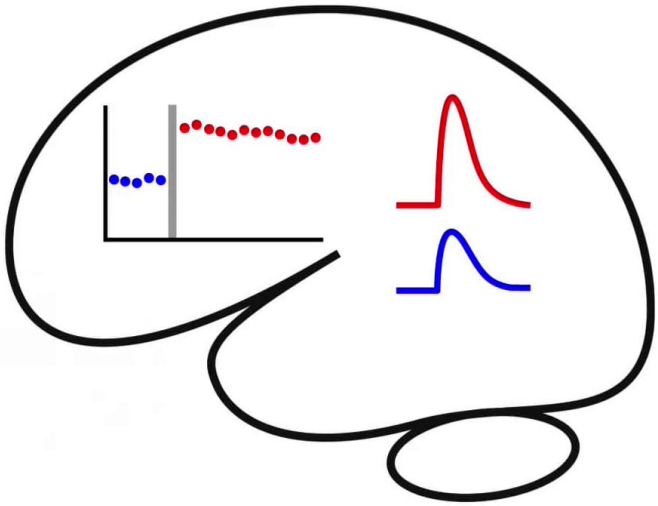
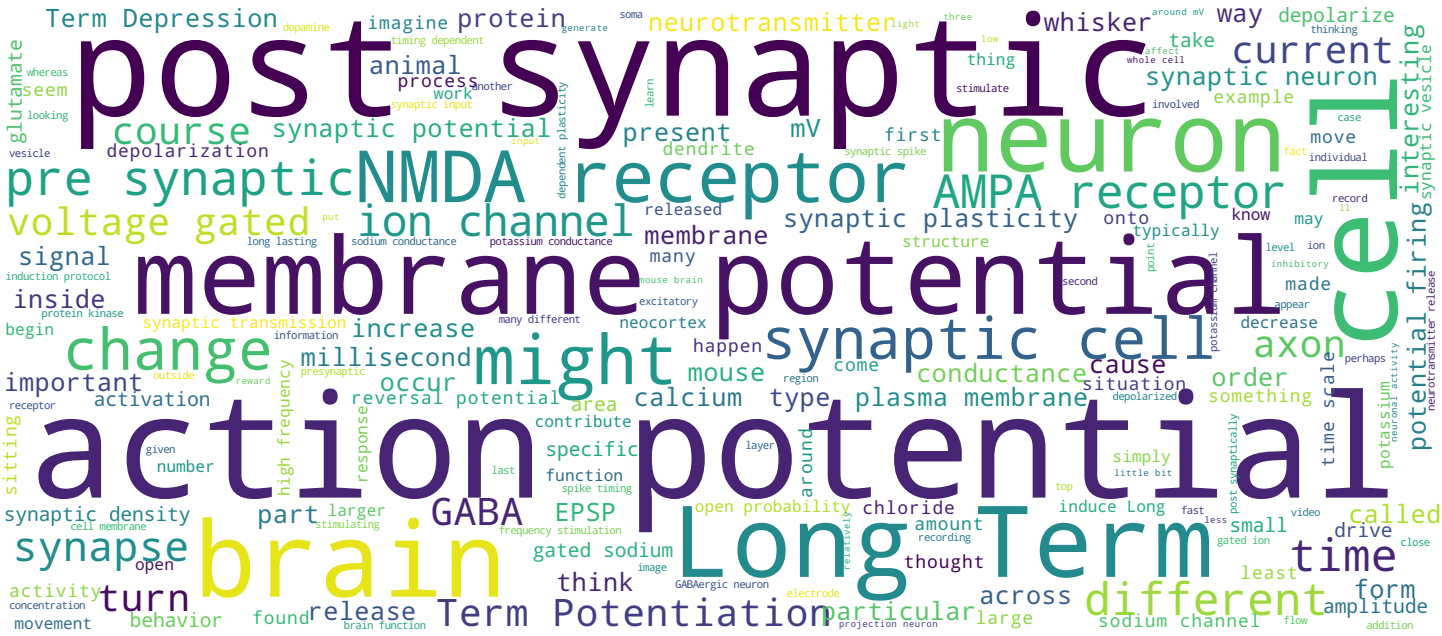
ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE



4.4 Synaptic plasticity

Cellular Mechanisms of Brain Function

Prof. Carl Petersen

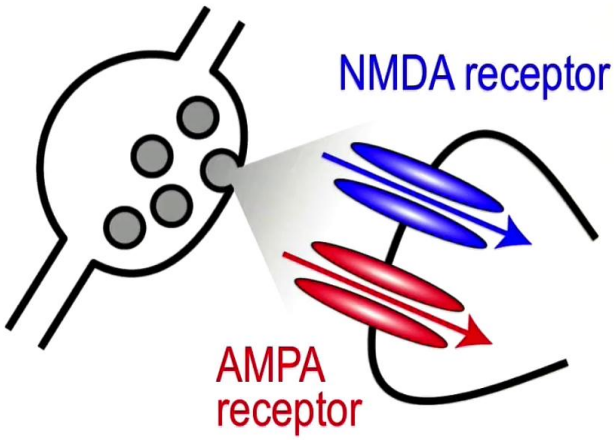


Search MOOC

Video

EPFL

Postsynaptic plasticity of glutamatergic synapses



Cellular Mechanisms of Brain Function

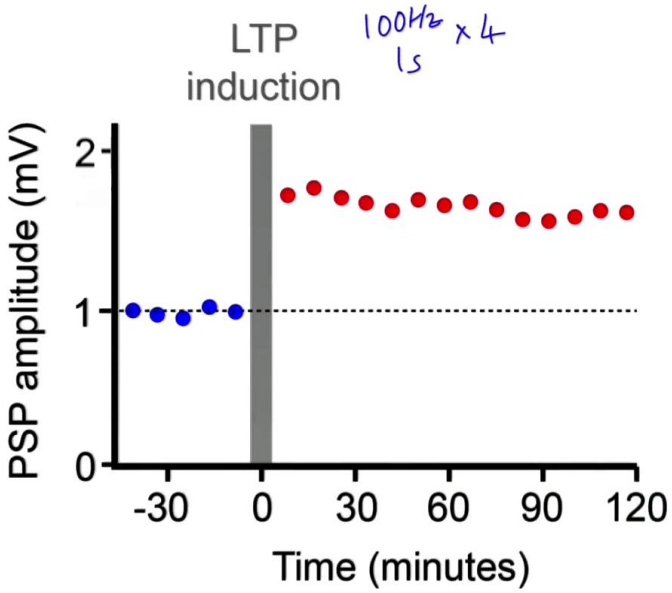
One of the most remarkable things about the brain is its ability to change in response to sensory experience. During development, sensory experience specifies how the neural circuits will wire in order to be able to process information in a sensible manner and throughout our lives, we learn through changing in the neural circuits inside the brain. The changes inside the brain are largely occurring at synapses, so-called *synaptic plasticity* changes how synapses function, and that's the topic of today's video. Much of the synaptic plasticity that takes place in the brain is so-called *post-synaptic plasticity* where there are changes in the receptor composition of the post-synaptic membrane at excitatory glutamatergic synapses. We've already discussed pre-synaptic plasticity, and that's the dominant form of plasticity on the millisecond and second time scale in the brain, but long-term forms of plasticity, the types of changes in the brain that might underlie memories that last for our lives, or at least for days, that is thought to largely occur through changes in the post-synaptic density. And that's what we'll focus on today. We'll think about changes that are largely driven by the NMDA receptor that induces synaptic plasticity and its changes in the AMPA receptor composition that largely underlie the long-term functional differences at synapses.

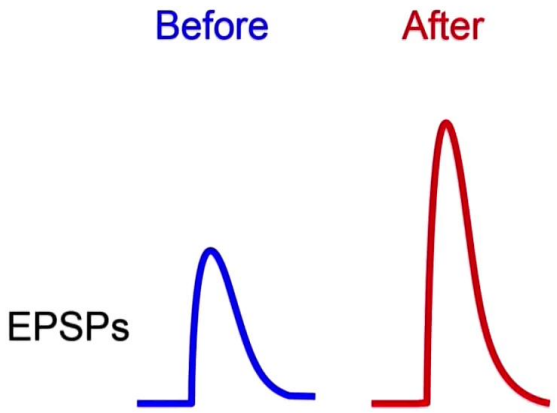
Notes

Summary

0m 05s

Long-term potentiation (LTP)





Cellular Mechanisms of Brain Function

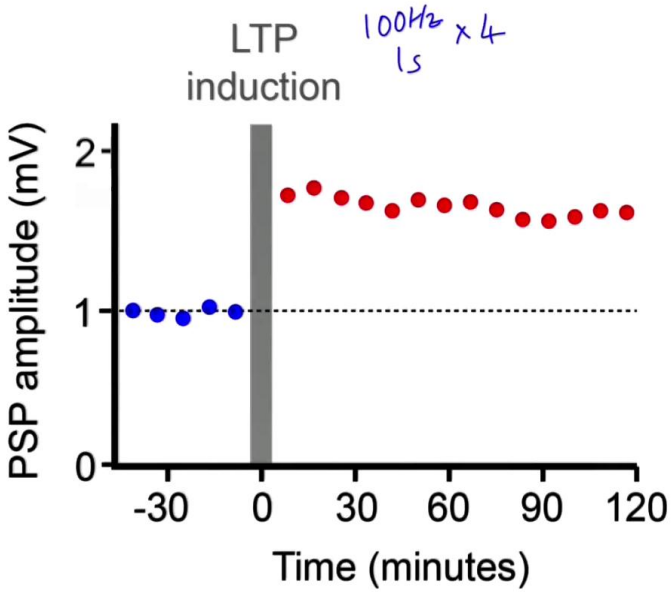
Bliss and Lomo discovered Long Term Potentiation in the hippocampus. They found that if they stimulated axonal fibers and recorded synaptic potentials in the hippocampus, they could evoke a stable baseline where each time they stimulated some fibers, they would get excitatory post-synaptic potentials, release of glutamate activating AMPA receptors, primarily. They then made a LTP induction protocol. LTP stands for Long Term Potentiation, and they did this through high frequency stimulation of the axons that they were stimulating, so they would stimulate axons, say, at 100 Hz for one second. That's a very typical protocol for inducing Long Term Potentiation. So they did that for one second, maybe a few times. You might want to repeat that 100Hz tetanic stimulation a few times, and then when they returned to stimulating as they'd been doing here during the baseline period, they found that the response amplitude had dramatically increased, and that's the phenomenon of Long Term Potentiation. That increase in the PSP amplitude can be very long-lasting. It can last, basically, for as long as you're able to record.

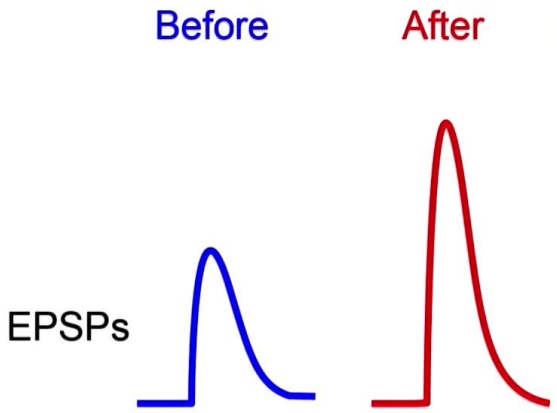
Notes

Summary

1m 50s

Long-term potentiation (LTP)





Cellular Mechanisms of Brain Function

In this case, we've plotted out two hours of recordings, but if you are able to record for much longer periods of time, these changes in synaptic efficacy can last for many days when recorded in vivo. So, this is a remarkable situation, where a brief change in the activity of the neural circuits can induce long-lasting and large changes in the fixing of synaptic transmission.

Notes

Summary

3m 21s

LTP induction

Experimentally, LTP is often induced by :

i) High frequency (100 Hz) stimulation of many axons
ii) Injecting depolarising current through whole-cell recording pipette during synaptic stimulation
iii) Pairing postsynaptic action potential firing with EPSP input

LTP induction requires :

i) NMDA receptor activation
ii) Postsynaptic cytosolic calcium increase
iii) Activation of protein kinases (CaMKII)

Cellular Mechanisms of Brain Function

How does that occur? Experimentally, you can induce Long Term Potentiation by a variety of ways. One of the most common ones, the one I just pointed out, is this high-frequency stimulation of many axons. You might put, for example, field stimulation electrodes where you might stimulate hundreds of axons at the same time. You stimulate these at high frequencies, and during that stimulation period where you stimulate every 10 milliseconds, what's happening post-synaptically is that you get EPSP's coming in. They summate, and often you get action potential firing coming in on top of this. So there's post-synaptic depolarization and often, action potential firing of the post-synaptic neurons. That's one of the most popular ways in which Long Term Potentiation can be induced. There are also other ways in which you can induce Long Term Potentiation where you don't change the way that you stimulate the pre-synaptic cells, and you just purely make post-synaptic changes. One way in which you can do that is in your whole cell recording electrode.

Notes

Summary

3m 55s

LTP induction

Experimentally, LTP is often induced by :

i) High frequency (100 Hz) stimulation of many axons
ii) Injecting depolarising current through whole-cell recording pipette during synaptic stimulation
iii) Pairing postsynaptic action potential firing with EPSP input

LTP induction requires :

i) NMDA receptor activation
ii) Postsynaptic cytosolic calcium increase
iii) Activation of protein kinases (CaMKII)

Cellular Mechanisms of Brain Function

If you're recording with a glass electrode the membrane potential of a cell, you can simply inject current and you can then, of course, depolarize the cell's membrane potential, so during a baseline period, the membrane potential of the cell might be sitting at, say, -70mV You get EPSP's driven here that are largely driven by the AMPA receptors. You can then depolarize the post-synaptic neuron. That then unblocks the NMDA receptor. You'll remember that there's a voltage dependent Mg block of the NMDA receptor. If you now have depolarized the cell and you gave the same stimulation to the pre-synaptic cell, you can now induce long-lasting NMDA currents. So, depolarizing the post-synaptic cell is another way in which you can induce Long Term Potentiation. And finally, you can also, again, it's a similar type of thing, you are also injecting currents, but here it's not a long-lasting depolarization, but you can simply inject brief currents to find action potentials in the post-synaptic neuron. If we are recording an EPSP, then we can make brief current injections in the post-synaptic cell to depolarize and find action potentials here during the actual EPSP that's occurring in the post-synaptic cell.

Notes

Summary

5m 10s

LTP induction

Experimentally, LTP is often induced by :

i) High frequency (100 Hz) stimulation of many axons
ii) Injecting depolarising current through whole-cell recording pipette during synaptic stimulation
iii) Pairing postsynaptic action potential firing with EPSP input

LTP induction requires :

i) NMDA receptor activation
ii) Postsynaptic cytosolic calcium increase
iii) Activation of protein kinases (CaMKII)

Cellular Mechanisms of Brain Function

So there are two ways here in which we can depolarize a cell. One is just simply just taking the membrane potential to depolarized potentials, and you may not meet any action potential firing. Another way is to get brief current pulses, find action potentials at the same time that an EPSP is arriving in the post-synaptic neuron. What all these different methodologies for inducing Long Term Potentiation have in common is that they induce activation of the NMDA receptor. That's the key event for most forms of post-synaptic Long Term Potentiation. We need to depolarize the cell, get the Mg out of the NMDA receptor, and what that then allows is for calcium influx to occur. You remember that AMPA receptors are not permeable to Ca, but the NMDA receptor, in addition to its interesting voltage dependence, also has Ca permeability so when we depolarize the cell either through high-frequency stimulation, injecting depolarizing current, or firing action potentials in the post-synaptic cell that unblocks the NMDA receptor. Glutamate is still bound to the NMDA receptor, and now, cytosolic Ca can increase in that post-synaptic area. That, in turn, causes activation of protein kinases.

Notes

Summary

6m 41s

LTP induction

Experimentally, LTP is often induced by :

i) High frequency (100 Hz) stimulation of many axons
ii) Injecting depolarising current through whole-cell recording pipette during synaptic stimulation
iii) Pairing postsynaptic action potential firing with EPSP input

LTP induction requires :

i) NMDA receptor activation
ii) Postsynaptic cytosolic calcium increase
iii) Activation of protein kinases (CaMKII)

Cellular Mechanisms of Brain Function

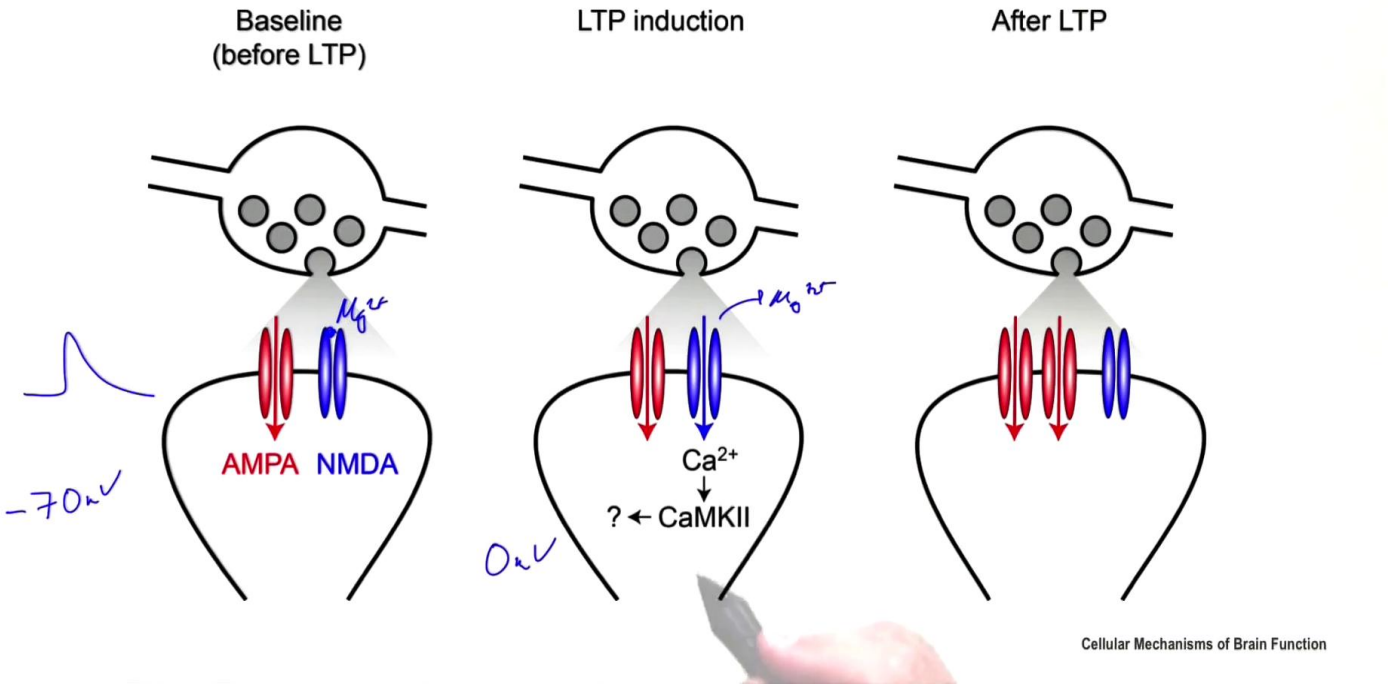
Many [cycling] molecules inside cells are sensitive to the cytosolic Ca ion concentration and at the post-synaptic density, there's a particularly high density of a Ca dependent protein kinase called *Calcium/calmodulin-dependent protein kinase II* or CaMKII, and activation of that molecule downstream of Ca increases is thought to be the most important signal that then, ultimately, leads to an increase in synaptic efficacy.

Notes

Summary

8m 03s

Postsynaptic mechanisms of LTP



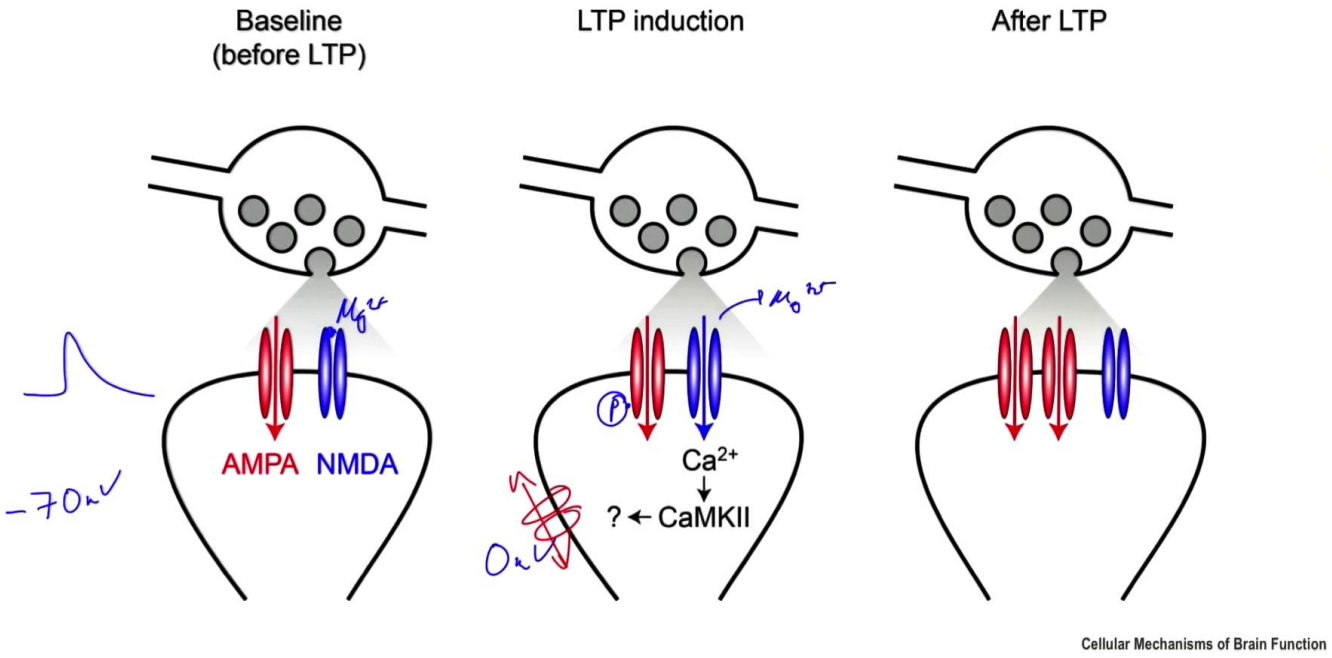
This is how we envisage the situation at the synapse. In the baseline situation action potentials will propagate down the axon, cause the release of neurotransmitter, glutamate from the pre-synaptic specialization, and that will largely activate AMPA receptors. We imagine here that under these baseline conditions, the membrane potential of the cell during rest is maybe around -70 mV. The NMDA receptor is blocked. There's Mg that's sitting here at negative potentials, and the released glutamate activates AMPA receptors, and that then gives rise to an excitatory post-synaptic potential. During the LTP induction protocol, we're depolarizing this post-synaptic neuron. Either because we're making high-frequency stimulation of many different axons, and so, the whole post-synaptic neuron is seeing a lot of glutamate across its entire dendritic operization, and thus depolarized, or because experimentally we've depolarized the membrane potential to, say, zero mV, which is a typical manipulation to do. That then gets the Mg out of the NMDA receptor so the Mg is now gone. The NMDA receptor can then contribute when glutamate is bound to the NMDA receptor.

Notes

Summary

8m 38s

Postsynaptic mechanisms of LTP



Cellular Mechanisms of Brain Function

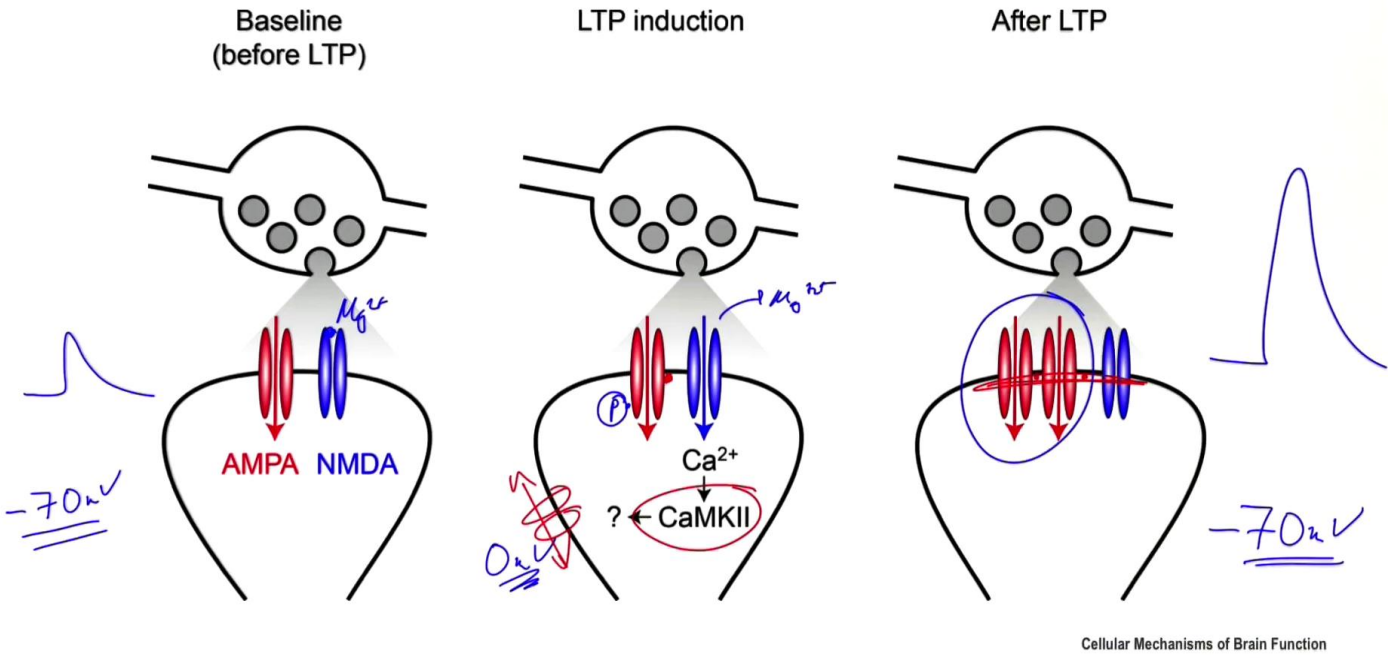
We're at these depolarized potentials and now Ca can flow in though the NMDA receptor and as mentioned, there's a high density of Calcium/calmodulin-dependent protein kinase II in this post-synaptic density region, and this kinase adds phosphate groups to a variety of different targets. One target is the AMPA receptor itself, so it can add a phosphate group onto the AMPA receptor and that seems to change the conductance of the AMPA receptor and make it larger, and that in itself might contribute to enhancing the amplitude of the post-synaptic potentials. However, what turns out to be the more important contribution to post-synaptic longterm plasticity is the recruitment of additional AMPA receptors onto the post-synaptic area. So AMPA receptors are actually floating around on the plasma membrane at many locations across the dendritic operization, and they're mobile. They diffuse in the two-dimensional plane of the plasma membrane. One of the things that seems to happen during Long Term Potentiation is the ability of the post-synaptic density to bind AMPA receptors and hold them tightly locked in place here at the post-synaptic density.

Notes

Summary

10m 04s

Postsynaptic mechanisms of LTP



Cellular Mechanisms of Brain Function

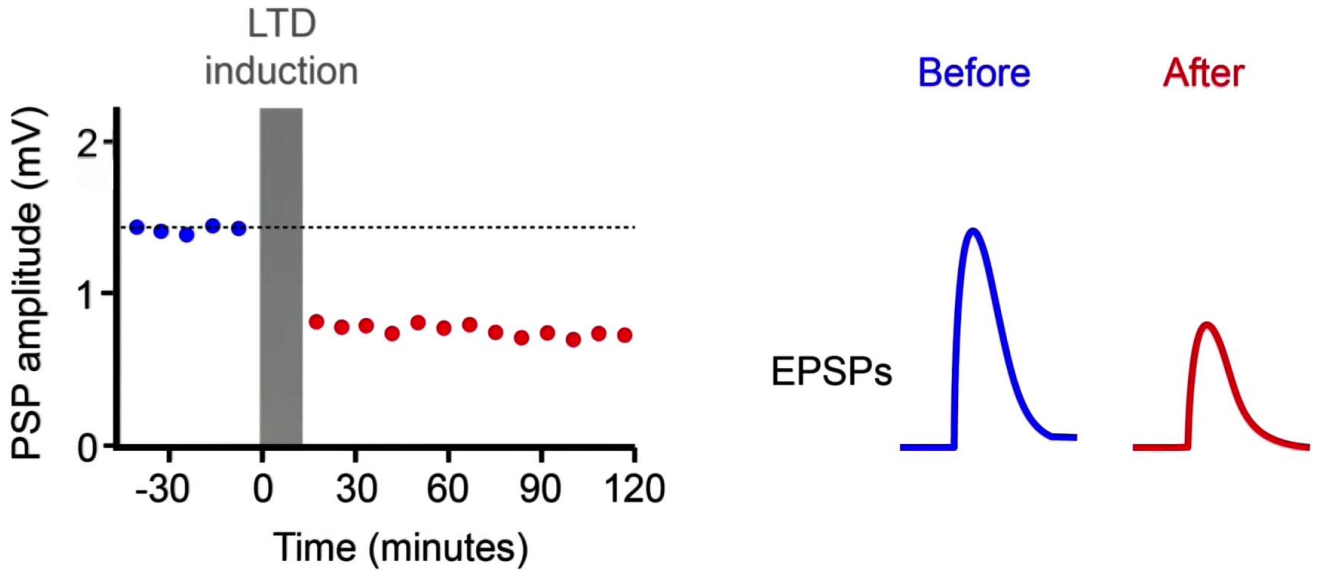
So, one of the major features that CaMKII is thought to do is to make more slots, as it were, binding partners here where AMPA receptors can bind tightly at this post-synaptic area here and you then simply recruit more AMPA receptors into the post-synaptic area, so whereas before we might have had ten AMPA receptors sitting in the post-synaptic density, after Long Term Potentiation, we might now have 20 AMPA receptors that have been driven in and bound here to the synapse through the activation of these cycling cascades downstream of Phosphorilation via CaMKII. The net result is that we have more AMPA receptors where we now return to the situation where we simply measure the potential, so we've done the LTP induction protocol, we depolarized here but only temporarily, while we were inducing synaptic plasticity. We then return to the same conditions as we had in our baseline recording period but now the post-synaptic potentials are much larger because we simply have more AMPA conductance at the present, post-synaptically.

Notes

Summary

11m 32s

Long-term depression (LTD)



Cellular Mechanisms of Brain Function

Now, if Long Term Potentiation were the only thing that went on in the brain, synapses would always get larger and larger, and that clearly isn't feasible, for all the synapses in the brain simply to grow. So it turns out that, luckily, there's a converse process called Long Term Depression that also takes place in the brain. Through the process of Long Term Depression the baseline synaptic efficacy, the post-synaptic potential amplitude can be made to grow smaller through a so-called Long Term Depression induction protocol. We start off with EPSP's that are relatively large in amplitude. We do the Long Term Depression induction protocol, and now, in a stable way across many hours or days, we can decrease the amplitude of these excitatory post-synaptic potentials.

Notes

Summary

12m 43s

LTD induction

Experimentally, LTD is often induced by :

i) Repetitive 1 Hz stimulation of many axons

ii) Injecting weak depolarising current through whole-cell recording pipette during synaptic stimulation

LTD induction requires :

i) NMDA receptor activation

ii) Activation of protein phosphatases (calcineurin)

LTD expression mechanism:

i) Calcineurin-mediated dephosphorylation of AMPA receptors

ii) AMPA receptors removed from synapse

Cellular Mechanisms of Brain Function

In order to induce Long Term Depression, typically, many axons are stimulated at an intermediate frequency of, say, 1 Hz so the baseline EPSP's might be stimulated with an interval of ten seconds, so we record baseline EPSP's. Then there's a period of stimulating at 1 Hz for many minutes, maybe for five or ten minutes, there's a constant 1 Hz stimulation of the same axons, and then we return to stimulating every ten seconds, and then it turns out that the EPSP amplitude has decreased in many different synapses across the brain. So, that's one way in which we can induce Long Term Depression, is through 1 Hz stimulation of many axons simultaneously. Another way of doing it is without changing the inter-stimulus interval of the pre-synaptic axons, but again just making post-synaptic manipulations where one can inject a weak depolarizing current through the whole cell recording pipette. So before, for Long Term Potentiation, we might have been depolarizing the cell to 0 mV, and then strongly unblocking the NMDA receptor In the induction of Long Term Depression, you might depolarize the cell, say, to -50 mV.

Notes

Summary

13m 44s

LTD induction

Experimentally, LTD is often induced by :

i) Repetitive 1 Hz stimulation of many axons

ii) Injecting weak depolarising current through whole-cell recording pipette during synaptic stimulation

LTD induction requires :

i) NMDA receptor activation

ii) Activation of protein phosphatases (calcineurin)

LTD expression mechanism:

i) Calcineurin-mediated dephosphorylation of AMPA receptors

ii) AMPA receptors removed from synapse

A sort of an intermediate situation where one might expect some degree of unblock of the NMDA receptors, but nowhere near as big an unblock of the NMDA receptor as you'd get at 0 mV. So the NMDA receptors are presumably partially activated, and indeed, many forms of Long Term Depression require an NMDA receptor activation, but it's at a smaller scale than for inducing Long Term Potentiation. Downstream of NMDA receptor activation, it's a little bit unclear what happens. Ca rises, or at least cytosolic Ca is required post-synaptically, but it's also possible that the NMDA receptor has additional cycling capabilities and it may be that protein-protein interactions between NMDA receptors and other cyclying proteins in the post-synaptic density are actually the ones that affect the expression of Long Term Depression. It's also known that the activation of protein phosphatases is essential for Long Term Depression, and in particular, the protein phosphatase cancineurin is essential for Long Term Depression. Phosphatases do the opposite of kinases, so a kinase adds a phosphate group to a protein, a phophatase does exactly the opposite: it'll take that phosphate away from the protein.

Notes

Summary

15m 21s

LTD induction

Experimentally, LTD is often induced by :

i) Repetitive 1 Hz stimulation of many axons

ii) Injecting weak depolarising current through whole-cell recording pipette during synaptic stimulation

LTD induction requires :

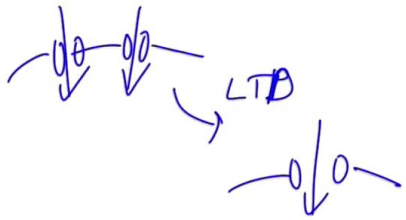
i) NMDA receptor activation

ii) Activation of protein phosphatases (calcineurin)

LTD expression mechanism:

i) Calcineurin-mediated dephosphorylation of AMPA receptors

ii) AMPA receptors removed from synapse



Cellular Mechanisms of Brain Function

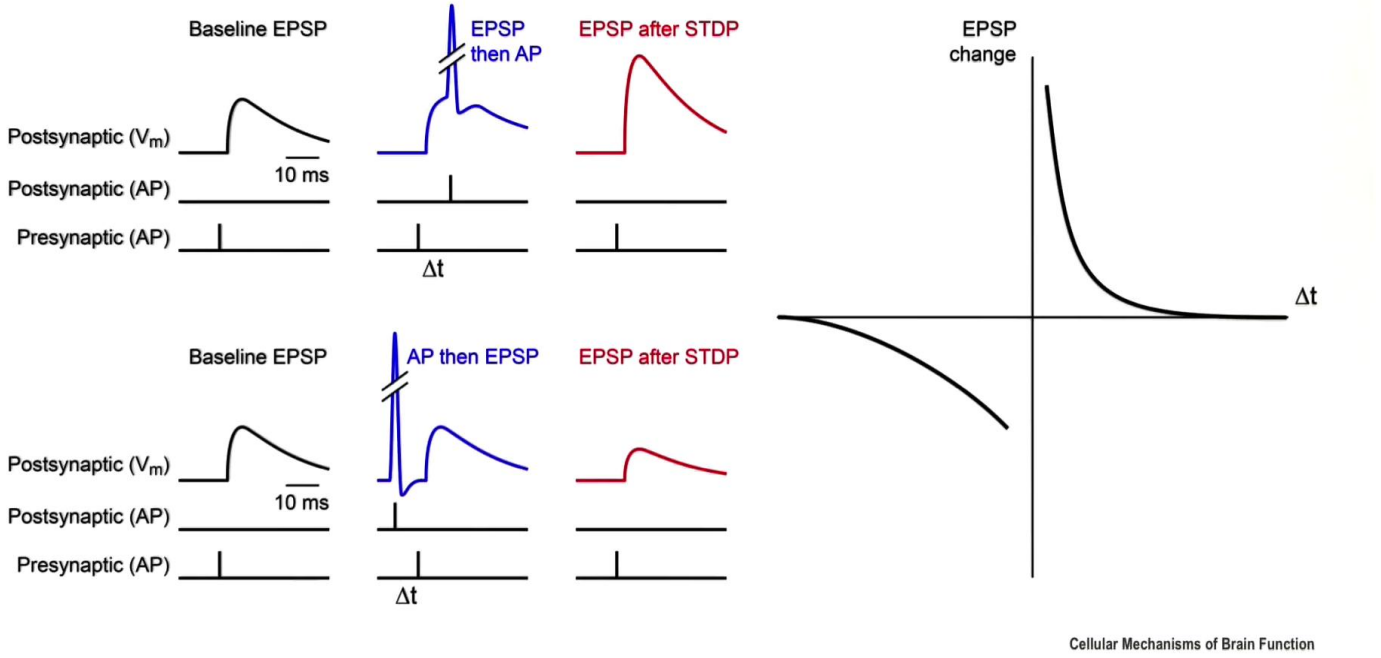
So in some respects, this process looks like the opposite of Long Term Potentiation, but in fact, there are interesting and important differences between LTP and LTD. They're not directly reversals of each other. In terms of what happens after the NMDA receptors have been partially activated and the protein phosphatases have been activated, presumable, there's a dephosphorilation event that occurs, and in particular it seems that, in part at least, directly dephospohrilating AMPA receptors appears to be a key aspect to Long Term Depression. After that, the AMPA receptors are simply removed from the synapse at least in part. And so, you start off with a situation where we might have many AMPA receptors post-synaptically, and after the Long Term Depression protocol, depression, we end up with fewer receptors post-synaptically, and so, we have less conductance, and therefore, we get smaller post-synaptic potentials. So that's the basis of Long Term Depression.

Notes

Summary

16m 51s

Spike timing-dependent plasticity (STDP)



Cellular Mechanisms of Brain Function

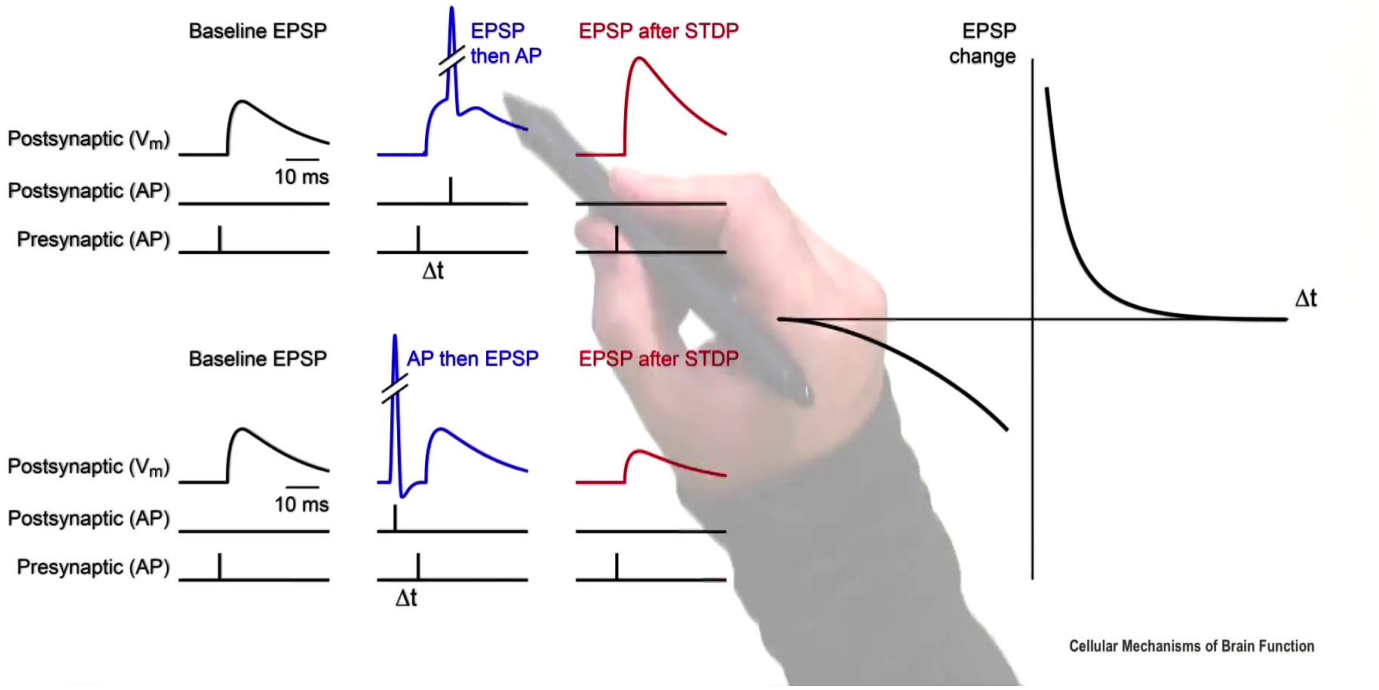
There's another form of synaptic plasticity that probably relates closely to NMDA receptor-dependent Long Term Potentiation and NMDA receptor dependent Long Term Depression that we've been talking about, but this is a mechanism that has at least a more physiological bend to it in the sense that it relies up`on action potential firing and the precise timing of those action potentials, so now we're not talking about long-lasting depolarizations or high frequency stimulation manipulations that experimentally, of course, can be carried out in a dish, but we have no idea whether they actually take place normally under physiological conditions inside the brain. Spike timing-dependent plasticity relies on the precise temporal relationship of an action potential in a pre-synaptic neuron and an action potential in a post-synaptic neuron, and of course, in the brain, we know that both pre-synaptic and post-synaptic cells fire action potentials, and there was an interesting discovery by Henry Markram and Beth [inaudible] that the precise timing of action potentials in the pre-synaptic and post-synaptic neurons can make a major impact upon the synaptic efficacy.

Notes

Summary

18m 01s

Spike timing-dependent plasticity (STDP)



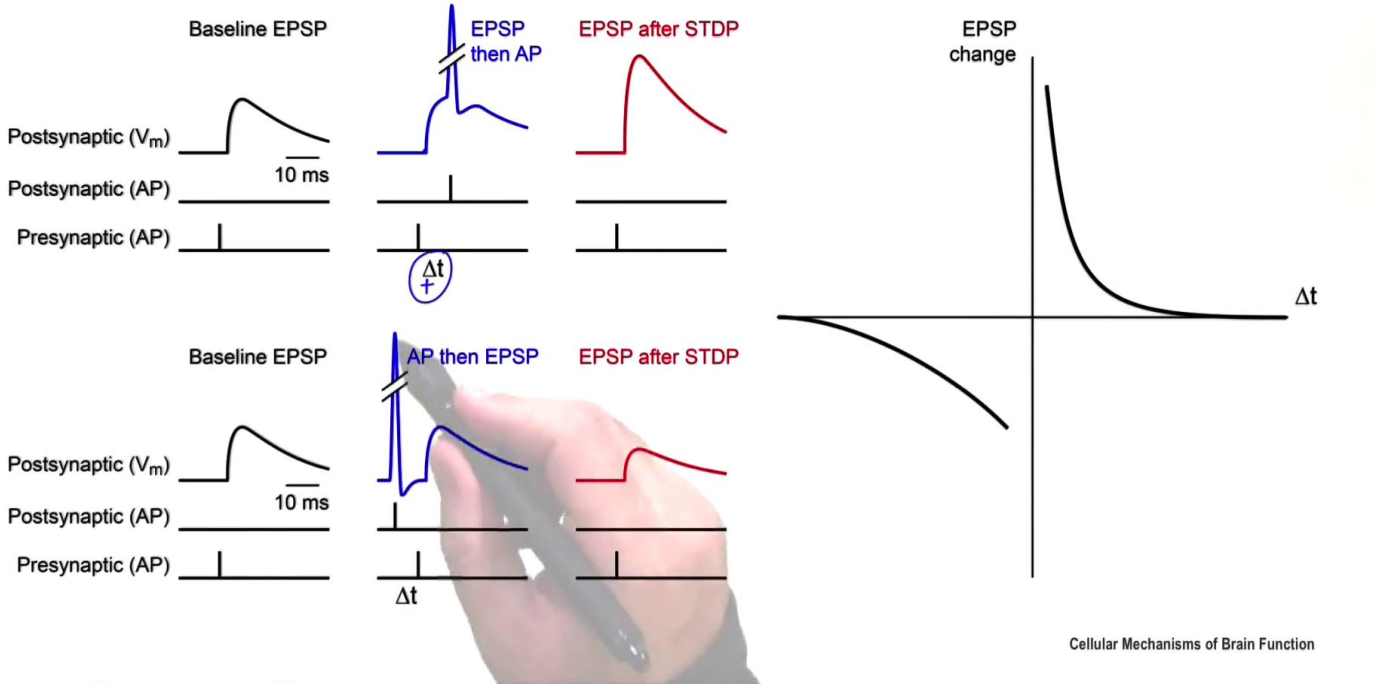
In particular, what they found was that if we imagine a synaptically connected pair of neurons where we have an action potential in a pre-synaptic neuron, that then releases glutamate onto the post-synaptic cell, causing, of course, a unitary excitatory post-synaptic potential. They then began to inject currents into the post-synaptic cell at the same time that there was also a synaptic input, so we have the pre-synaptic action potential that releases glutamate onto the post-synaptic cell as before causing the post-synaptic potential, but now, in addition to that EPSP there is also a current that's being injected into the post-synaptic cell, and that then makes it fire an action potential riding on top of the post-synaptic potential. When one then goes back and looks at what happens at the EPSP when we just stimulate the pre-synaptic cell, now the EPSP has grown. It's important to note that typically this process, this pairing process of pre-synaptic followed by post-synaptic action potential, is typically repeated many times, maybe a hundred times, in order to generate a robust increase in the efficacy of the connection between the pre-synaptic and the post-synaptic neuron.

Notes

Summary

19m 18s

Spike timing-dependent plasticity (STDP)



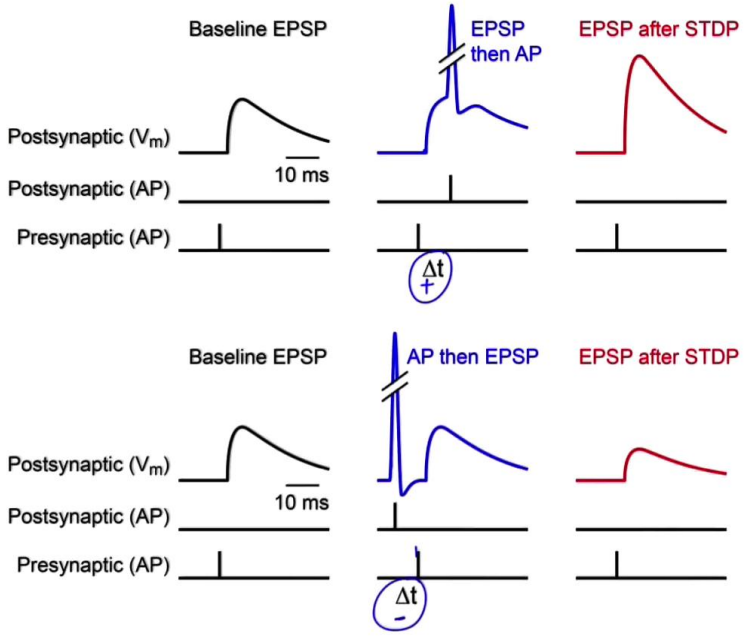
And so, we go from a small baseline EPSP to a large EPSP after the Spike Timing Dependent Plasticity protocol has been run, and in particular it's with a delay in the post-synaptic spike relative to the pre-synaptic spike. At these so-called positive delta-T intervals, that causes an increase in the efficacy of the EPSP. Remarkably, if you move the timing of the action potential to be just ten ms before the pre-synaptic action potential, then the plasticity reverses sign. So here again we're looking at a unitary synaptic connection, action potential in the pre-synaptic cell, post-synaptic potential in the post-synaptic cell. An action potential can then be evoked in the post-synaptic neuron by injecting current into the post-synaptic cell firing an action potential, and you can do that at a time that precedes the action potential in the pre-synaptic cell, so the pre-synaptic cell evokes an EPSP just like it did before, but now that EPSP is preceded by an action potential here during the spike timing-dependent plasticity induction period where again you might pair a hundred times the action potential and the EPSP, but now the timing is very different to before.

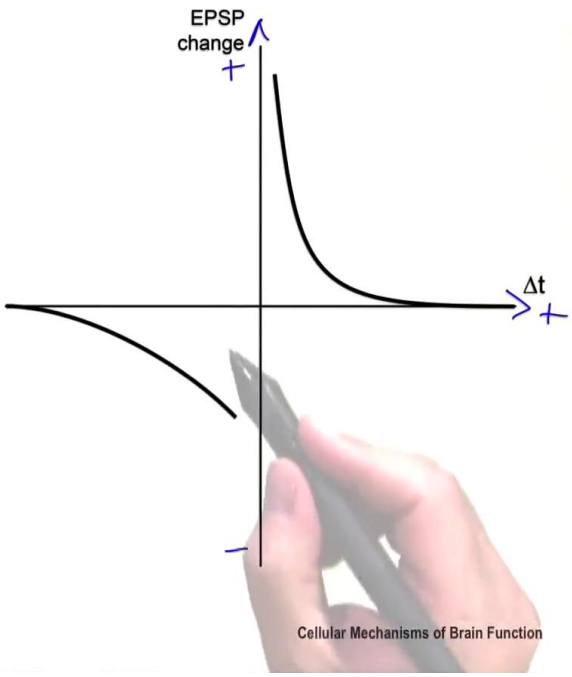
Notes

Summary

20m 37s

Spike timing-dependent plasticity (STDP)





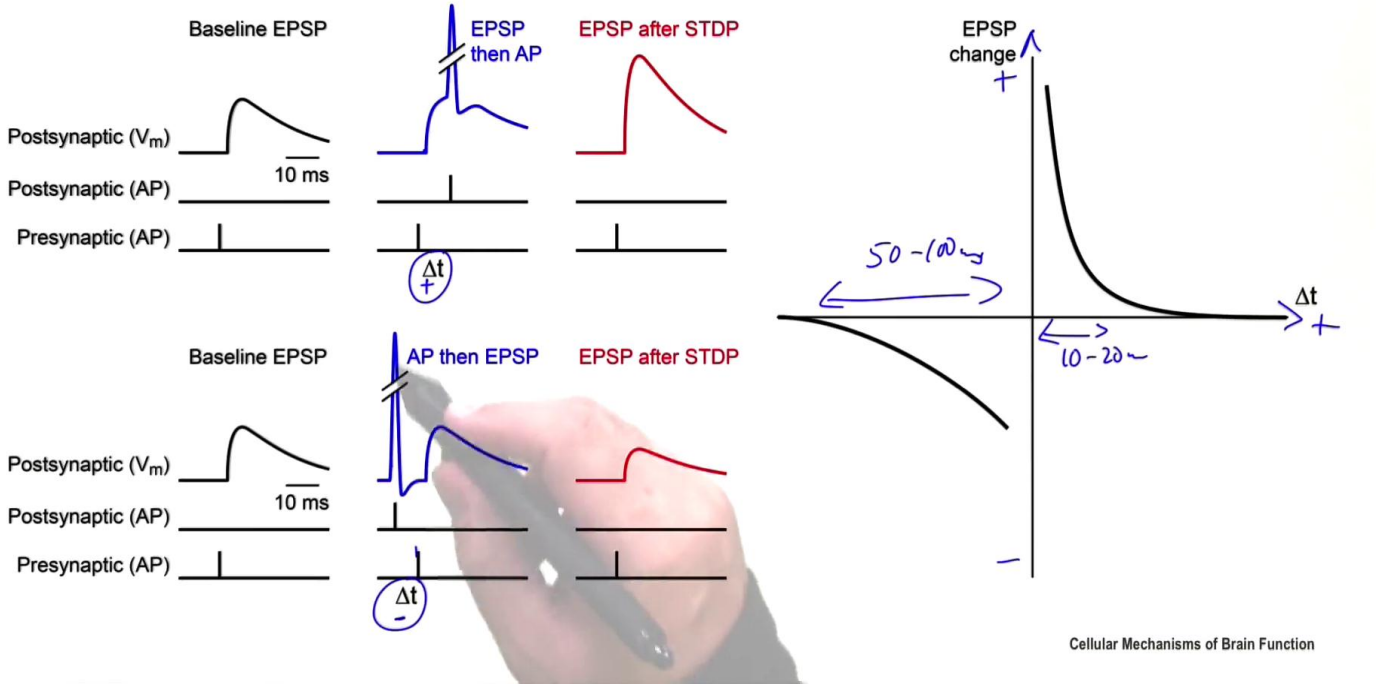
Here, the action potential was riding on top of the EPSP. Now the action potential precedes the glutamatergic input onto the cell. And what is found is that the EPSP now decreases in amplitude and so we now have a decrease in the efficacy of the EPSP when we've reversed the timing of the pre- and the post-synaptic cells, so this is at so-called negative delta-T intervals where the post-synaptic cell fires before the pre-synaptic cell. By measuring what types of plasticity happen when you vary this time interval between pre-synaptic and post-synaptic spikes, you can build up a timing of the plasticity of the change in EPSP amplitude, so that's what's plotted here on the Y axis where positive values here indicate increased enhanced EPSP size and the negative values are decreased amplitudes in the EPSP. Here on the X axis we're looking at the difference in the timing between the post-synaptic spike and the pre-synaptic spike at positive times, that's when the post-synaptic cell fires after the pre-synaptic cell, and that then gives rise to enhanced synaptic plasticity. When we have the timing the other way around, the post-synaptic cell fires first. That gives rise to decreases in the EPSP.

Notes

Summary

22m 05s

Spike timing-dependent plasticity (STDP)



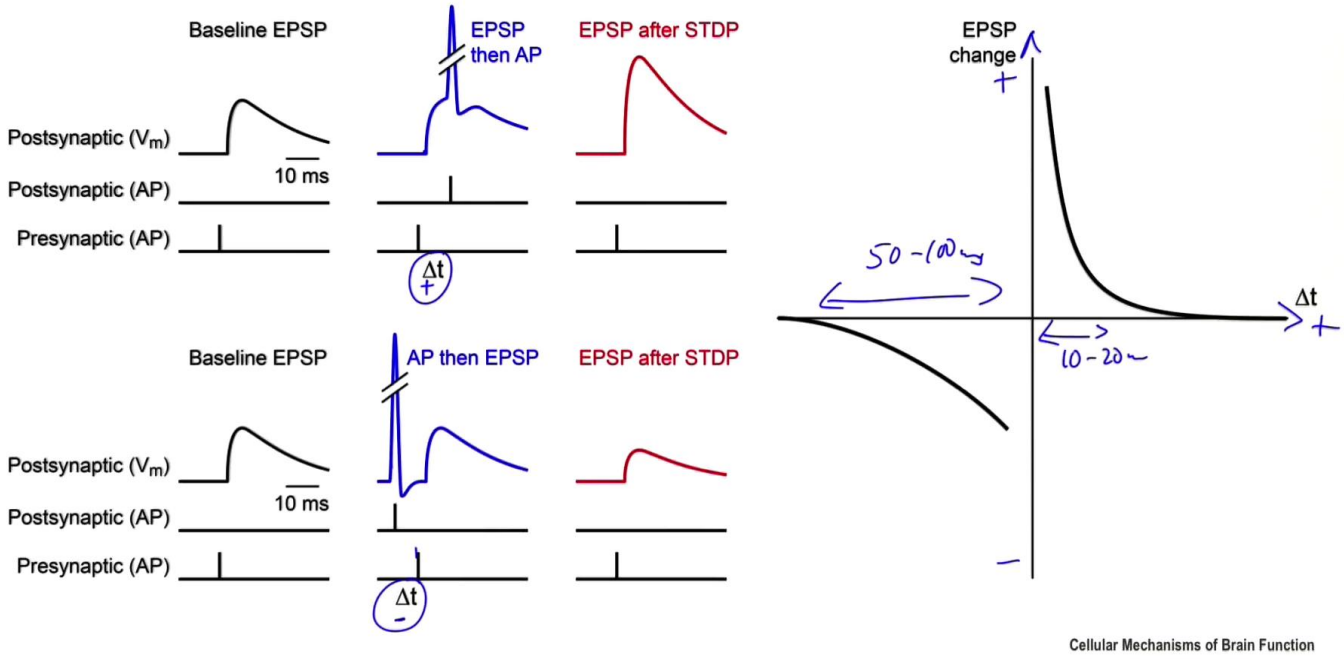
In this temporal relationship to synaptic plasticity, the so-called spike timing-dependent plasticity (STDP) has been now found at a large variety of synapses in the brain, so it appears to be an interesting, and perhaps general, rule. What's remarkable is really the short timescale here where we're thinking about ten, twenty ms and maybe 50 to 100 ms on this side here where on this millisecond time scale, the order of the action potential firing makes a very big diference to the types of plasticity that are involved. To some extent, this makes sense, so this EPSP didn't just come at a random time. It came at a time when the neuron actually fired action potentials. So one might then think that this input to the cell was useful and something that should be kept and maybe even strengthened, and that's what happens here in spike timing-dependent plasticity. Apparently useful inputs that contribute to firing the post-synaptic cell get strengthened. In this scenario, the action potential occurred before the glutamate was released from the pre-synaptic neuron. Clearly, the firing of the post-synaptic cell has nothing to do with what the pre-synaptic cell was doing.

Notes

Summary

23m 33s

Spike timing-dependent plasticity (STDP)



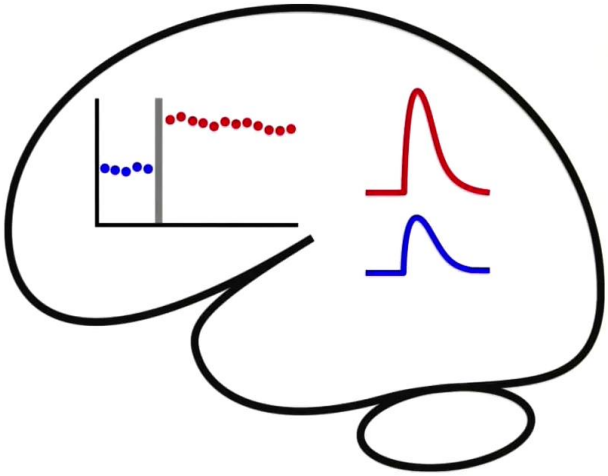
This input from the pre-synaptic cell might not be a particularly useful input for that cell. It certainly doesn't contribute to this artificially flat spike that's done under these experimental conditions. So, the cell may think that this synapse is not a particularly helpful one for the function of the neuron, so it may be the reason for why the depression of that EPSP occurs when the action potentials occur in an uncorrelated way with the pre-synaptic neuron.

Notes

Summary

25m 00s

Postsynaptic plasticity



Cellular Mechanisms of Brain Function

Changes in the post-synaptic receptor composition, the number of AMPA receptors in particular that are present at the post-synaptic density are an important way in which the synapse strength can be regulated between two different neurons. It's the activity of these neurons, and in particular the depolarization of the post-synaptic cell concomitant with the release of glutamate from the pre-synaptic cell that is typically involved in setting the plasticity and the direction of the plasticity that occurs in these different paradigms. Strong depolarization or action potentials riding directly on top of EPSP's coming in strengthen that synaptic connection, and the strengthening appears to occur, at least in part, through the insertion and recruitment of AMPA receptors that are diffusing on the plasma membrane but then bind onto post-synaptic density proteins and get locked onto the post-synaptic density when they can contribute to driving post-synaptic potentials. On the other hand, weak depolarization or action potentials occurring at times that are different than when the synaptic inputs arrive tend to cause a depression of the synaptic inputs, so there's a strengthening of what appear to be useful inputs, and there's a weakening of inputs that appear to not contribute to the post-synaptic firing.

Notes

Summary

25m 33s