GERALD SCHNEIDER: We're still on this first topic, primitive cellular mechanisms. And we'll be on that for the entire session today, talking mainly about secretion in neurons. We started that before, when we talked about excitatory and inhibitory postsynaptic potentials and summation effects.

Is action at a synapse always one way? Well, if it's a chemical synapse, the information flows always in one direction. It doesn't mean there's nothing that goes the other direction.

There is some communication, but the electrical changes generally are going one direction. There are such things as electrical synapses. They're not very common in the mammalian nervous system, where the action can go in both ways.

We talked about Otto Loewi. And remember, he discovered some pretty good evidence for chemical transmission at synapses. He was in the peripheral nervous system, the autonomic nervous system, working with the innervation of the frog heart.

And what was that acceleran stuff, the accelerator substance? Norepinephrine. And what was the vagus substance? Acetylcholine. Those were the first two transmitters discovered.

So now, let's talk about synapses. And we're really dealing not just with secretion, but with membrane specializations for irritability as well. So these will be the topics now, under secretion.

And I've taken some pictures from the book. At the left there, they show one neuron connected to another, sort of a cartoon. And then they enlarge it to show the little terminals that are usually enlarged where they make a contact.

And then the far right, you have a picture somewhat like the cartoon based on electron micrograph studies of what a synapse looks like. And it shows the little vesicles containing neurotransmitter in the terminal. And it shows some of them releasing neurotransmitter into the synaptic cleft.

How big is the synaptic cleft if you're looking with an electron microscope and you can measure it? Anybody know? It was initially given an Angstrom units, 200 angstroms, about 20 nanometers, if I'm converting that right.

So here's the book cartoon of a chemical synapse, showing the actions at the arrival of an action potential. It shows other things arriving there, too. You see that? It shows a synaptic vesicle.

Well, it's just to point out that the terminals are constantly being replenished with materials from the cell body. These things are being transported by antegrade transport. But that is not related to what happens when an action potential arrives.

The action potential arrives and depolarizes the membrane of the synaptic terminal. And that causes an influx of calcium ions, which you see there. And the influx of calcium ions causes a molecular cascade that causes these vesicles to bind to the presynaptic membrane and release their neurotransmitter into the synaptic cleft.

So then what happens? So they diffuse, and the molecules diffuse across that little gap. And some of them will bind, then, to receptors in the postsynaptic membrane. Yes?

STUDENT: [INAUDIBLE]?

GERALD SCHNEIDER: I'm sorry, in what?

STUDENT: [INAUDIBLE].

GERALD SCHNEIDER: There's usually so much material that that doesn't happen very much. But yes, in studies of motor neurons, they have been able to deplete the terminals that. Way and there's a few other-- now what happens?

So it binds to a receptor. Well, when it binds the receptor, it causes changes in the receptor. What is a receptor? It's a protein embedded in the membrane, postsynaptic membrane. When it binds to a ligand, which in this case would be the neurotransmitter released at that terminal, it causes a conformational change, which will cause a channel to open up and result in either hyperpolarization or depolarization of the membrane, depending on the receptor molecule.

Now, it also shows a few other things there. It shows a transporter here, but it's just a means for re-collecting some of the transmitter molecules in the synaptic cleft, reforming, recycling that membrane, forming new vesicles. There are also sometimes autoreceptors for reuptake.

Now, this will vary depending on the type of synapse and the neurotransmitter. In the case of acetylcholine, most of the acetylcholine is actually destroyed by an enzyme, acetylcholinesterase, after it's released. And that's what stops the action at the synapse. In the case of other molecules like norepinephrine, there's a lot of reuptake. The terminals take the transmitter up again, and then it, through these transporter molecules, gets inside the vesicles again as they reform.

Now, this just shows a cartoon of the receptors in the membrane. And look at the one on the left. This is a ligand gated ion channel, an ion channel that is change gated by when it binds to a ligand, which is the neurotransmitter.

The little neurotransmitter there is shown in green. And when it binds to that protein, you get a change so that ions can pass through the membrane. So ions flow across the membrane and cause the membrane to depolarize or hyperpolarize.

There are other kinds of receptors that act a little differently, where the neurotransmitter doesn't bind to a channel molecule. This is the G protein-coupled receptor. It has slower action, sometimes called a metabotropic receptor.

Note there that they show a G protein bound to the receptor molecule. And when the transmitter binds, they call it here an activation of the G protein that actually dissociates. And a piece of it then can diffuse and bind to nearby channel molecules.

And when it does so, then the ion channel will open. But that molecule that moves through the cell like that is often called an intracellular messenger, communicating the information that the neurotransmitter has been bound, and the channel should open. The end result is similar-- the flow of ions through the membrane.

So let's just now review some of these things we've been talking about. I'm going to put some of these questions a little bit differently. First of all, these are all about electrical properties of the neural membrane. So what are the forces acting on ions at the cell membrane? Electrostatic forces and concentration gradient.

The concentrations are very different. You'll have, again, have forces on these ions. These are the forces acting on the ions.

So how do they pass through the cell membrane? Well, they need these channels. They need ion channels to go through, because the membrane is otherwise not very permeable beyond it.

What are some of the measures of electrical properties? I asked for four of them here. One of them, of course, would just be the potential difference between inside and outside. You can measure that with a tiny electrode.

What are other things that are electrical properties? You remember when we talked about properties that affect speed of decremental conduction. The membrane has capacitance, and there's resistance across the membrane that you can measure, and resistance along the axial direction of an axon.

These are all measures of electrical properties that affect how the membrane behaves. So how are these things different from copper wires? It conducts. Which conducts faster? The copper wires-- much faster when dealing with electrons, not with these ions and the slower processes involving diffusion of ions through the membrane.

So how fast is conduction? See, if I ask the question like that, you've got to ask me a question, or you've got to give a pretty elaborate answer. How fast is conduction?

Well, it depends on what kind of conduction we're talking about-- decremental conduction. And we know that the speed of decremental conduction can vary a lot depending on resistance and capacitance in the membrane. And we talked about the effects of myelin.

What about non-decremental conduction? How fast is that, the action potential? What does it depend on? Two things-- what?

What affects rate of conduction of the action potential in an axon? The size of the axon, and myelin. So if you're an invertebrate and you don't have myelin like a squid, how fast do you think the action potential can go?

We'll make the axon really big. The squid giant axon can be a millimeter in diameter. How fast can the action potential go down that membrane? About 20 meters a second.

Well, we don't have 1 millimeter-thick axons in us, and yet we have much faster conduction because of myelin. What would be the conduction of the large axons, largest axons we have, with myelin, according to your text? About 120 meters a second, according to the text, about six times the speed of a squid giant axon.

So how far do they conduct? What's the answer to that one? Well, if it's decremental conduction, not very far because it gets weaker and weaker the further you go until it peters out.

What about the axon? Well, as far as the axon goes, that's right. It goes to all parts of the axon. It's non-decremental. It goes everywhere.

So what would be the longest axon? Well, in the periphery, probably from your big toe to the spinal cord. In the central nervous system, probably from your motor cortex to the lower enlargement, lumbar enlargement, of your spinal cord to the motor neurons that are controlling the feet.

Next question, triggering of spikes-- how does that happen and where does it happen? First of all, where are spikes normally triggered?

We can trigger them artificially anywhere there's an axon by tweaking the axon mechanically or electrically. Where is it normally triggered? At the axon hillock, the initial segment of the axon. And what causes it to be triggered? Depolarization that reaches the threshold for triggering the all-or-none response.

A few more questions there-- I didn't discuss the refractory period before. What's the refractory period of an axon? Yes.

STUDENT: [INAUDIBLE].

GERALD SCHNEIDER: Right after an action potential fires, there's a little time period when it can't fire another action potential. That's correct. It takes a little bit of time to recover.

So the time when it can't fire an action potential is called the refractory period. We talk about a relative refractory period when the threshold can fire but the threshold isn't is as high, and then when it's completely recovered. Antidromic activation or antidromic conduction-- question in the back?

STUDENT: [INAUDIBLE].

GERALD SCHNEIDER: Opposite of the normal direction, so how could that happen? It's often due to mechanical, or it can be due to electrical stimulation. We can stimulate an axon right in the middle of its course.

So you hit your elbow hard here, and we call it your funny bone because of the way it feels. You're triggering action potentials in the nerve from your forearm and hand. And that's why it feels so weird in your forearm and hand.

It's not that you've changed the forearm and hand at all. You've just affected the nerves there. But you've caused the action potentials to go in both directions, orthodromic, toward the central nervous system, and antidromically back to the sites of origin of the axons. Yes.

STUDENT: [INAUDIBLE]?

GERALD SCHNEIDER: Which question, louder please?

STUDENT: [INAUDIBLE].

GERALD SCHNEIDER: Oh, the four measures? These are just the measures we talked about when we gave when we talked earlier about membrane properties-- potential difference across the membrane, capacitance of the membrane, resistance across the membrane, and the axial resistance along the axon. Now, this last question I'm going to spend a little more time on. I want you to understand all of these questions, the answers. That's why I've given it to you and gone over it, though a little bit quickly.

What influences the potency of synaptic input? That is, what are the conditions that favor the triggering of an action potential? You look there in the next picture.

Proximity of an excitatory synapse to the axon hillock because of decremental conduction-- the closer that synapses to the axon hillock, the more likely an excitatory postsynaptic potential is to trigger an action potential. The number of synaptic contacts formed by one axon, because you can have one axon that's forming multiple synapses on a cell. And the more it forms, then the more likely an action potential arriving over that axon will have in triggering an action potential in the next cell. That's because of its spatial summation. And of course because of temporal summation, the rate at which they arrive will also affect it.

So let's just draw a couple of cells now to illustrate this. Let's draw a pyramidal cell. Remember the Betz cell? Here's the nucleus, and here's a long dendrite with some various branches. And here's the axon. We'll draw the axon to look like that.

And we want to know what-- let's say we have a terminal here, another terminal here, another terminal here. Now, if we have one action potential arriving over each of those terminals, the one that's closest, this one, is going to be most likely to cause an action potential because it's so much closer. We might be able to make one that's further out just as likely if it, in fact, has many terminals. And that can happen because that'll give us more spatial summation.

Because now, one action potential coming over that axon is going to travel down all those little branches, in most cases, anyway, and cause the excitatory postsynaptic potential at every one of the terminals. Well, is it possible to get really reliable transmission at a synapse so that every time an action potential arrives, it triggers an action potential in the postsynaptic cell? With this kind of arrangement of a pyramidal cell in the cortex, that's very unlikely.

But there are cells where you get one-to-one transmission. For example, in the auditory system, in the cochlear nucleus, there's one cell type there which gets input from large axons coming from the cochlea, where we want to preserve the timing really precisely. So these cells are often called magnocellular nucleus cells.

And here's a big axon, the auditory nerve coming in. And here's what it does-- it forms a terminal like this. So the action potentials come in here. Well, so what? It's formed a big terminal.

Well, there's many synapses there. And this is just a cross section. And we can see many synaptic specializations. At each one of them, we have synaptic vesicles.

You can always identify the synapse in the electron micrograph by these little collections of synaptic vesicles, and also by thickening of the membrane. So one terminal can have many synapses. And if we looked at this, we did a three-dimensional reconstruction, we could find over 100 synapses.

The result is that when one action potential arrives, there's so many synapses that are activated that it triggers enough-- you can notice that the cell here is a little, bare cell without dendrites. It had dendrites when it was developing. That was discovered at Harvard a few years ago by Dr. Jhaveri, who works in the building sometimes here.

You get so much spatial summation that every time an action potential arrives over the presynaptic cell, it will trigger an action potential here. So those are the extremes. The extremes, then, would be this cell and, say, an action potential here, way out on the tip of the dendrite, having very little effect by itself.

Now let's talk a little bit about neural hormones. You know what hormones are, released by endocrine glands. Well, then what are neural hormones?

Can be illustrated by discussing this reflex, the milk let-down reflex. When the baby starts to suckle, milk does not come out immediately. The reason is that a reflex has to be triggered.

And it's an unusual reflex-- sensory input from the nipple reaches the hypothalamus by a polysynaptic pathway. In the hypothalamus, there are neurons that rather than exciting other cells with action potentials, secrete a substance into the bloodstream, oxytocin, which then affects the smooth muscle.

And oxytocin does several things. It will cause the milk to be released. It also causes uterine contractions, and it's involved in the birth process. This is an enlargement of the posterior pituitary. It's often called the neural hypophysis, at the very base of the twin brain or base of the hypothalamus.

Its location is defined here by the optic chiasm, but that has nothing to do with the function. It just gives you the location. That's where the fiber is coming from-- the eyes, or many of them are crossing over.

Right near that structure, there are two nuclei, the supraoptic nucleus and the paraventricular nucleus, where they're neurons whose axons go down this little stalk to the posterior part of the pituitary gland. The anterior part of the pituitary, this part, the anterior pituitary, is a gland and isn't part of the brain at all. It's gland tissue like other endocrine organs.

But the posterior part is part of the brain. And the axons from these two nuclei terminate not on neurons there, but they terminate on capillaries, on blood vessels. And some of them release oxytocin, some of them release vasopressin.

In the case of the milk let-down reflex, the axons involved are releasing oxytocin, sometimes called Pitocin. And that causes the milk letdown, and also can cause uterine contractions. Many women when they're nursing can feel that. It can actually give them the sexual experience, at least feels similar.

And that's because of this neurohormonal reflex. But that's not the way, of course, most reflexes work. You could say the synaptic gap is rather large in that case.

So let's talk a little more about other kinds of synapses. There are multiple types. We've been talking about axosomatic and axodendritic terminals, where an axon terminates on the usual receptive surface of neurons, the dendrites or cell body. And those can be either excitatory or inhibitory, depending on whether they're causing depolarization or hyperpolarization.

But there's other types of synapses, as well, all these other types listed. So let's talk here about the axo-axonal synapses first of all, so you can see how these can have a somewhat different kind of function. We know a little more about the axo-axonal synapses than we know about some of these others.

There are synapses between dendrites and other dendrites. There are synapses between dendrites and axons. We know not very much about them. We'll say a little more about the reciprocal synapses and serial synapses and synapses at a post-synaptic site in minute.

In this picture, I'm showing a little diagram of a cell in black there that is synaptically connected to another cell through this green axon. And I am showing that if an action potential arrives over the green axon, I've shown the action potential in green there on the graph. I'm showing the triggering of a slight depolarization, so it's an excitatory post-synaptic potential.

Now, in addition, I've shown another axon in red that's terminating on the terminal of the first axon. And then in the graph, I'm showing what would happen if an action potential arrives over the red axon just in advance of the action potential arriving over the green axon. And it's also causing depolarization, but in this case, the depolarization is of the presynaptic membrane of the green axon.

So the result, and you see that right here, now when the action potential arrives over the green axon, note that instead of this big action potential, it's now a smaller action potential, because it started from a different point. The result will be, because the membrane potential change is less, there will be less release of neurotransmitter. And you'll have a smaller EPSP.

And because of that effect, it's called presynaptic inhibition. It's a different use of the term "inhibition." It's called an inhibition because it's reducing the effect of the other axons' terminals.

So my question then is, could you get presynaptic facilitation? And what would be required for that? Just using the same logic, what we described here, you can imagine that if this red axon here caused a hyperpolarization, increased the membrane polarization of the green axon, then the action potential, when it arrives, would be bigger because more neurotransmitter would be released.

And you could get larger EPSPs. So that would be presynaptic facilitation. And there is evidence for these things, particularly for presynaptic inhibition, in the dorsal horn of the spinal cord.

I know a lot of people get confused with presynaptic inhibition, but study those pictures and try to understand it. What's critical is to realize that what's causing the release of neurotransmitter is the membrane potential change happening when the action potential arrives. So if it's a smaller action potential, you'll get less release.

And we can make the action potential smaller by depolarizing the membrane a little bit so that the axon causing the presynaptic inhibition is not directly affecting that cell sitting there. It's affecting just the axon, just another axon, and its effects. So let's say a little bit more now about these other types of synapses. I'll draw them here.

First of all, the reciprocal synapse-- let's say we're looking at a pre and a postsynaptic membrane here. And we can see the synapse here. We know that this synapse would be going in this direction because we see where the synaptic vesicles are. Also, there's often asymmetry in those thickenings of the membrane.

But sometimes nearby, you find another synapse that seems to be polarized in the opposite direction. That would be called a reciprocal synapse. One thing to understand here is that-- let's say that this is number one, and that's where an action potential first arrives.

When you get depolarization of that other membrane, you could get release of neurotransmitter in the nearby synapse even without an action potential. I think that's important to understand when you're dealing with some of these synaptic configurations. Synapses don't require action potentials, though normally, many axons, of course, they release their neurotransmitter when an action potential arrives. But any sudden potential change can cause release.

So in this case, you could have the action potential arriving from here causes a depolarization. That could then depolarize that membrane and keep it-- affect that terminal immediately afterwards. It's like an immediate feedback affecting their further action of the originally presynaptic site.

What about a serial synapse? Sometimes in the electron microscope, we see a dendrite sandwiched between two other cells. And we'll see a synapse here. And then, we'll see another synapse here.

So this synapse is polarized this way, this synapse is polarized this way across the dendrite. We would call that a serial synapse. There's a number of examples of it, not always very well understood.

But we can say something about how that might work. We know that the effect of the first synapse there on the way to that second one is operating will depend on membrane polarization in that dendrite. So other influences on the dendrite coming from outside this little local area will affect the action.

Now if we let this one, two, and three be the three cells involved, the effect of cell one on cell three will be influenced by the level of polarization of that dendrite in between, which could be affected, of course, by a number of factors from outside. So it's a kind of very local gating mechanism, very difficult to study because this is happening at such a microscopic level.

In addition, we see these are two of the extra kinds of synapse you can see. We also will sometimes see a terminal that has an ending, and we won't see any membrane on the other side. It'll end. It won't have any membrane immediately opposed to it.

And at first, it was thought these were just artifacts, the methods. But [? Clonier ?] in Canada is an anatomist who kept seeing them. And he identified them in the neocortex, frequently being axons using norepinephrine, which we'll abbreviate NE, as a transmitter. And he postulated that these were the way that you could get norepinephrine released into the extracellular space and it was not destroyed right away.

And we don't know of an enzyme that does destroy it, so it would diffuse to the extracellular space and be taken up by cells. It could influence many cells in the vicinity. They can modulate their action. So we know that kind of synapse also exists, synapses without a specific post-synaptic site. Yes.

STUDENT: [INAUDIBLE]?

GERALD SCHNEIDER: They have vesicles. And they often have a thickening, as well, that has to do with the molecules needed to bind to the vesicles cause the release of transmitter. I can't tell you for sure whether they really look identical to these other synapses.

So when we look, consider, this variety of terminals, some people have begun to think that we should really think of these complexes of synapses as the functional units, realizing that quite a lot of computation is happening at these complexes of synapse. Sometimes, we have a synaptic arrangement that's enclosed in glial cells, and sometimes, it's difficult to figure out exactly what it's doing.

Our models have lagged behind the anatomy in this case. And that's still true. Most of the models deal only with the standard axosomatic and axodendritic synapses, and not these other types. And yet there's many places in the nervous system where we see a great many of these other terminals.

So any questions? You think you understand presynaptic inhibition? You have to know something about how transmitter is released, and how that we're using inhibition in a slightly different way. Yes.

STUDENT: [INAUDIBLE].

GERALD SCHNEIDER: First of all, make sure you know what I'm showing here. Just this could be a dendrite or it could be a cell with a terminal. And we have to assume there's a synapse there. I'm not showing the actual synapse.

And then we have another axon terminating on the first axon with an axo-axonal contact. I'm assuming that the synapses in either case here cause depolarization. Now before, remember we always said that depolarization was excitatory, but that's because we were talking about an axon terminating on a dendrite or cell. We weren't talking about axo-axonal synapses.

We have to use our terms a little bit differently when we're talking about axo-axonal synapses. So just you've got to think about what's happening when you get these changes. So I'm showing there the action potential arriving and causing an EPSP in this dendrite or cell. That's what this shows.

Now I'm showing that if an action potential arrives here, it likewise causes a depolarization. But if that depolarization-- and if I didn't have the other action potential, it would look just like that. It would be a little depolarization. It would disappear.

But now, if it arrives just before the other action potential arrives, you'll see that the amount of change in membrane polarity when the action potential arrives is less because it started out in a more depolarized state. That causes less release of neurotransmitter at the synapse there between the green axon and the black cell. So the EPSP is smaller. And that's why we say it's an inhibition.

Then I'm saying if you used the same logic, and we say that this is not causing depolarization-- I should have drawn another color. And if you have your notes there, and you take, let's say-- we'll just show another one here, and we'll say that the blue one causes hyperpolarization rather than depolarization. And that action potential arrives, just like this one. Now what does the green one do?

It starts out like this, and then shows the action potential. The height is greater. It'll release more neurotransmitter. I shouldn't have done it higher there, but the point is it starts out lower point, so now you get a larger effect at that synapse. So that's facilitation. It facilitates or increases the effect of that first synapse. Yes.

STUDENT: [INAUDIBLE]?

GERALD SCHNEIDER: That's right, the height of the spike is affecting the amount of release of neurotransmitter. Why? Because more calcium comes in. All right, well, that's all we have time for.