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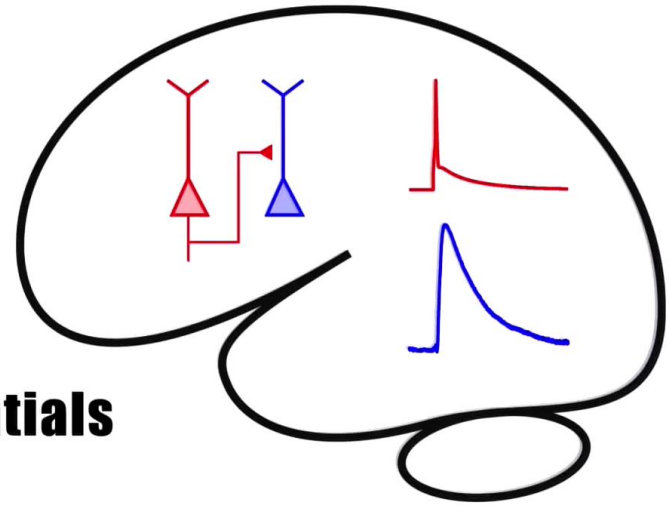
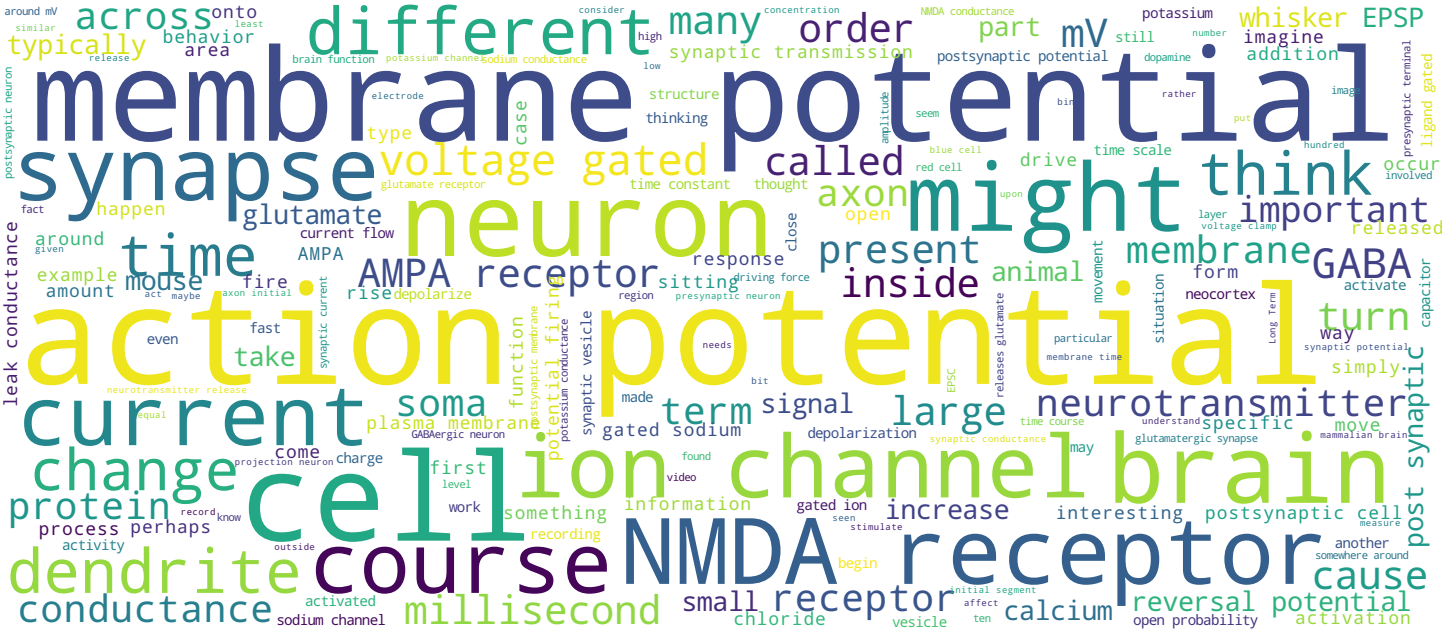


4.2 Postsynaptic potentials

Cellular Mechanisms of Brain Function

Prof. Carl Petersen

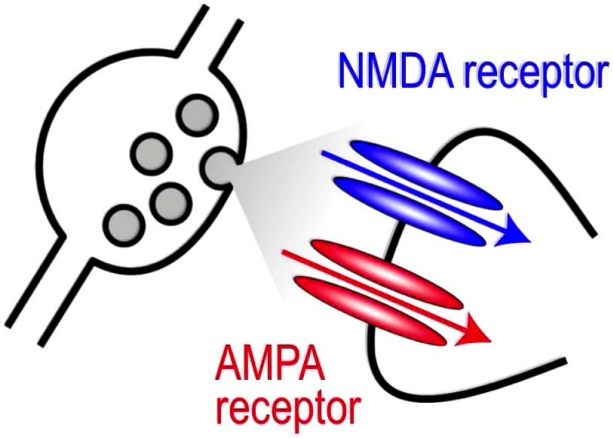


Search MOOC

Video

EPFL

Glutamatergic excitatory postsynaptic potentials



Cellular Mechanisms of Brain Function

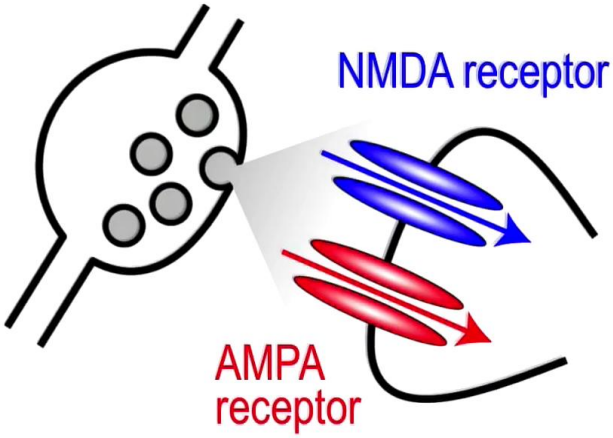
In the last video, we saw that there are two important major types of ligand-gated glutamate receptors. These are the receptors that are sitting in the postsynaptic membrane, and respond through the release of glutamate from presynaptic terminals. We explored the function of these ligand-gated ion channels in isolated patches of membrane, and found that there were two different types of glutamate receptors: the AMPA receptor, that was extremely fast, and the much slower NMDA receptors, that in addition were found to be voltage dependent. In this lesson we'll explore how these receptors function at real synapses, in situ, in the brain. These receptors are, of course, placed in the postsynaptic locations immediately adjacent to presynaptic release sites, so the action potential invading an axon, and a presynaptic nerve terminal, will cause release of glutamate from the presynaptic specialization, and that will act on the postsynaptically located receptors. And so now instead of considering what happens in response to a 1 millimolar pulse of glutamate for 1 millisecond, we'll consider the more physiological situation of where an action potential evokes release of glutamate, and that acts on these receptors present in the postsynaptic membrane.

Notes

Summary

0m 06s

Glutamatergic excitatory postsynaptic potentials



Cellular Mechanisms of Brain Function

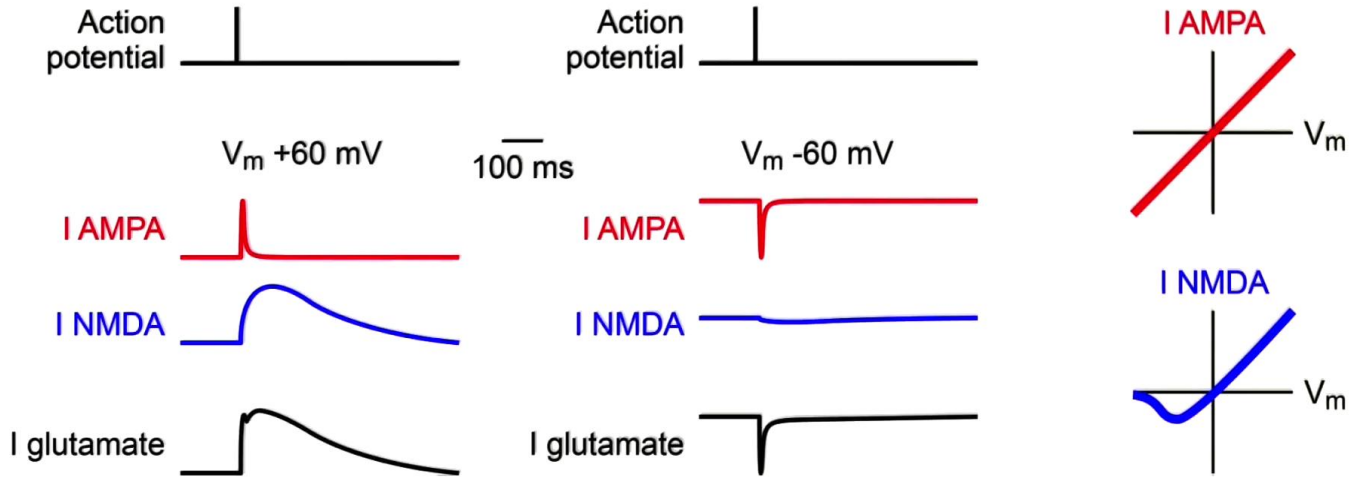
We'll also think about how the integration of those postsynaptic conductances occurs in the postsynaptic neuron, and how those conductances are changed into membrane potential changes that in their turn can effect the ligand-gated ion channels themselves, through the voltage-dependence of the NMDA receptor, and we'll also think about what happens in terms of dendritic integration, and how those potentials are filtered across the dendrites before they reach the final integration site in the soma and the axon initial segment.

Notes

Summary

1m 33s

EPSCs - excitatory postsynaptic currents



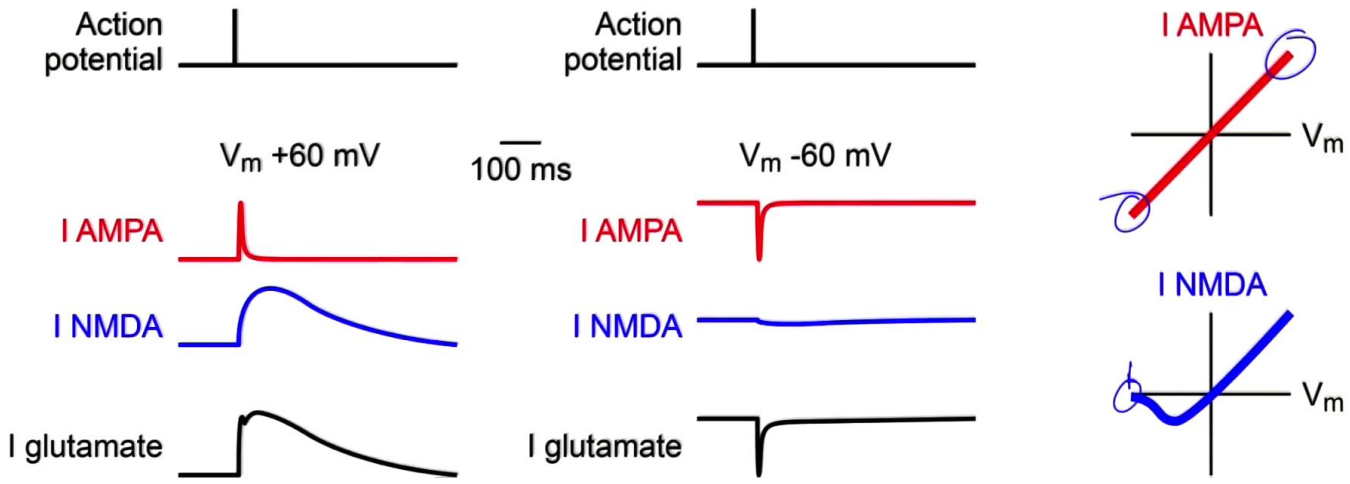
So here now we have a schematic drawing of what happens at a real synapse, where we're considering a presynaptic neuron, that fires an action potential, perhaps in response to a current injection in the experimental setting, and simultaneously, we're recording from a small, compact cell, that's voltage-clamped and synaptically connected to the presynaptic neuron. So the action potential invades the presynaptic nerve terminal, it releases glutamate, and with a short delay of around 1 millisecond, there's an activation of the postsynaptic glutamatergic currents. And at a negative membrane potential postsynaptically, the total synaptic current that's recorded here is brief, and fast, and it is almost entirely dominated by the AMPA component. AMPA receptors, just like the isolated patch measurements that we discussed in the previous video, give rise to short, 2 millisecond or so duration conductance changes that here are then measured through the voltage clamp amplifier in terms of a excitatory postsynaptic current. That's an EPSC, an excitatory postsynaptic current. The NMDA receptors are, however, largely blocked at negative potentials.

Notes

Summary

2m 08s

EPSCs - excitatory postsynaptic currents



Cellular Mechanisms of Brain Function

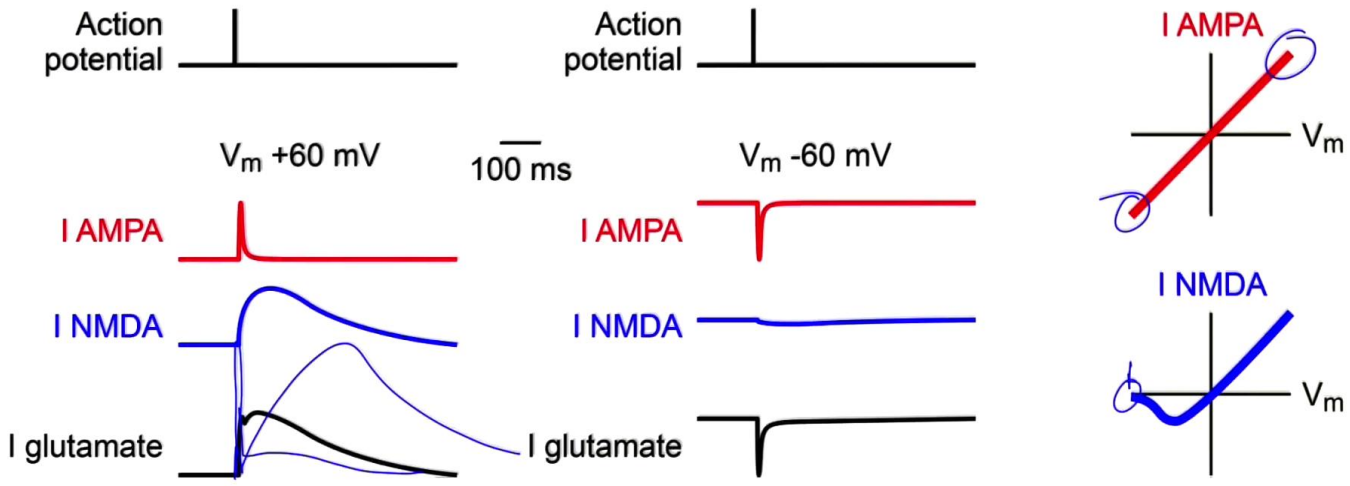
The magnesium ions from the extracellular solution enter the NMDA receptor, and block it at negative potentials. And so at typical resting membrane potentials of a neuron, somewhere around -60 mV, the NMDA conductance is basically shut. The AMPA conductance is large, and the total excitatory postsynaptic current, the EPSC, has this fast kinetics, dominated by the AMPA receptor. If we now change the postsynaptic membrane potential, still in voltage clamp mode, so now we voltage clamp our small, compact neuron to be at +60 mV, the AMPA receptor looks as before, except now, of course, the current is outward, rather than inward, we're sitting over here, reversal potential for AMPA and NMDA receptors is close to 0 mV, so the amplitude and kinetics of the AMPA receptor are similar, but now the NMDA channels can contribute. Magnesium has been expelled from the ion channel pore, it no longer blocks, and we get a considerable current flowing through the NMDA receptor, and it's the summation of these two that give rise to the total EPSC recorded at positive potentials. A fast AMPA component, and a slower, longer-lasting NMDA component. Now different synapses have very different ratios of AMPA and NMDA receptors that are present.

Notes

Summary

3m 32s

EPSCs - excitatory postsynaptic currents



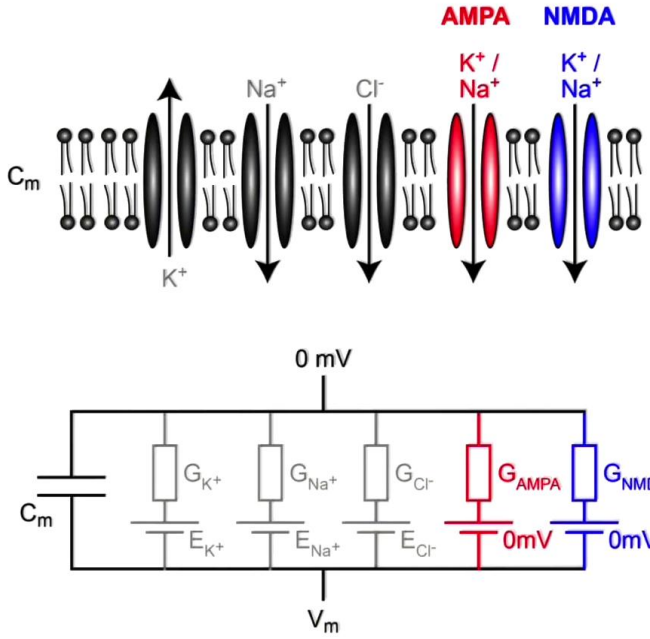
Some synapses are almost entirely dominated by AMPA receptors, whereas other synapses are almost entirely dominated by NMDA receptors. But in most synapses, there's a fair mix, where both AMPA and NMDA receptors are present in roughly even quantities in terms of the total synaptic currents. And so although there are cases where there's a large AMPA, and just a very small NMDA, or small AMPA and very large NMDA, most of the time there's a mix, and both AMPA and NMDA contribute importantly at most glutamatergic synapses.

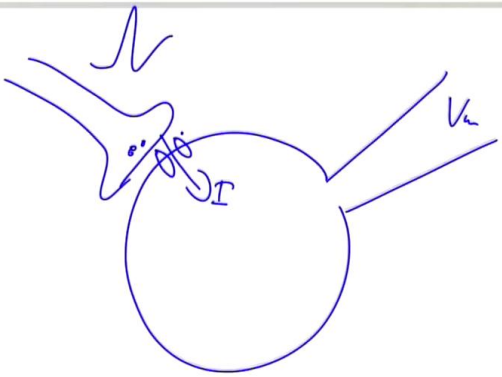
Notes

Summary

5m 02s

EPSPs - excitatory postsynaptic potentials





Cellular Mechanisms of Brain Function

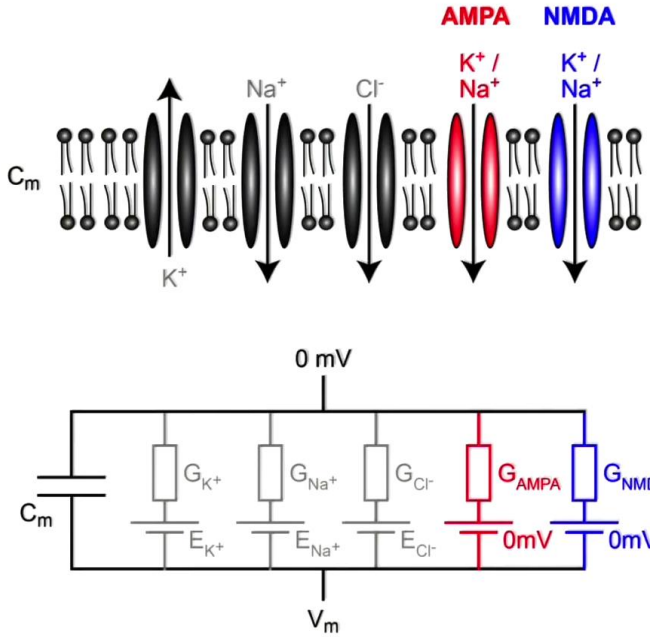
Now we'd like to know, in the physiological situation, where the postsynaptic membrane is *not* voltage clamped, but rather that the membrane potential is free to swing under the influence of these ionic channels that are present in the plasma membrane, how now do these postsynaptic conductances of the AMPA and the NMDA receptor interplay with membrane potential? And so we imagine that we have a membrane potential recording from a small, compact neuron that receives a glutamatergic input. The action potential comes down, the axon releases glutamate, and of course it activates the ion channels that are sitting here, the glutamate receptors, the AMPA and the NMDA receptors, and that of course causes then a current flow through the AMPA and NMDA receptors. And we've already considered the relationship between current flow and membrane potential in our electrical equivalence circuits, where we found that the phospholipid bilayer could be thought of as a capacitor, that we draw here, in the electrical equivalence circuit, and the individual ion channels, with their different ionic permeabilities, can be thought of as conductors, or resistors, alternatively, with a specific driving force relating to their reversal potential.

Notes

Summary

5m 43s

EPSPs



$$I_m = I_C + I_K + I_{Na} + I_{Cl} + I_{AMPA} + I_{NMDA}$$

$$I_C = C_m \cdot dV_m/dt \quad I = \dot{Q} = C\dot{V}$$

$$I_K = (V_m - E_K) \cdot G_K$$

$$I_{Na} = (V_m - E_{Na}) \cdot G_{Na}$$

$$I_{Cl} = (V_m - E_{Cl}) \cdot G_{Cl}$$

$$I_{AMPA} = V_m \cdot G_{AMPA}$$

$$I_{NMDA} = V_m \cdot G_{NMDA}$$

Cellular Mechanisms of Brain Function

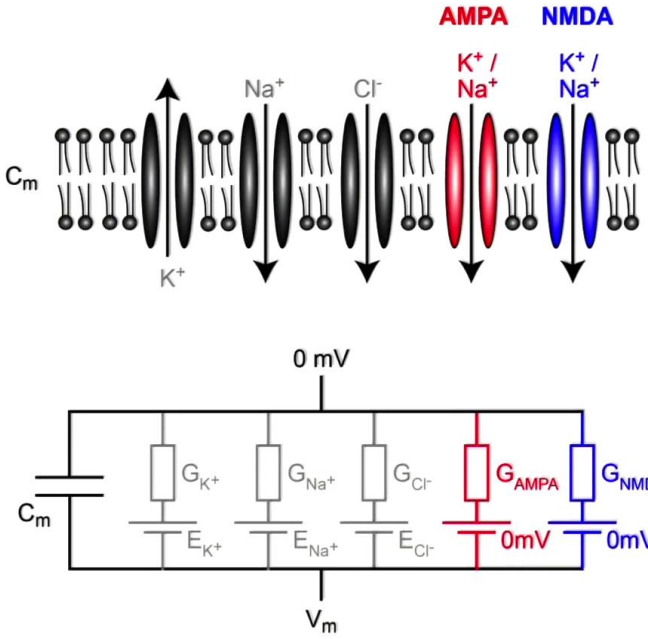
So we have potassium, sodium and chloride conductances, and now, for the synaptic conductances, we can add the AMPA and the NMDA conductances that have reversal potentials close to 0 mV, and that then are involved in determining the membrane potential of the cell. We also already know the quantitative description of how membrane potential and currents interrelate. So the total membrane current is made out of different components. There's the capacitative component, that's the filling on charging of the capacitor, that then relates to the change in membrane potential over time, so that's the typical equation here, from Q = CV, we take the derivative of that, and that then gives us that the current is equal to dVm/dt times the capacitance. We also have our various leak conductances relating to potassium, sodium and chloride conductances, that we can also just rewrite in a single term, here, that the leak is equal to the membrane potential, minus some leak potential, times the leak conductance overall, and the leak here is simply the resting membrane potential of the cell in the absence of synaptic conductances, and typically that's sitting at around -70 mV.

Notes

Summary

7m 03s

EPSPs



$$I_m = I_C + I_K + I_{Na} + I_{Cl} + I_{AMPA} + I_{NMDA}$$

$$I_C = C_m \cdot dV_m/dt \qquad I = \dot{Q} = C\dot{V}$$

$$I_K = (V_m - E_K) \cdot G_K$$

$$I_{Na} = (V_m - E_{Na}) \cdot G_{Na} \qquad I_{Leak} = (V_m - E_m) G_L$$

$$I_{Cl} = (V_m - E_{Cl}) \cdot G_{Cl}$$

$$I_{AMPA} = V_m \cdot G_{AMPA}$$

$$I_{NMDA} = V_m \cdot G_{NMDA} \left(V_m \right)$$

Cellular Mechanisms of Brain Function

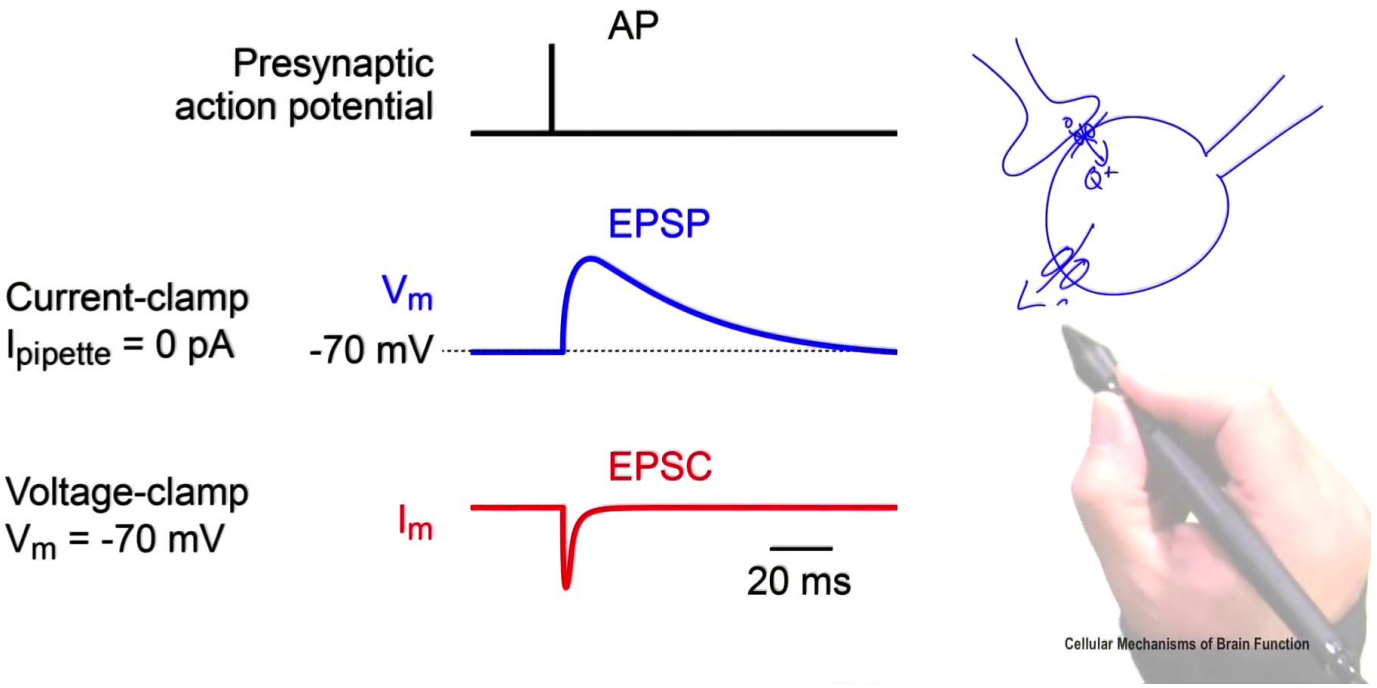
Now we also add the synaptic conductances here, and of course the current flow through each of these synaptic conductances relates to the driving force, or the membrane potential, the 0 mV reversal potential, so it's simply the membrane potential, times the conductance of the different channels. And of course for the NMDA conductance we also have to, in addition, think that this is actually voltage dependent, in addition, of course, to its dependence upon the presence of glutamate released from the presynaptic terminals. Now, importantly, when we think about these currents, and their relationship to voltage, we need to think about the charging and discharging of a capacitor. And so there's a big difference between the synaptic currents that are flowing, and the influence on the membrane potential, both in terms of how the leak conductances will determine how large that potential is, postsynaptically, how large the EPSP is in response to a given conductance, and of course the membrane capacitance will also affect the kinetics of how those currents are translated into membrane potential changes.

Notes

Summary

8m 34s

EPSPs *vs* EPSCs



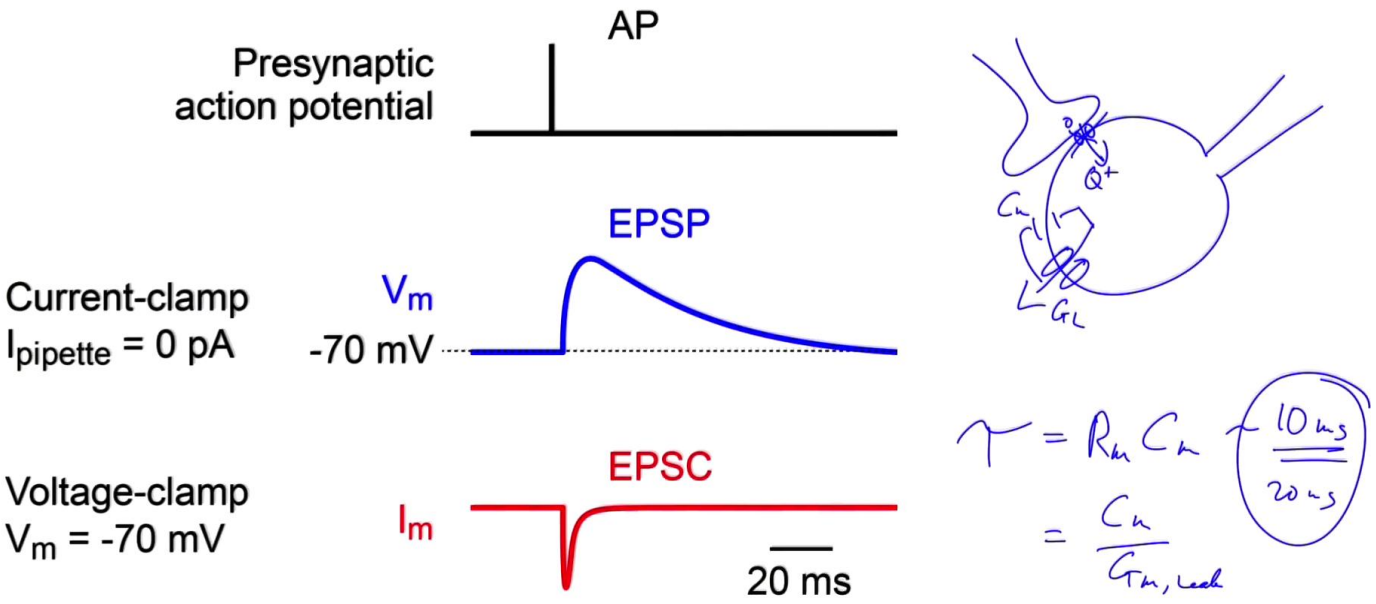
And so if we now try to directly compare, for the same synapse, the same conditions, presynaptic action potential gives rise to a fast EPSC. If we're talking about hyperpolarized conditions at -70 mV, we only need to think about AMPA receptors, the NMDA receptor is blocked, so we have these brief, transient AMPA conductances, lasting about 2 ms, and that then generates a 2 ms EPSC, the current follows the conductance in voltage clamp mode, and we see these rapid synaptic currents. Now in terms of the membrane potential, the situation is a bit more complicated. So we imagine, again, a synapse here, the release of glutamate. We have the synaptic currents that are, as stated here, about 2 ms in duration, then the conductance closes, and that is then closed, but there's still a lot of charge that entered during that EPSC. And the K phase of the EPSP is determined by how that charge then discharges the capacitor, and that is, of course, through the leak conductances. So we have the leak conductance here, we have our membrane capacitor here, and essentially the charging that occurs due to the EPSC, that causes the depolarization of the membrane, the decay phase of the EPSP, that's determined here through the leak conductance and the membrane capacitance.

Notes

Summary

9m 47s

EPSPs *vs* EPSCs



Cellular Mechanisms of Brain Function

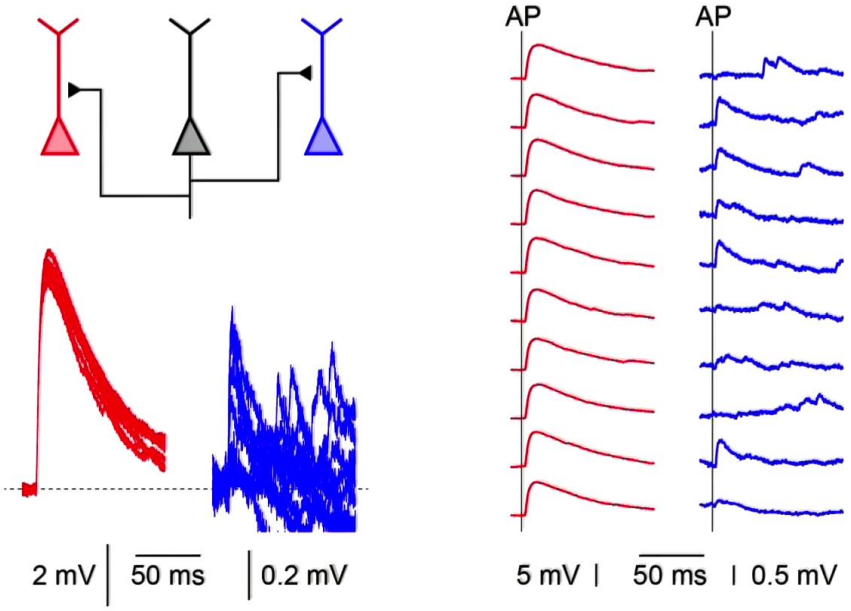
And you'll remember from our previous studies that there's a membrane time constant that is related here to the membrane resistance, times the membrane capacitance, and of course the membrane resistance here is simply 1 over the membrane conductance, or the leak conductance, if you like. And typically these membrane time constants are on the order of many tens of milliseconds, so it's somewhere 10, 20 ms in duration for the membrane time constants, And that's then the conversion factor, if you like, between the EPSC, which has this rapid time constant, and the EPSP, that's through the filtering here, the discharge properties of the membrane capacitor that has a built-in time constant sitting somewhere around 10 ms, and so there's a major difference in the time course between EPSCs and EPSPs, when EPSP is a much slower and longer-lasting event than the underlying conductance that drives it.

Notes

Summary

11m 24s

Unitary EPSPs



Lefort, Tomm, Sarria & Petersen, 2009

Cellular Mechanisms of Brain Function

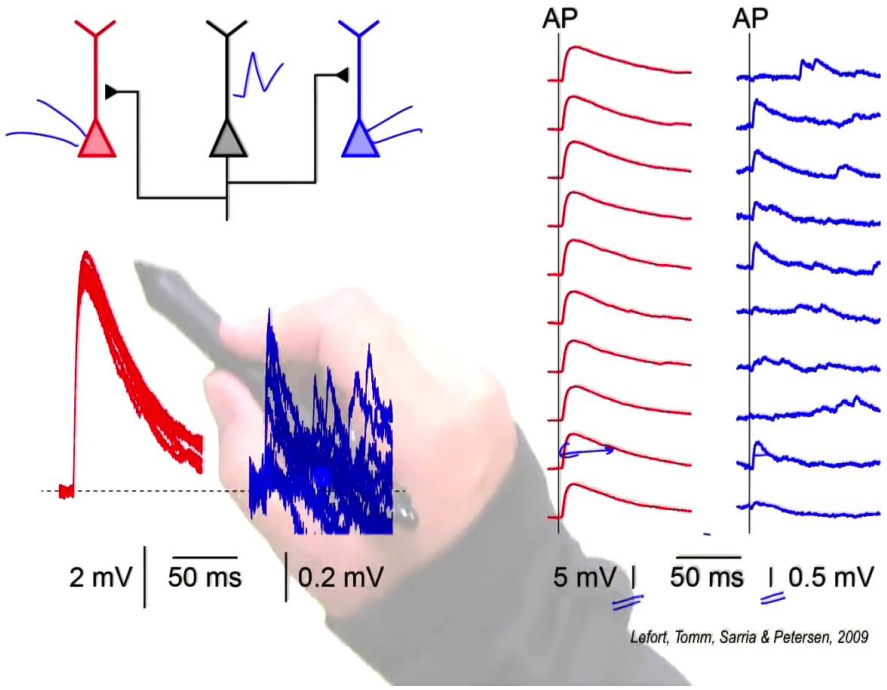
So far we've been looking at schematic example-type drawings of how EPSCs and EPSPs are. Now I'd like to look at real data, how synaptic transmission looks like in physiological conditions, at least in brain slice-type recordings. In this particular example, we're recording simultaneously from three different neurons. There's a presynaptic neuron that we stimulate to fire an action potential at a well-controlled point in time, and simultaneously we record from two postsynaptic neurons, a red neuron and a blue neuron, each of which is synaptically connected, and so the action potential here propogates down the axon, releases glutamate onto the red cell, and also simultaneously releases glutamate onto the blue cell. And it turns out that the properties of the postsynaptic potentials are really very different in this example, between these two cells, postsynaptically. These potentials can be thought of as unitary potentials, in the sense that a major and important unit of information in the brain is one cell firing a single action potential. And we then measure the so-called unitary postsynaptic potentials again in single cells, at the somatic location here, how the action potential of one neuron here influences the postsynaptic membrane potential of two other neurons.

Notes

Summary

12m 30s

Unitary EPSPs



Cellular Mechanisms of Brain Function

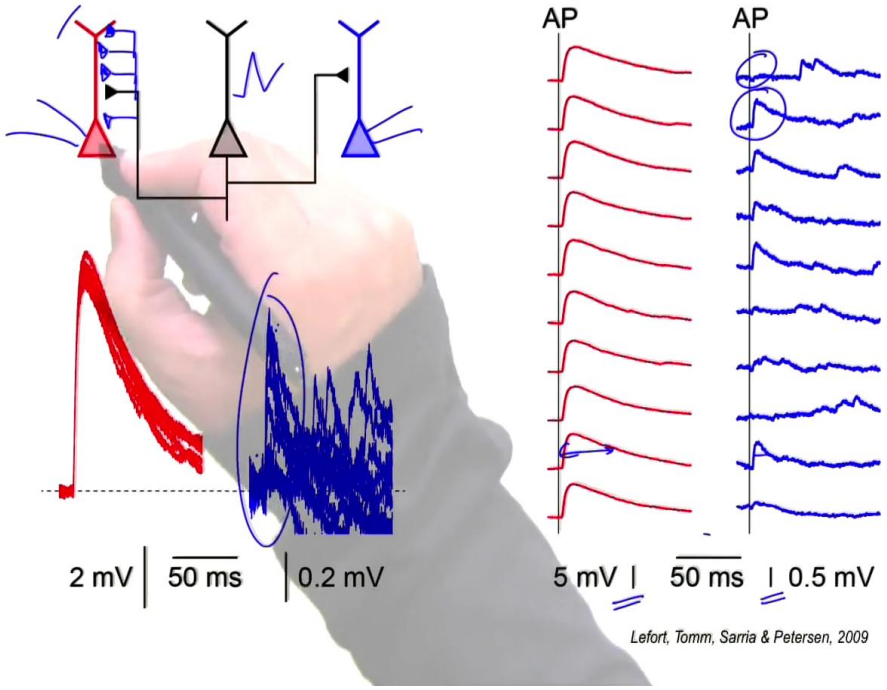
And in this particular example, an action potential in the black neuron induces a large depolarization in the red neuron, so let's look at the scale bar here. This is about 0.5 mV depolarization, lasting some tens of milliseconds in the red cell, whereas in the blue cell you'll see that the amplitude is much smaller, there's a different scale bar, it's about ten times smaller, and also the duration of the PSP in this case is also much faster, the decay time here is maybe 10 ms, whereas here maybe it's 30 ms, and so there are differences in the amplitude and the kinetics of the responses, and in addition there's also an obvious difference in the reproducibility, or the variability of the postsynaptic potential. Here we have ten consecutive trials, and action potential is evoked in each one, and in the red cell you see that there's a relatively constant depolarization that's measured. Here we superimpose those ten trials, and you see that it's almost the same postsynaptic depolarization we see in the red cell, whereas in the blue cell there seems to be enormous variability, sometimes there's a response, sometimes there isn't, and that corresponds to failures and successes, as we record here.

Notes

Summary

14m 09s

Unitary EPSPs



Cellular Mechanisms of Brain Function

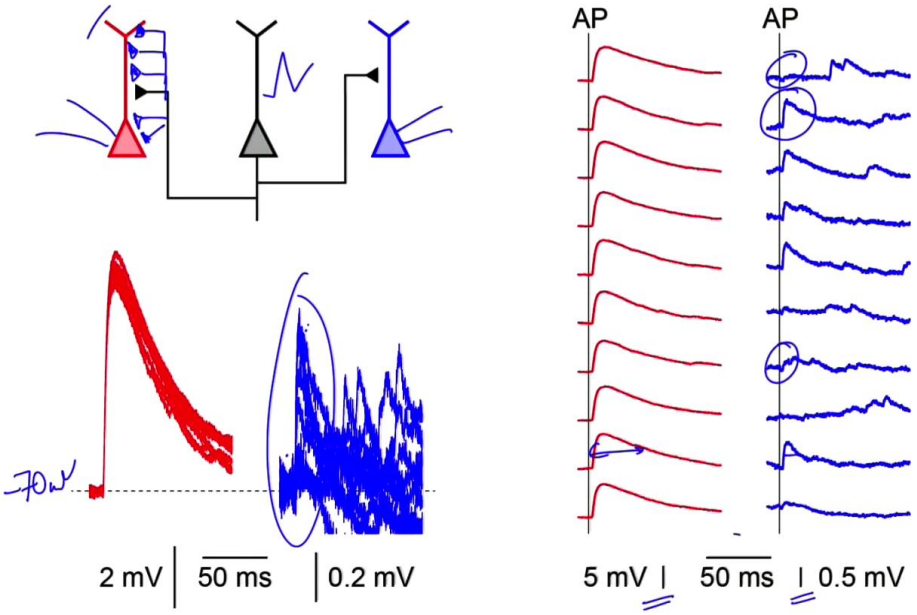
And we can envisage a sort of a simple explanation for why we might have this type of large-amplitude, reliable transmission, compared to this small-amplitude, unreliable synaptic transmission, and part of the reason for this explanation then might be that there's many different synapses here, that actually independently form release sites and postsynaptic contact sites between this single axon here. It might make multiple contacts, say it might make 10 different synapses, each of which can independently have released glutamate onto this red cell when an action potential is released, and that will then increase the amplitude of the response, and in addition decrease the variability, because all though these might be independently releasing glutamate or not, in the probabilistic manner of synaptic transmission, if we have 10 synapses, then the chance that some of them will be releasing simultaneously, and the variance here will decrease, whereas for the blue cell, it really might be just a single synaptic contact, and then the action potential either causes release of a neurotransmitter or it doesn't, and then we can get this all-or-none type of synaptic transmission.

Notes

Summary

15m 28s

Unitary EPSPs



Lefort, Tomm, Sarria & Petersen, 2009

Cellular Mechanisms of Brain Function

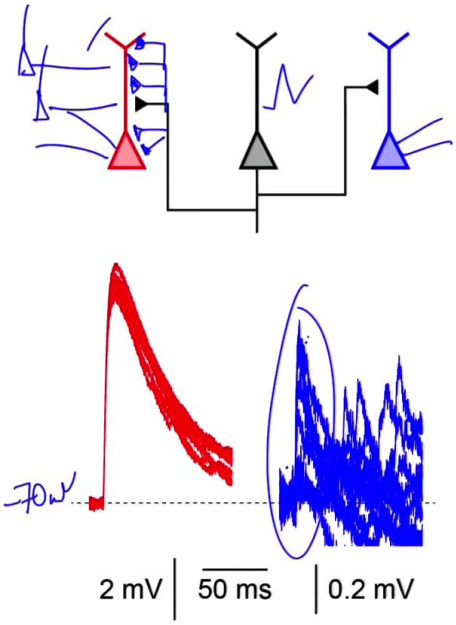
And of course there's also some smaller amplitude responses, and that might then correspond to vesicles that have less glutamate in them than other vesicles. So typically when we think about synaptic transmission in the brain, there are small-amplitude PSPs, and even this one, which is amongst the larger that are seen at most synapses. This is still a small depolarization, compared to what's needed in order to fire an action potential. So here the postsynaptic cell might be at -70 mV, we get a 5 mV depolarization, but we're still more than 20 mV away from action potential threshold, and so unitary inputs onto most cells don't cause postsynaptic action potential firing. And what you need in order to get action potentials fired in postsynaptic cells are perhaps inputs from many cells around it, that all provide input, perhaps at the same time, onto the postsynaptic cell, so that you can get a larger degree of summation, and then you can cross action potential thresholds, and fire.

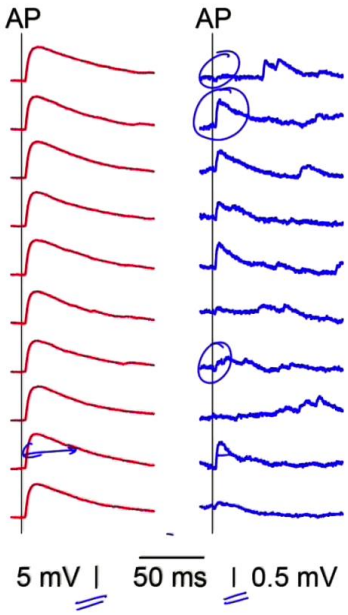
Notes

Summary

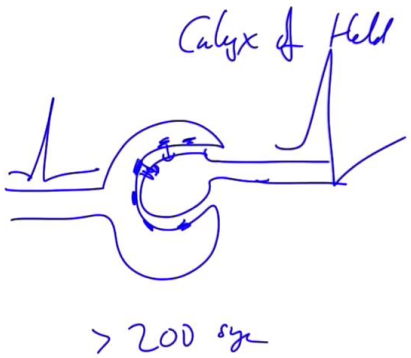
16m 48s

Unitary EPSPs





Lefort, Tomm, Sarria & Petersen, 2009



Cellular Mechanisms of Brain Function

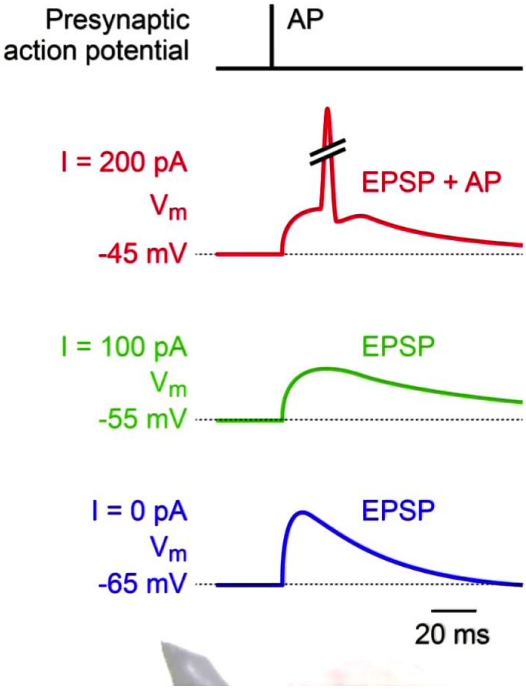
Although this is the most common situation, where we have relatively small unitary EPSPs, on the range of a few millivolts, lasting a few tens of milliseconds, there are other examples in the brain, and one important one that's studied, in much detail, is the so-called *Calyx of Held* synapse, where an individual axon comes and envelops the postsynaptic cell, and has really a large number of release sites present in it, maybe some 200 or more synapses, and because the action potential comes in, and it then releases glutamate onto the postsynaptic cell, which has many receptors, this then causes automatically an action potential to fire in the postsynaptic neuron, and so there are cases where an action potential is converted into an action potential in the postsynaptic cell through a large number of synaptic connections, like, for example, here in the Calyx of Held, an example from the auditory brain stem. But for most synapses in the brain we need to think about small depolarizations, lasting relatively short amounts of time, and that these potentials need to be integrated, postsynaptically, in order to have further processing of information in the brain.

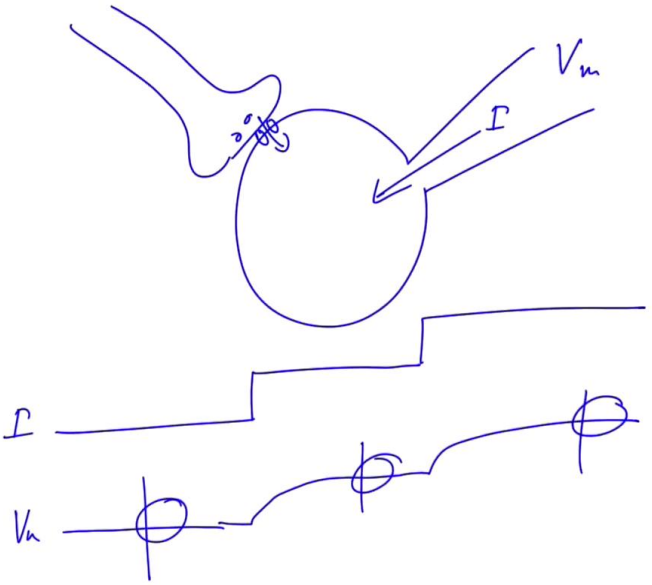
Notes

Summary

17m 56s

Postsynaptic voltage-dependence of EPSPs





Cellular Mechanisms of Brain Function

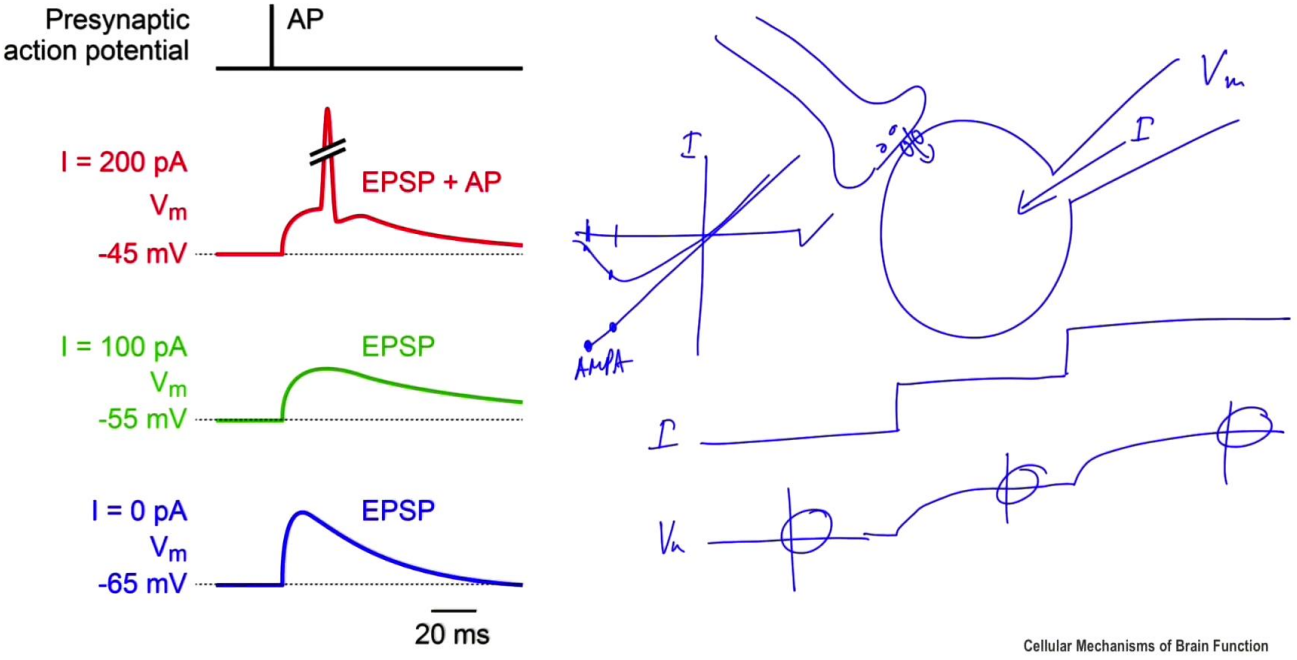
We can begin to explore this process of postsynaptic integration artificially, at first, by thinking about what happens as we simply depolarize the postsynaptic cell. And so we can imagine having a recording electrode sitting on a cell, that's receiving a synaptic input, glutamate is being released, opening AMPA and NMJ receptors, and we're measuring the membrane potential of the cell. And in addition to measuring the membrane potential of the cell, we can also use this electrode to inject current. And so we can inject 0 pA of current, in which case we measure the membrane potential at rest, so this is the current being injected. We can inject some current, and that will then cause a filling of the membrane capacitance, a depolarization. We can depolarize, even inject more current, and cause further depolarization, and then we can, of course, stimulate the presynaptic cell at different time points, and see what happens to the PSP at different membrane potentials. And here are examples, schematic drawings of what might happen. At -65 mV the membrane potential is relatively hyperpolarized.

Notes

Summary

19m 24s

Postsynaptic voltage-dependence of EPSPs



Cellular Mechanisms of Brain Function

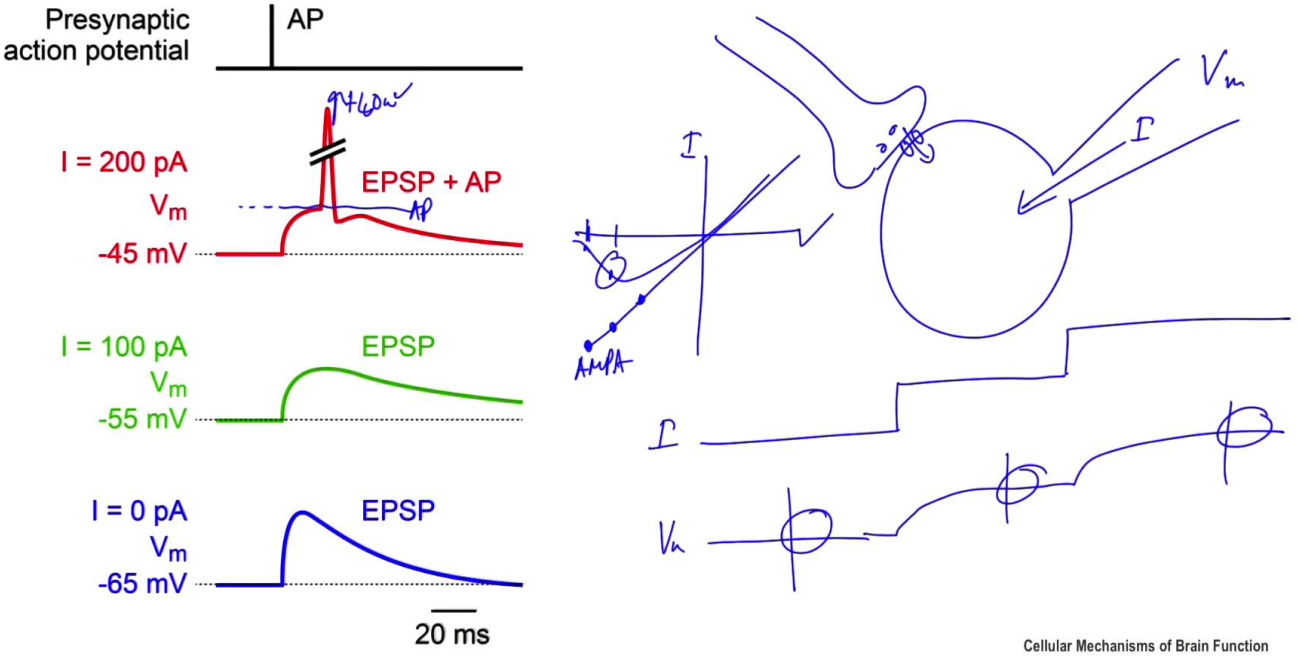
The NMDA receptors don't get activated, and so we have an AMPA-driven EPSP, the rapid 2 ms conductance of the AMPA receptor, and then the discharge of the membrane, through the membrane time course, discharging through the leak conductances. If we depolarize the postsynaptic cell, here by 10 mV, and it gives the same presynaptic action potential, same amount of glutamate is being released, same activation of AMPA receptors, but now, in addition, also perhaps some contribution of NMJ receptors, because we're depolarized a bit. And so there are now two different phenomena that are going on. If we think about our current voltage relationships, we've gone from having large currents, to having somewhat smaller currents, and so there might be a decrease in the amplitude of the EPSP. if we're just thinking about the AMPA component, but on the other side we have the NMJ component that might now be making a larger contribution. And so we can imagine that perhaps at slightly later times during the PSP the AMPA component is supplemented by an NMDA component, and the EPSP might have a slightly longer time course, and a smaller overall amplitude, because of the change in the driving force, that is also, of course, involved in helping the NMDA receptor get recruited.

Notes

Summary

20m 43s

Postsynaptic voltage-dependence of EPSPs



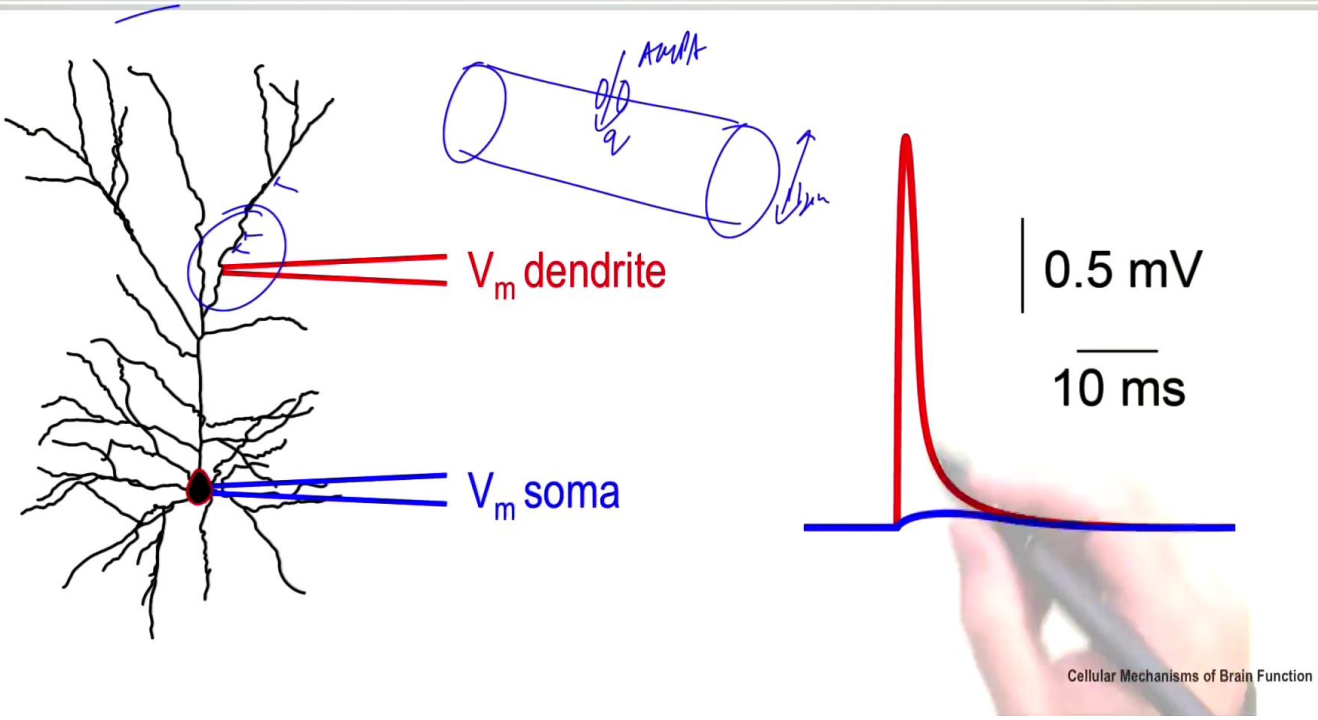
If we depolarize even further, there'll be a further drop in the amplitude of the response, because we're moving towards smaller and smaller currents, the driving force for the AMPA receptor has decreased, but we're, of course, much closer to AP threshold, and if we hit AP threshold, an action potential wlll be fired in the postsynaptic neuron, and the membrane potential will zoom up to something like +14 mV. And so you can see here that there are some relatively complex membrane potential dynamics that we need to think about. As we depolarize, the driving force gets smaller, but at the same time we're also recruiting more NMDA receptors, and so, again, depending upon how much NMDA receptors are present at the synapse, you can get quite different effects of depolarization at different synapses.

Notes

Summary

22m 11s

Dendrites



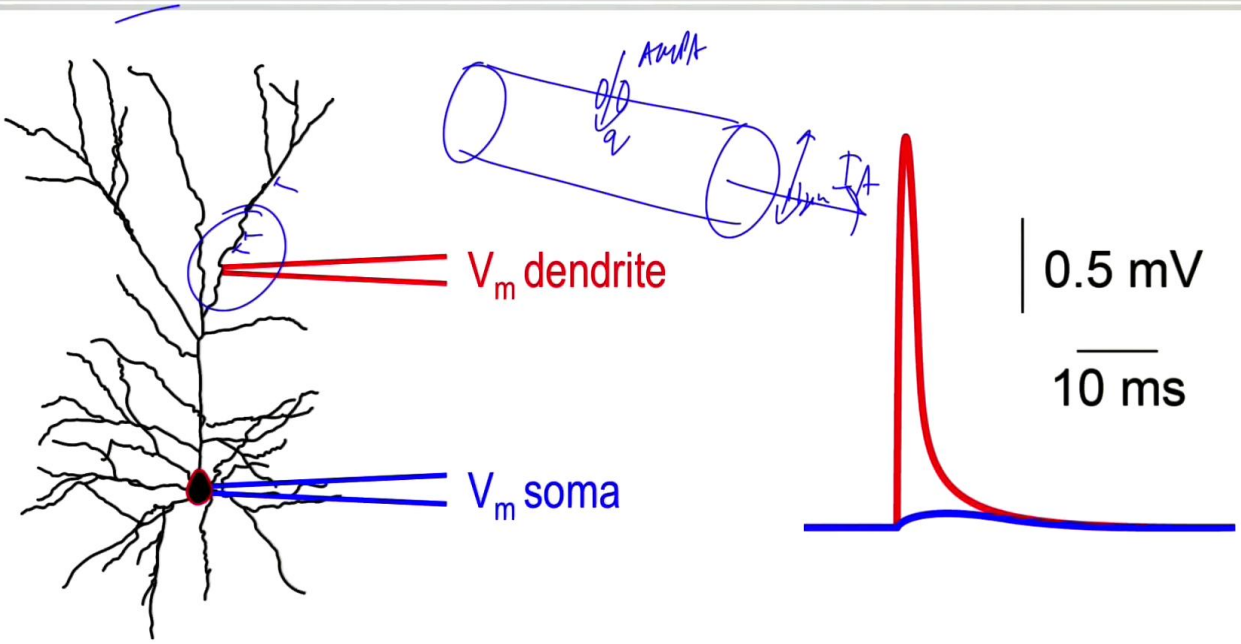
The situation is, in fact, much more complicated because these synapses that we've been talking about are typically distributed over the dendrites of a neuron, and so there will be glutamatergic inputs that are distributed all over the dendrites, and, in fact, relatively few synapses are present on the actual soma of a neuron, and so, typically, the input that arrives on a cell occurs on dendrites at electrotonically remote locations to the soma. And so if glutamate is coming in at synapses close to our recording site here, because there's relatively little membrane here, so these are small, the dendrites are something like 1 micrometer or so in diameter. And the opening of the AMPA and NMDA conductances here, then the charge that comes in here, will then cause a considerable change in the voltage, because there's relatively little membrane here that needs to get charged. And so you get large membrane potential changes here in dendritic areas, because of the small surface area, and these are also very fast in their time course, because the amount of membrane, again, here, is relatively low, and there's a rapid flow of current away from this, down the axial direction of these cables that are, ultimately, the dendrites that we're thinking about.

Notes

Summary

23m 03s

Dendrites



Cellular Mechanisms of Brain Function

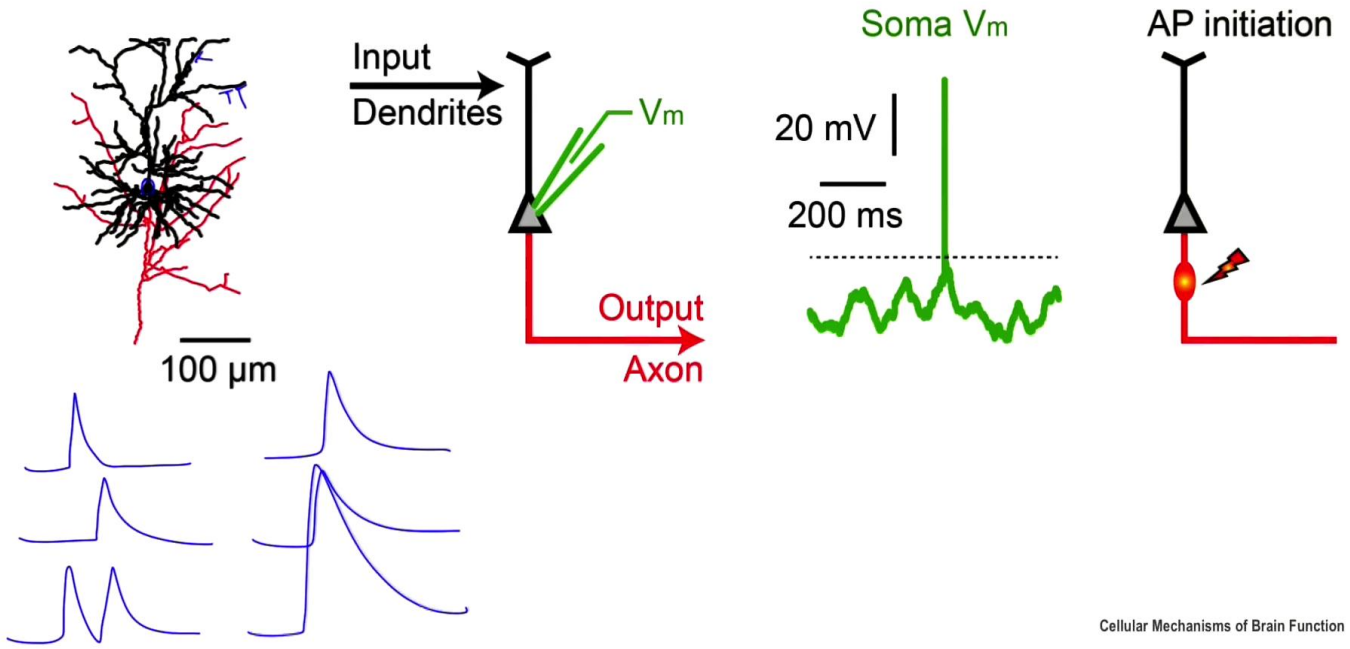
And so the membrane potential has these rapid, and large amplitude excursions, when synaptic conductances are opened, and those potentials, of course, spread passively down the dendrites, and are filtered, in time, because of the cable properties of the dendrites, and so what's ultimately seen at the soma is a much slower, and smaller amplitude version of this synaptic potential that's been recorded here in the dendrites.

Notes

Summary

24m 31s

Temporal and spatial summation of PSPs



Cellular Mechanisms of Brain Function

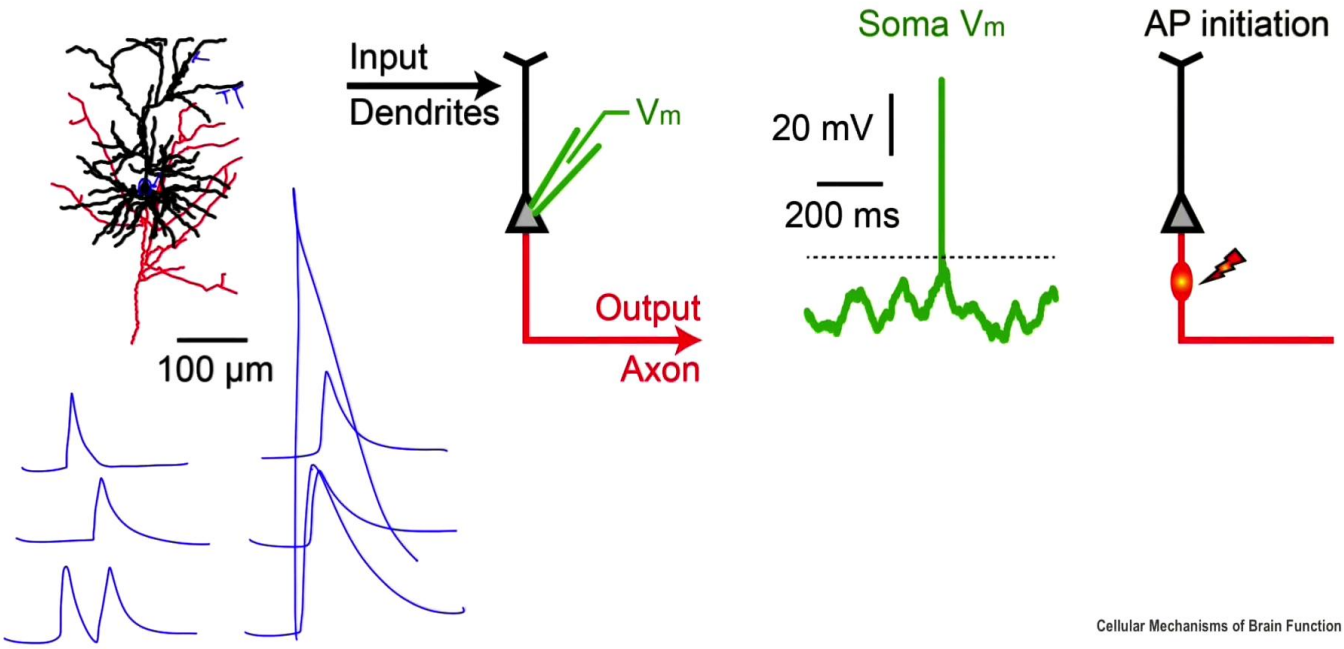
So this gives rise to even further complexity as to how synaptic integration occurs in real neurons. So if we have our cell body here, and there are synapses that are distributed across the dendritic arborization of the cell there will be a barrage of membrane potential fluctuations that occur, some of them at the same time, and others at different times, across the dendritic arborization. And if there are conductances that are synaptic inputs that come at slightly different times then they may not give rise to summation, but if, on the other hand, these synapses occur at the same time then of course you can get much larger depolarizations here, and so there's a summation process, and that summation process can take place also locally on dendrites, and that can even be very helpful, in terms of activating NMDA receptors. You'll remember that the NMDA receptor is blocked at hyperpolarized potentials, but, especially in these dendrites, where the individual synaptic events have large amplitudes, if you just have a few of them occurring more simultaneously we can get very large depolarizations in the dendrites that are likely to activate NMDA receptors extensively.

Notes

Summary

25m 00s

Temporal and spatial summation of PSPs



And so these distal areas here might be involved in communicating with the soma largely through activation of the voltage-gated NMDA receptors that might further drive voltage-gated sodium conductances. And so the process of dendritic integration, in both terms of time and space, is very complex, and there can be highly nonlinear phenomena going on in the dendrites, as well as, of course, there can be proximal inputs close to the soma that in themselves give rise to large potentials in the soma. And so what we typically see at the membrane potential level, at the soma is then the summated input of the synapses across the dendrites, and it's when the membrane potential at the soma, or more precisely at the axon initial segment, crosses the threshold, that an action potential is fired, giving rise to the output of that cell. So that's, in a sense, the essence of the neuronal computation, how you take these postsynaptic potentials, integrate them at the axon initial segment, and decide whether to fire an action potential, or not.

Notes

Summary

26m 24s

EPSPs – excitatory postsynaptic potentials

- Approximately 80% of synapses in the brain use glutamate.
- Glutamatergic EPSPs are driven by fast AMPA and slower, voltage-dependent NMDA conductances.
- EPSPs are larger and faster in dendrites, giving rise to smaller and slower EPSPs in the soma.
- For most cell-types, many uEPSPs must summate in order to reach action potential threshold.

Cellular Mechanisms of Brain Function

And so we've now begun to consider what happens at glutamatergic synapses in the brain. These glutamatergic synapses are very important to think about because they make up about 80% of all the synapses that are present in the brain, and so we absolutely need to understand how these work if we want to understand how the brain functions. The postsynaptic responses are composed of rapid AMPA conductances, and much slower, longer-lasting NMDA conductances that in addition have a voltage dependence to them. And it's that voltage dependence of the NMDA receptor that gives rise to complicated membrane potential dynamics. Individual, unitary PSPs that come into the soma are typically small in amplitude, they may be one or two millivolts in amplitude if you're lucky, and they last some tens of milliseconds. But typically they're not sufficient to drive postsynaptic action potential firing. For that we probably need the convergence of many tens or hundreds of presynaptic neurons, all to find action potentials with some degree of synchrony so that we can get this postsynaptic temporal integration on the time scale of the PSP, which is somewhere around 10 to 20 to 50 ms, depending again upon how much depolarization there is postsynaptically, and to what extent the slower NMDA receptors are being activated.

Notes

Summary

27m 36s

EPSPs – excitatory postsynaptic potentials

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Cellular Mechanisms of Brain Function

And so the total conversion of activation of postsynaptic conductances, downstream of an action potential in the presynaptic terminal, is a complicated phenomenon, and it's still something that's actively being investigated in research, in terms of how these dendritic inputs are integrated in real neurons during real behavior in the mammalian brain.

Notes

Summary

29m 07s