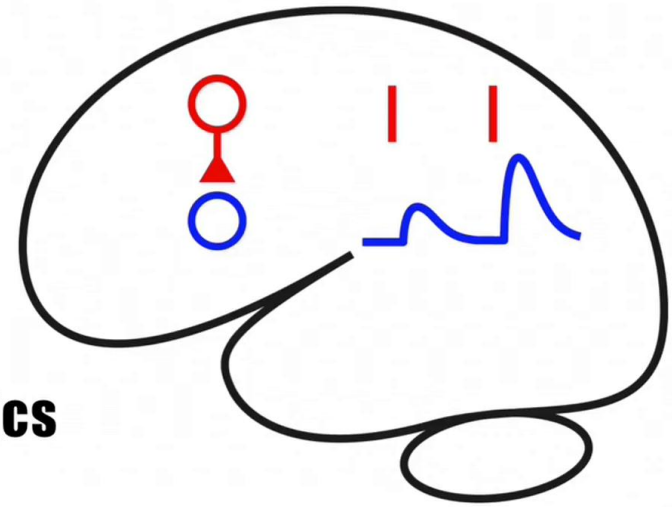
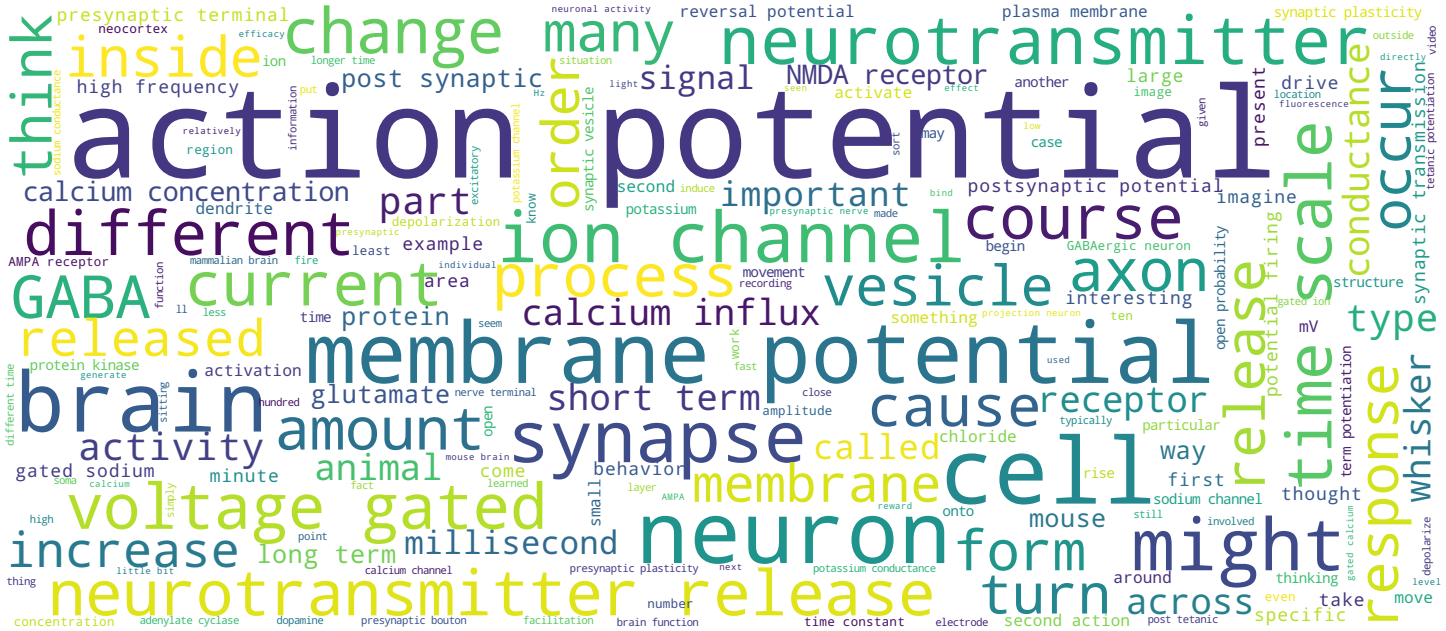


3.3 Presynaptic dynamics

Cellular Mechanisms of Brain Function

Prof. Carl Petersen



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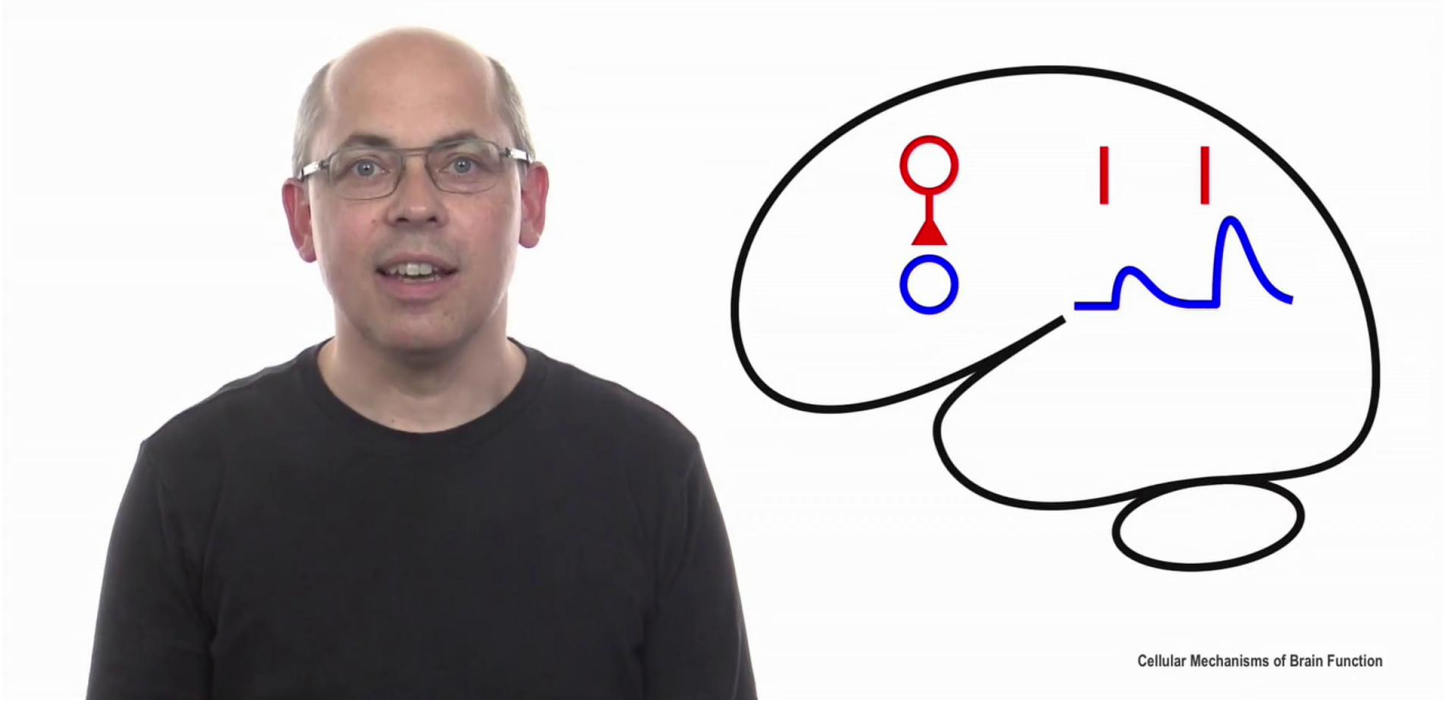
Video

EPFL

History-dependence of synaptic transmission



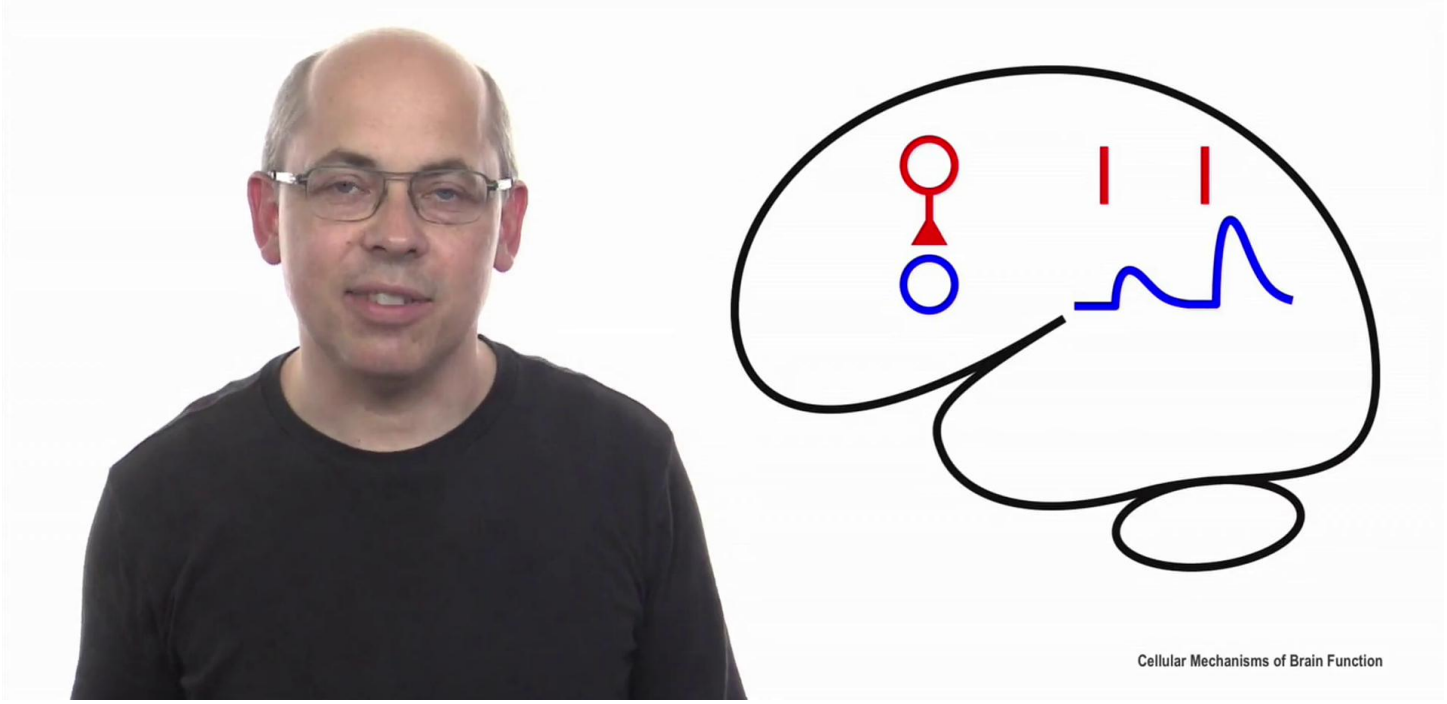
We've now learned about the complex process coupling an action potential in a presynaptic bouton to neurotransmitter release through complex molecular machinery. The action potential firing rate in a neuron makes a large difference about its synaptic transmission. Some neurons, some types of cells in the mammalian brain, fire action potentials at very high rates, almost continuously. So, some cells fire at 100 Hz: that's an action potential every 10 milliseconds, almost continuously throughout our lives. Other neurons fire much more sparsely and selectively. They might be silent for minutes, and then fire a brief burst of five action potentials within a few milliseconds of each other, and then remain silent again for many minutes. There are thus diverse patterns of action potential firing and the brain has adapted to make use, enhance, and suppress some of the information transmitted by action potentials in different time scales. The amount of neurotransmitter that's released in response to an action potential is therefore dependent upon the history of activity in that particular axon. If an action potential occurs immediately *before*, then that leaves an imprint upon the synapse.

Notes

Summary

0m 04s

History-dependence of synaptic transmission



And that can change the amount of neurotransmitter that's released in response to subsequent action potentials. And that process of so-called *presynaptic plasticity* is what we're gonna study in today's video.

Notes

Summary

1m 37s

Presynaptic dynamics

1. Short-term (milliseconds)
   - Facilitation
   - Depression
2. Post-tetanic potentiation (minutes)
3. Long-term presynaptic plasticity (hours)

Cellular Mechanisms of Brain Function

The modulation of neurotransmitter release in response to activity of that same axon is called presynaptic short-term plasticity, or presynaptic dynamics. It can thought of as occurring on three different time scales, which also relate to three different mechanisms that are at play in the presynaptic terminal. We can have short-term synaptic plasticity: that's a form of short-term dynamics that occurs on a time scale of less than one second, typically 10 milliseconds; 100 milliseconds is the time scale of interaction between neighboring action potentials when we're thinking about short-term synaptic plasticity. It can be divided into two forms: *facilitation*, where subsequent action potentials *increase* the amount of neurotransmission, and *depression*, where consecutive action potentials induce less and less release of neurotransmitter. There are other forms of presynaptic plasticity that occur on much longer time scales: postsynaptic potentiation, that occurs on the *minute* time scale, and long-term presynaptic plasticity, that can last hours, days, perhaps even a lifetime and might ultimately contribute to forming memories in the brain.

Notes

Summary

1m 53s

Presynaptic dynamics

1. Short-term (milliseconds)
   - Facilitation
   - Depression
2. Post-tetanic potentiation (minutes)
3. Long-term presynaptic plasticity (hours)

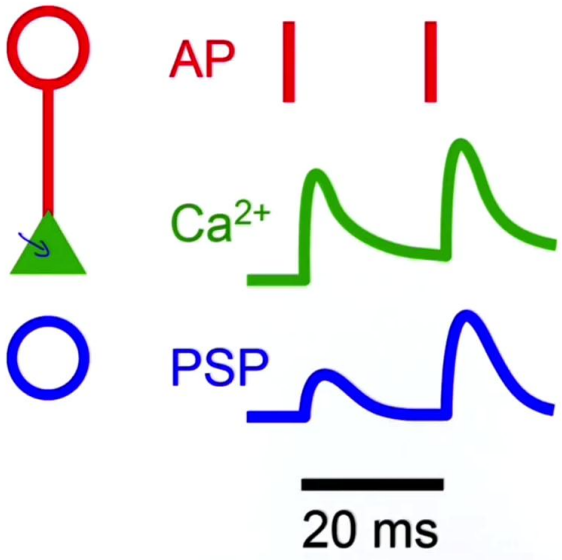
These two longer-lasting plasticities rely upon complex signaling cascades downstream of activity, and calcium, whereas these are *immediately* related to the calcium and the amount of neurotransmitter vesicles available. We will talk about bit about each of these four different forms of presynaptic short-term plasticity in the next slides.

Notes

Summary

3m 21s

Short-term dynamics: Facilitation



Release rate ~ $[Ca^{2+}]_i^4$

$(1.2)^4 \approx 2$

A 20% increase in Ca^{2+} causes a doubling of neurotransmitter release.

Cellular Mechanisms of Brain Function

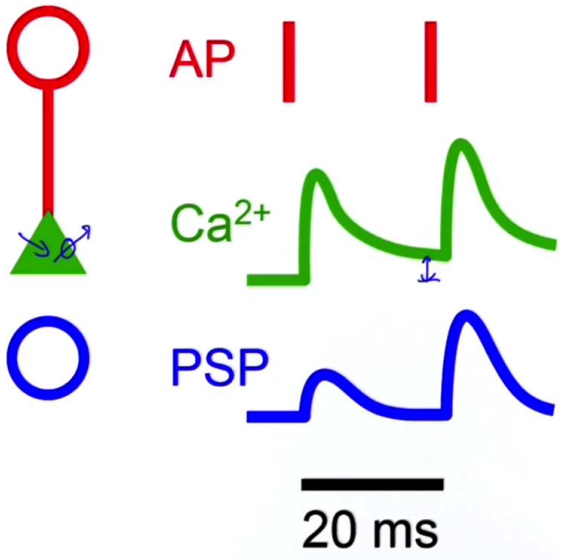
We'll begin by thinking about facilitation. In the process of facilitation, we imagine a connected pair of neurons where action potentials in the red neuron propagate down to the presynaptic bouton, calcium influx causes neurotransmitter release, and then postsynaptic potentials are evoked in the blue neuron. One action potential causes calcium influx, causes a postsynaptic potential. Then we'll envisage a second action potential, occurring shortly after the first one: in this case, on the time scale of 20 milliseconds later. The second action potential induces a large amount of neurotransmitter release, and therefore also a larger postsynaptic potential. That's the process of *facilitation*. The mechanism underlying presynaptic short-term facilitation is thought to be an accumulation of calcium in the presynaptic terminal. So, the first action potential induces a calcium influx that activates the voltage-gated calcium channels; calcium then floods into the presynaptic bouton, and that's what causes neurotransmitter release. There are a number of different calcium binding proteins, of course, including the Synaptotagmin: that's the effector for neurotransmitter release.

Notes

Summary

3m 48s

Short-term dynamics: Facilitation



Release rate ~ $[Ca^{2+}]_i^4$

$(1.2)^4 \approx 2$

A 20% increase in Ca^{2+} causes a doubling of neurotransmitter release.

Cellular Mechanisms of Brain Function

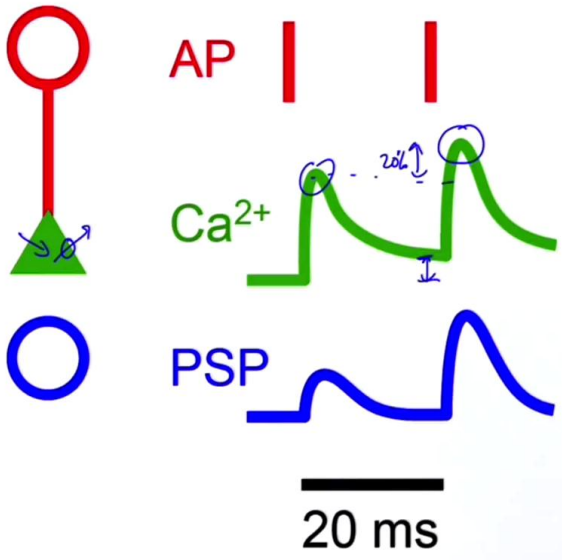
But there are many other proteins that also bind calcium. They become calcium buffers. There are also proteins that are involved in sucking the calcium out of the presynaptic terminal: calcium pumps that are involved in reducing the calcium concentration. And so, in the 20 milliseconds that follow the action potential, there's a gradual reduction in the calcium concentration in the presynaptic terminal; and that depends on the activity of the pumps, the diffusion of the calcium away from the entry site at the voltage-gated calcium channels, and the binding of various calcium buffers. When the second action potential arrives, there may, then, be a little bit of residual calcium left in the presynaptic terminal. We may not have reached the equilibrium baseline situation. Equally, some of the buffers may be saturated; and when the second action potential occurs, and calcium floods in, those buffers won't be able to bind calcium; and there's already an elevated baseline; and so the peak calcium concentration that's reached in response to the second action potential can be higher than that in response to the first.

Notes

Summary

5m 08s

Short-term dynamics: Facilitation



Release rate ~ $[Ca^{2+}]_i^4$

$(1.2)^4 \approx 2$

A 20% increase in Ca^{2+} causes a doubling of neurotransmitter release.

Cellular Mechanisms of Brain Function

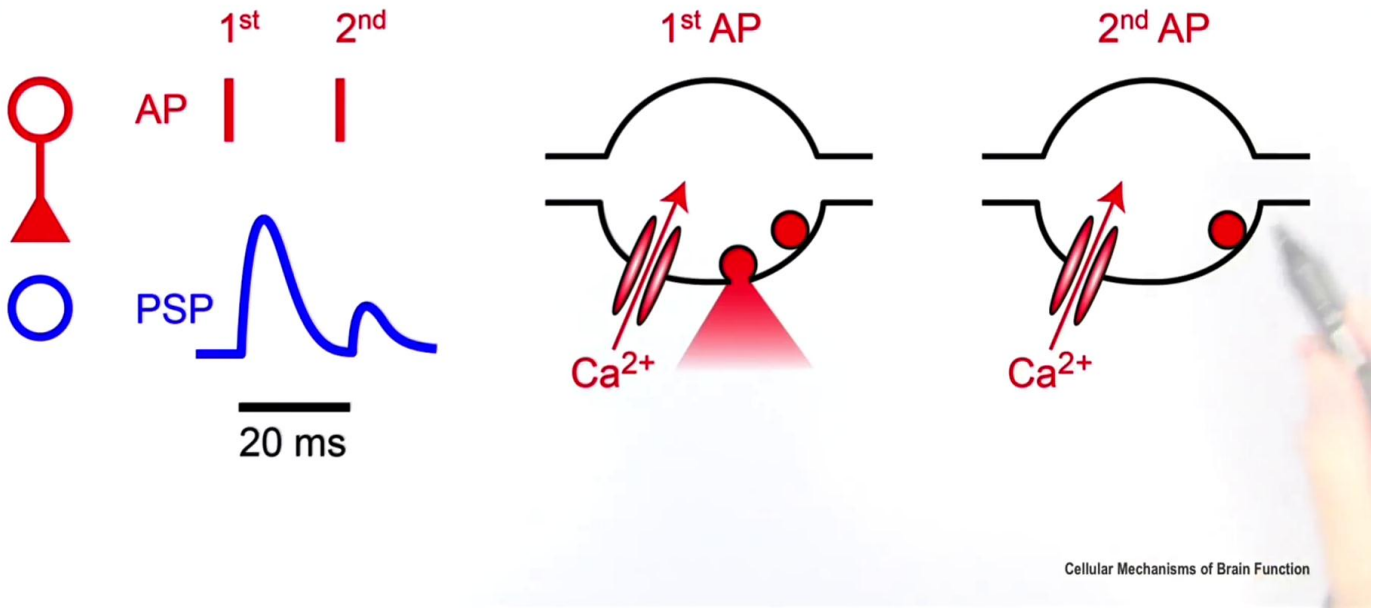
And even if that's only, say, a 20-percent increase in the peak calcium concentration, that can make a major difference to the amount of neurotransmitter that's being released. In the last lesson we discussed that the release rate of vesicles depended upon the fourth power of the concentration of calcium. And so, if we have a 20-percent increase in the calcium concentration, we put that to the fourth power: that induces a doubling in the amount of neurotransmitter release. So, even small changes in the amount of peak calcium influx reached in response to an action potential can have a large impact upon the release of neurotransmitter. And in the process of short-term facilitation, it is thought to be increased calcium signals that give rise to increased amounts of neurotransmitter release. And that's the process of short-term facilitation, that typically lasts less than a second, and is typically, sort of, studied on the time scale of action potentials that are 10 milliseconds, 50 milliseconds, or 100 milliseconds apart.

Notes

Summary

6m 19s

Short-term dynamics: Depression



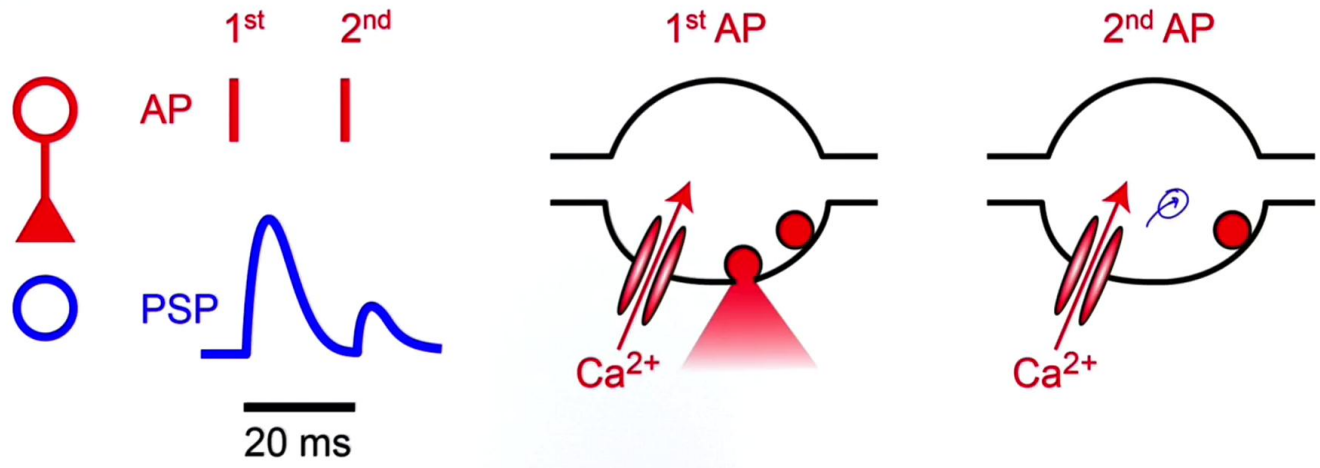
There's another process of short-term synaptic plasticity that does the converse: *depression.* In the process of depression, the second action potential gives rise to a smaller postsynaptic response because of less release of neurotransmitter compared to the first action potential, when those action potentials are separated by a few tens of milliseconds. In the process of synaptic depression, we imagine that the first action potential is quite efficacious, and it releases a large amount of neurotransmitter from the presynaptic nerve terminal. After that neurotransmitter has been released, the vesicles need to replenish. And in the time space of 20 milliseconds, perhaps, there's very little time for the vesicles to replenish; and so, in response to the second action potential, less neurotransmitter is released. We can envisage the situation here: in response to the first action potential, there might, for example, be two release-ready vesicles. The action potential induces calcium influx; one of these is released and causes a postsynaptic potential. In response to the second action potential that first vesicle is now gone; It's probably somewhere in the recycling process, trying to load up with neurotransmitter.

Notes

Summary

7m 28s

Short-term dynamics: Depression



Cellular Mechanisms of Brain Function

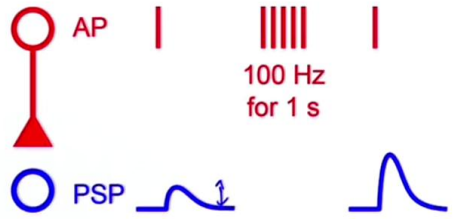
So there's only one vesicle, now, that's left; and the action potential causes the same calcium influx; and, in this case, there's, then, a reduced probability of releasing a neurotransmitter.

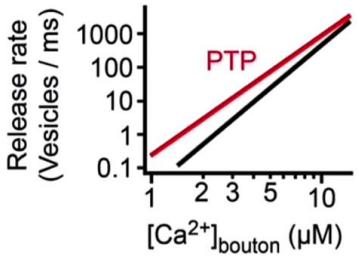
Notes

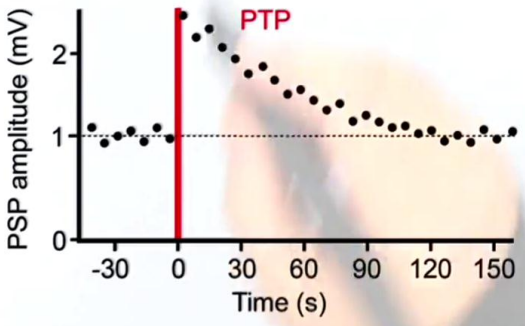
Summary

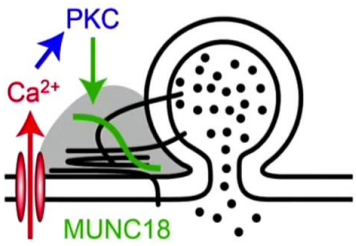
8m 50s

Post-tetanic potentiation









Cellular Mechanisms of Brain Function

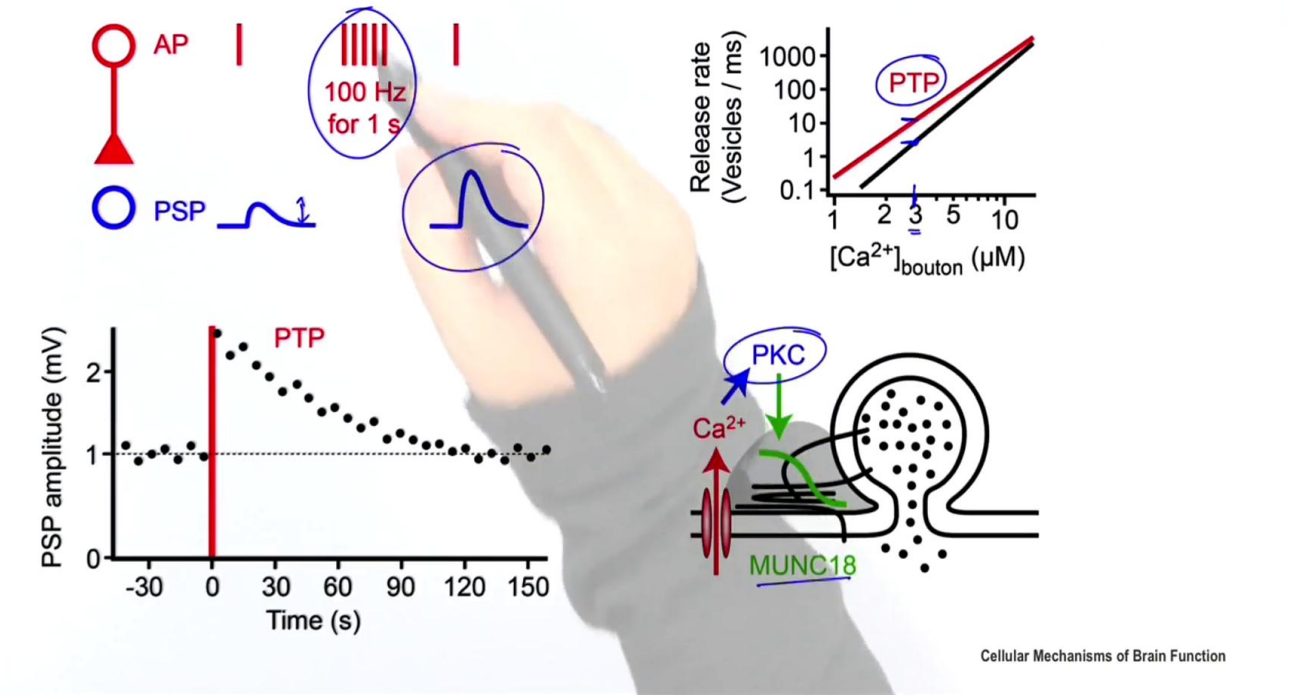
It's also possible to modulate presynaptic release on longer time scales; and this typically involves high-frequency stimulation of the presynaptic nerve terminal and activation of additional signaling pathways. These sort of longer-lasting forms of presynaptic plasticity only occur at certain types of synapses. So, most types of synapses have the short-term forms of synaptic plasticity, and only certain ones have, for example, *post-tetanic potentiation*, or long-term potentiation, that we'll discuss next. And so, at synapses that express post-tetanic potentiation, we can imagine having a high-frequency burst of action potential where we might fire the presynaptic cell at 100 Hz for one second: so, that's 100 action potentials and each one separated by a 10-millisecond time scale. And we can have a baseline, where we stimulate, perhaps, once every 10 seconds, or once every 20 seconds. That gives us our baseline postsynaptic potential. We can plot the amplitude of that, in the form of these dots here, across time. So we stimulate, perhaps, every 10 seconds: we see some variation in the postsynaptic potential; then, we give our high-frequency tetanic stimulation, the 100 Hz.

Notes

Summary

9m 05s

Post-tetanic potentiation



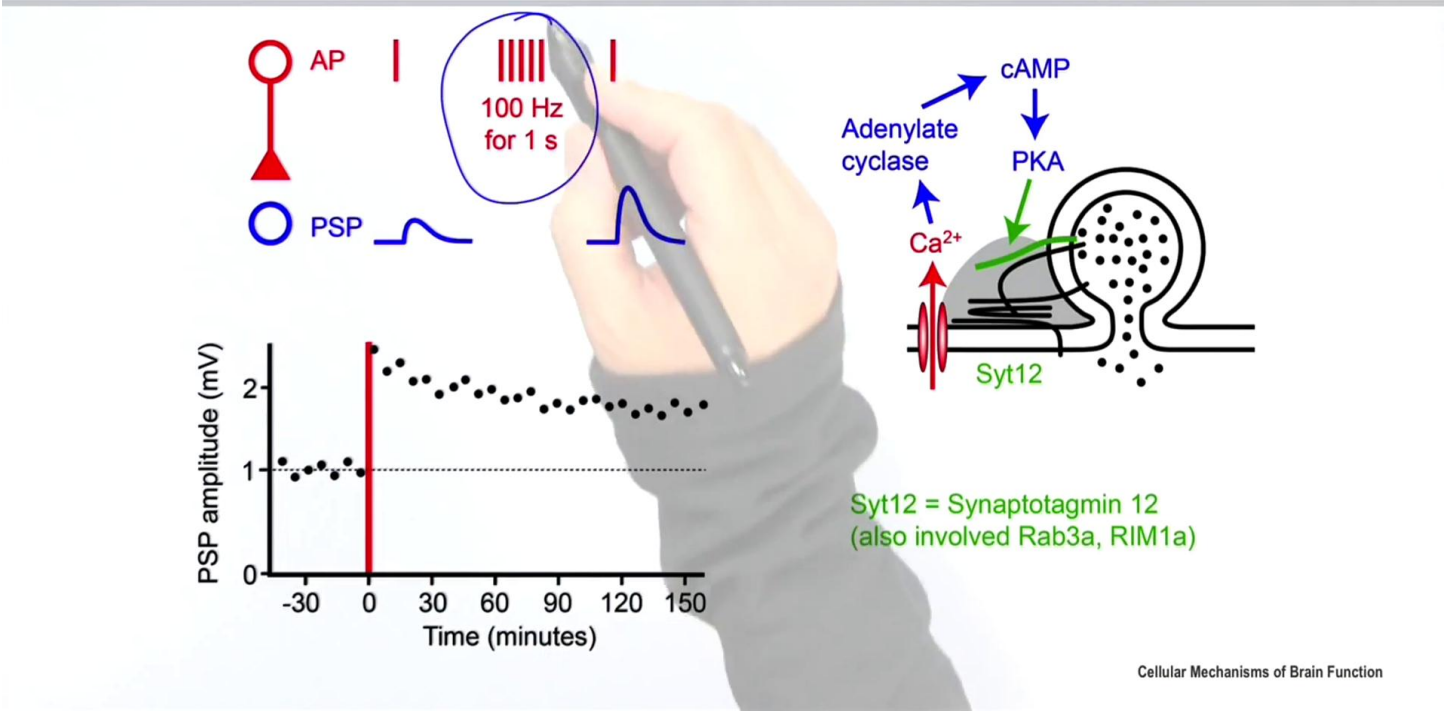
That causes a massive influx of calcium through the voltage-gated calcium channels. That rise in calcium activates an enzyme called protein kinase C that depends upon calcium to activate it: so, there's a large calcium influx during this one second of high-frequency stimulation that activates protein kinase C; and one of the targets of protein kinase C is part of the molecular machinery involved in neurotransmitter release. It's a protein called Munc-18; and if that becomes phosphorylated by protein kinase C, then the release rate at any given calcium concentration is increased. And so, if our action potential induces, say, 3 micromolar calcium in the presynaptic cell under baseline conditions, after the post-tetanic potentiation -- this 100 Hz stimulus; after the activation of protein kinase C in the phosphorylation of Munc-18, three micromole of calcium will now induce a much higher release rate; and that's, then, what we see here. After the post-tetanic potentiation stimulation, we go back to our stimulation of action potentials every 10 seconds or so, and we now see that the release of neurotransmitter is enhanced; and it can be enhanced for a time of many seconds.

Notes

Summary

10m 23s

Presynaptic long-term potentiation



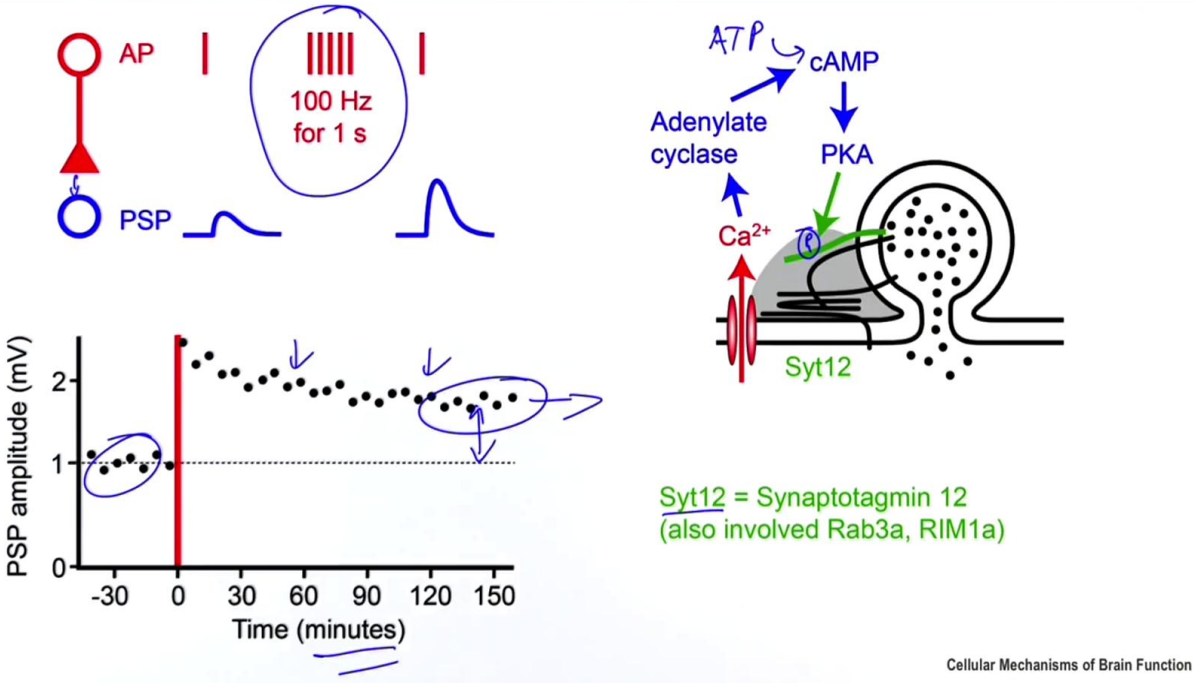
So, here we're in seconds, so this is one minute. And, after one minute, there's still a substantial enhancement in the release from this synapse, compared to the baseline. So, a brief period of high-frequency activity can induce a long-lasting change here over a period of about a minute, where there's a substantial increase in neurotransmitter release. And that can, of course, affect brain function in important and interesting ways, where one can imagine holding a short-term memory of activity at the synapse for a period of a minute. We can also have much longer terms of presynaptic plasticity, in so-called long-term potentiation. Again, this only occurs at *some* types of synapses in the brain. Again, we have a high-frequency train of stimuli in the presynaptic cell that induce the long-term potentiation; we have baseline PSPs that come in; we stimulate every now and then, and we see that there's a relatively-reliable postsynaptic potential that comes in. We give our high-frequency tetanization, the amplitude of the PSP, that, we recall, postsynaptically increases because of an enhanced release of neurotransmitter.

Notes

Summary

11m 44s

Presynaptic long-term potentiation



Cellular Mechanisms of Brain Function

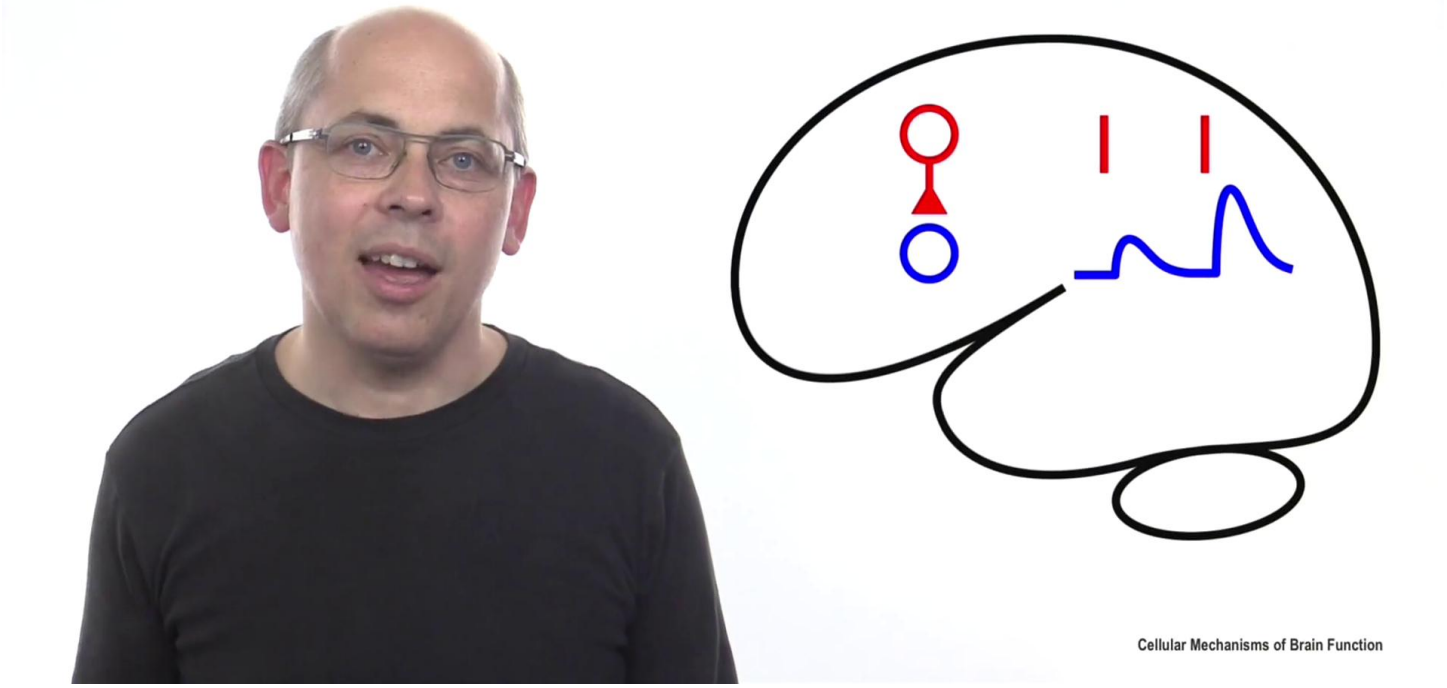
And molecularly, what's thought to be happening at synapses that express long-term potentiation is that the calcium influx during the high-frequency train activates an enzyme called adenylate cyclase. There are calcium-dependent forms of adenylate cyclases, and so the calcium that floods in during the presynaptic train of action potentials activates adenylate cyclase; that, in turn, turns ATP into cyclic AMP. That's the job of adenylate cyclase. Cyclic AMP is an important signaling molecule that activates another protein called protein kinase A; and that phosphorylates one of our favorite proteins here in the release machinery: a Synaptotagmin. Not the standard Synaptotagmin that's responsible for calcium-dependent release, but another one, another isoform, Synaptotagmin-12, at least in some cases where it's been studied. And the phosphorylation of Synaptotagmin-12 causes this long-lasting enhancement of neurotransmitter release, known as presynaptic long-term potentiation. And this is something that can take place on many minutes', on the hour time scale. So one hour, two hours later, there's still a large increase in the efficacy of synaptic transmission at the synapse, and that can maybe go on for days.

Notes

Summary

13m 00s

Presynaptic dynamics



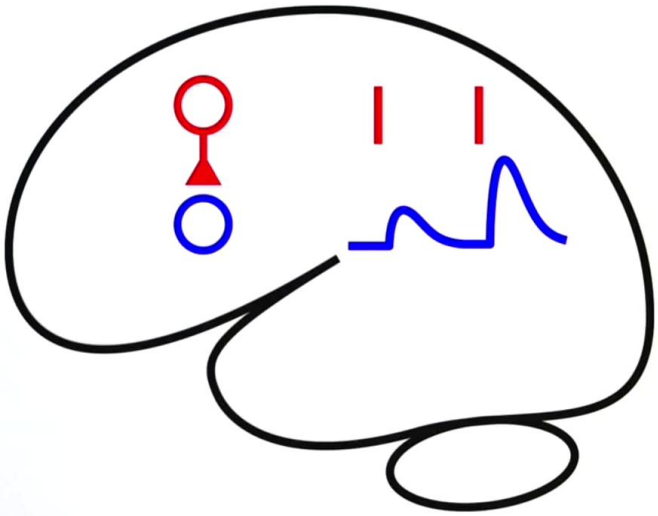
So the amount of neurotransmitter that's being released at a synapse depends on a large number of things; and one of them is the recent history, the activity of that individual bouton in its past. If it just received another action potential before, then the calcium concentration will rise to higher levels with the next action potential, and that can induce presynaptic facilitation: something that occurs on the 10- to 100-millisecond time scale. Equally, the release of a lot of vesicles from the presynaptic terminal leads to a process of depletion. The vesicles need to dock and refill with neurotransmitter before they can be released again; and so there's also a process where we need to refill and reload vesicles. And again, that process of replenishment of the vesicles that are depleted by a previous action potential can take place on the time scale of 10 to 100 milliseconds. So there are these short-term facilitation and depression dynamics that affect nearly all synapses in the brain. Other synapses are able to be modified on longer time scales through signaling processes involving kinases that are calcium-sensitive, for the most part.

Notes

Summary

14m 23s

Presynaptic dynamics



Cellular Mechanisms of Brain Function

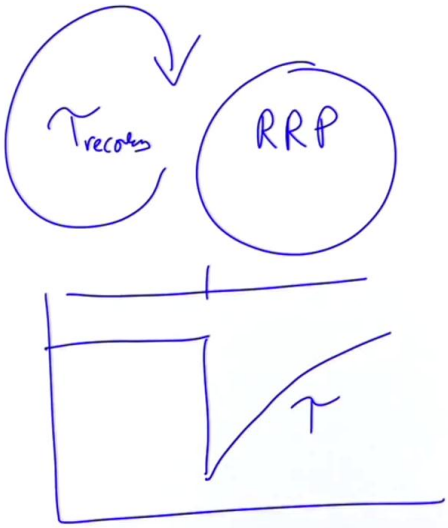
And so, they can sense the activity of the presynaptic terminal; and, through phosphorylating different enzymes or changing the amount -- availability -- of vesicles, can then change the efficacy of neurotransmitter release. And some of those modifications can last for minutes or hours.

Notes

Summary

15m 39s

Modeling of presynaptic dynamics



Cellular Mechanisms of Brain Function

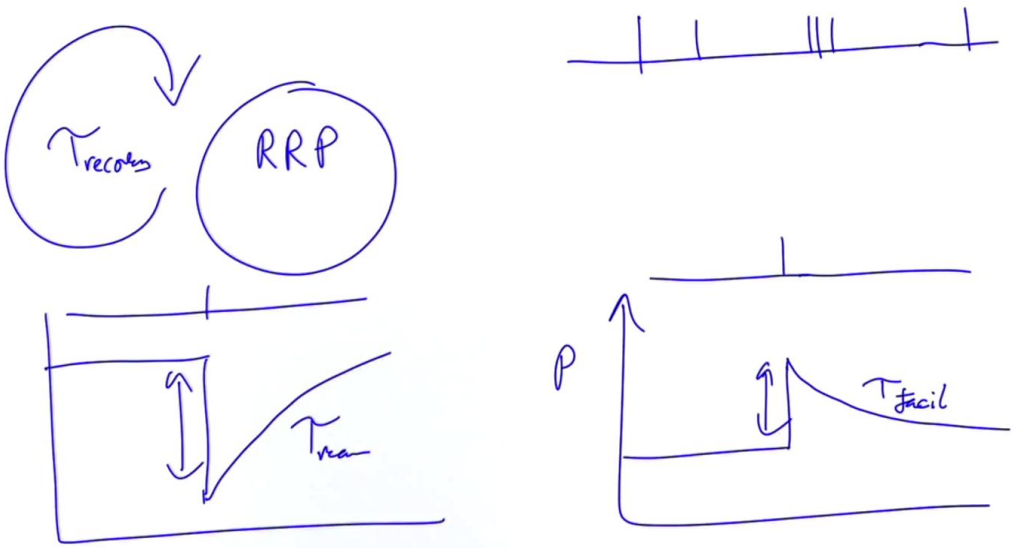
In order to begin thinking about how these modulations of neurotransmitter release can occur in the brain and at different synapses -- and, in particular, when we start thinking about how *many* neurons interact with each other -- it's useful to come up with some computational models, some simple models that, nonetheless, provide reasonable descriptions about the types of changes that occur in synaptic transmission on different time scales. And so one useful way of thinking about it is by bringing in exponential time courses that will help model different events. And so, if we imagine that there's a readily-releasable pool of vesicles, and they, then, need to be replenished, and that will take some sort of time course, here, that we can give an exponential recovery rate to a readily-releasable pool: So, we have a given number of resources and when an action potential is fired, some of those resources are used up; there's an exocytosis, a release of vesicles; and then those vesicles need to recover. And that can be thought of as occurring on some exponential recovery time constant. Equally, we know that there's a process of facilitation, so that when calcium floods into the presynaptic nerve terminal, then the release probability in response to an action potential goes up.

Notes

Summary

15m 58s

Modeling of presynaptic dynamics



Cellular Mechanisms of Brain Function

And so, if we have an action potential that then causes an increase in release probability, which we can think of as an increase in the calcium concentration that, again, lasts for a given amount of time. So, we can think of a facilitation time constant. And so, we have two different time constants. We can also have, of course, different amplitudes for these effects; and by putting, simply, two different, exponentially-dependent time constants together in some sort of releasable, pool fashion, where action potentials then convert resources into released neurotransmitter, and some of those get used up, we can then generate very complex patterns of interactions, with... we can imagine modeling spike trains with quite complicated dynamics. And it turns out that simple models, with just a few variables in them, can actually recover quite a lot of the dynamics that occur at real synapses in the brain. And so, there are simplifications to the complexity that we see at the molecular level. We can have empirical, much simpler models that do a relatively good job of modeling synaptic transmission, at least on short time scales. And of course, in future work, more detailed models need to be generated in order to fully understand the synaptic process of transmission.

Notes

Summary

17m 30s

Presynaptic dynamics

- Presynaptic efficacy varies depending upon recent activity.
- On the millisecond time scale: calcium summation drives facilitation, and vesicle depletion results in depression.
- Calcium-dependent kinases signal presynaptic plasticity on longer time-scales.

Cellular Mechanisms of Brain Function

And so, we've learned that not all action potentials are equal. An action potential will certainly cause calcium influx into the presynaptic bouton, and neurotransmitter release; but the amount of neurotransmitter release and the amount of calcium influx depends upon the recent history of action potential firing in that axon. Action potentials occurring within some tens or hundreds of milliseconds of each other can induce facilitation through summation of calcium concentrations in the presynaptic terminal, and they can induce depression through the depletion of synaptic vesicles and a reduction in the readily-releasable pool. On the longer time scales, the calcium influx that occurs, particularly during high-frequency firing, can induce changes in calcium-activated signaling cascades. Calcium activation of protein kinase C can cause post-tetanic potentiation lasting for a minute or so, whereas calcium activation of adenylate cyclase and cyclic AMP signaling pathways can cause long-lasting forms of potentiation at the presynaptic nerve terminal that probably contributes to the formation of memories. As a result, changes in the efficacy of presynaptic neurotransmitter release are prominent, and form an interesting way in which the brain can auto-regulate its amount of neurotransmitter release from its synaptic terminals.

Notes

Summary

18m 56s