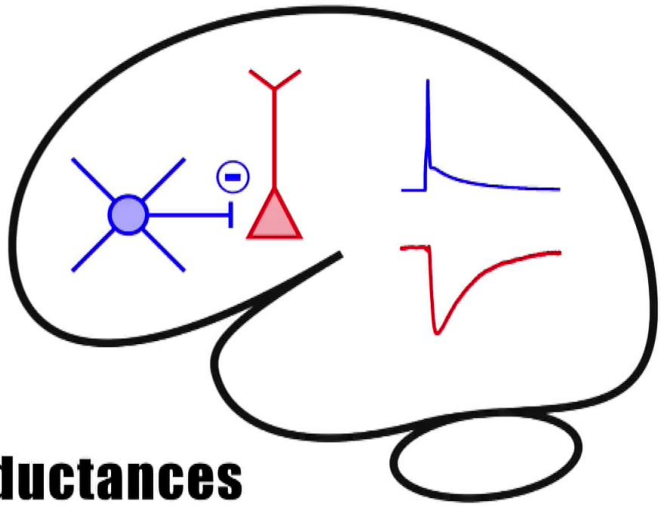
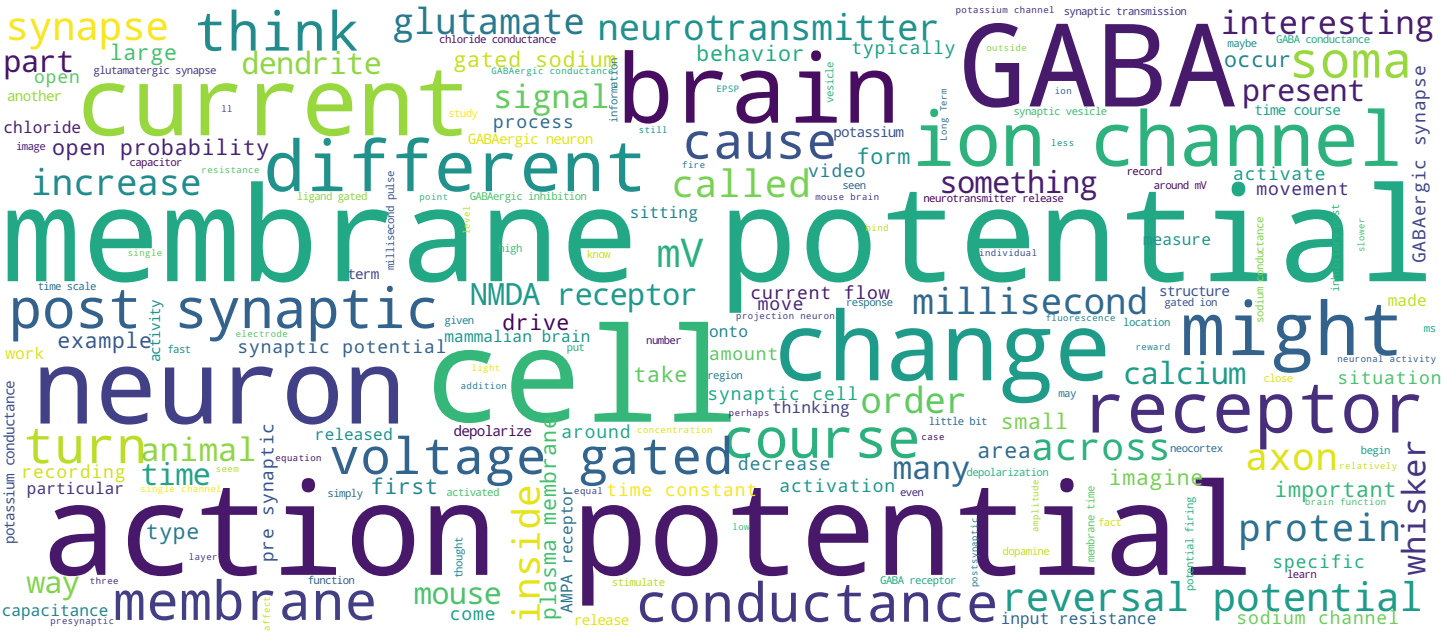


5.2 Inhibitory synaptic conductances

Cellular Mechanisms of Brain Function

Prof. Carl Petersen

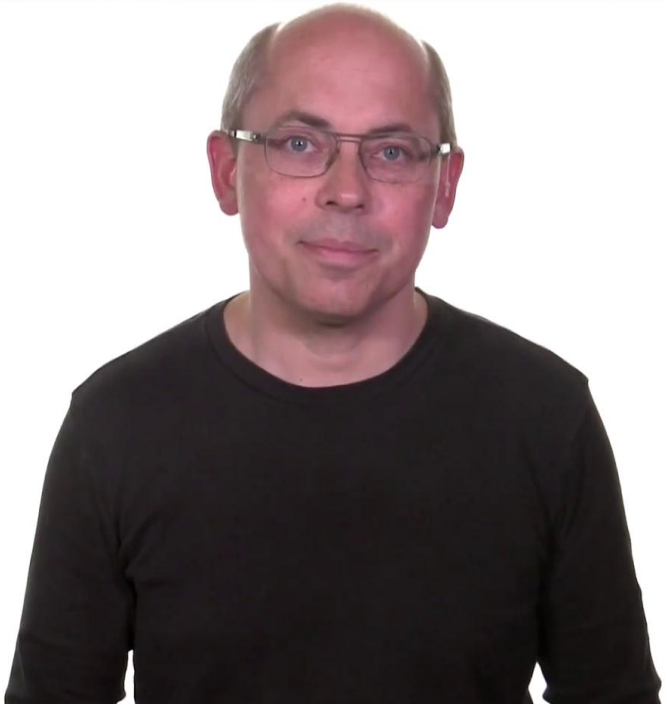


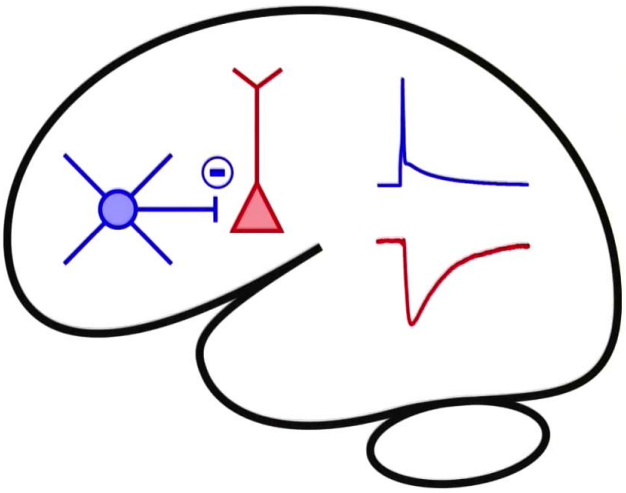
Search MOOC

Video

EPFL

GABAergic inhibitory postsynaptic potentials





Cellular Mechanisms of Brain Function

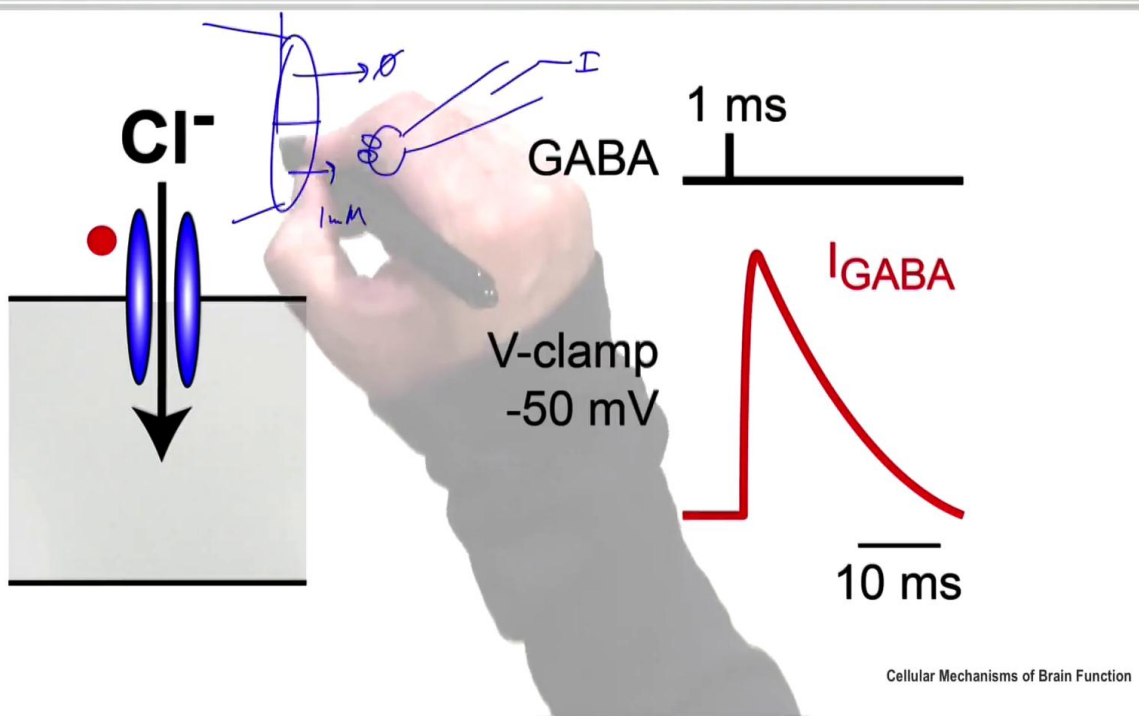
In the last video, we saw that GABA is a main inhibiting neurotransmitter of the mammalian brain. GABA acts via two distinct mechanisms. At the synapse. GABA activates GABA-A receptors, ligand gated ion channels permeable to choride, and here it drives a hyperpolarization. GABA also acts extra-synaptically upon GABA-B receptors. Here the GABA-B receptor is a seven transmembrane protein. It's metabotropic, it activates G proteins, and downstream of that it activates a Potassium conductance, also causing hyperpolarization. There are two distinct mechanisms for GABA inhibition, and in this video we're going to take a closer look at the GABA-A mediated inhibition. The GABA-A conductance is a chloride conductance. Chloride reverses at around -18 mV, so typically, when a pre-synaptic GABAergic neuron fires an action potential, it propagates down its axon, releases GABA, it acts upon GABA-A receptors and causes a hyperpolarization in the post-synaptic neuron. That's the fast hyperpolarizing action of the GABA-A receptor. In this lesson we're going to look in more detail at the fast inhibition mediated by GABA-A conductances and see a little bit more about the specific details of how it works.

Notes

Summary

0m 05s

The $GABA_A$ receptor is a fast ligand-gated channel



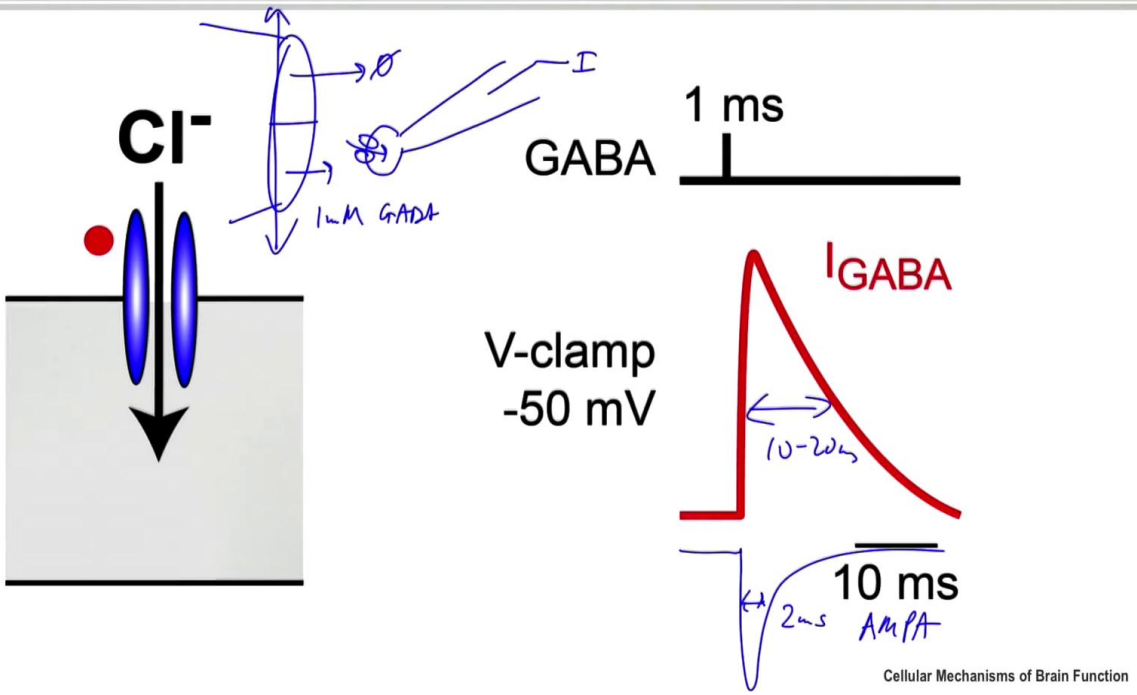
The GABA-A receptor is a chloride channel. GABA binding to the GABA receptor increases the open probability of the receptor, so in the absence of GABA, if we are recording with an electrode looking at the single channel, then the openings and closings of this receptor, it'll be closed. If then you add GABA to the recording pipette, you'll see that the open probability increases and we have single channel currents that come with a conductance of something like 10 to 30 pS. So GABA increases the open probability of the GABA-A receptor. It's of course also interesting to note what the time course of activation of the GABA currents are, and in particular, when we're thinking of synaptic release of GABA, we're thinking about brief pulses of GABA that may well reach 1 millimolar concentrations. So, in the same way that we thought about analyzing the AMPA receptors, we can also record the currents evoked by brief GABA applications onto patches of membrane containing the GABA receptor. And so, we can have a laminar flow electrode which has either no GABA or contains maybe one millimolar GABA. We mount this onto a piezo device and we can then give brief one millisecond pulses of GABA to our patch of membrane containing GABA-A receptors.

Notes

Summary

1m 44s

The $GABA_A$ receptor is a fast ligand-gated channel



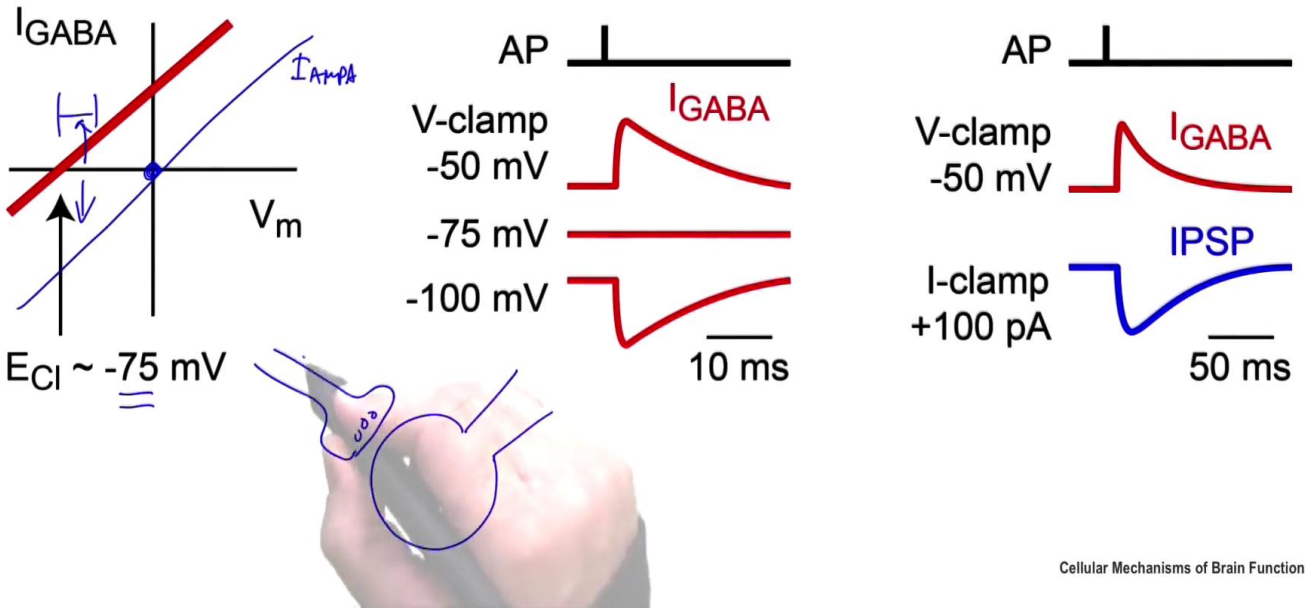
We can then measure the resulting current under voltage climb, so we keep the membrane potential clamped, and so we measure the current flowing through the GABA receptor. Here you can see a typical recording like this. One millisecond pulse of GABA almost immediately activates the GABA conductance. Increased open probability chloride flux, and we get an outward current. The GABA disappears. It's only a one millisecond pulse, but the current remains on for some ten to 20 milliseconds. That's the duration of the GABAergic conductance that's mediated by a single one millisecond pulse of GABA. So it's a fast conductance that's mediated by the GABA-A receptor, but it's interesting to note that this is still much slower than the AMPA currents that are mediated by glutamate at glutamatergic synapses, so if you do the equivalent experiment and last week this is what we looked at, one millisecond pulse of glutamate activate an AMPA conductance and that lasts maybe only two ms. The GABAergic conductance here is five to ten times lower than the AMPA conductance of the glutamatergic synapses. So GABAergic inhibition is fast, but it's much slower than the AMPA mediated excitation.

Notes

Summary

3m 28s

Inhibitory postsynaptic potentials - IPSPs



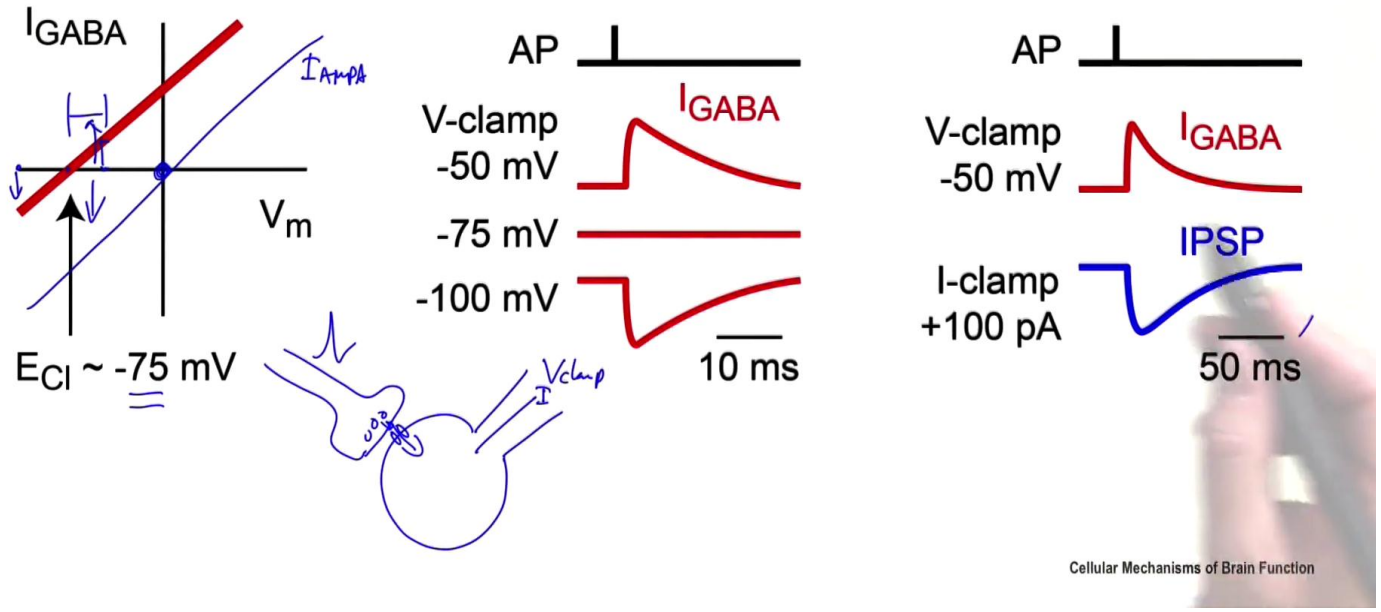
Let's see how those conductances, then, are reflected in post-synaptic membrane potential changes. So the GABA currents are chloride currents. They therefore reverse at the chloride reversal potential, something like -75 mV. The GABA conductance is basically linear, so we can draw a linear current-voltage relationship so this is a current evoked by a GABA pulse and this is a membrane potential of which that current is being recorded. The equivalent AMPA current would look something like this, wherein a pulse of glutamate will cause a current and here it reverses close to zero mV. For GABA, it reverses close to -75 mV and the interesting range of membrane potentials, physiologically, is something around -75 to -40 mV. That's where the membrane potential of a neuron typically is. Here we have an outward current for GABA and we have inward currents for AMPA so inhibition and excitation. If you now think about the synaptic situation, we might imagine having a tight small cell that we can consider as iso-potential. We have a GABAergic synapse that's made here. An action potential invades, releases GABA, and activates the GABA-A currents and we then measure here in the Voltage clamp mode we measure the current flowing through the GABA receptor.

Notes

Summary

4m 56s

Inhibitory postsynaptic potentials - IPSPs



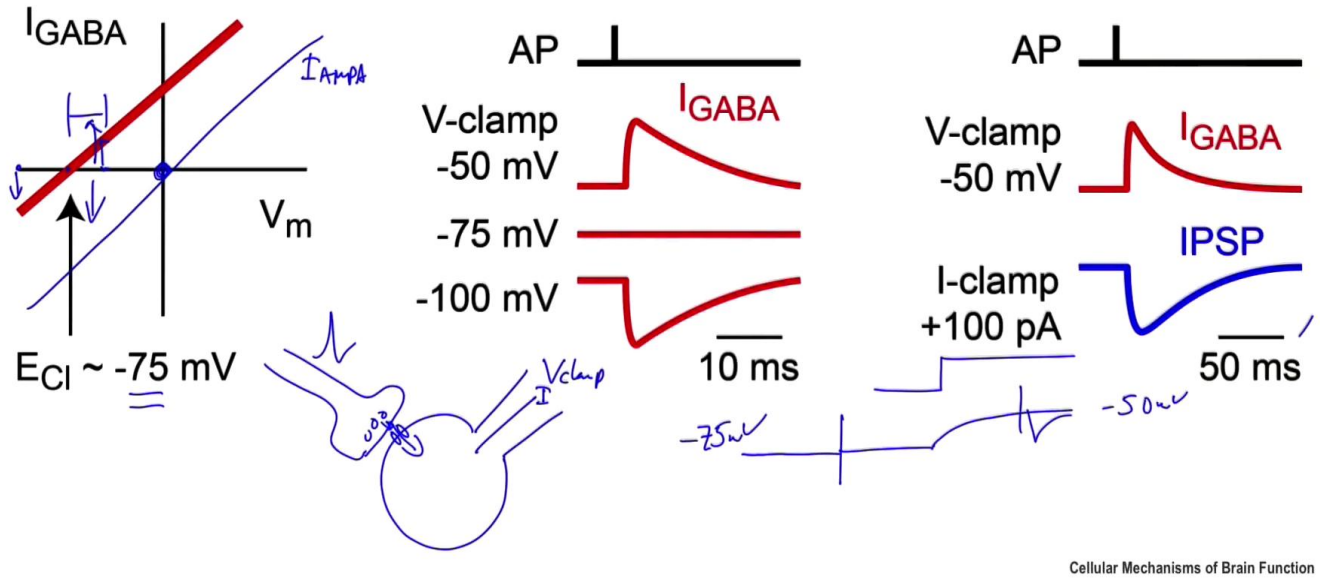
The action potential causes release of GABA and we can then see the synaptic conductances here at different membrane potentials. At -100 mV we have an inward current. At -75 mV no current flow, and at positive potentials to the red, to the reversal potential there of -50 mV we have an outward current, and it's linear and symmetrical around the reversal potential with the time course of around ten ms just as we saw for the isolated receptor with a one ms pulse of GABA. So that's the synaptic GABA conductance that tries to bring the membrane potential to around -75 mV and has a time course of 10-20 ms. If we now think about this situation in current clamp mode, where we're now measuring the membrane potential and we let the membrane potential swing freely depending upon the conductances that are activated, we see that there's an inhibitory post-synaptic potential that has a time course of a little bit longer than the GABA conductance, the GABA currents themselves. And that's because, of course, we have the membrane time constants that we need to discharge the capacitor after we've charged with our currents, we need to think about this and additional filtering because of the capacitance of real cells.

Notes

Summary

6m 30s

Inhibitory postsynaptic potentials - IPSPs



Cellular Mechanisms of Brain Function

Now, in this case, when we're thinking about the GABAergic conductance I've indicated that we're adding 100 pA to the current of the cell that we're recording from. So at resting membrane potentials, maybe we're sitting close to the reversal potential for chloride at -75 mV, so as we stimulate an action potential in the pre-synaptic cell, and the post-synaptic cell is at -75 mV, we're not going to see a response. We're here at the reversal potential, there's no current flow, and so there's no change in membrane potential. We need to depolarize the cell in order to see the inhibitory post-synaptic potentials. We can do that by injecting 100 pA of current, so here if we inject 100 pA of current we'll charge the membrane of the post-synaptic cell. Maybe we depolarize it to -50 mV and now, when we stimulate an action potential in the pre-synaptic cell, we get the hyperpolarizing inhibitory post-synaptic potential that lasts some tenths of milliseconds.

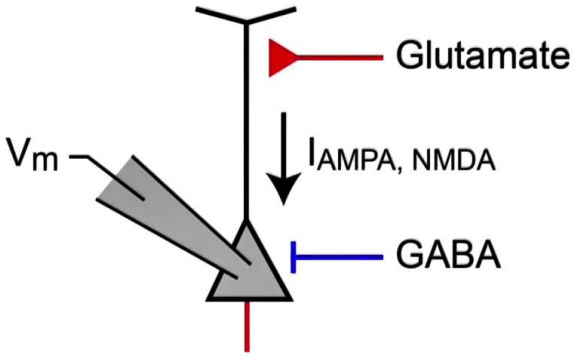
Notes

Summary

7m 56s

Shunting inhibition

The resting V_m is often close to the chloride reversal potential.
If $V_m = E_{Cl}$, then there is no flow of current and therefore no IPSP, but there is nonetheless a conductance, which changes the input resistance.



Now, it's interesting to note that even though the membrane potential of cells is often close to the chloride reversal potential and therefore you actually don't record an inhibitory post-synaptic potential when GABA is released, there is nonetheless an impact upon the integration of the post-synaptic cell in terms of, say, how excitatory conductances are integrated in that neuron. That comes about because there's a change in the overall membrane resistance. I'll illustrate that with a simple example here. We can imagine for example a glutamatergic excitatory conductance coming into the dendrites of a cell. That then causes current flow into the dendrite that'll then go towards the soma, so there'll be conductances from glutamate that mediate current chart flow via the AMPA and NMDA receptors that contribute to changing the membrane potential of the soma. At the soma we can imagine that there are GABAergic synapses that are present here, a chloride conductance that maybe is reversing at exactly the same as the membrane potential of that cell. Nonetheless, activating this GABA conductance will change the impact of that glutamate. Why is that? Let's think about the electrical equivalent of the cell soma.

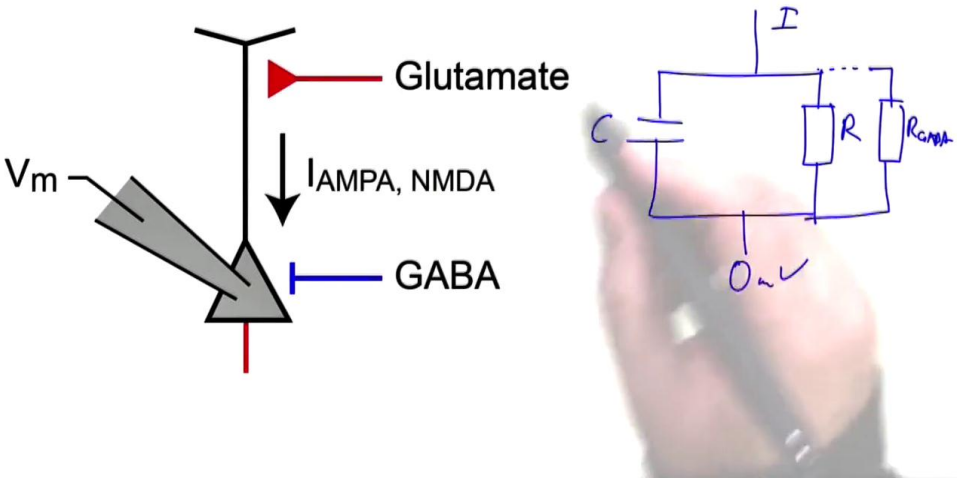
Notes

Summary

9m 06s

Shunting inhibition

The resting V_m is often close to the chloride reversal potential.
If $V_m = E_{Cl}$, then there is no flow of current and therefore no IPSP, but there is nonetheless a conductance, which changes the input resistance.



Cellular Mechanisms of Brain Function

We have current coming into the soma from the dendrites. That'll contribute to charging the membrane, the capacitance of the cell, and also, of course, some of that current will flow across the leak conductances that are present in the plasma membrane. That current, of course, in the end goes out into the extracellular space where there's zero mV potential by definition. So we have a capacitor of the soma, and we have resistance of the soma. What we can do with the GABAergic conducting send is to add on an additional conducting pathway here so the GABAergic conductor here can then be added and it changes the total resistance of the soma. By changing the so-called input resistance of the soma, that then changes the integrative properties of how currents flowing into that soma affect membrane potential. We can think about the equations that govern the membrane potential changes here that we've already dealt with in our previous weeks of study, so the potential here across the cell is equal to the current flow times the resistance, and then we have the time course for those changes that are the charging of the capacitor here and the membrane time constant is equal to the resistance times the capacitance.

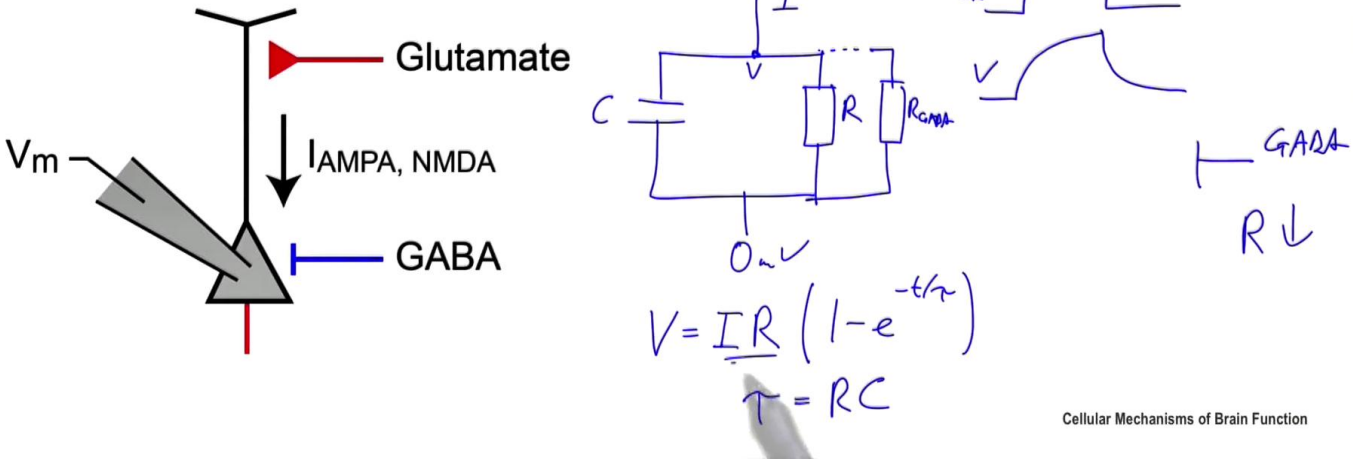
Notes

Summary

10m 36s

Shunting inhibition

The resting V_m is often close to the chloride reversal potential.
If $V_m = E_{Cl}$, then there is no flow of current and therefore no IPSP, but there is nonetheless a conductance, which changes the input resistance.



That's the exponential charging function here. So if we have a square current pulse flowing into the cell soma, that causes a change of membrane potential, a charging of the capacitor. You turn the current off and the capacitor discharges, so this is the Current and this is the Voltage. Now, let's imagine that we put the GABAergic inhibition on. The change here is a decrease in the membrane resistance. We've added more conductance to the membrane of the soma. It's reversing the same as the resting membrane potential of the cell, so we can simply just think of it as a change in the resistance of the membrane. So we decrease the resistance of that membrane. That has two impacts, if we look at this equation here. The first is that the steady-state voltage is going to become less because that depends upon the input resistance of the cell, and the other impact is that the membrane time constant is going to change, it's going to decrease, so we've got a decrease in the membrane time constant, and if we now look at how the membrane potential would change, it's faster, so the overall time constant here is faster than it was, but also, the overall change in membrane potential is smaller.

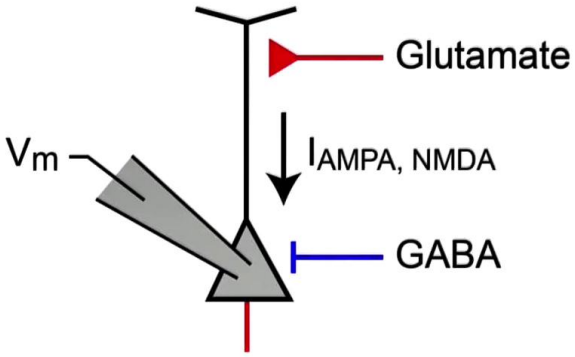
Notes

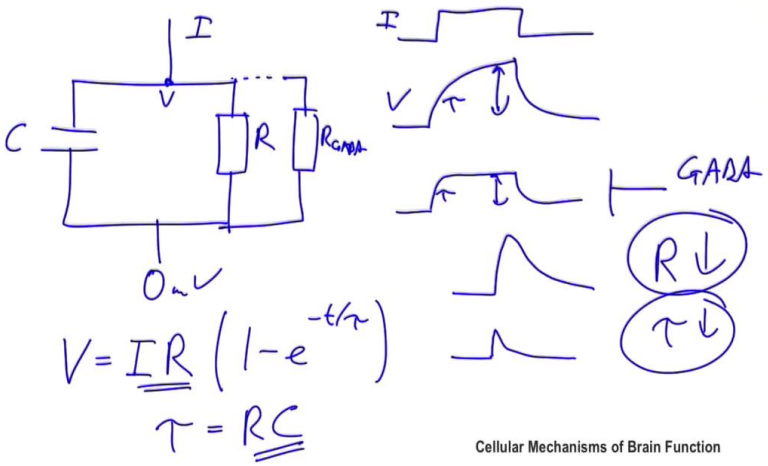
Summary

12m 11s

Shunting inhibition

The resting V_m is often close to the chloride reversal potential.
If $V_m = E_{Cl}$, then there is no flow of current and therefore no IPSP, but there is nonetheless a conductance, which changes the input resistance.





Cellular Mechanisms of Brain Function

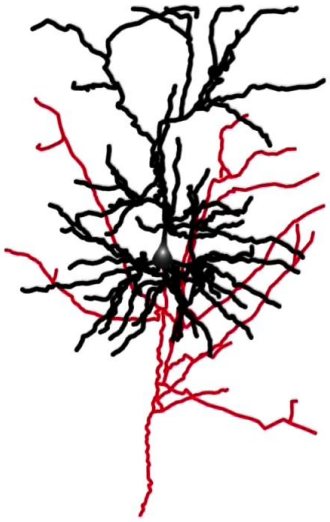
So by activating a GABAergic conductance, even if it's at the same membrane potential as the actual cell that we're recording from, and there's no inhibitory post-synaptic potential per se, that'll still cause an inhibitiion of excitatory glutamatergic inputs coming in, so here we thought about steady state injections of currents, but we'll have the same situation if we think about glutamatergic inputs coming in, brief currents, where if we have at resting conditions an EPSP that looks like this, then we turn on the GABAergic conductance and the EPSP gets smaller, and also a bit faster, because we've changed the membrane time constant and the input resistance of the cell soma. So shunting inhibition is another important form of inhibition in addition to the hyperpolarizing inhibition mediated by charge flowing through the GABA receptor.

Notes

Summary

13m 36s

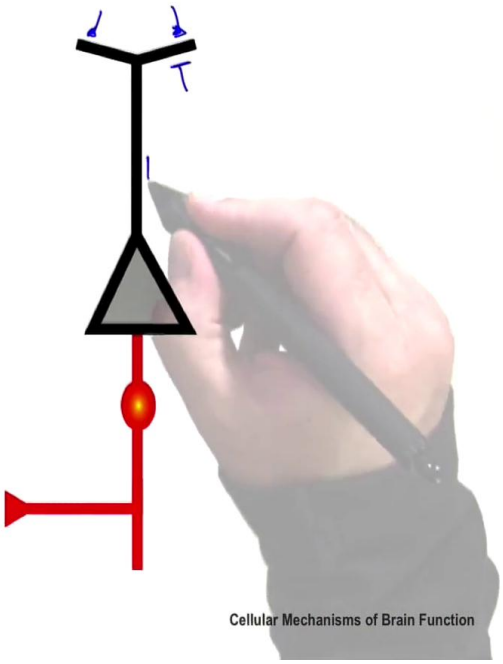
Target structures of GABAergic inhibition



Dendrites

Soma

Axon (AIS)



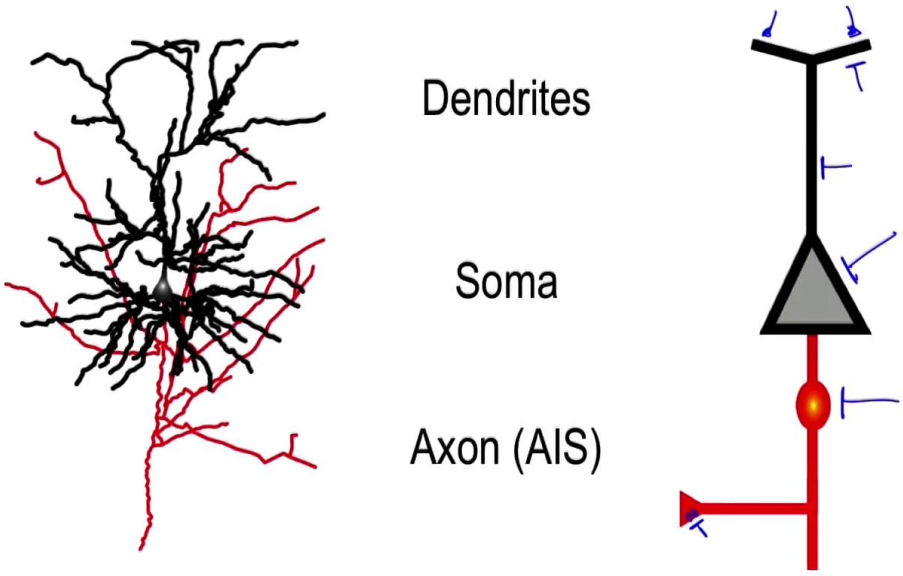
Now, GABAergic synapses are made on a large variety of subcellular compartments. GABAergic inhibition can occur here on the distal dendrites, so we have GABAergic input right here in the distal dendritic operizations, and presumably, a GABAergic input here will have a large effect upon the nearby excitatory synapses coming in here, but might not affect GABAergic synapses occurring on other dendritic branches. There might be specific inhibition that's localized to individual dendritic arborizations. So there could be a high degree of spatial specificity as to where the GABAergic inhibition might function. There are also GABAergic inhibitory synapses all over the basal and more proximal dendrites, and interestingly, there are also GABAergic synapses that are directly placed on the soma, and that's something that you won't find usually for excited glutamatergic synapses that are sitting on the dendrites, but not on the soma, so GABAergic inhibition is different and prominent on the cell bodies, where it could affect the input resistance and the integration of the synaptic current flowing in from the dendrites in this divisive way, by changing the input resistance of the cell soma.

Notes

Summary

14m 39s

Target structures of GABAergic inhibition



Cellular Mechanisms of Brain Function

Interestingly, there are also GABAergic synapses directly on the axon initial segment. Again, there are no excitatory synapses in this area, but inhibitory synapses are prominent here at this site, where action potentials are initiated in most cells. In GABAergic inhibition, then might not affect dendritic integration at all, but might simply form an editing function where it decides whether a cell can output an action potential or not, independent of what synaptic computations are occurring in the rest of the cell. Then, finally, in the spinal cord, but not anywhere else in the mammalian brain, there are also GABA-A synapses directly here on the pre-synaptic specializations, and that only occurs in the spinal cord, but these synapses at other locations occur throughout the mammalian brain, and each one probably performs a slightly different function.

Notes

Summary

16m 03s

GABAergic synaptic conductances

- Synaptic $GABA_A$ conductances last ~10 ms, reversing ~-75 mV.
- $GABA_A$ synaptic input causes hyperpolarising inhibition when V_m is depolarised.
- $GABA_A$ synaptic input also causes shunting inhibition due to decreased membrane resistance.

Cellular Mechanisms of Brain Function

So in this video we've seen that the GABA-A conductance lasts some 10 to 20 ms and has a reversal potential somewhere around -75 mV, depending upon the local chloride concentrations. The GABA-A conductance can mediate inhibition in two slightly different ways, both of which, of course, depend upon the chloride conductance mediated by the ligand gated GABA-A receptor. The first one is hyperpolarizing inhibition. This occurs when the membrane potential is depolarized relative to the chloride reversal potential, and that's simply a movement then of chloride ions in negative charge inside the cell, causing a change in membrane potential. The other sort of inhibition relies upon a conductance, on a change in the input resistance of a cell, so even if the membrane potential is actually sitting at the same equilibrium potential as chloride, there can still be a significant impact upon the integration of excitatory inputs that ligend gated a chloride conductance will decrease the input resistance of the soma and the excitatory synaptic input that arrives at the soma then causes a smaller change in membrane potential if the GABA-A conductance is open.

Notes

Summary

17m 02s

GABAergic synaptic conductances

- Synaptic $GABA_A$ conductances last ~10 ms, reversing ~-75 mV.
- $GABA_A$ synaptic input causes hyperpolarising inhibition when V_m is depolarised.
- $GABA_A$ synaptic input also causes shunting inhibition due to decreased membrane resistance.

Cellular Mechanisms of Brain Function

So there are multiple different ways in which GABA can cause inhibition, and furthermore, it's complicated by the spatial distribution of the GABA-A input that'll presumably have many different effects depending upon where exactly the GABAergic synapses are activated. We'll learn more about the sub-cellular targeting of GABA synapses in subsequent videos.

Notes

Summary

18m 23s