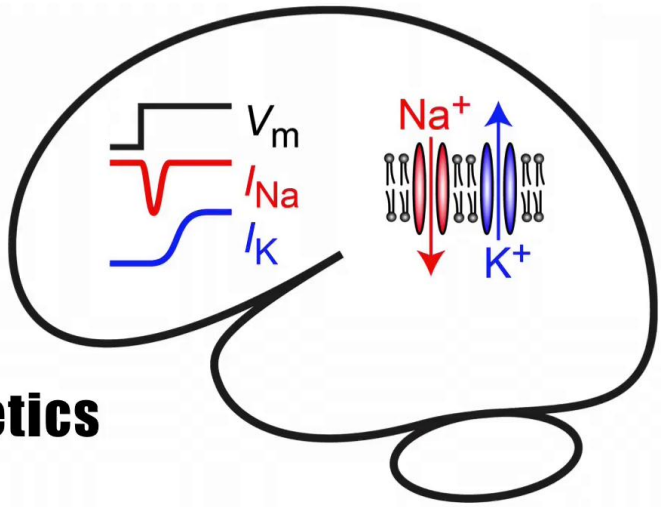
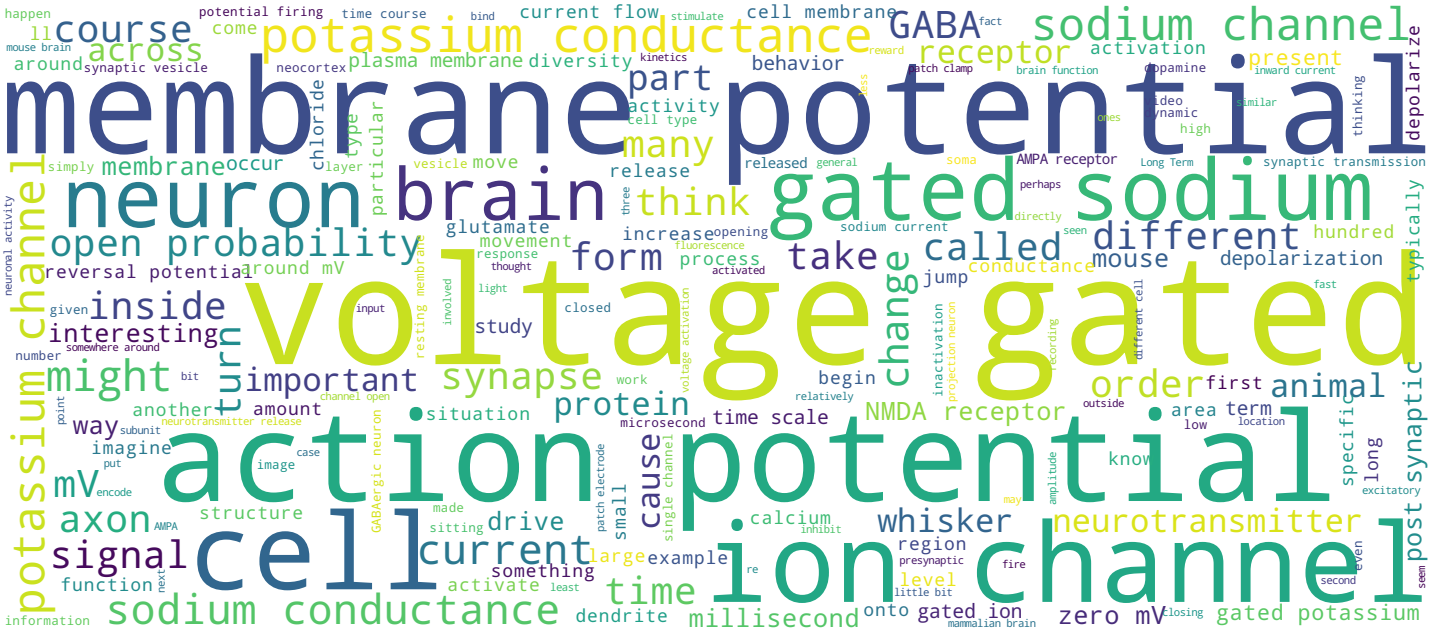


2.2 Voltage-gating kinetics

Cellular Mechanisms of Brain Function

Prof. Carl Petersen



Search MOOC

Video

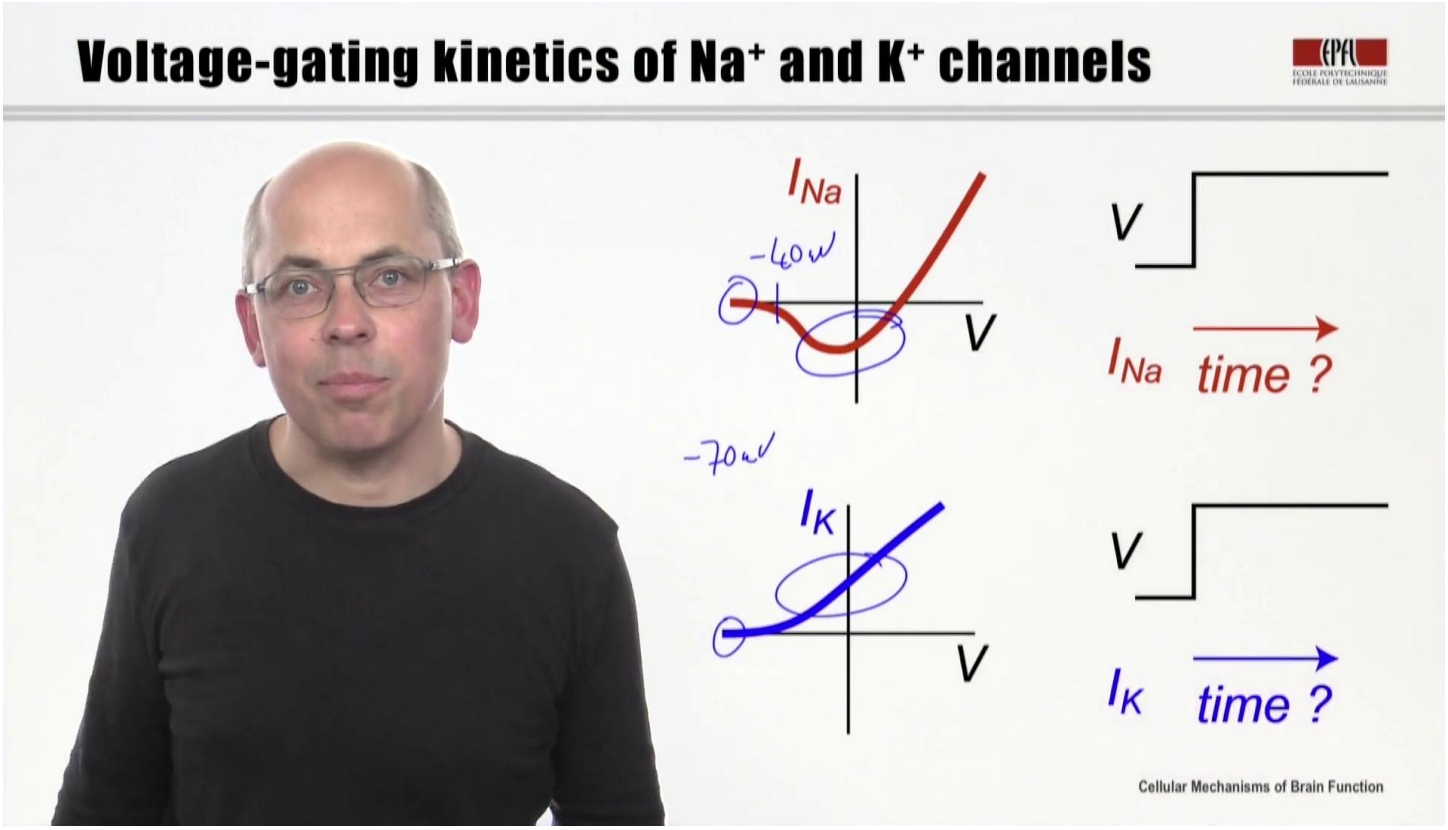
Voltage-gating kinetics

In the last lesson we learned about an important and interesting family of ion channels: the voltage-gated ion channels. For a voltage-gated ion channel, the open probability depends upon the membrane potential. Furthermore, we can see that there's a complicated situation where the opening and closing of the voltage-gated ion channel changes membrane potential, and that change in membrane potential in turn affects the open probability. And so, we can envisage complex interactions between the voltage-gated ion channel function and membrane potential. The dynamics of those interactions depend upon the channel kinetics, how rapidly it is changed in its open probability by the membrane potential. The voltage-gating of the ion channel depends upon changes to the 3D conformation, the structure of the protein ion channel itself, and this does not occur instantaneously. The opening and closing of the ion channel, the individual opening and closing, they occur on the microsecond time scale. The voltage gating, the change in the open probability of the ion channel, occurs on slightly longer time scales and it's those dynamics that we're going to study in today's lesson.

Notes

Summary

0m 05s

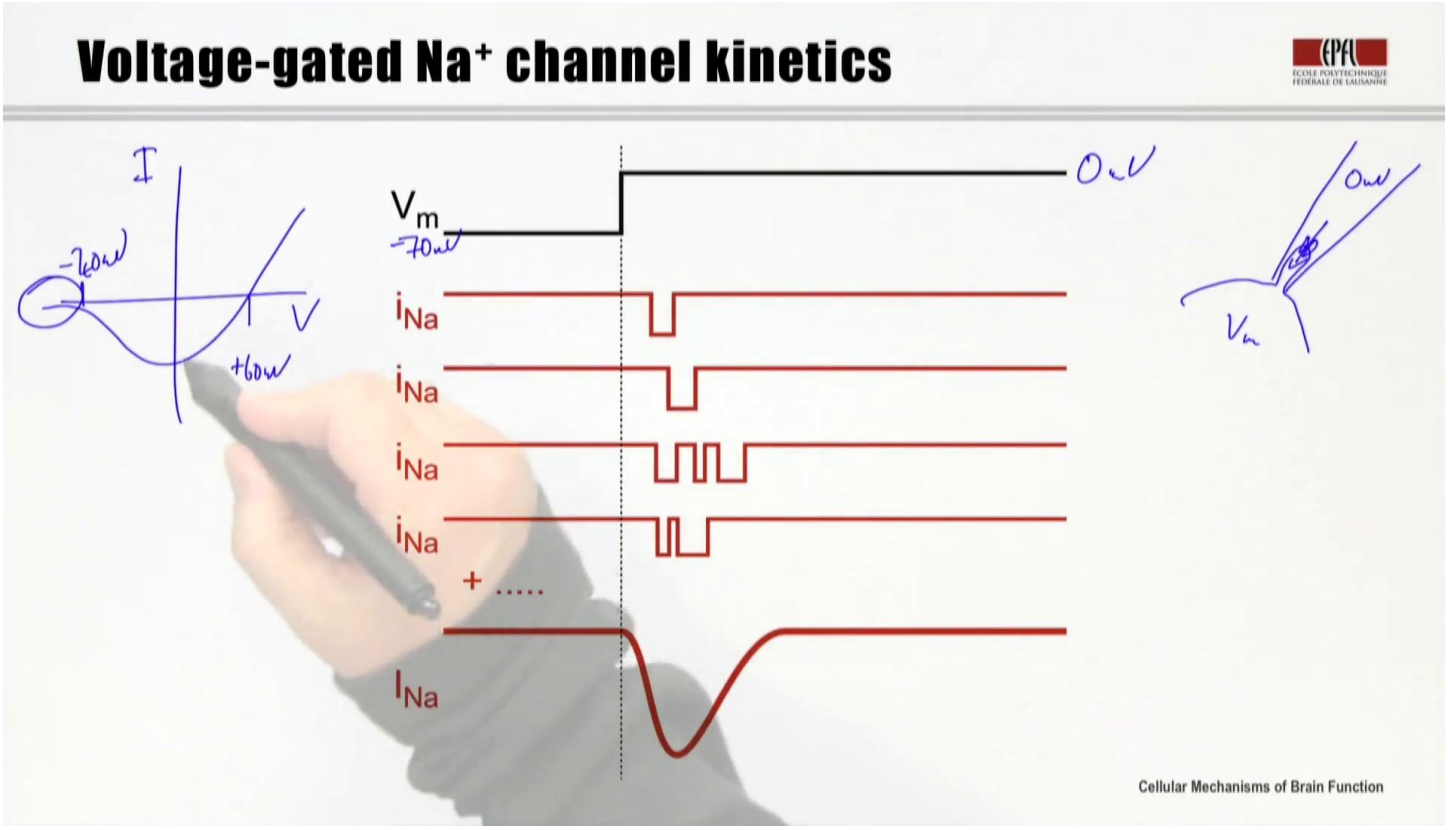


We're going to focus again on the voltage-gated sodium and potassium conductances that we began to study in the last lesson. These, as we remember, are largely closed at resting membrane potentials of around -70 mV. They only become activated as we depolarize, as we go beyond -40mV and above, the open probability of the voltage-gated sodium potassium conductances increases dramatically causing an inward sodium current and an outward potassium conductance. In order to understand how they dynamically interact on the cell membrane in real cells, we need to know about the gating kinetics. If we rapidly change the membrane potential, what happens to the sodium current in time?

Notes

Summary

1m 26s

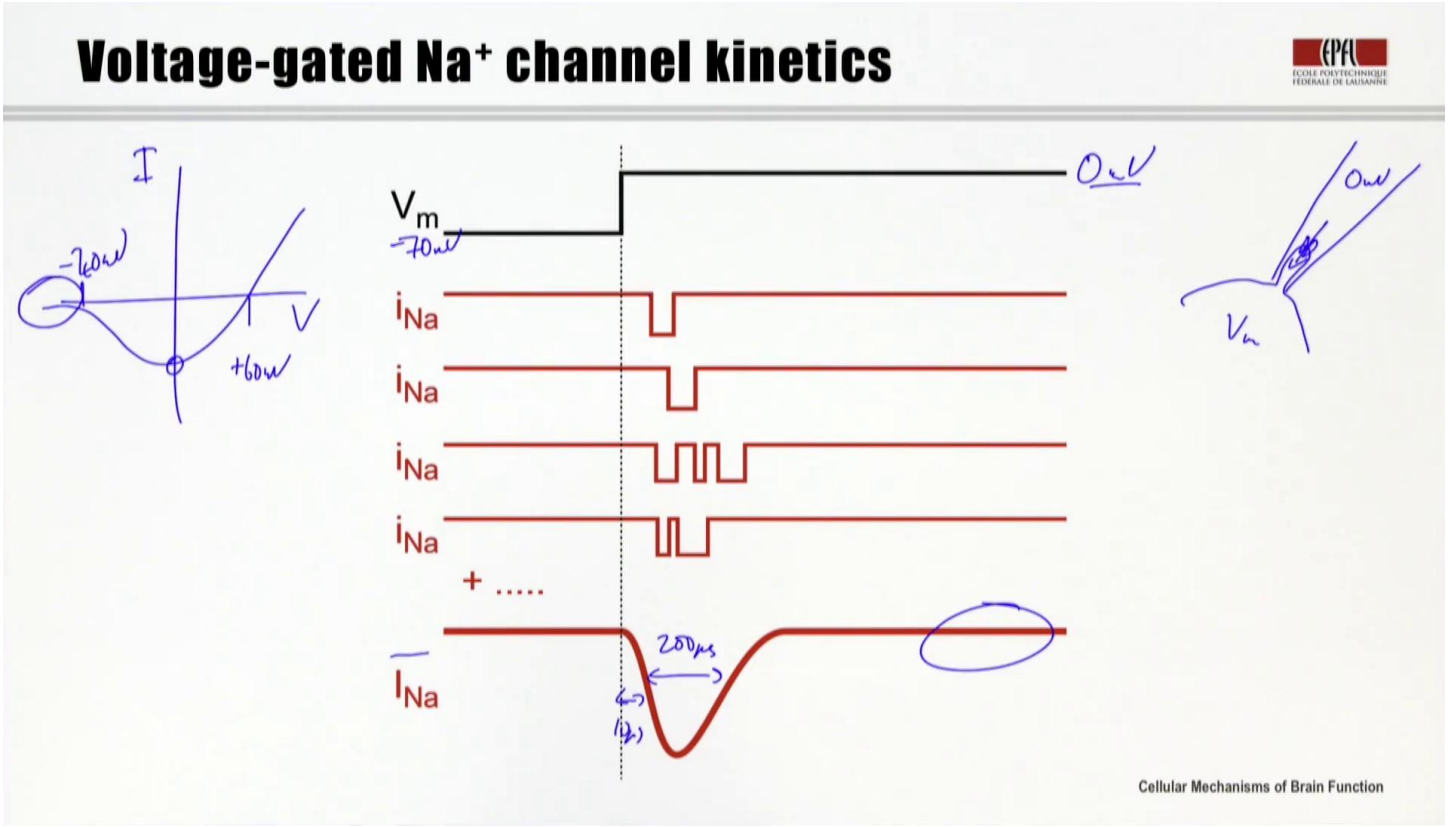


For the voltage-gated sodium conductance, we can imagine a situation where we have a patch clamp electrode sitting on a piece of membrane, we suck a bit of membrane into the patch electrode, and in this patch would be voltage-gated sodium channels. For a given membrane potential we can, using the patch clamp amplifiers, change that membrane potential. We can then activate these voltage-gated sodium conductances. We know that the current/voltage relationship for a sodium conductance is something like this: a reversal potential right here, at around +60 mV activating somewhere around -40 mV and enclosed, basically, at hyper-polarized potentials relative to this. So let's take a situation where we start at -70 mV. At some given time we jump the membrane potential to 0 mV and we're going to be studying the single-channel currents flowing through an individual ion channel inside the patch electrode. So as we go from -70 mV to zero mV, initially, the open probability is very low. The ion channel is closed at -70 mV. We then jump to zero mV. Now we have an inward driving force, so we're expecting an inward current to happen.

Notes

Summary

2m 18s

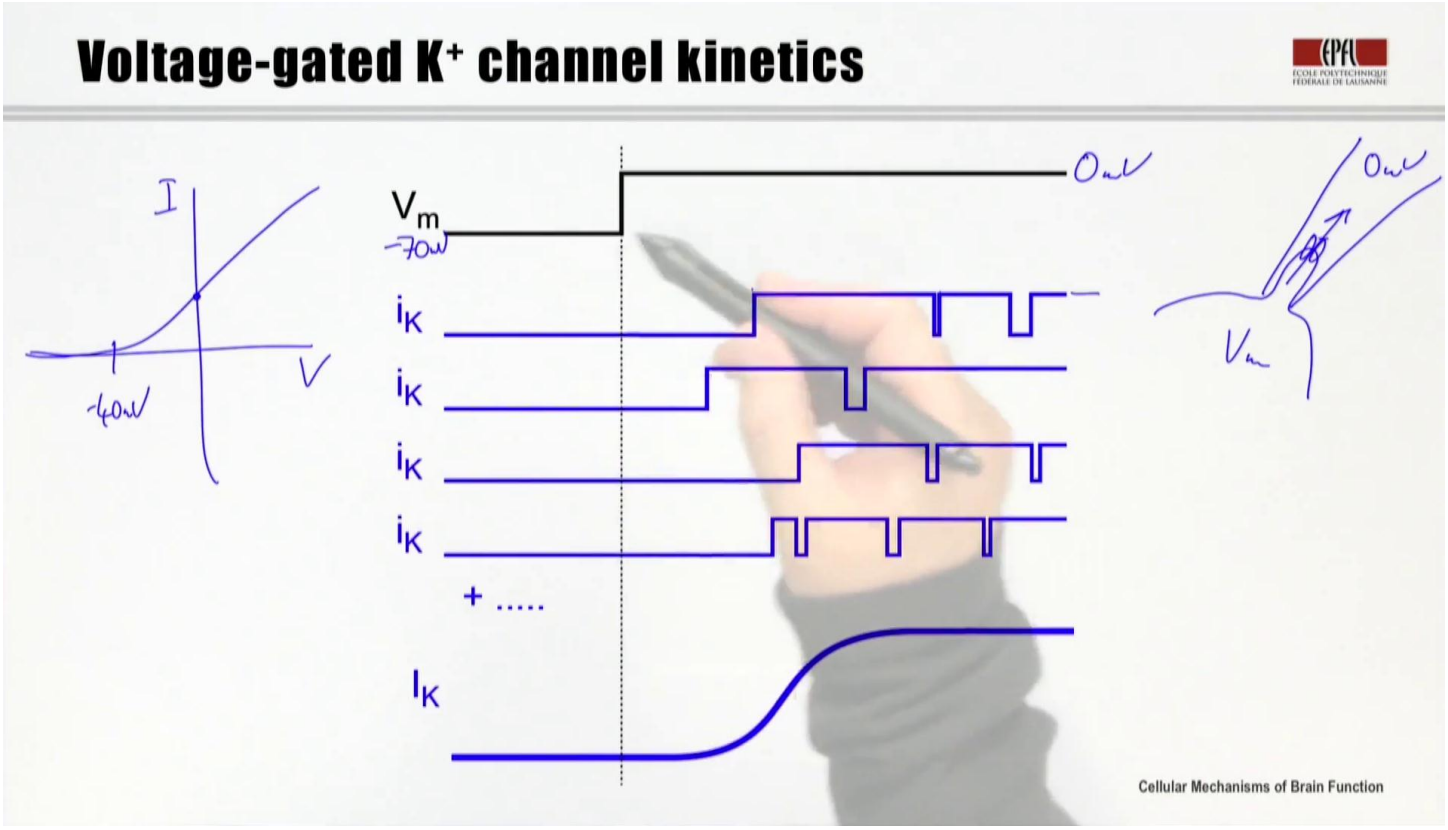


Initially, nothing happens, but then, after a short delay, this ion channel opens, stays open for a brief period of time, closes again, and then remains closed for the duration of the depolarization to zero mV. On the next trial when we repeat this again, -70 mV, no current flow, we depolarize to zero mV, short delay, ion channel opens, stays open, closes, and then again, remains closed for the duration. In this case here, the ion channel is open for a slightly longer duration here with some stochastic opening and closings. And you can imagine repeating this over and over again for hundreds of trials, or alternatively, summating that current across a whole cell membrane and doing just a single voltage step and seeing that summated average currents across the sodium channels, and either way, we get the same picture. We make the voltage step from -70 to zero mV. After a brief delay, inward current is activated. This takes, maybe some ten microseconds or so, and then the sodium conductance remains high for a period of about 200 microseconds, and then it closes. The voltage-gated sodium channel inactivates rapidly on that time scale of hundreds of microseconds. Fast, brief, transient voltage-gated sodium conductance is activated by a prolonged step to zero mV.

Notes

Summary

3m 47s

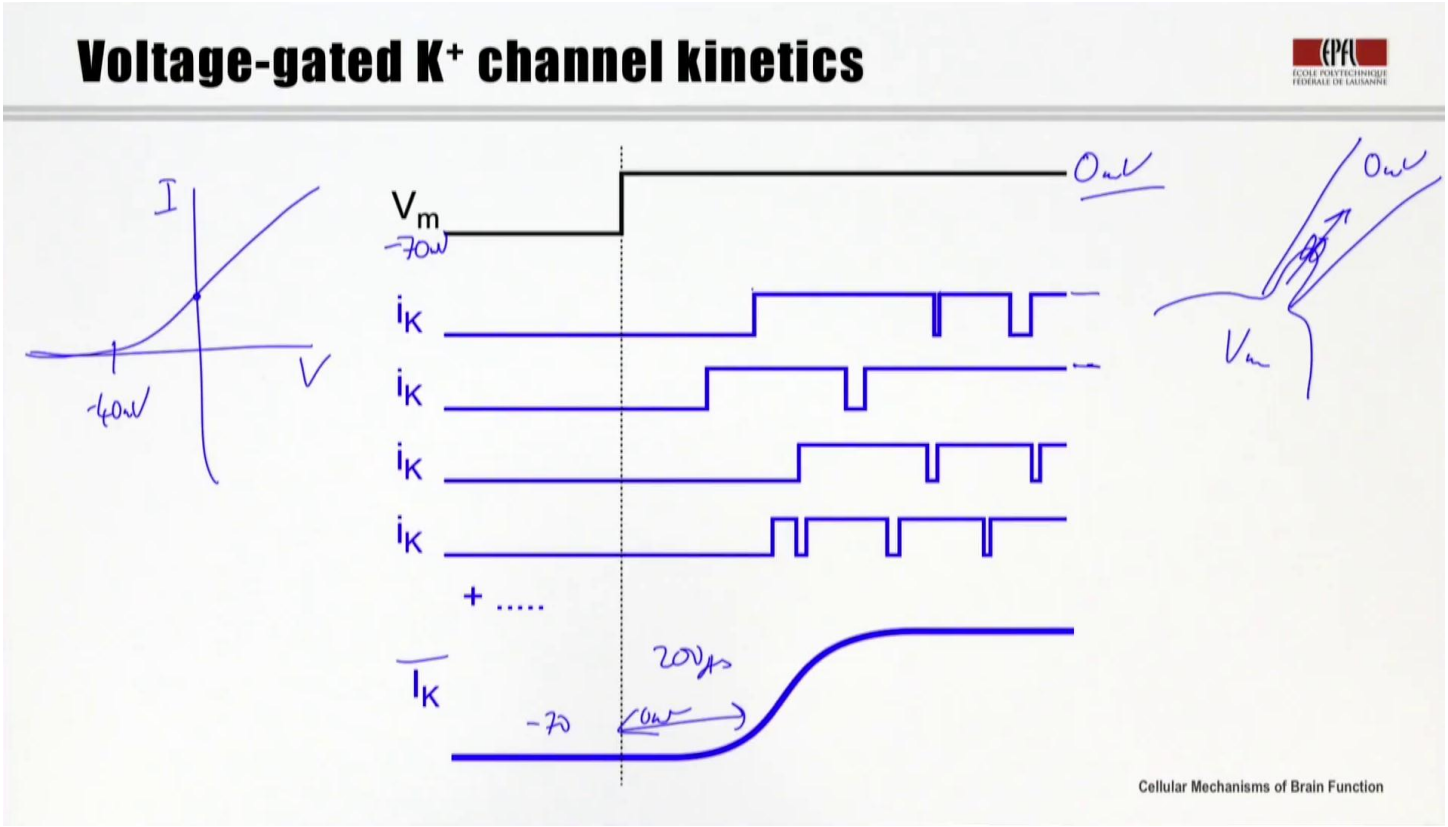


For the voltage-gated potassium conductance, things are rather different. Again, envisage a situation where we have a glass patch electrode sucking a bit of membrane inside it and inside this membrane we now have a potassium conductance. We can choose the membrane potential through the patch clamp amplifier, and again we take a situation where we start at -70 mV, the ion channel is closed, we have our current/voltage relationships that are characteristic, which are closed until somewhere around -40mV. We jump to zero mV, we have an outward driving force and we now study what happens at the level of single channels as we make that jump in voltage from -70 to zero mV. Here we're looking at the single channel current through our patch electrode, we make the voltage jump, and initially, nothing happens. There's a long delay, and then at some time, the channel opens, stays open, briefly closes, opens, briefly closes, opens again, and this ion channel will remain open as long as we keep the plasma membrane depolarized to zero mV. In another trial we do the same. We jump from -70 to zero mV with a delay, the ion channel opens, closes, opens, and stays open for as long as we care to keep the patch of membrane depolarized.

Notes

Summary

5m 21s

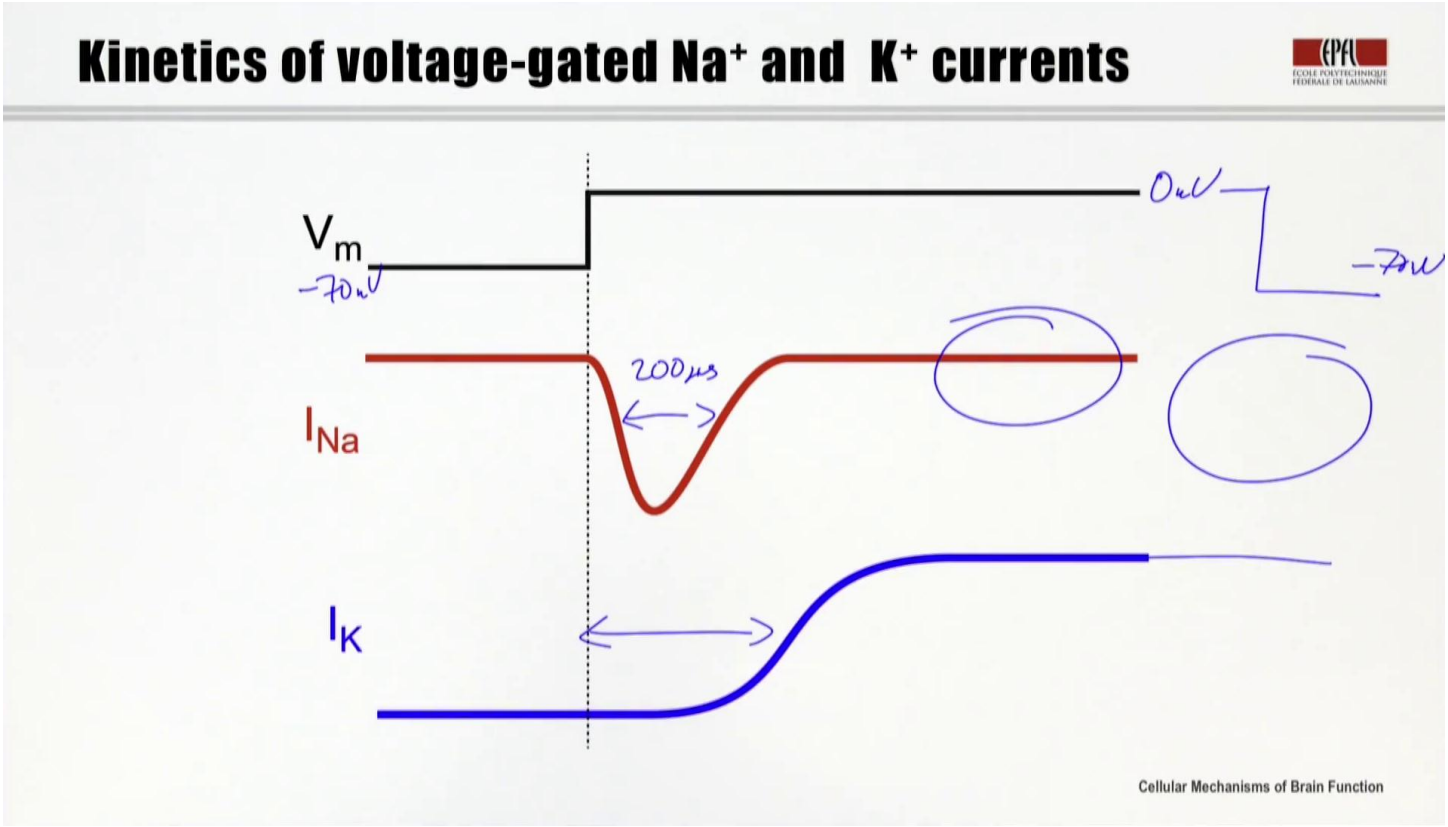


We can, again, summate this across multiple ion channels that are present in the cell membrane, or we can repeat at the level of individual ion channels and get the mean current flow for the potassium conductance. And either way we get the same picture, we jump from -70 mV to zero mV. There's a delay, nothing happens for a few hundred microseconds, so about 200 microseconds, nothing happens, and then the open probability of the voltage-gated potassium conductance increases and we see an increase in the current flow through the voltage-gated potassium channels.

Notes

Summary

6m 52s

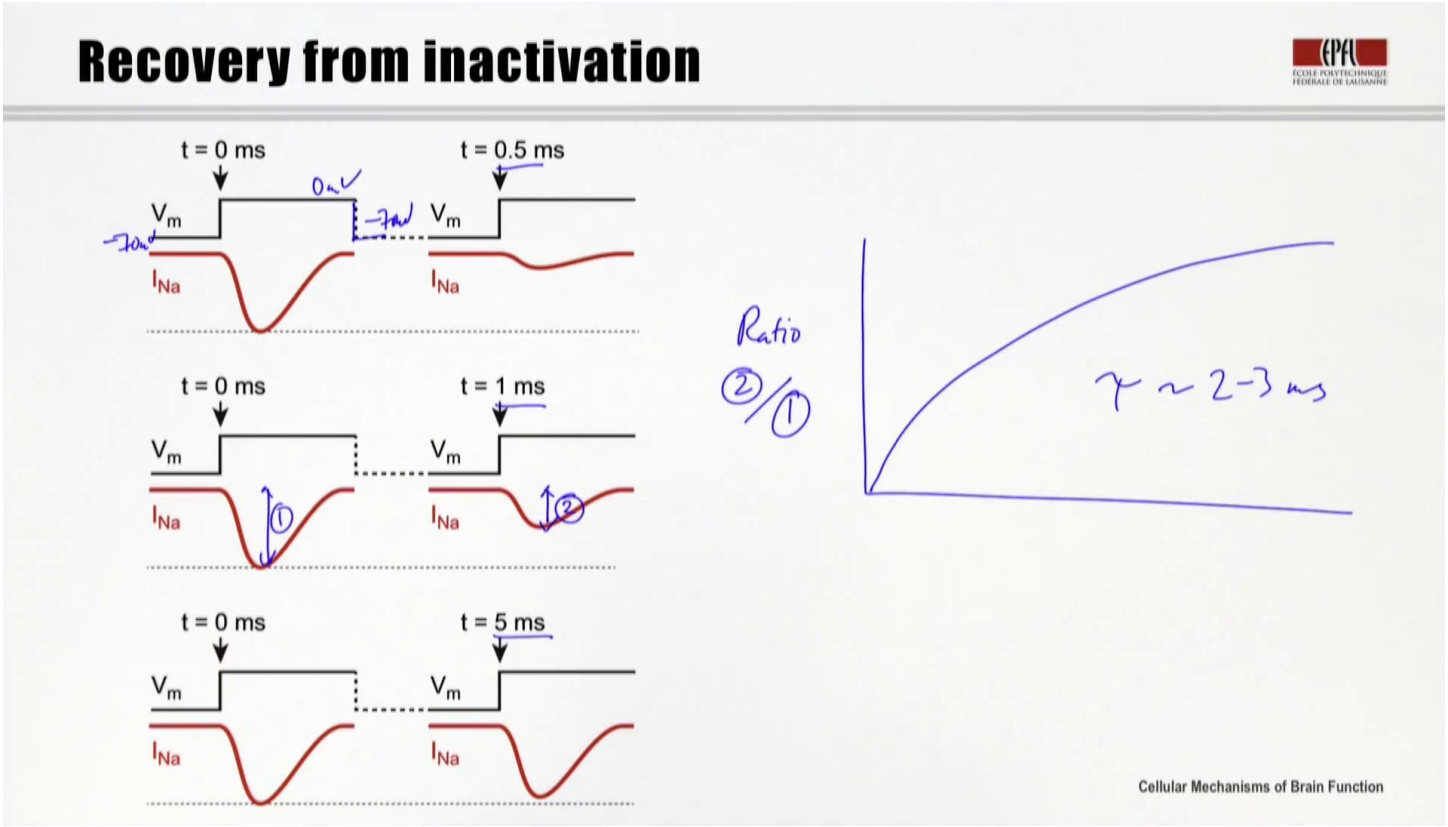


We can directly compare the kinetics of the voltage-gated sodium and potassium currents by putting them on the same graph. So again, we imagine going from our hyper-polarized to our depolarized state that activates both the voltage-gated sodium and the potassium conductances are both activated somewhere positive to -40 mV, but the major difference is in the time course. The voltage gated sodium conductance is fast and transient. The voltage-gated potassium conductance is delayed and long lasting, without inactivation. The transient sodium conductance lasts something like 200 microseconds, and the potassium conductance is delayed by that same order of magnitude, some hundreds of microseconds delay the activation of the potassium conductance that then remains active and doesn't inactivate, whereas here, the sodium conductance has fully inactivated after just a few hundred microseconds of the depolarization. However, the voltage-gated sodium channel doesn't remain inactivated forever. We can take that membrane potential, hyper-polarize it again, say, to -70 mV, and under those circumstances, the sodium channel de-inactivates and can go through another round of this while we can make a step activation and will again see the transient voltage-gated sodium conductance. The de-inactivation doesn't occur instantaneously, but again, takes some time.

Notes

Summary

7m 29s

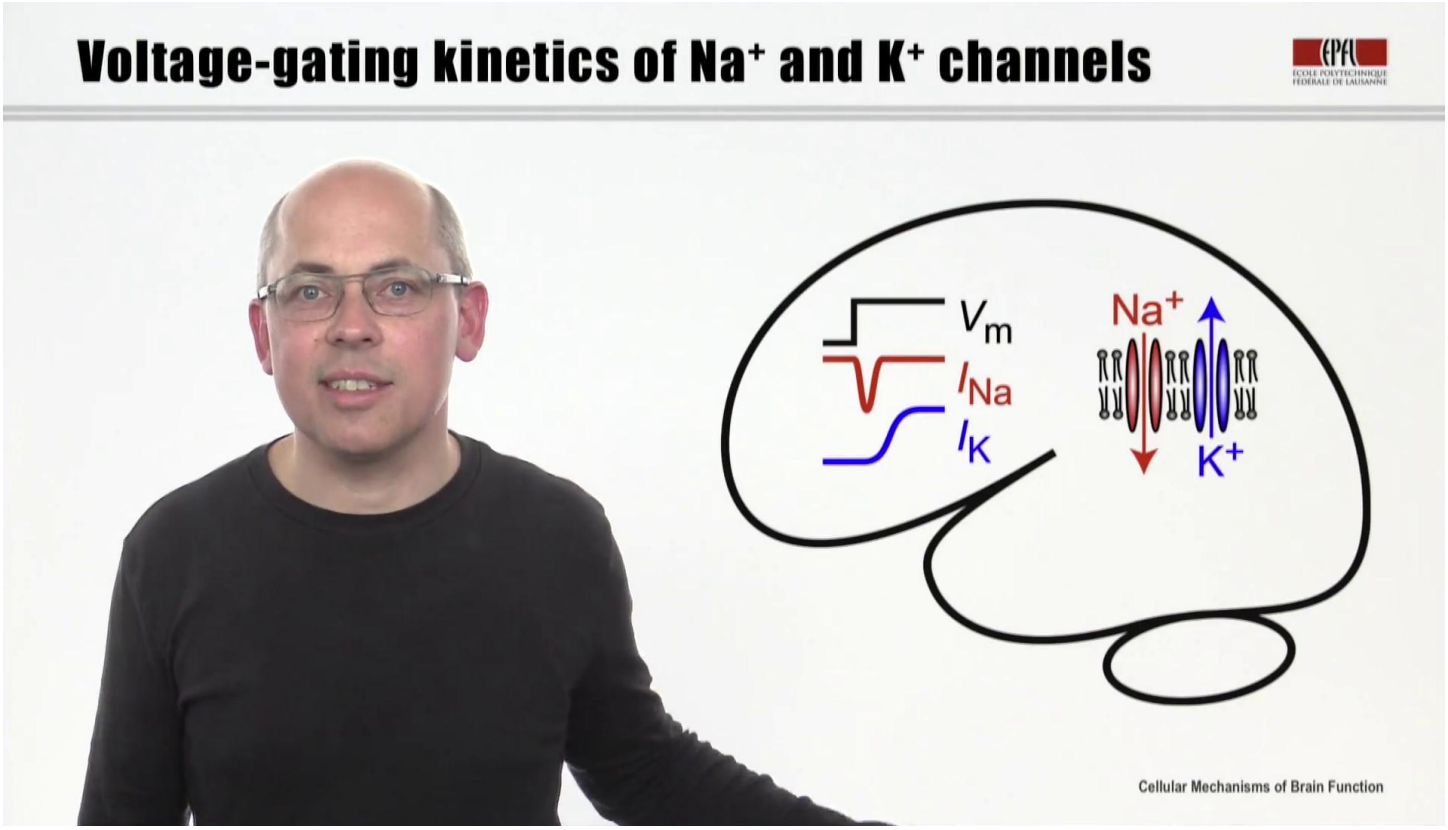


We can study the recovery from inactivation by doing two pulse experiments. And so, as before, we go from our hyper-polarized to our de-polarized state. We see the transient voltage-gated sodium current that becomes activated by this depolarizing step and then at some later time, after we've re-polarized again back to -70 mV, we can then study how long it takes before we recover our full sodium current. If we wait half a millisecond, we get some recovery, but not much. If we wait one millisecond, the recovery is already better. and after about five milliseconds, we're almost back to the full voltage-gated sodium current that we had from controlled conditions. And so, we can plot an exponential recovery time course for the voltage-gated sodium conductance if we think of this as the second peak, and this as the control, first peak, we can look at the ratio of the second activated voltage-gated sodium conductance compared to the first one, and we find that there's a recovery time constant with an exponential form here, and the exponential for the recovery from inactivation is on the seven millisecond time scale.

Notes

Summary

9m 10s

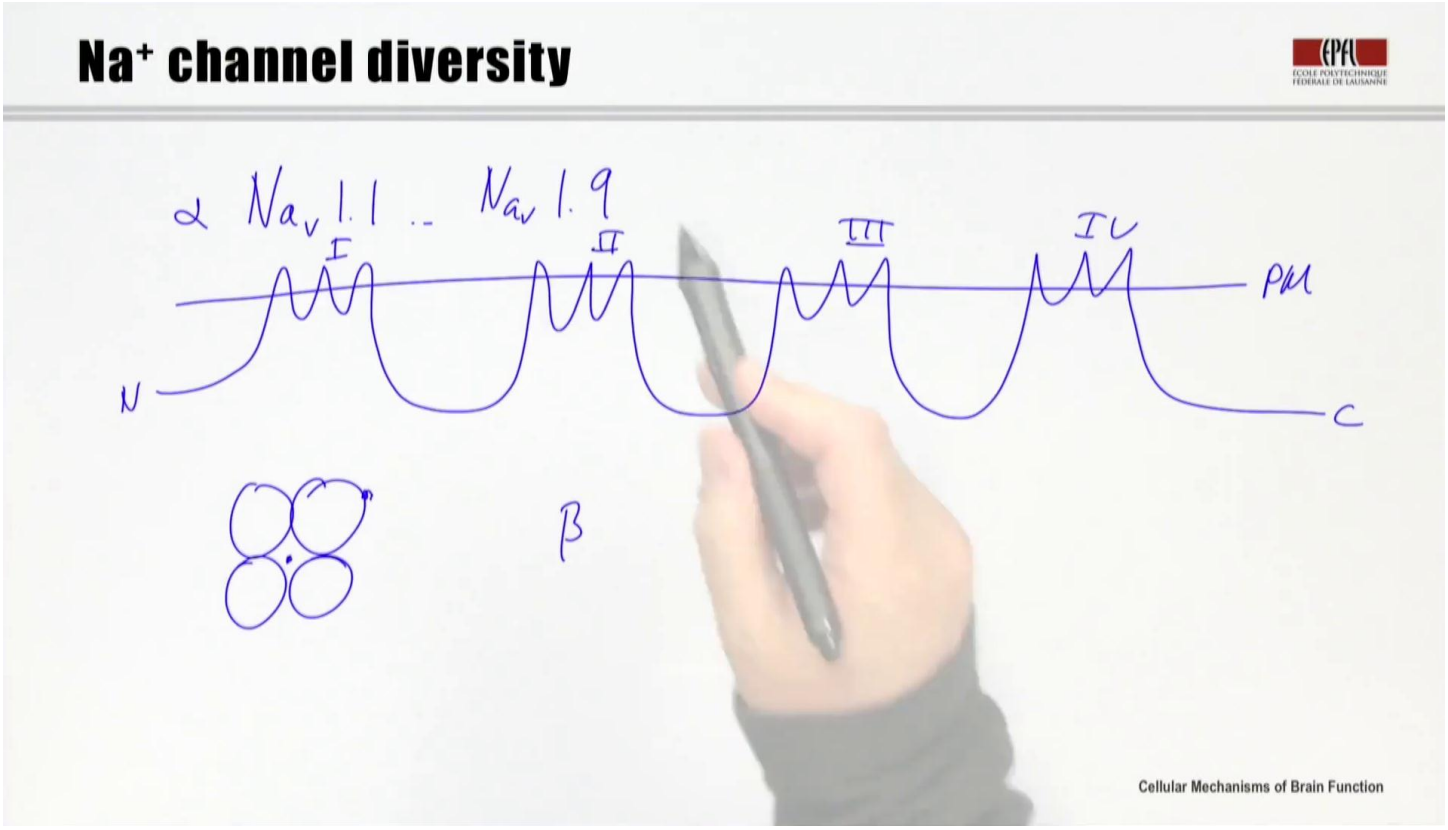


So we've seen some important features of the kinetics of the activation and inactivation of the voltage-gated sodium and potassium conductances. Both voltage-gated sodium and potassium conductances are interactive at resting membrane potential, around -70 mV. Above -40 mV the open probability of both sodium and potassium conductances increases dramatically, but the sodium conductance is rapidly activated in the time domain lasting a few hundred microseconds is then inactivated, whereas the potassium conductance is delayed. It takes some hundreds of microseconds before it even opens, and then, it doesn't inactivate, but remains open for as long as the membrane is depolarized. Now, this is true in general of the voltage-gated sodium and potassium conductances that one sees, but there's also some diversity as one goes across different species and across different cells in the same species, and we'l have a little look at the basis of that in the next slides.

Notes

Summary

10m 36s

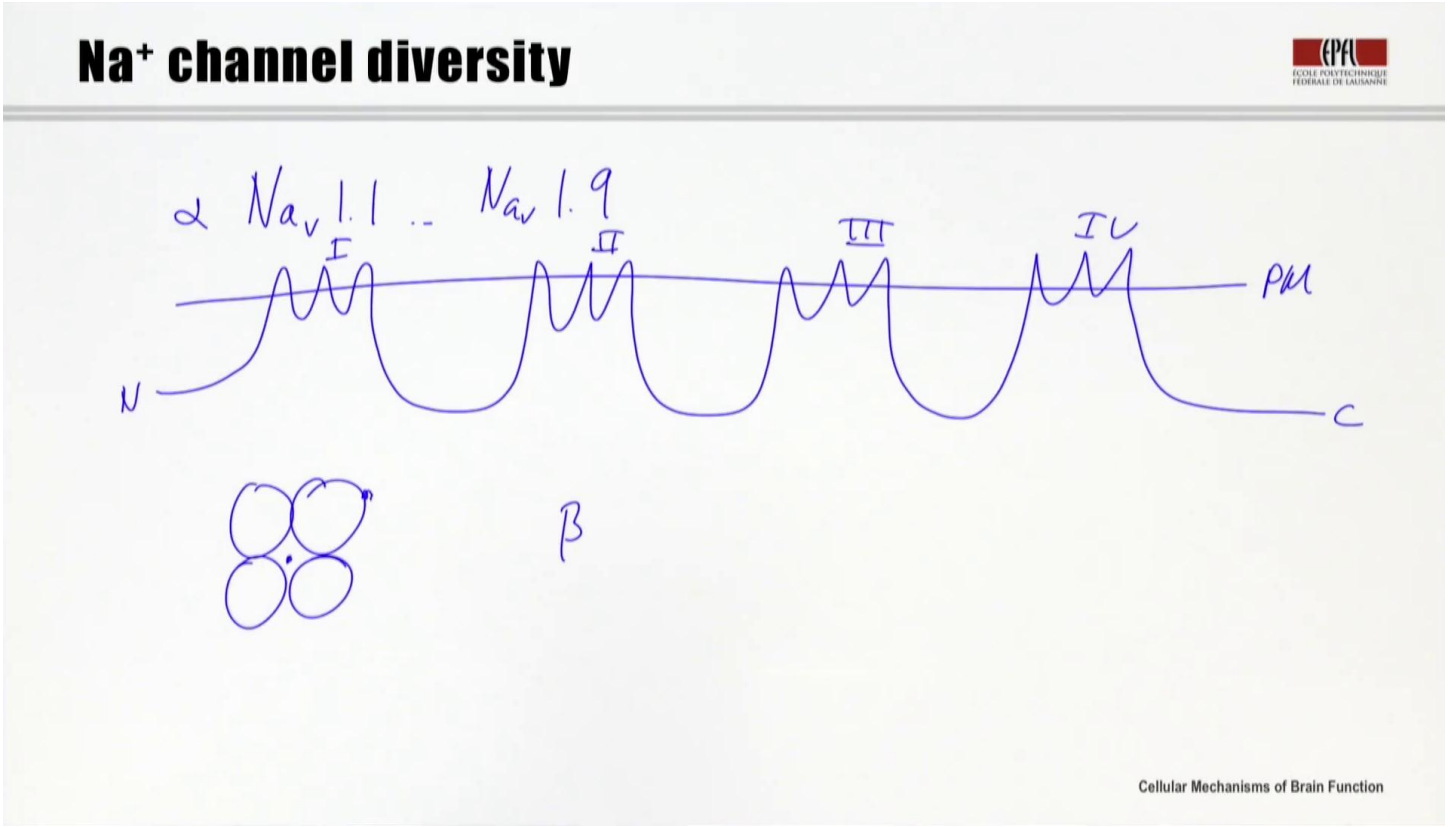


The voltage-gated sodium channels are encoded by a family of nine genes that are given the nomenclature NaV1.1 through to NaV1.9. All of them encode the voltage-gated sodium channel in a single gene, so it's one long string of amino-acids that has transmembrane domains and it has four subunits that are all part of the same string of amino-acids so this would be the N terminal, the C terminal, and here's subunit I, II, III, and IV and these are then the trans-membrane regions that will ultimately sit in the plasma membrane and will then form the four subunits of the ion channel, the center of which forms the ion conducting channel pore. Associated with this so-called alpha subunit of the voltage-gated sodium channel is a much smaller Beta subunit that sits somewhere tightly associated to the ion channel proteins encoded by the Alpha subunit. Together this provides some diversity. There are nine different sodium channel proteins, there are four different Beta supplements, and they can then encode slightly different functions in terms of the single-channel conductance and the detailed kinetics and the voltage activation.

Notes

Summary

11m 42s

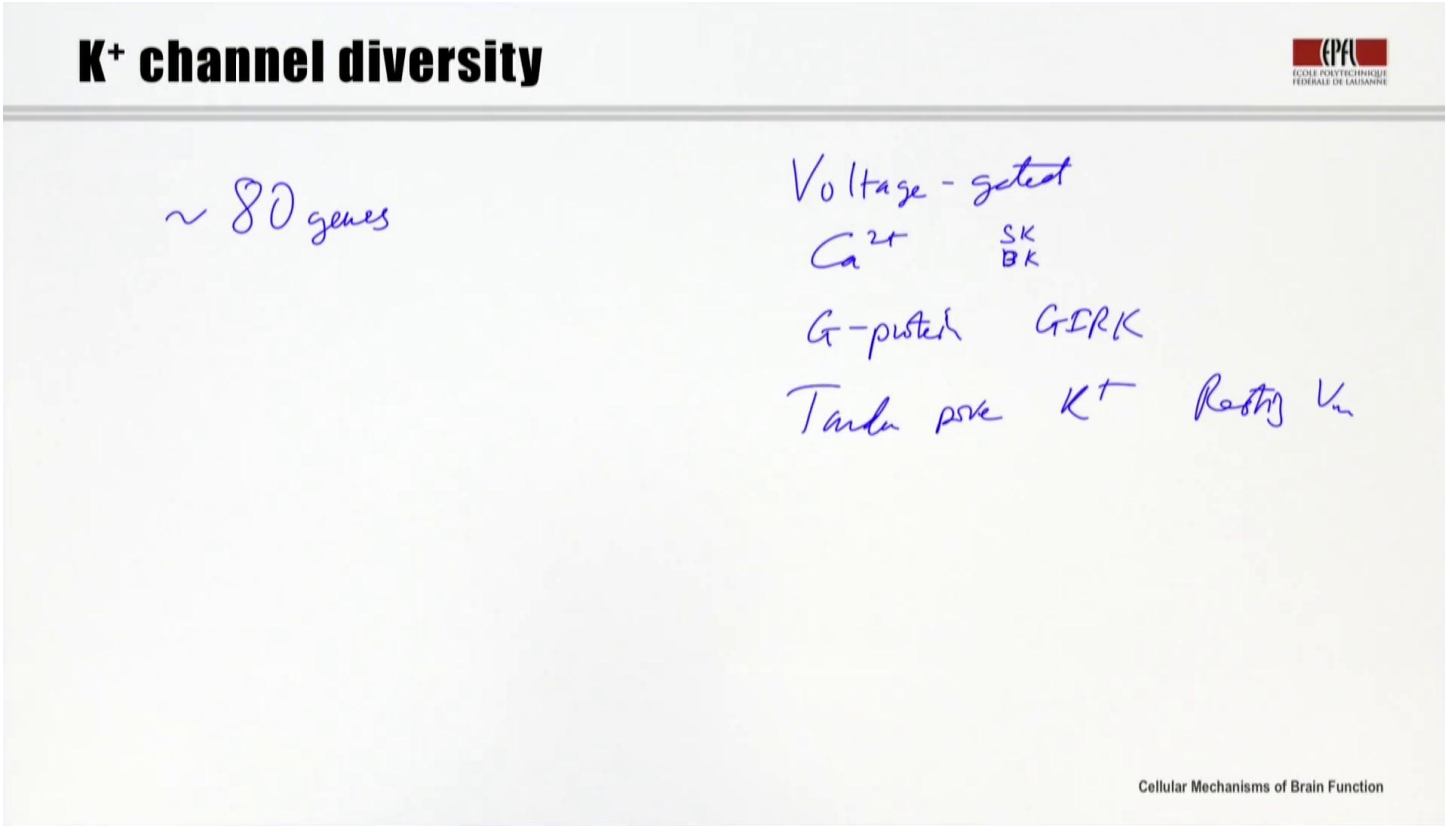


Another very important aspect that's different between the different isoforms is the cell types in which they are expressed, and also the sub-cellular localization of the voltage-gated sodium channel. As we'll learn in the next lesson, the density of the voltage-gated sodium channel is regulated very precisely, and some small subregions of neurons have very high densities of voltage-gated sodium channels and that makes a big difference to the functioning of neurons. There's also some diversity in terms of the time course of the voltage-gated sodium channel, and in particular, some subtypes of voltage-gated sodium channels have much less inactivation than what we've discussed.

Notes

Summary

13m 13s



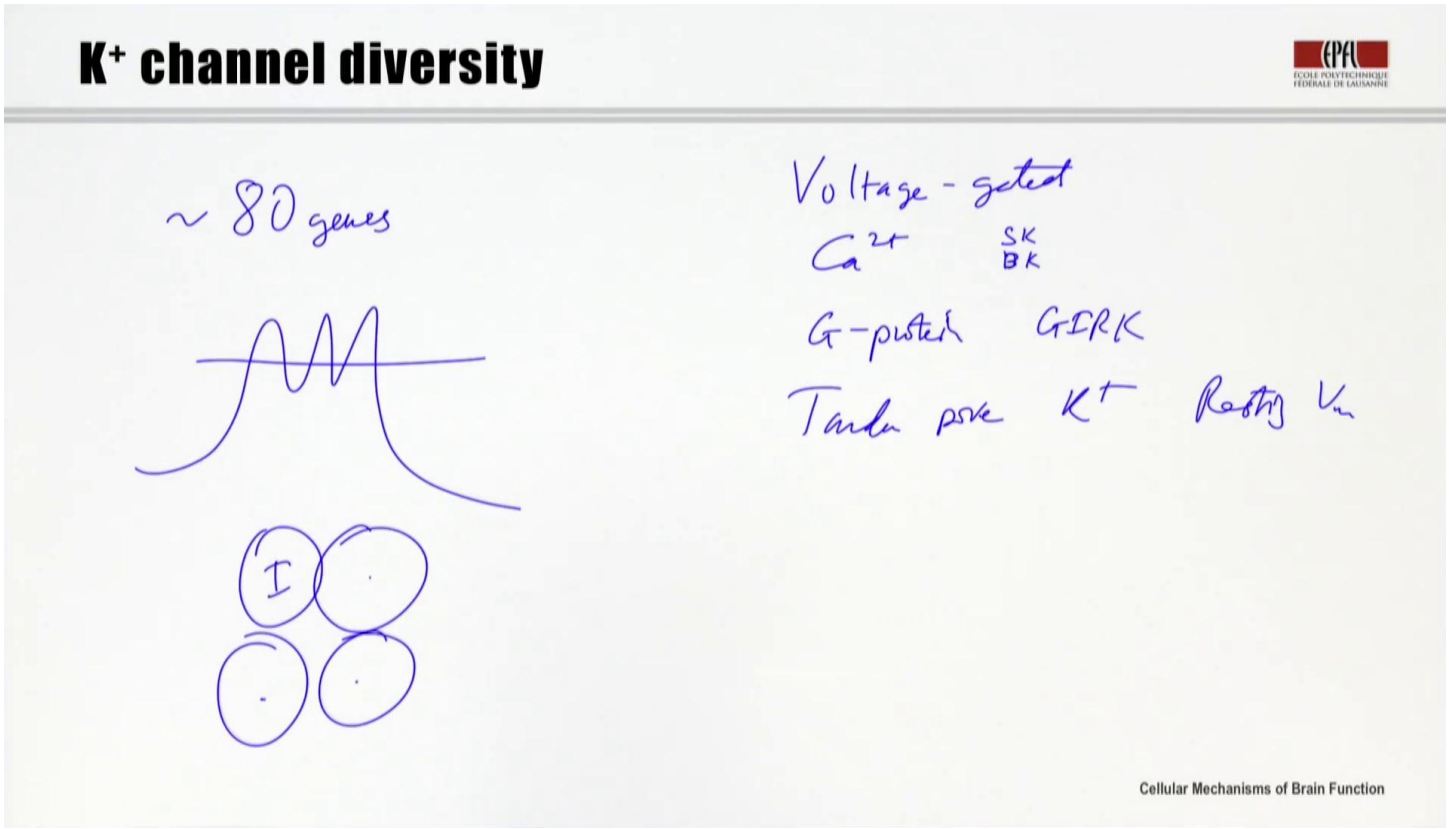
Potassium channels are an even more diverse family of ion channels. There's something like 80 different genes in the mammalian genome that encode potassium channels. Not all of the potassium channels are voltage-gated. They are an important family of the potassium channels, and are certainly the ones that are most interesting to us in terms of thinking about the complex dynamics of membrane potential but they're not the only ones. There are also potassium channels that are gated by the intracellular calcium concentration, calcium activated potassium channels that are so-called BK and SK channels, and there's another family of proteins, of potassium channels, that are so-called G-protein coupled ion channels, these are the so-called GIRK channels, and there are the Tandem pore potassium channels that are involved in setting the resting membrane potential. The voltage-gated potassium channels in themselves have extensive diversity. Some of the voltage-gated potassium channels have some degree of inactivation but on a much longer time scale than what we saw for the voltage-gated sodium channels.

Notes

Summary

14m 00s

K+ channel diversity



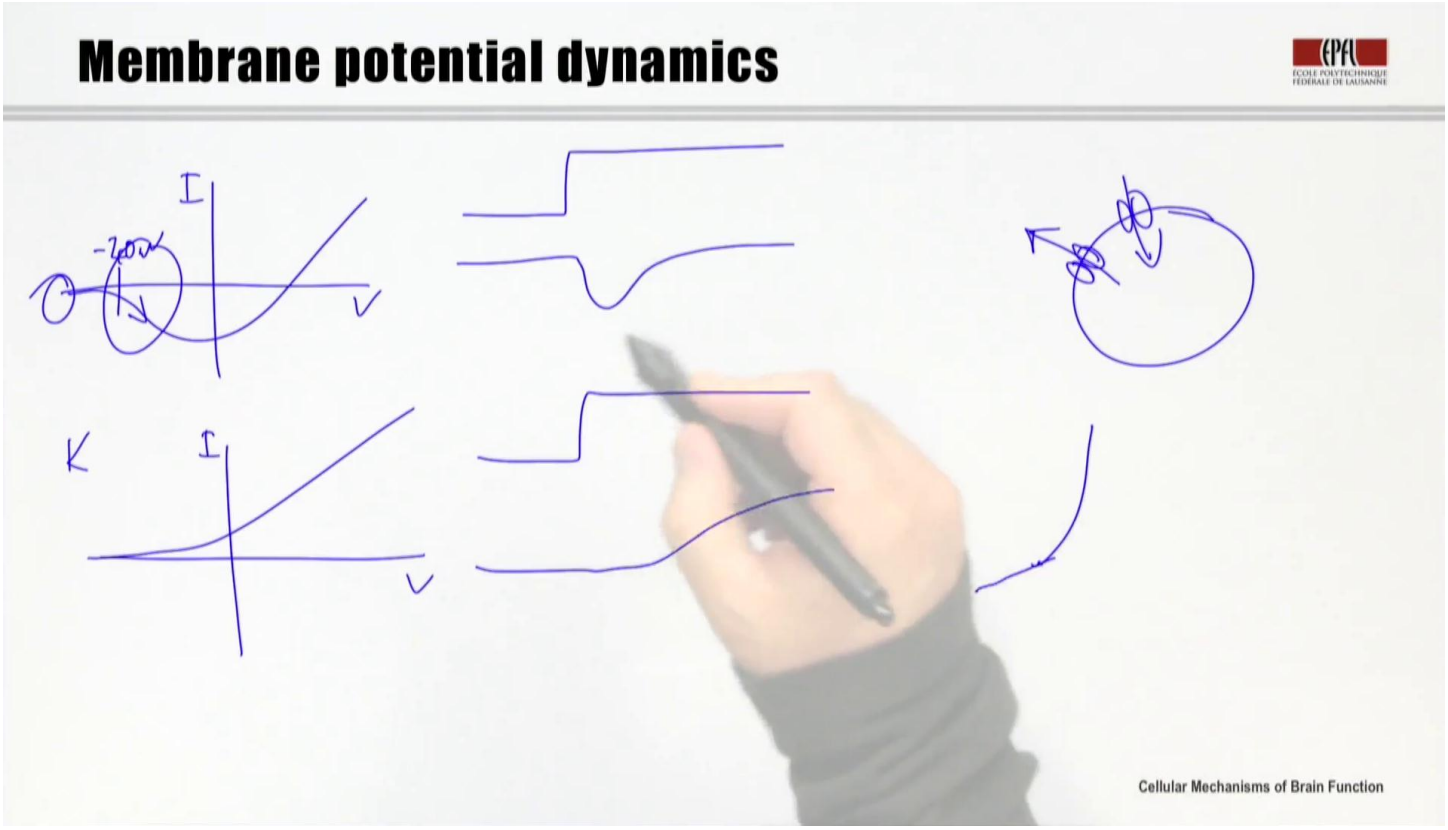
Cellular Mechanisms of Brain Function

The potassium channels are also different in the sense that they encode individual subunits rather than the whole potassium channel in itself and so, one gene will encode the six transmembrane regions of the potassium channel, but it will only encode one subunit of that, so one gene will encode one subunit and another gene might mix together with that and form other parts of the subunit of the potassium channel, so we can generate even more diversity by mixing different proteins together to form the voltage-gated potassium channels. The diversity in the voltage-gated potassium channels causes a great deal of the diversity in terms of how neuronal membrane potential changes in different cell types and in different compartments of the same cell.

Notes

Summary

15m 25s



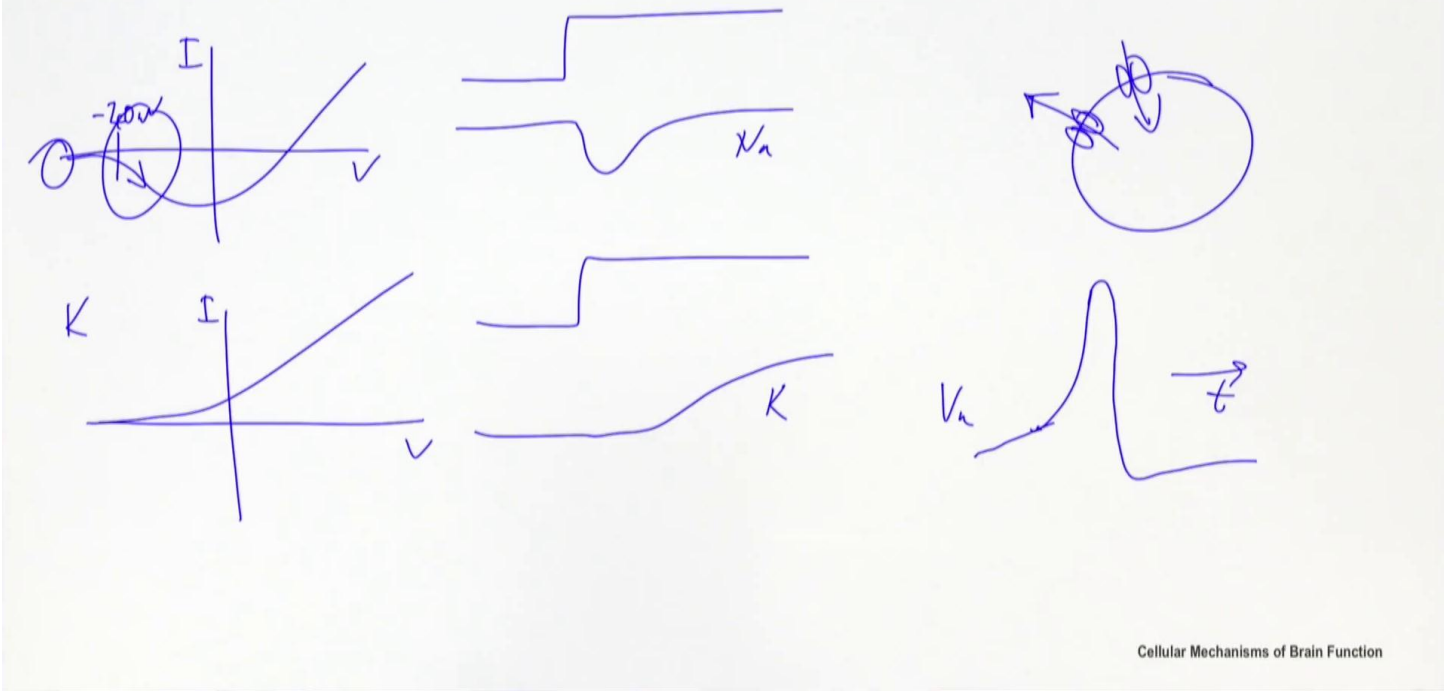
So now we've learned a bit about the voltage activation of the sodium and the potassium conductances. We have the voltage activation of the sodium conductance, and we have the voltage activation of the potassium conductance, both of which are activating somewhere positive to -40 mV and closed at resting membrane potentials. We also know something about the dynamics of the opening of the voltage-gated sodium conductance. It opens rapidly and then inactivates, whereas for the potassium conductance, we have a slower rise that takes some hundreds of microseconds. We can then begin to think about what happens inside a cell that might express both the sodium and the potassium conductances. If we think now about the different time courses of these, you can imagine that if we take the membrane potential a little bit depolarized and we get into this regime where the sodium channel begins to activate, we could then get this brief activity of the voltage-gated sodium conductance that will drive a depolarization for the inward current through the sodium conductance. This will then inactivate, and at the same time, while the sodium conductance inactivates, the potassium conductance is activating, driving a hyper-polarization.

Notes

Summary

16m 18s

Membrane potential dynamics



We'll see it's exactly this dynamic interaction between the sodium and the potassium conductances giving rise to brief transient excursions in the membrane potential with time that drives the so-called action potential. That action potential is what we'll be studying in the next lesson.

Notes

Summary

17m 48s

Voltage-gating kinetics of Na^+ and K^+ channels

- Voltage-gated Na^+ channels open rapidly in response to depolarisation, and then inactivate rapidly.
- Voltage-gated K^+ channels are activated more slowly by depolarisation, but they do not inactivate.

Cellular Mechanisms of Brain Function

So to summarize this lesson, we've learned some interesting details about the kinetics of activation and inactivation of voltage-gated sodium and potassium channels. The voltage-gated sodium channel activates rapidly, then inactivates rapidly, and remains inactivated until the membrane potential hyper-polarizes again, and then, after a few milliseconds, it's de-inactivated and ready for the next voltage pulse. The voltage-gated potassium channels, on the other hand, are slowly activated by depolarization. It takes them a few microseconds before their open probability increases, but then they remain open for as long as the membrane potential is depolarized. The complex interplay between time, space and membrane potential and the opening of these voltage-gated ion channels causes very interesting and complex dynamics in membrane potential, and ultimately underlie the action potential signal, which is the 0 and 1 signal that we'll go on to study in the next lesson.

Notes

Summary

18m 10s