in your nervous system were excitatory as these appear to be then we would be a mass of convulsing protoplasm. In other words, it would be like our town where all of the intersections have nothing but green lights. In other words, we'd have collisions and chaos and total confusion. Luckily, synapse has come in two basic forms which is where we're going now. The type that we just discussed, which brings about depolarization, is called an excitatory synapse, in effect a green light, that is it allows for transmission in the manner that we described. And the neurotransmitters that are known to be of this category include these compounds, some of which may be familiar. Acetylcholine, norepinephrine, serotonin and glutamate, with actually glutamate being the most common but all of these cause sodium influx and therefore bring about the D word, depolarization. They promote depolarization by either an increase in sodium permeability, or in some cases, a decrease in what? Understand that if we increase sodium permeability, sodium would go which way? And that would depolarize. If we decrease potassium permeability then less potassium would leave and that also would cause depolarization. So these are two means to achieve the same result which is depolarization. And the voltage that occurs on the postsynaptic side is called an EPSP which is not a structural thing, it's an electrical thing. EPSP stands for Excitatory Postsynaptic Potential which basically depolarizes the postsynaptic cell and therefore leads to the T word, successful transmission. Excitatory synapsis are countered by or basically antagonized by, what do you think? Inhibitory. Now, let's just speculate if excitatory transmitters bring about depolarization, what do you imagine an inhibitory synapse would do? Hyperpolarize. And the transmitters that are important in these types of synapsis include the following, GABA, which is an acronym for Gamma-Aminobutyric Acid. No, you don't have to know that. Dopamine, maybe you've heard of it, serotonin, you just did earlier, and glycine, these are all inhibitory neurotransmitters. And the immediate question is what?

[Inaudible Remark]

Why could serotonin be an inhibitory and also an excitatory? Why isn't it one or the other? In certain parts of the brain, the postsynaptic cell reacts differently to the same stuff. In this case, of course, promoting hyperpolarization. How do you promote hyperpolarization? Well, here's a new ion nd what's that?

>> Chloride.

>> And what charge does chloride have? And if we increase chloride permeability, more of it will go in bringing what charge to the inside then? Negative, and that amounts to H word, hyperpolarization. If we increase potassium permeability, what charge this potassium have and which way is that going to go? Out. So understand that both of these achieve the same net effect. They make the voltage not? Less negative but what? More negative, further from, T word? And therefore harder to excite. The voltage that these then produce have the appropriate name IPSP. I've have it here in red to symbolize its opposite effect to the EPSP, but the words are inhibitory postsynaptic potential, essentially working against depolarization. Now, of course, I guess the question still is unclear. Why do we need inhibitory synapsis if all we had were excitatory synapsis, then action potentials would faithfully and always be T word, what's that? Transmitted, and there'll be no checks, no balances, no ability to stop or block or even filter extraneous or superfluous sensory or motor activity. And very simply put, if you took away inhibitory, you'd have only what? And that would lead to an overwhelming barrage of sensory input to the brain which would be mind blowing literally. And at the same time, it would allow an overwhelming number of motor action potentials to reach muscles and that would cause all manner of

seizures and tremors and twitches and cramping. So, essentially the inhibitory synapsis allow for a reduction in transmission and therefore a proper communication across synapsis in the central nervous system. This illustration came from your text and it's a simplified illustration of what we're trying to convey. Here's a postsynaptic neurons seen in green. And remember there are tens of thousands of synapsis reduced in this illustration to just three. We have A, B and C. A and B are shown in green so they must be what variety? And C is shown as red so that must be inhibitory. The excitatory fibers tend to-- where is the D word, tend to what? Depolarize, whereas, the inhibitory tend to, H word? Hyperpolarized. So, my point is what happens in the postsynaptic cell at any given moment is a function of the ratio of green to red. Simply put, if green predominate, will action potentials be transmitted? Yes. If red predominate, then action potentials will be blocked or at least reduced in frequency. So, here for instance, this graph shows A by itself producing depolarization. Then A, again depolarization. But if we have A plus B or A, A, B, B, B, what is this? This reaches the so-called kicking point which is what? Threshold where an action potential occurs. If we see the effect of C, C by itself doesn't depolarize, it makes the voltage more negative and what's the H word for that? Hyperpolarization. So, at any given second, any given nanosecond in your nervous system, there are literally a barrage of excitatory and inhibitory activities occurring across all of the trillions of synapsis within your brain. So, the effect of these excitatory and inhibitory couldn't be overvalued or overestimated. And there are, as you probably would guess, various drugs that act not on axons but most psychoactive or neuroaffective drugs don't act on axons, they act here at synapsis by altering either excitatory or inhibitory activity. So let's go through a few, because in doing so, you'll appreciate the value and the interaction of inhibitory versus excitatory synapsis. So here on the left, we have bar graphs, green and red, which at the moment show equal activity of what? Excitatory versus what, inhibitory. So this is the status quo, in other words peaceful coexistence where excitatory activity is balanced or matched by inhibitory synaptic activity. As we go through these lists of synaptically effective drugs, we can classify and we will classify then very broadly into two categories which make perfect sense. If a drug is a stimulant or if a drug is a depressant, can be deduced, that is figured out from the information that's up here. Oftentimes, you don't need that because it's fairly common knowledge. Amphetamines and cocaine, what's their reputation? Do they put people to sleep or do they wake them up?

>> Wake them up.

>> All right. So right away, would that be a stimulant or a depressant?

>> Stimulant.

>> And noticed that that matches perfectly with this information. So, to be exact, do those cocaine have any effect apparently on inhibitory synaptic activity, compare this to this? No. So, these don't affect or change inhibitory synaptic activity but they do apparently have what effect on excitatory transmission, they what? Therefore, increasing the what? The number of EPSPs and does this sort of-- well, provided jolt to people. And of course, it's famous for its excitatory stimulatory effect on the nervous system. Next are barbiturates. And before we consider their final effect, what does this information suggest? Barbiturates tend to increase or decrease excitatory synaptic activity? Decrease it. And apparently, at the same time can also cause what effect on inhibitory synaptic activity? So, we're inhibiting the excitatory synaptic activity but we're boosting or stimulating inhibitory synaptic activity. So, in other way, we are decreasing what? EPSPs and increasing IPSPs. The net effect would be to drive these resting potentials more negative which would make synaptic transmission more or less likely? And so, what would be the classification of these compounds, are they stimulants or depressants? Very powerful depressants use medically to treat among other things epileptic seizures. But at least historically, they have been available by prescription and abused. At least two famous celebrities were killed by either an accidental or deliberate overdose, Judy Garland, Marilyn Monroe, people you probably don't know because, well, they're dead and been dead for a long time. But what's interesting is these barbiturates, which can kill people accidentally, can also be legally used in the state of Oregon today to kill people who are terminally ill. And in fact, quite thankfully, the state of California has passed a law so that in June 9th, you can also secure these drugs especially in the form of a brand name called seconal and you can do what to yourself? You can go to sleep and never wake up. And why would that be therapeutic? Well, I guess the trade off is what? Months of torture and pain and agony or a gentle peaceful death. Of course, I'm editorializing here but I'm happy to see that law passed. So, can barbiturates be abused and actually, of course, produce unwanted results? Yes. But they do have medical and therapeutic advantages. So, to repeat, stimulant or depressant?

>> Depressant.

>> Moving on, caffeine and nicotine, hardly any guess work there. And noticed that their work, not by changing inhibitory synaptic activity, but by boosting what? Excitatory synaptic activity. Next and curiously, a compound that really has no medical value, at least no beneficial medical value, and what is the reputation that you know for strychnine?

>> Rat poison.

>> It's a poison, it's a rat poison actually or any kind of poison will kill you too. So, how does it work? Does it have any effect apparently on excitatory synaptic activity?

>> No.

>> No. Does it have some effect on inhibitory activity? In fact, it reduces it dramatically. So, let's be clear. It's taking away the red lights, it's reducing inhibitory postsynaptic potentials and living what unchecked? Excitatory potentials. Now, would that be a stimulant or a depressant? It'd be a stimulant. And you say, well then, how would that kill people? It would just sort of wake him up. Well, not really, because if you allow too many motor action potentials through these synapses, they're going to go out to what? And these muscles are going to be contracting uncontrollably. And what muscle would be most impacted by an inappropriate delivery of motor action potential through the neuromuscular junction? Not the heart because actually the heart is autorhythmic. But this one here, the D word, diaphragm. And when that contracts uncontrollably, you're not breathing, that is you're not moving air. So these are indeed lethal, not because they are depressants but because they cause an overstimulation across, let's say, motor synapsis and therefore lead to what's called, [inaudible] of the diaphragm, in other words respiratory arrest. But there's nothing that's stated in this information that restricts this affect to motor nerves. Could this effect also occur across sensory synapsis? And if so, what would the effect be? Now, we're taking away as before the what? And living unchecked a lot of EPSPs. This answers an interesting paradox because a lot of drug dealers that sell this, what's this? Cocaine, actually mix a little of this in because it's cheaper. And why would you put strychnine in the cocaine you're selling your best friends? Well, that would tend to make them feel a little more happy about the whole thing. That is they get an extra boost off of it as long as it wasn't too much over the top. But, again, that's kind of a-- well, let's say, an unconsumable business practice for drug dealers. Next, moving on to this compound which enjoys a familiar reputation, who hasn't heard of Valium. And so what does it apparently do based on this information? Does it have any affect on excitatory synaptic activity? Apparently not but it does boost or increase the number and the frequency of IPSPs. That said, is it a stimulant or a depressant? A depressant? And especially helps to calm and relax muscle so its main effect is to chill people out and of course it has the capacity for abuse as do most of these things for that matter. Now, here's one additional item that, of course, shouldn't be left off anybody's list of drugs that influence CNS synapsis, because never mind all of these. What's the most popular widely used and abused agent that acts on the central nervous system? It's alcohol. And we think of alcohol as a fun, recreational drug and it's legal and just about every place that I know of. What's it do? It tends to reduce what? Excitatory activity and at the same time tend to increase a little bit the what? Inhibitory activity. So with that said, how would you classify alcohol? Is it a stimulant or a depressant? It's a depressant. And that is sort of counterintuitive to a lot of people because they say, hey, I go to bars all the time and those people aren't asleep at the wee of hour, you know, having fun and interacting. It does tend to make them a little more social but is it possible to kill yourself with alcohol right there on the stool? It's possible. In fact, some fraternities have tested this theory and they've invented these large funnels with hoses that go straight into the esophagus so that we can really pour gin and vodka down there so we can get the maximum effect as quickly as possible. And are people actually occasionally killed by this? Yeah. Ask the relatives of any winehouse who basically did exactly that with probably five bottles of vodka and was found dead due to what, due to alcohol intoxication. So, this is just an illustration of how important this normal natural balance between excitatory and inhibitory synaptic activity is. And many of these drugs are used appropriately and therapeutically, some are not. So naturally, proper use of this is something we hope for. All right. So, turning the page literally and without any real segue, we're going to switch gears into our final topic for today at least which is taking all of those information that we have now and putting it into an actual physiological circuit or context. Let's just back up, we discussed what equilibrium potentials are, we discussed what resting potentials were, we discussed what these are, action potentials, we discussed how they're generated, how they're P word, propagated, how they're T word, transmitted, and how they can be blocked or boosted at synapses by a virtue of IPSPs and EPSPs. So all of that is very valuable, very essential, fundamental information but now we're going to put those ideas into a working circuit, a circuit

of the nervous system which in fact is the simplest one possible, known as simply the reflex arc. Simple because it doesn't involve the brain and essentially is a mechanism for bringing about very rapid response or an immediate change of the individuals muscles to bring about usually an involuntary motor response to a stimulus. Now, why is it called an arc? A-R-C is not a circle, an arc is half a circle, right? So it has a definite beginning and a definite end. Why is it called a reflex? Because what's not involved in the decision or in the process in anyway? The brain. So this is a straight through spinal cord circuit that doesn't involve any thinking and it's certainly familiar to you in the simple example of walking barefoot and then stepping on a sharp rock or maybe a tack. What happens as soon as your foot makes contact with something like that? Your foot is withdrawn. Is that a choice that you made? Did you analyze? Did you ponder? No. It was all just that quick and of course we know it as a reflex. What are the necessary components in such a response? In order for a reflex to work, there has to be something in your foot. Something in the skin that's reacting to this offending stimulus and that something is called a receptor, a receptor for touch, a receptor for pain, a receptor for heat, whatever the stimulus exactly might be. And this receptor is connected to and has an effect on an afferent nerve, a sensory nerve which then carries that information into the spinal cord where it may or may not synapse with an interneuron but sooner or later the information will be exiting the spinal cord by way of an efferent nerve, also known as a motor nerve, and these train of action potentials will end up in a muscle that is most likely a skeletal muscle and that will bring about movement, contraction, of that muscle which will elevate your leg or otherwise remove the foot from the offending stimuli. So, this is diagrammed in every textbook on the topic and here we see a tack which is making its presence known here on the big toe. It's going to stimulate what cells in that skin, R word, receptors, that will cause action potentials to be propagated toward and into the spinal cord then those action potentials will be transmitted across synapses on to interneurons and eventually on to outgoing efferent nerves. What's the other word for efferent nerve? Motor nerve, which is going to take that information to a muscle and cause a synapse there called the neuromuscular junction and that brings about contraction. Now, don't get me wrong. Does the brain receive this information? Are you aware of the disturbing contact with this tack? Yes. Does this information travel up to the spinal cord and are you made aware of this event? Sure. But did your brain decide to bring about those contraction? No, because that has already been completed by the time the brain even gets this information. So, to be clear what's the advantage of this if the brain is not involved? The advantage is that it produces an instant involuntary motor response which prevents obviously any further what? Any further injury. So it's designed as a protective mechanism against ongoing pain and suffering here. So, we use this as a starting point as we discuss circuits in the nervous system because it is so fundamental and at the very least it will acquire a receptor, a sensory nerve, a motor nerve and an effector. We naturally we'll talk about muscles as effectors at a later date. We've already talked about motor nerves. We've talked about sensory nerves and we'll remind you that what's the difference between an action potential which is propagating along a sensory nerve and one which is propagating along a motor nerve, the only difference is what?

>> Direction.

>> Direction. So in short, if you understand the action potentials, you understand all of these because it's basically propagation followed by transmission across one or more synapses. So, in terms of the components that are listed here, the one thing that begs our attention now is a receptor. We have to understand a little bit more about what's going on in receptors and specifically the array of receptors that we have at our disposal as human beings. So here's the definition. A receptor is a cell or group of cells which is designed to respond to what?

>> Specific.

>> A specific environmental energy form. If you're highlighting anything, that S word is important, specific, not just any but a specific environmental energy form which from now on will be called simply a stimulus. And this stimulus can be externally applied, as in the case of this thumbtack making contact with the toe, or could be an internal stimulus as a result of ischemia that means poor blood flow through let's say blood vessels, so can you have pain in your chest which is not the result of external but rather internal stimuli? Of course. So, this stimulus whatever it is can be from the outside environment or can be coming from the internal environment. And as we now start to list receptors, certainly the familiar sensations are here to see. They are listed as sensory types, also called modality. What are the modalities of sensation that the human being is apparently aware of or has receptors for? Light. Do we have receptors that respond to light? And they're not on your foot are they? They're only found where actually?

>> Retina.

>> On the retina of your eye. So if I hold my hand up to that light, I'm not going to see anything because I don't have, what are these called? Photoreceptors. Do photoreceptors react to sound? If someone shouts at your eyes, do you see anything as a result? You're in a totally dark room, someone comes up and says, hey, you're not going to see any light, right? Because photoreceptors are S word, what is it? Specific. They only react to light and light is not as simple as you might think because light has various wavelengths, right? You know what I mean, the rainbow, and so there's red light, blue light, green light and all of that. So we have a quite array, quite a different variety of photoreceptors but fundamentally they are sensitive to? Light. Then we have receptors that are sensitive to sound and we know where these are. That is they're not in your foot. They're in your inner ear actually. These can be called auditory receptors or acoustic receptors. Fundamentally, from anatomy, you know that the disturbance that we call sound is basically waveforms, that is movements of disturbing air which impact, what? The tympanic membrane and set in motion those ear ossicles. Remember that? Stapes plunging in, scala vestibuli, OK? You got all that, OK? So, we won't review that. But ultimately, we disturb those hair cells along the spiral organ and those are fundamentally the acoustic receptors. Actually, they are mechanoreceptors because they're reacting, at that point, to physical movement of the basilar membrane which leads us to mechanoreceptors, much more familiar and perhaps more obvious in the skin. Do we have receptors that respond to physical touch or stretch of the skin or a pressure applied to the skin? Yeah. So these are all varieties of so-called mechanoreceptors. Do these react to light? No. So again, they are specific. We have a group of receptors called chemoreceptors which are absolutely incredible if you think about the human's ability to discriminate different kinds of odors and different kinds of taste. The numbers are well over tens of thousands of different discrete taste and smells. So these are quite discriminating and collectively they are called chemoreceptors because they're reacting to chemicals in the air that we breathe or in the solutions that we consume as food or drink. Then of course we have thermoreceptors. They react, you would guess, to changes in temperature. So, in your skin you have receptors that are dedicated to increasing temperature and those responding to decreasing, call them simply heat receptors and cold receptors. You might think we're pretty well done. That is, these are the big five and they certainly are the ones that are the most familiar, the most valuable, the ones that we can easily recognize. But what's incredible about the human body is that we have way more than just those five. Here's a list of human senses and here we see vision, hearing, smell, taste. OK, so far, we're still within the big five. Do you have the ability to detect gravity? You do. Do you have the ability to detect linear acceleration or circular rotation? Do you have that ability? Yup, semicircular canals and the vestibular apparatus. Touch, pressure, warmth, cold, OK, that's familiar. Muscle stretch, tendon stretch, joint position, something we take for granted, but yet as you sip there, are you at least approximately aware of where your knee is? Yeah. And your feedback you're getting there is with receptors in the joint which are responding to the position or status of that joint whether it's moving or not. And this was still not done because as we go to the second page, you have receptors for acidity in the CSF. What's the CSF? Cerebrospinal fluid. You have receptors that are monitoring osmotic pressure. Yeah, believe it or not. And you have receptors that are monitoring for you, what? Blood sugar concentration. Are you aware of your blood sugar? Can you say, oh yeah, it's 86 right now. No. But is it being monitored for you sort of in the background? Absolutely. And so these are chemoreceptors responding, in this case, to sugar. Do you have receptors for pain or physical injury? Naturally you do. Lung volume, et cetera, oxygen concentration, believe it or not, oxygen is being monitored too. So my point is that these are the obvious and important ones that we think about, but there are lots that we are never even aware of because these receptors are working in the background and taking care of general housekeeping which we probably are better of not knowing about. With that said, are humans sensitive to magnetic influences? I find this fascinating because we all know that whales or pigeons, do they navigate over long distances pretty amazingly so? And, you know, there's no signs underwater there for the whales to look at. There's no GPS that they're taking advantage of, but yet they navigate successfully to the same breeding sites, you know, thousands of miles away. So some animals have quite the ability to use the magnetic fields of this earth to navigate, that is to find their way north, south, or whatever. So that's impressive and certainly just one of other examples that shows that the human being is or is not the most sophisticated when it comes to sensory receptors. Your dog beats you in what category here? Your dog beats you out here and eagles beat you out in this category. So, before we start to think of ourselves as the epitome of evolution, there are plenty of other animals that put us to shame here in some of these categories. But fundamentally, these are dedicated to and respond to what? Specific environmental stimuli. But interestingly, sometimes these can be tricked so to speak. You all probably have gone to Mexican restaurants and there's this cup there which contain salsa, right? And they call that hot sauce or something, right? Is it really hot?

>> No.

>> No. You put a thermometer in there, it's pretty cold. But when you put it on your tongue, what do you experience? You experience the sensation of heat. Don't you say, "That's hot." And someone next to you saying, "What you mean, hot, hot or spicy hot?" Don't you say that? So you say, or it's not hot, hot, it's spicy hot," but yet it's still the same, it's still hot, right? What am I getting at? The receptors that we're talking about are chemoreceptors and they're acting to-- acting on or reacting to the chemistry of these-- or whatever it is, jalapenos whatever. But it does stimulate also the, what? The thermoreceptors giving you a false sense of? Heat. And in fact, drug companies have taken advantage of that. Maybe, you know, some of these creams, they're called icy hot or whatever. Basically, they contain capsaicin which is the same ingredient coming from, well, jalapenos and stuff. And is this cream actually hot? It's not actually hot but it does stimulate, what? The thermoreceptors and gives you the impression of what? Hot and it makes you feel better and you say, "Well, that feels good," even though it's not hot at all. So, what's my point? Some of these receptors can be overwhelmed and here's a fun one too. Photoreceptors are supposed to react to what?

>> Light.

>> Just to light, but if you close your eyelids and press on your eyelid, don't do this now please. But if you press on your closed eyelid, you will actually see light even though your lids are what? Closed because the pressure of your finger will stimulate successfully, what? The photoreceptors which are supposed to be sensitive only to what? Light. This falls into the familiar catch phrase, he was sucked in the face so hard that what? He saw stars and that's not just make believe. It's because of the effect on the photoreceptors. So, receptors are specific but they can be tricked, that is they can be stimulated occasionally by other modalities which brings about these bizarre examples that we just mentioned. In the time we have left, we've got a knockout receptor mechanisms which you would think an impossible chore because we have so many receptors to consider. We're not going to go through each and every receptor because it would be too time consuming. Instead, we're going to provide a generic explanation of how receptors work in general. And basically, all receptors work by transforming some energy form into an electric response which is we're about to see is called a receptor voltage or a receptor potential. So for the simplicity of it, we're not going to pick on a photoreceptor but rather these which are called pacinian corpuscles. They are tiny mechanoreceptors, smaller than the head on a P-I-N, pin, and these are buried in the dermis of your skin and they resemble this design here, that is they look like a very microscopic onion which layer upon layer of membranes which are fluid filled in the voids between them. So that this little structure here, if you were to touch it, would be soft and cushy like a marshmallow. What are these called? Pacinian corpuscles. This is one cut in cross-section. If we cut right through there, this is what it looks like and this is the axon which penetrates the center of the corpuscle and these are the membranes which are wrapped in concentric fashion around this core. So that if I touch here, what's going to happen? Will this be rigid or soft? And will these membranes dimple in or otherwise be deformed by this poke? Yes. So that's how they work. They are sensitive to touch, specifically sensitive to changes in pressure as applied to the skin or the vicinity of these receptors. So here are the steps. Here are the steps in bringing about activation of pacinian corpuscles. First, we have to stimulate, that means we have to apply some physical contact with these membranes that brings about membrane distortion. The membranes form layers which are called lamellae. So when I touch this, the lamellae, what's the D word? Deformed. That is they're basically going to collapse as we put pressure against them. This will cause a nonselective increase in permeability across this axon which is buried in the center of this receptor. And let's remember, what is the resting voltage that is probably enforced here in this axon? Negative 70 millivolts. So this increase permeability, notice, is not selective. It causes an increase permeability, what to? All ions. Now that's interesting because it causes sodium ions to go in but also potassium ions to go out. And if you think about that, well, that would be a wash, positive in, positive out, but more sodium goes in than potassium out. With that said, what's going to happen to this negative voltage if more sodium goes in than potassium out?

>> Positive.

>> It's going to be less negative. It's going to be the D word, it's going to be depolarized. And that local depolarization which is happening right here is called an RP, a resting-- I should say, a receptor potential, because of course, it has been produced in this area of the receptor. A receptor potential is fundamentally different from an action potential in many ways. Here's an action potential. What did we say previously about its amplitude? Always the same. It's duration? Always the same. In fact, we use the phrase all or none. Receptor potentials are not all or none. They can be higher voltage or lesser voltage. They can last long or short. And so they have what's called the graded amplitude which you would guess correctly would be due to what? What would determine the size, the amplitude of this voltage called the receptor potential?

>> The magnitude of the touch.

>> The magnitude of the touch. If we touch harder, we're going to get more ions to move therefore more D word, more depolarization. And the duration of this voltage is not fixed. It can change. It can be long or short, once again depending on what? How long you stimulated. The longer you stimulate, the longer the voltage. So, the duration tends to match or at least be proportional to the duration of the stimulus. Finally, this voltage doesn't go anywhere. That is, it's produced here and stays here. So we say it's not propagated into the spinal cord. With that said, what good is it if it doesn't go anywhere? This voltage doesn't have to go anywhere. It goes only as far as the first node where it triggers what? Remember, action potentials carry only-- I should say nerves carry only, what?

>> Action potential.

>> Action potentials. So what happens at the first node, is this RP, what is it? Will trigger a series of APs. What are those? And those then will be propagated along from node to node. Eventually reaching the spinal cord, eventually reaching the brain, eventually being interpreted as you would expect, in this case, some sort of contact, some sort of pressure. We said all along that action potentials, what was that catch phrase, are always what? All or none. There's no such thing as a big or a small action potential. So, we lead now to this idea of intensity coding. How does the brain determine how strong a stimulus is? It's not based on the size of the action potential but rather the F word? Frequency. So here's just a graphic illustration of that idea. Blood vessels have pacinian corpuscles in them, in the walls of a blood vessel. What goes through blood vessels? Blood. And is that under pressure? Yes. And when that pressure is high, the vessel is pushed, is otherwise made to stretch, right? And there are receptors in the walls of blood vessels called? And they're going to react to changes in blood pressure. Here are some blood pressure numbers, 40, 60, 90, 130 millimeters of mercury. Notice, these are action potentials and notice they're all the same A word, what's this? Amplitude. Notice, at 40 there are no action potentials. At 60 whoa, at 90 whoa, at 130 whoa. So what is the relationship between stimulus intensity and action potentials? The stimulus intensity is going to determine what about the action potentials, their frequency or their amplitude? Frequency. And so, frequency is the way in which this system is going to judge, calibrate, or determine the intensity. So simply put, how does the brain know that this blood pressure is higher than that blood pressure? These action potentials are not greater in amplitude, they're greater in frequency which is dictated by incidentally the size of the receptor potential which brings us to our next graph which shows just that relationship. Here is a moderate stimulus of a short duration and here's a more intense stimulus of a much longer duration. So, in case this graph is unclear, nothing-- and then we stimulate this receptor for how long? And do we-- we stimulate it then we not stimulate it, then over here we stimulate it and keep it stimulated until where? Right. So this is the application of the stimulus. This is the removal of the stimulus, all right? Great. How does these-- How do these affect the receptor potentials? This is the receptor potential that results from a moderate but brief stimulus. Notice that it reaches threshold but quickly subsides. Why does this voltage fall? Well, the stimulus has been what? Has been removed. Then we come over here and we see the receptor potential jumps up again and then as time goes on, it eventually disappears especially as we remove or take away the stimulus. Notice this though the receptor potential here tends to fall in voltage even though the stimulus is what? Maintained. That's a curious thing because you'd expect this to be equally maintained. The consequence of that fact is that we get, as we've said, a brief or low frequency of action potentials here. Why are these action potentials closer together? Greater voltage of this. What is this? This is the receptor potential. And as that voltage falls, what happens to the action potentials? They become less frequent. An interesting and consistent effect for nearly all receptors. But before we discuss and explain that, we can at least appreciate that the sensory action potential, F word, what is that? Frequency, is determined by the receptor potential amplitude. This is the receptor potential amplitude which produces a greater, F word? And this is a lesser voltage which produces a lesser frequency. The interesting thing which we'll leave you with is this concept of receptor adaptation which is simply this, a decrease in sensory action potential what? Despite what, what's happening as far as the stimulus itself? Has the stimulus changed at all?

>> No.

>> But yet the receptor potential falls off and with it so does the frequency of action potentials. That's called what? Receptor adaptation. Numerous examples, here's a watchband around my wrist. I put the watch on this morning, was I aware putting it on. Did I fear the application? Yes. Am I aware of it now? I'm not aware of that. In fact, sometimes in the morning I forget to put my watch on and then later in the day I go, "Oh, there's no watch there." So what's going on

here? Have the receptors, what's the A word? Adapted. Because this stimulus is now, what's the M word? Maintained. And even though it's maintained, what happens to the receptor potential is that it falls and eventually what happens to action potentials? They are-- or become less frequent. Now, that will happen to and does happen to you with anything that is in a sustained unchanging situation whether it's a wedding ring or a belt around your waist or watchband or so forth. In fact, it can happen to other receptors. Never mind these which apparently are responding to pressure. An example I always use because I love it, you know, I go into an auto supply place, Pep Boys for instance, and they have tires in there and I love the smell of rubber. So you go in there and it's like, ah, rubber, I just like that smell. Now, if this is not getting it for you women, we'll take you to the mall where you open a candle shop and you get blown away by all of that. OK. So you like that. But here's the interesting thing, you step into these candle shops and you get overwhelmed with these odors right off the bed but then as you're shopping in there, what do you notice or maybe you haven't? But can you continue to smell those? Not really. What's happened to the olfactory receptors, what? It's the A word? They've adapted because the stimulus is constant. The only way you can regain that is to walk out of the store and then what? Walk back in. So, I know, that's interesting isn't it? What's the good of that? This is the physiological significance of receptor adaptation, plain and simple. The brain has limited computer power and why should it be bothered by something that's not changing? What's important to your brain? What's important is something is changing. If it's not changing, do you need to be reminded? Watchband, watchband, watchband, wedding ring, wedding ring, wedding ring, shoes on your feet, shoes on our feet. No, I don't want to be bothered by that. They're still there, it's all good. What do I care about? Not that something is unchanging but the fact that suddenly, it's what? So if I take this watchband off, will I feel it? If I take this wedding ring off, will I feel that removal? Yes. So the beauty of receptor adaptation is that it allows the brain, the master computer there, to devote attention to what's important and what is important is something that is changing. It's very important for you to realize that this concept, what is it?

[Inaudible Remark]

Has nothing to do with your brain, that is you're not, don't tell me this that you are deciding not to feel it. If you're deciding not to feel it then you could decide to feel it, right? So I'm going to try. Feel that watchband, feel that, come on, feel that watchband. Now, I can-- feel it, come on, I can't feel it, do I have? So it has nothing to do with up here, it's all out here. It's all the function of the receptor. Do all receptors adapt to the same rate? No, and luckily so. Let's look at a few. We talked about a pacinian corpuscle which is what's responding to watchbands and so forth. Here are PPS, an acronym for pulses per second, frequency of action potentials. And here's time of stimulation, unchanging stimulation. So notice, in the first half a second, the pacinian corpuscle responds, but after that, what happens to this red line, it goes to what? Zero. So a pacinian corpuscle is only sensitive for, what is this? Half a second. And hair receptors don't do much better. So if you don't believe me, you can do this at home when you're totally bored. You can pick out one of these hairs on the back of your hand. Yup, there it is, and you can take a toothpick or something and bend it over. So, here we go. Here's the hair magnified. You're going to what? Bend it over. And you hold it there. Will you feel that? Yes, you will. But if you will hold it there, will you continue to feel it in that position? No, because after the first second that has totally what? Adapted. The only way you can get that sensation back is to do what? Then you'll feel that. But if you do this, you'll feel that but then you won't feel anything because it's what, R word? Receptor adaptation. So, what receptors adapt quickly are clearly these two. But some don't adapt very quickly, for instance, do we have receptors that monitor the position of your joints, the position and tension of muscles that act on those joints? Sure. So if I hold my hands out like this and keep them motionless for as long as I can, do I at some point say, "Whoa, I can't feel it anymore." No. In fact amazingly, I can always point to where that is. If I hold it there for the longest time, I'll still be able to say, "it's right there. Oh no, it's over there." What's my point? If this adapted as quickly as hair receptors or pacinian corpuscles then you'd be sitting there and it would be time to go and you'd have to say, "All right, where are all these joints. Oh, they're still there, OK, good. Let's get going." No. But you don't because you know where they are all the time because they adapt quickly or slowly?

>> Slowly.

>> So in summary, what are some fast adapting ones? Well, pacinian corpuscles, smell is another one. But slow adapters are those that give us information about the position of our joints in space. And also, in somewhat paradoxically, pain receptors. Do pain receptors adapt quickly or slowly, apparently what? And you think, OMG, that's too bad. It would be better if they were fast adapting but actually not. Why would it be bad for pain receptors to adapt quickly? Pain is responding to injury, right? So, if they're adapted quickly, you could say what? Oh, hang on for five

seconds, it will go away. And of course, it's not really going away and so let's be real as we will later. Is pain a good thing or a bad thing?

>> Bad.

>> You're going to be tempted to say it's a bad thing but it's a very good thing and so it's important for us to be reminded that there is injury, injury, injury, injury so that we take notice and that we avoid further injury or at least take remedies for whatever is the cause of this injury. So that's it. So I went [inaudible] over. We're done for tonight. See you tomorrow for an exciting lab, I hope.