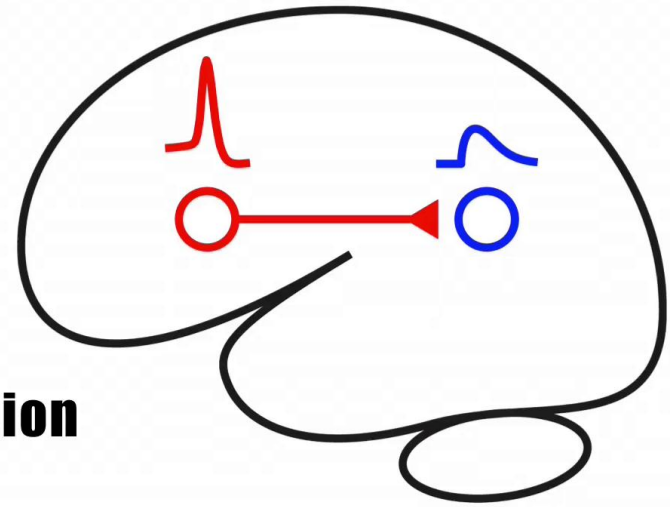
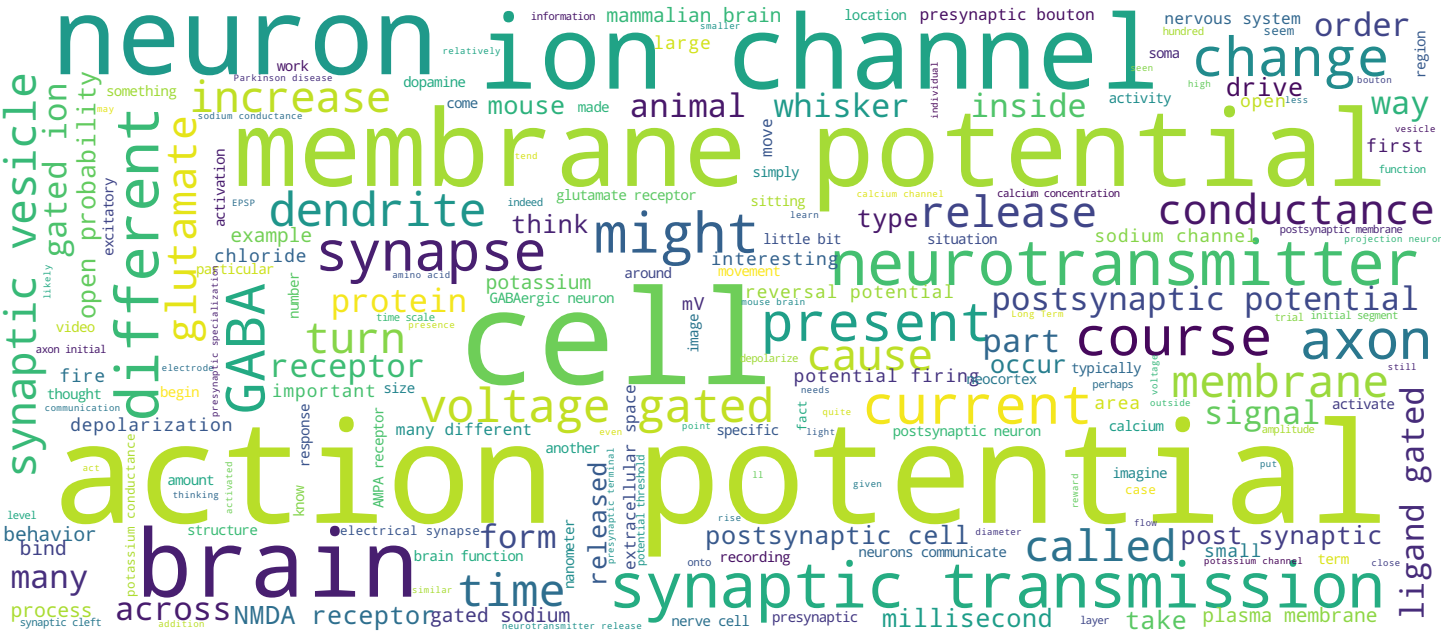


3.1 Synaptic transmission

Cellular Mechanisms of Brain Function

Prof. Carl Petersen



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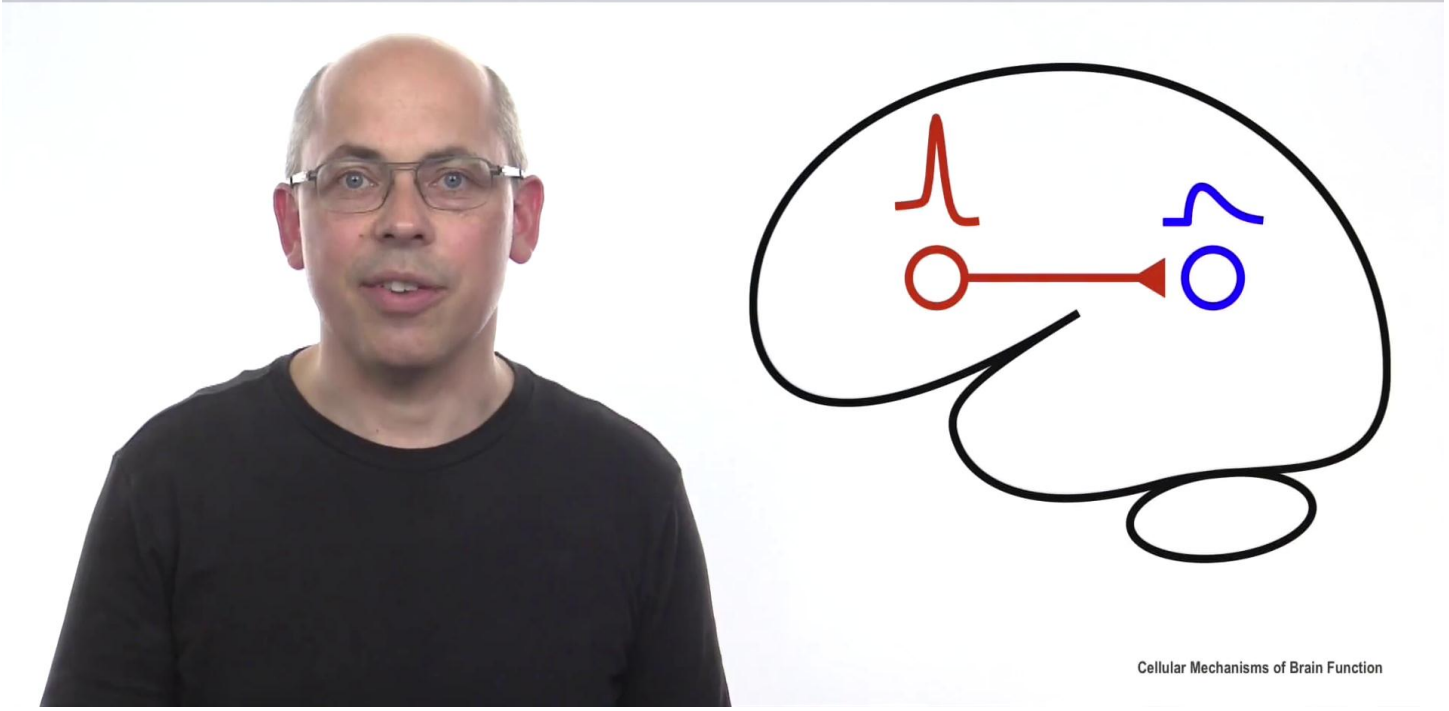
Synaptic transmission



Welcome back to week three of Cellular Mechanisms in Brain Function. Over the last two weeks, we've considered extensively the membrane biophysics of electrical signalling in single neurons. The brain is composed of many neurons and these neurons communicate with each other. A single neuron might communicate and send messages to hundreds of thousands of other neurons and equally, that neuron will receive signals from hundreds of thousands of other neurons. The communication between different nerve cells in the brain sending specific messages to each other, underlies the complex and important computational powers of the mammalian brain. Neurons communicate to each other at specialized junctions called synapses. Typically, an action potential in a presynaptic neuron causes that action potential to travel down the axon of that neuron and when it reaches the presynaptic bouton, it releases a neurotransmitter substance, a chemical that binds to receptors on the postsynaptic cell and causes a change in the membrane potential of that cell. That process of synaptic transmission is the main way in which neurons communicate with each other and signal to each other.

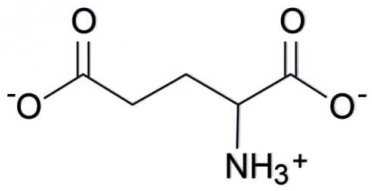
Notes

Summary

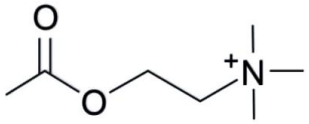
0m 03s

Diverse neurotransmitters

Glutamate



Acetylcholine

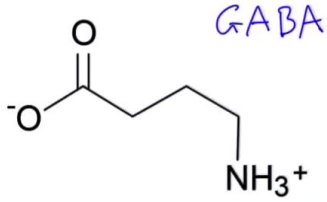


Met-enkephalin

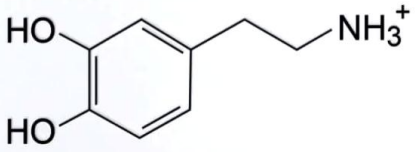
Tyr - Gly - Gly - Phe - Met

γ-aminobutyric acid

GABA



Dopamine



Oxytocin

Cys - Tyr - Ile - Gln - Asn
Gly - Leu - Pro - Cys

Cellular Mechanisms of Brain Function

There are many different neurotransmitters present in the mammalian brain, and here, I show just a small handful out of that total diversity. The most important two neurotransmitters in the central nervous system are glutamate and gamma-aminobutyric acid, that's typically written, simply, in it's short form as GABA. So glutamate is the amino acid that we know that forms parts of proteins and glutamate is the main excitatory neurotransmitter in the brain. A release of glutamate causes postsynaptic neurons to increase the probability of firing action potentials. GABA, on the other hand, is the most important inhibitory neurotransmitter, and a neuron that releases GABA will tend to decrease the probability of the postsynaptic cells firing action potentials. A given neuron will release one neurotransmitter from its axon. And so, a neuron might be glutamatergic, in which case, from its axon -- along all its different synaptic specializations -- it'll release glutamate; and a different neuron will release GABA from its axon. And so glutamate and GABA make up the vast majority of synapses in the central nervous system. The first neurotransmitter that was identified, however, was acetylcholine.

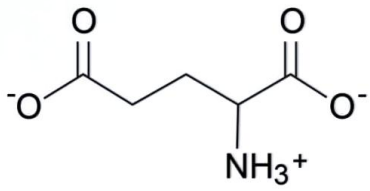
Notes

Summary

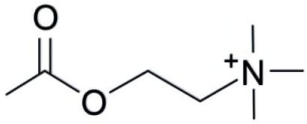
1m 33s

Diverse neurotransmitters

Glutamate



Acetylcholine

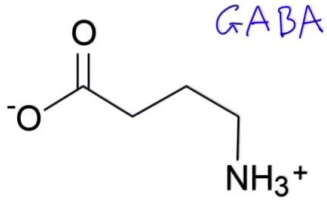


Met-enkephalin

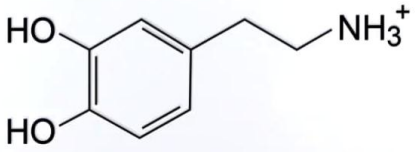
Tyr - Gly - Gly - Phe - Met

γ-aminobutyric acid

GABA



Dopamine



Oxytocin

Cys - Tyr - Ile - Gln - Asn
Gly - Leu - Pro - Cys

Cellular Mechanisms of Brain Function

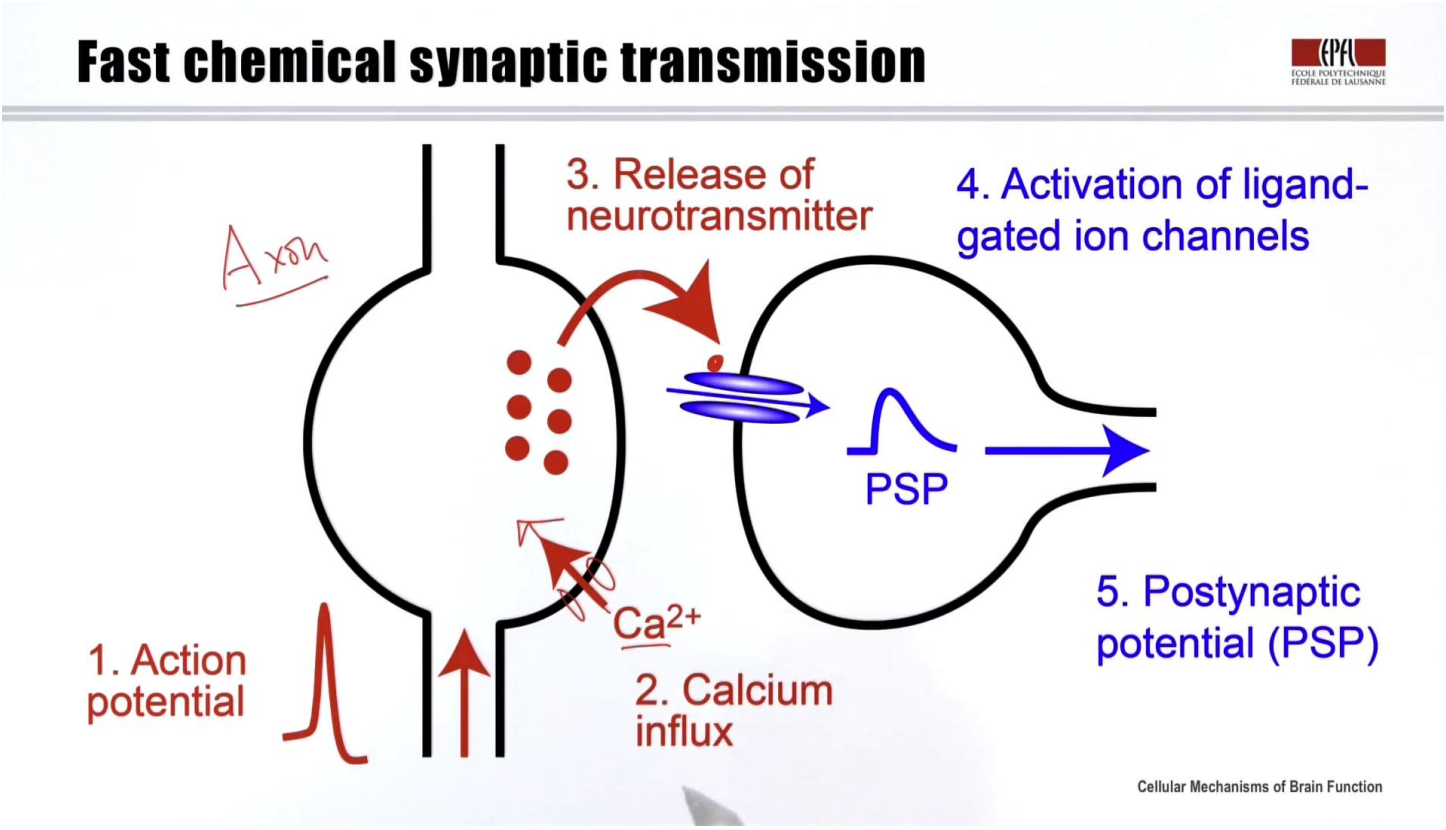
And that has an important role in regulating heart function, and, most importantly, it is the neurotransmitter at the mammalian neuromuscular junction. So a motor neuron will release acetylcholine from its nerve ending, and that acetylcholine will bind to acetycholine receptors that are present on muscle; and that forms the first step in initiation of contraction of that muscle. Dopamine is another interesting neurotransmitter. Dopamine function is thought to be highly involved in reward-based learning, and deficits in dopamine function appear to be important components in diseases such as Parkinson's disease, in which case there's a deficit in the regulation and release of dopamine. Equally, dopaminergic dysfunction is also thought to be a key player in schizophrenia, and dopamine is part of a family of neurotransmitters called the catecholamines. These small molecules are complemented by slightly larger neurotransmitters, made out of small peptide chains. And so one neuropeptide, met-enkephalin, is composed of five different amino acids and here another one, oxytocin, has nine different amino acids in it. And of course, there are many different neuropeptides that signal as neurotransmitters; and indeed, this is just a small subset of the total number of neurotransmitters that are present; and indeed, new neurotransmitters are continually being discovered.

Notes

Summary

3m 07s

Fast chemical synaptic transmission



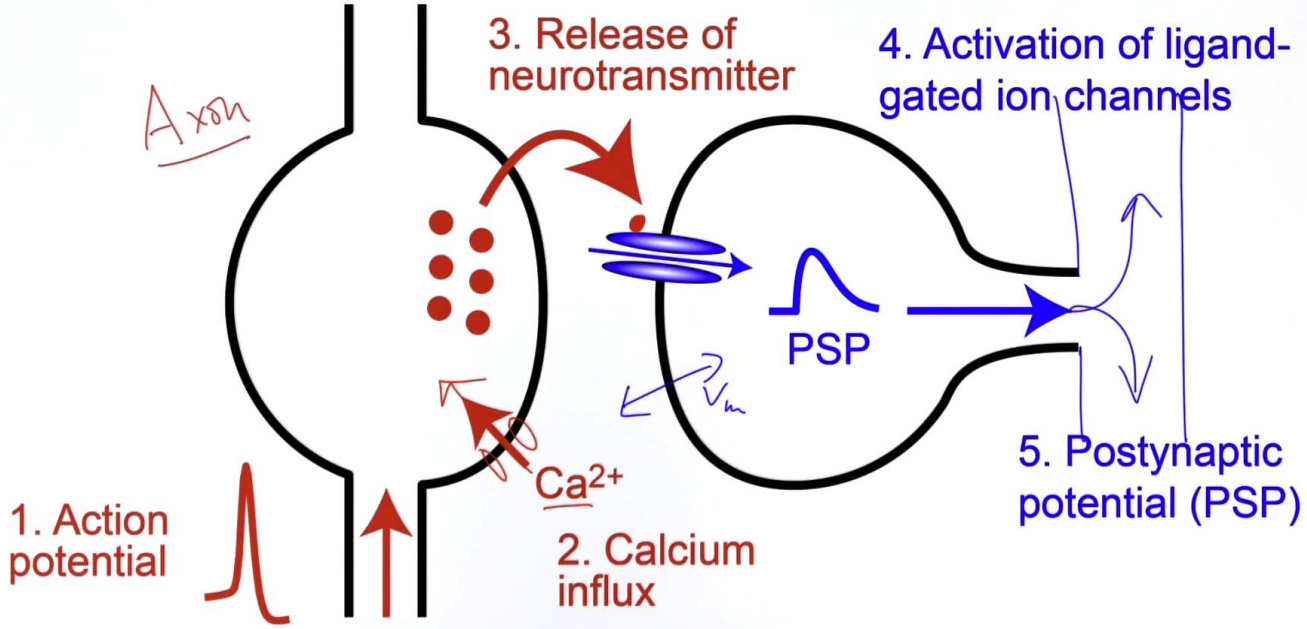
The basic process of fast chemical synaptic transmission that dominates neuron-to-neuron communication is schematically shown here in five important steps. We have the presynaptic axon. An action potential is traveling down the axon; it invades the presynaptic specialization, the bouton. At the bouton, there are present a set of voltage-gated calcium channels. And so these are voltage-gated ion channels, similar to the potassium and sodium channels we've already considered, except they conduct calcium ions. And so they're activated by the depolarization of the action potential, and the voltage-gated calcium channel then increases its open probability, and allows an influx of calcium to occur into the presynaptic bouton. That elevation in calcium concentration causes the release of neurotransmitter that's stored, and it's released into the extracellular space, into the synaptic cleft. There's some 50 nanometers of extracellular space here. The neurotransmitter diffuses and binds to a neurotransmitter receptor that's present in the postsynaptic membrane. For fast chemical synaptic transmission, the binding of the neurotransmitter to the receptor is onto a so-called ligand-gated ion channel.

Notes

Summary

4m 48s

Fast chemical synaptic transmission

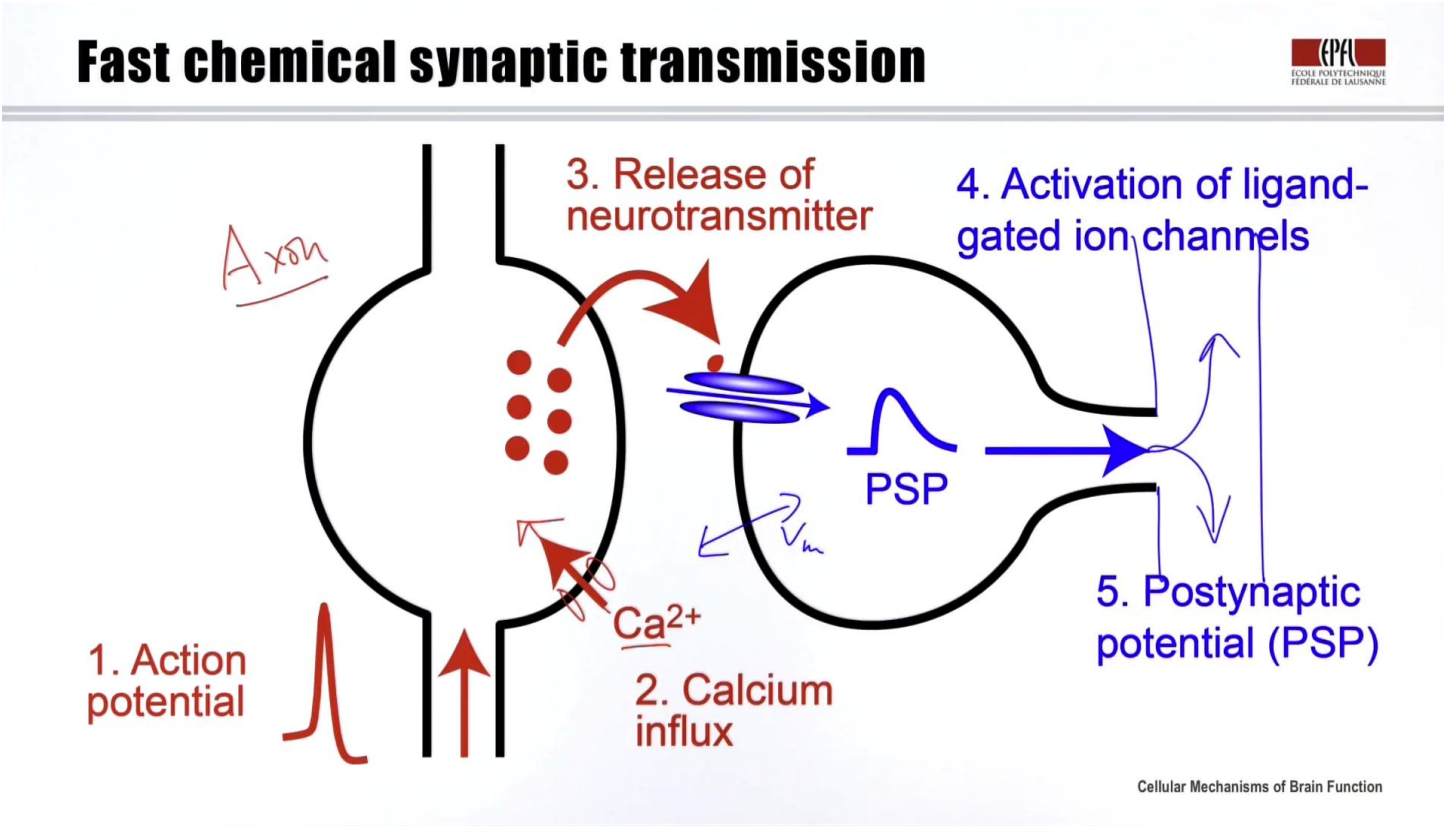


That's a protein, it's an ion channel very similar to the other types of ion channels that we've already considered; but the open probability of this ion channel is not gated by voltage or anything else, but it's gated by the presence or absence of a neurotransmitter. And so, that released neurotransmitter binds to a ligand-gated ion channel, and the binding of that neurotransmitter increases the open probability, and that then causes an influx of ions that then changes the membrane potential of the postsynaptic cell and causes a so-called postsynaptic potential. The synapses are typically on dendrites that are far from the somatic area of the neuron. And so there's a dendrite that connects the synapse, and the flow of current from the postsynaptic potential; and the postsynaptic current, then, needs to cut across the cable properties of the dendrites before it reaches the soma and the axon initial segment; and of course, it's the axon initial segment that forms the trigger point for an action potential in the postsynaptic cell. And so, a typical postsynaptic cell will have many hundreds or thousands of synapses.

Notes

Summary

6m 23s



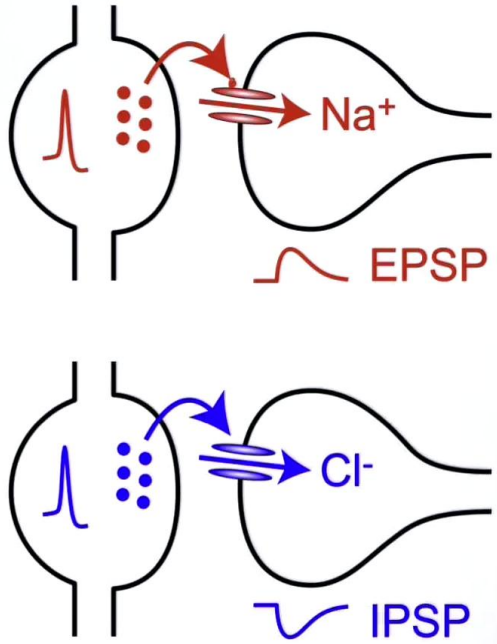
Some of them will be excitatory synapses; some of them will be inhibitory synapses; and the potentials here will be summated at the level of the axon initial segment; and that will then be the place where the postsynaptic neuron decides on whether it should fire an action potential in turn; and if it fires an action potential, the axon of that cell can then come back, and we'll have another process of synaptic transmission with different partners somewhere in the brain. The process of synaptic transmission is extremely rapid. The action potential has a time course of about 1 millisecond, there's a short delay for getting calcium into the bouton and the release process also takes a short delay, but the postsynaptic potential typically occurs with a latency of within 1 millisecond of the action potential in the presynaptic terminal. So, synaptic transmission is a very fast process, and neurons can communicate with each other on the millisecond timescale.

Notes

Summary

7m 41s

Excitatory and inhibitory synapses



Glutamate activates postsynaptic ionotropic glutamate receptors permeable to Na^+ and K^+ with reversal potential ~0 mV causing an excitatory postsynaptic potential (EPSP).

GABA activates postsynaptic ionotropic GABA receptors permeable to Cl^- with reversal potential ~ -70 mV causing an inhibitory postsynaptic potential (IPSP).

Cellular Mechanisms of Brain Function

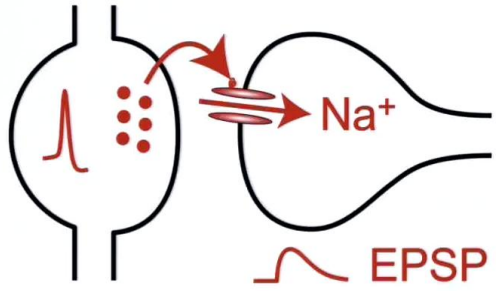
Synapses can be excitatory and inhibitory. And here, we illustrate the two major forms of synapses that are present in the central nervous system. An excitatory synapse typically releases glutamate from its presynaptic specialization. That release of glutamate acts upon glutamate receptors: these are so-called ionotropic glutamate receptors -- that is, that they're ligand-gated ion channels activated by the presence of glutamate -- and the glutamate receptor is permeable to both sodium and potassium, and they're a little bit more permeable to sodium. The reversal potential of these ionotropic glutamate receptors is somewhere around 0 millivolts. 0 millivolts is depolarized relative to action potential threshold, and so the excitatory postsynaptic potentials, the EPSPs that are made in the postsynaptic neuron, tend to depolarize the cell beyond action potential threshold and tend to increase action potential firing in the postsynaptic neuron. And that's why glutamate is an excitatory neurotransmitter. The major inhibitory neurotransmitter is GABA, and release of GABA from the presynaptic terminal, binds to ionotropic GABA receptors, GABA_A receptors.

Notes

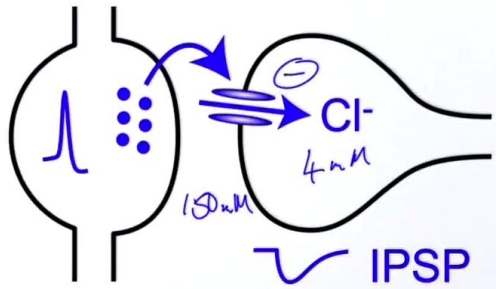
Summary

8m 45s

Excitatory and inhibitory synapses



Glutamate activates postsynaptic ionotropic glutamate receptors permeable to Na^+ and K^+ with reversal potential ~0 mV causing an excitatory postsynaptic potential (EPSP).



GABA activates postsynaptic ionotropic GABA receptors permeable to Cl^- with reversal potential ~ -70 mV causing an inhibitory postsynaptic potential (IPSP).

Cellular Mechanisms of Brain Function

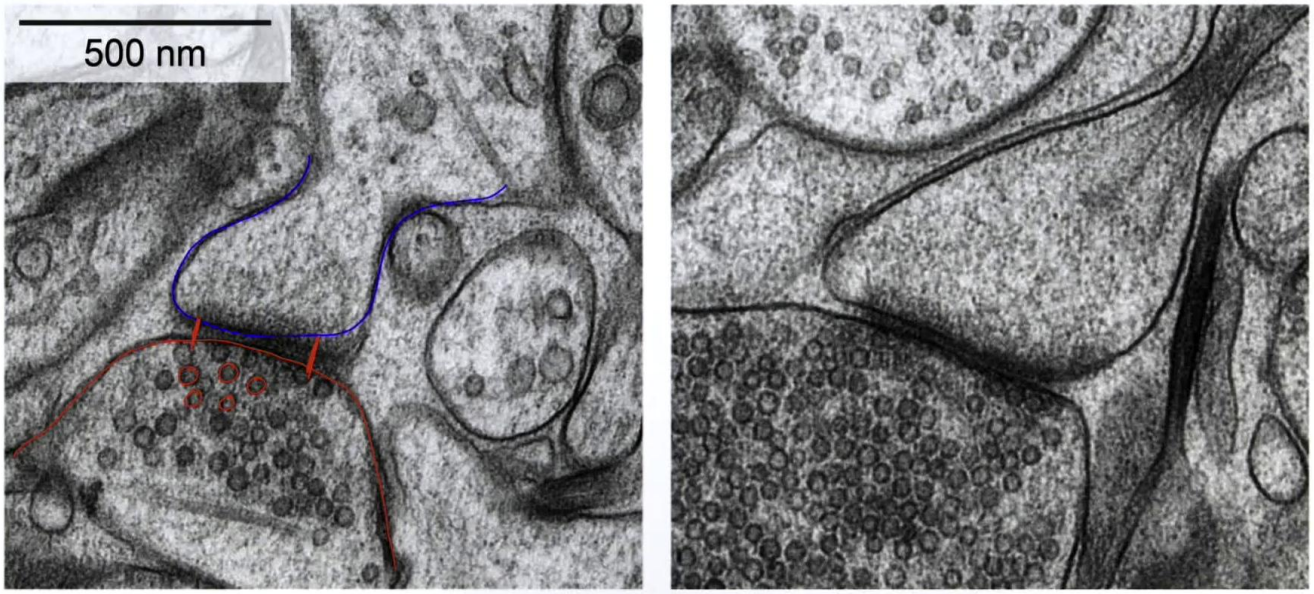
They turn out to be conductors of chloride, and chloride, as we know, is present at low concentrations intracellularly, at high concentrations extracellularly; and so chloride wants to enter a cell, carrying negative charge with it, causing hyperpolarization of the membrane; and that then causes inhibitory postsynaptic potentials, IPSPs, that take the neuronal membrane potential more negative than action potential threshold, and thus causing a reduction in action potential output. So we have excitatory and inhibitory types of neurotransmission.

Notes

Summary

10m 06s

Electron microscopy of synaptic structure



Korogod, Petersen and Knott

Cellular Mechanisms of Brain Function

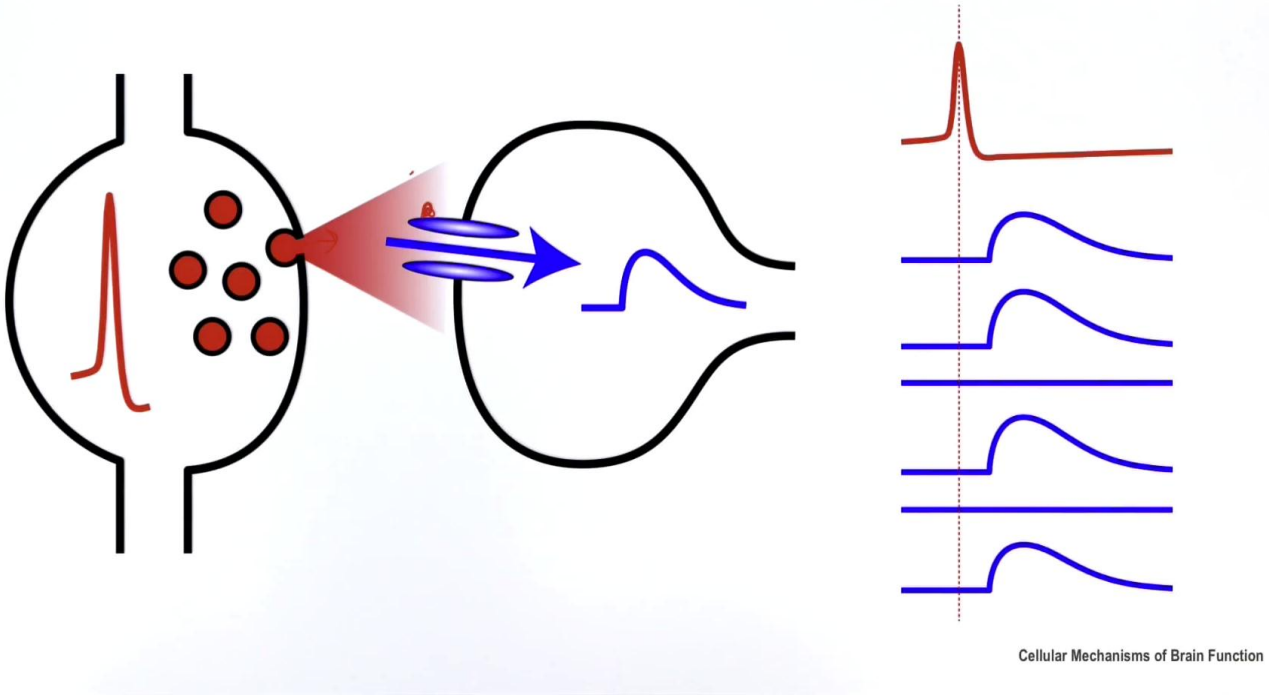
The structure of synapses can be observed at high resolution using electron microscopy. Synapses turn out to be small, typically smaller than 1 micron. On this scale bar here, we have a 500 nanometer distance and this synapse here, shown in the left, has a size of about 200 nanometers; and this synapse here is larger: it has a size of about 500 nanometers; and they're entirely typical synapses found in the central nervous system. You will see the two compartments that we've already discussed. There's the presynaptic membrane, and there's the postsynaptic membrane, here. The distance between the presynaptic and postsynaptic membrane is very short -- it's on the order of 50 nanometers -- and you can also see that it's rich in this dark stuff here, electron-dense material, proteins that link the pre- and postsynaptic specializations and hold them tightly apposed to each other. Also obvious are these so-called round synaptic vesicles. They're around 40 nanometers in diameter and they're filled with high concentrations of neurotransmitter. And what the incoming action potential does, is cause these synaptic vesicles, that are in close apposition with the presynaptic membrane, to release the contents into the synaptic cleft.

Notes

Summary

10m 46s

Quantal release of neurotransmitter



Cellular Mechanisms of Brain Function

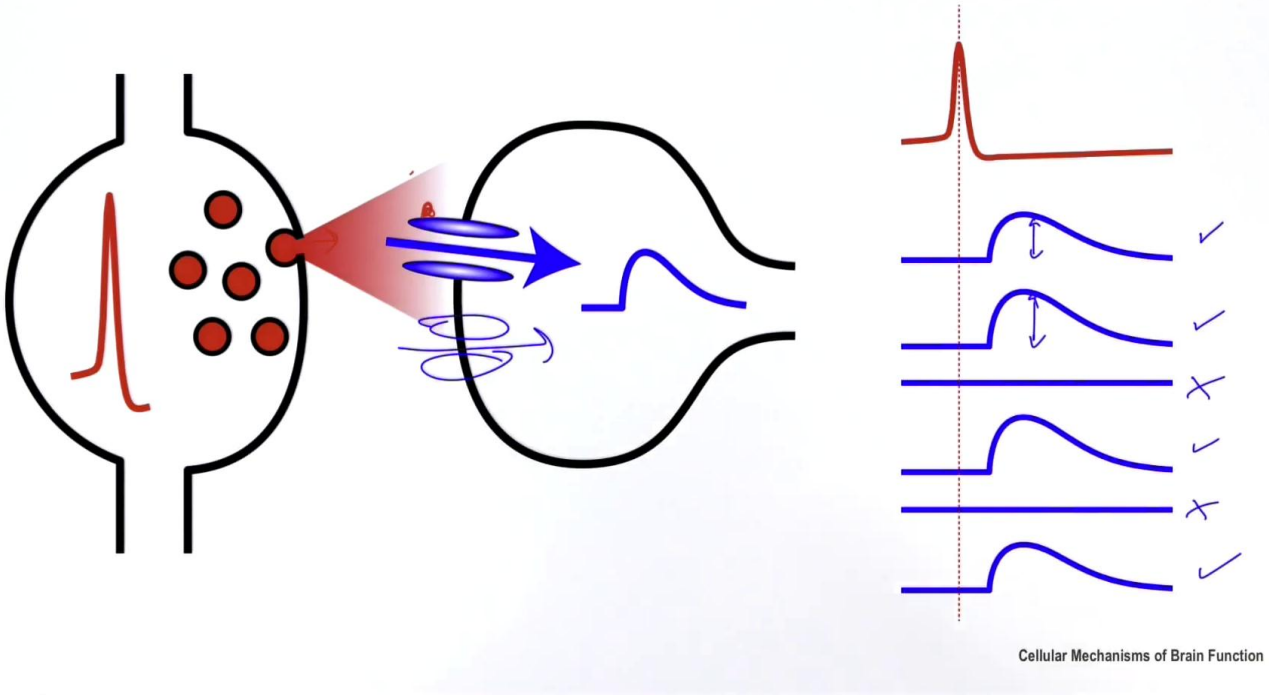
We see that schematically drawn here. The action potential invades the bouton; the synaptic vesicles are, in fact, enveloped by lipid membranes just the same as the lipid membrane that we have at the plasma membrane; and these lipid bilayer membranes also envelope the synaptic vesicles -- they're 40 nanometers in diameter -- and upon action potential firing, calcium influx, the synaptic vesicles fuse their membrane with the presynaptic membrane. That fusion of the membrane causes exocytosis; the contents, the neurotransmitter inside the synaptic vesicle, is released; and that neurotransmitter molecules then diffuse into the synaptic cleft, something like 40, 50 nanometers. Their diffusion is rapid; the neurotransmitter binds to its ligand-gated ion channel and causes a conductance. The presence of these synaptic vesicles, then, raised the idea that synaptic transmission might be quantal in nature. An action potential might release a vesicle, or it might not release a vesicle. And so there could be a quantized, all-or-none form of communication at individual synapses.

Notes

Summary

12m 19s

Quantal release of neurotransmitter



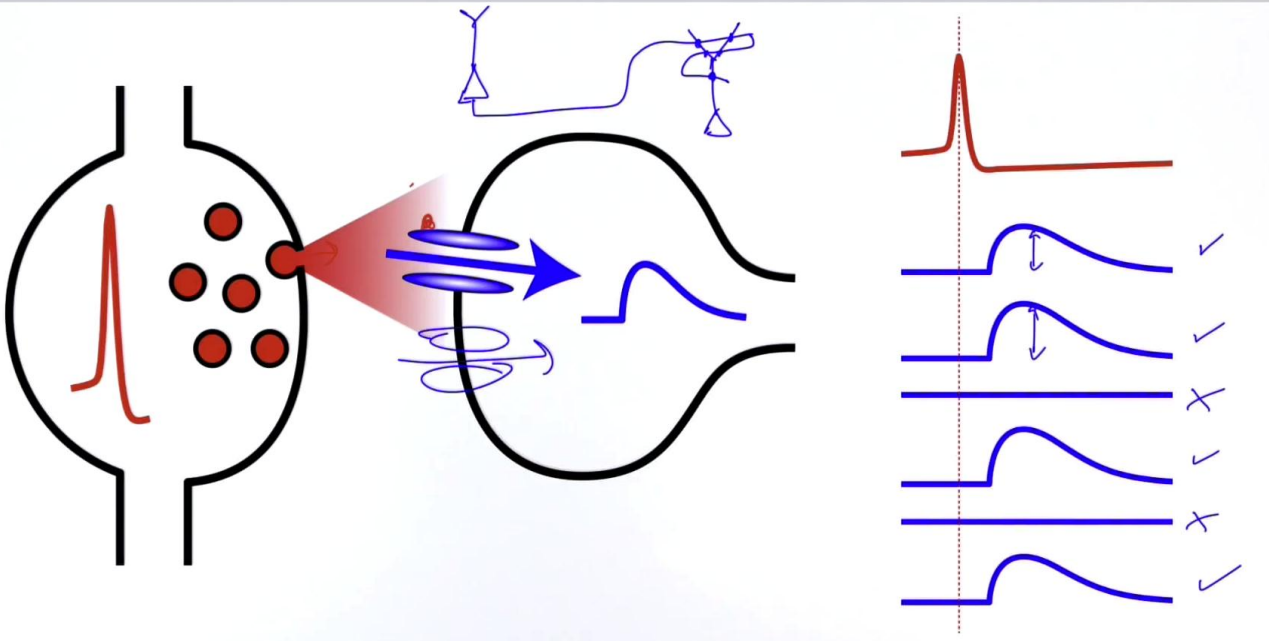
And indeed, the first measurements of synaptic transmission, at the frog neuromuscular junction, by Sir Bernard Katz in the 50's, showed exactly this: that neurotransmitter occurs in quantized packages; and this is schematically illustrated here. Here we have an action potential in a presynaptic axon; it causes calcium influx; the action potential is reliable, but the synaptic transmission has failures. So on this trial, there's synaptic transmission; there's release of neurotransmitter; activation of the ligand-gated ion channels; a nice postsynaptic potential is formed here also. But on *this* trial, the action potential failed to cause exocytosis, and no substance was released; and therefore, there's no postsynaptic response. And here, there's again a success; failure; success. And you can see that these have roughly the same size. There's a little bit of variation in amplitude, and that's probably because there's different amounts of neurotransmitter present or because the neurotransmitter reaches a little bit further and can, perhaps, activate more postsynaptic receptors. So, there's some variability here; but the major feature is an all-or-none synaptic transmission caused by the all-or-none exocytosis of individual synaptic vesicles.

Notes

Summary

13m 36s

Quantal release of neurotransmitter



Cellular Mechanisms of Brain Function

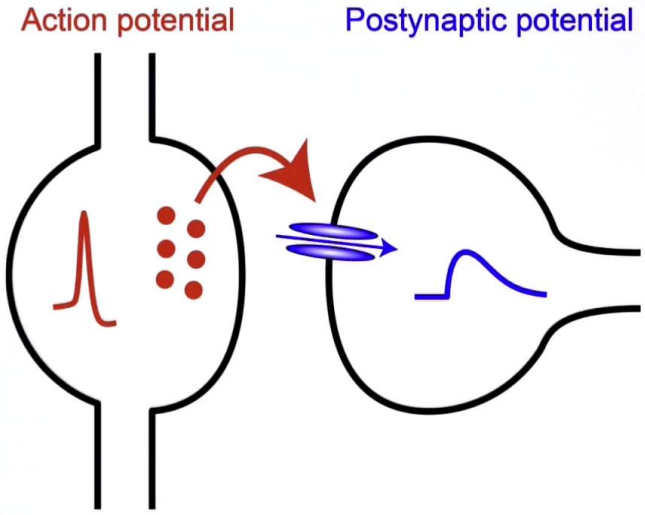
There's, then, some variability and randomness in the process of synaptic transmission at individual synapses; and therefore, if a neuron needs to communicate a very important message to another nerve cell, then typically, it'll do so by having multiple synapses. So if this is one cell, and this is its axon, that axon might then make multiple contacts with a postsynaptic cell, if it was going to make a very important message that had to be reliably communicated. And so this axon might come back and forth, and it might make many different synapses here. And then the stochastic variations that occur at individual synapses are then averaged out, by having many synapses, or many different active zones, that then give rise to a statistically average, well-defined quanta amount of neurotransmitter, sensed postsynaptically.

Notes

Summary

15m 01s

Synaptic transmission



Cellular Mechanisms of Brain Function

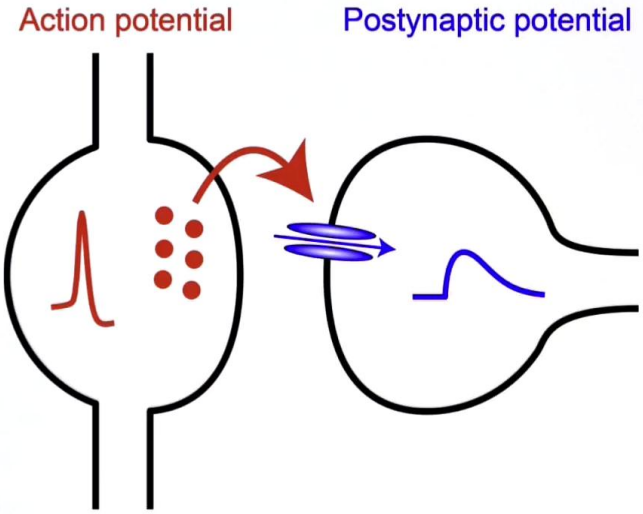
So we've now seen some fundamental aspects about how neurons communicate with each other. Neurons communicate through chemical synaptic transmission, where an action potential in a presynaptic cell travels down the axon, causes release of neurotransmitter from presynaptic boutons. They then act at postsynaptic ligand-gated ion channels that cause postsynaptic potentials. There are many synapses down a single axon and one neuron releases the same neurotransmitter onto many different postsynaptic target cells. Equally, an individual neuron receives synaptic inputs distributed across its dendritic arborization from many other neurons. Those synaptic inputs can be excitatory and inhibitory; and what the postsynaptic cell needs to do is to summate the excitatory and inhibitory conductances, and see whether it, too, should fire an action potential. And that final integration occurs at the axon initial segment, close to the somatic location of the cell. And so the way that neurons communicate with each other, then, is through large networks of synapses passing messages from one cell to another, integrating those specific messages, and seeing whether the resulting computation is sufficient to drive an action potential in the postsynaptic neuron.

Notes

Summary

15m 59s

Synaptic transmission



Cellular Mechanisms of Brain Function

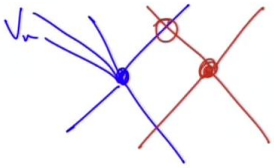
And all of this communication takes place at the millisecond timescale, allowing rapid computations to take place in the mammalian brain. Now, although chemical synapses are the most important signals in the mammalian brain, they're not the only ones. And in the next three slides, we'll show three variations on the theme of neuron-to-neuron communication.

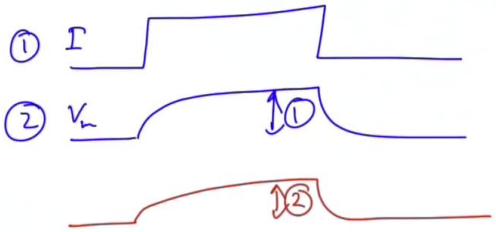
Notes

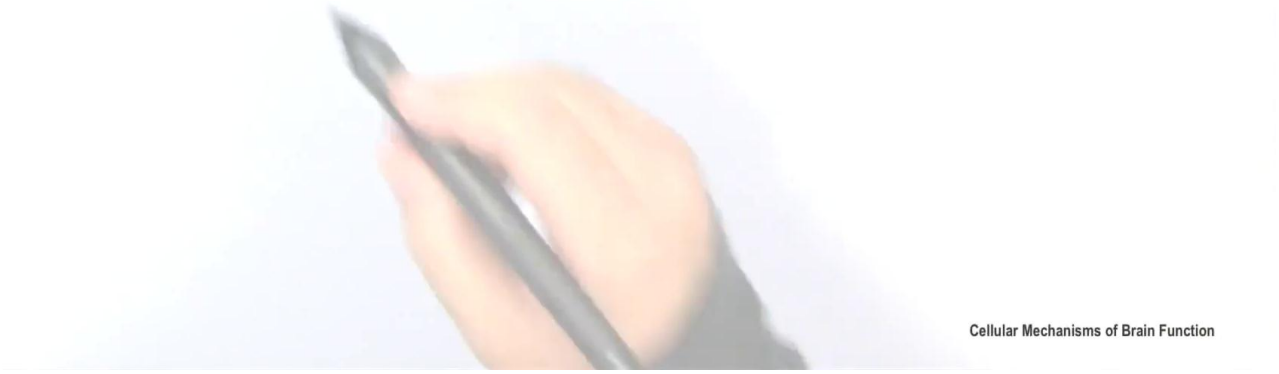
Summary

17m 32s

Electrical synapses







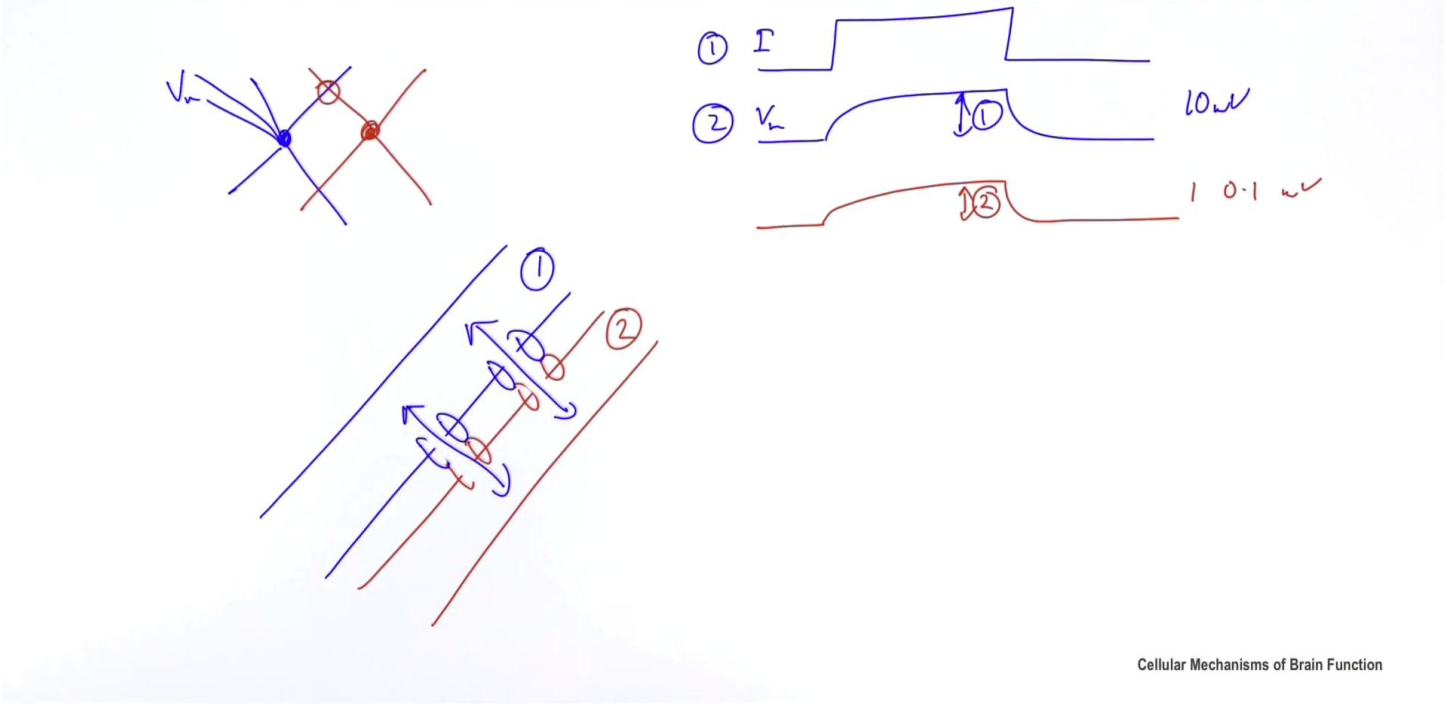
The first aspect is that not all synapses, and not all communication between neurons, occurs through chemical messages. There are, in fact, also electrical synapses that are present in the mammalian nervous system. And so one neuron may have axon and dendrite that looks like this, and another cell may have axon and dendrite that overlap and, perhaps, in one location, they come into close contact with each other and they might form an electrical synapse. Electrical synapses are rare in the mature mammalian brain, but during early development, many cells are, in fact, electrically coupled. If we then take cell one and inject some current into it while we're making a recording of the membrane potential of the cell through a glass electrode -- so, we can inject the current into cell one; that will then cause depolarization of that cell; and its membrane potential; and if these cells are electrically coupled to each other, then, in cell two, we will then also get a depolarization. The size of that depolarization, here in cell two, would be much smaller than the depolarization present in cell one. There's quite a lot of resistance at the gap junction coupling between these two cells.

Notes

Summary

17m 57s

Electrical synapses



Cellular Mechanisms of Brain Function

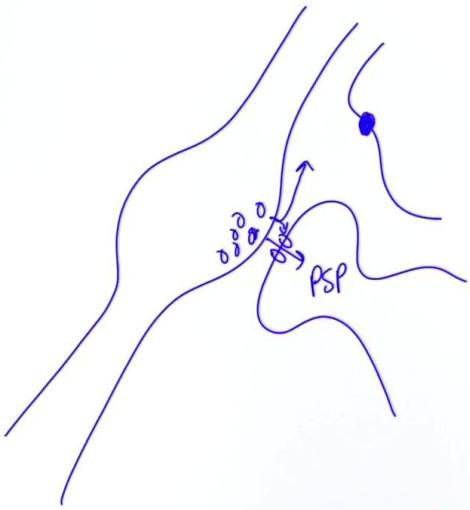
And so the scale here: if this, say, is 10 millivolts, then the postsynaptic cell might depolarize by 1 or 0.1 millivolts. So there's a big change, a drop in potential across electrical synapses. The electrical synapses are formed by specialized junctions, so-called *gap junctions*, where if this is the membrane of cell one, and we have the membrane of cell two sitting close by it -- these could be axons or dendrites -- then, the way that they communicate is through special proteins that are sitting here in the plasma membrane; they're present on both sides of the so-called electrical synapse; and they then create gap junctions, where current can flow directly between one cell and another.

Notes

Summary

19m 28s

Volume transmission



Cellular Mechanisms of Brain Function

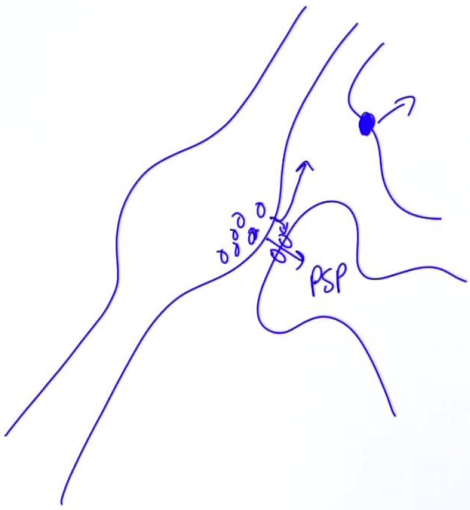
Another important feature of synaptic transmission is that there is a diffusive component, where a presynaptic bouton -- that's filled with neurotransmitters, of course -- releases those vesicles onto the postsynaptic specialized structure, and activates an ion channel -- ligand-gated ion channels -- to cause postsynaptic potentials, as we've already discussed. But: that neurotransmitter will also leak out of the synaptic cleft and go into the extracellular space; and here, it can also bind to neurotransmitter receptors, causing distinct actions at a distance from the actual one-to-one synapse. And so there's a highly specific, one-to-one communication of synaptic transmission, and then there's a more general, volume synaptic transmission, where this neurotransmitter diffuses out; of course, the concentration goes down; and the speed of transmission is also, of course, reduced in this extracellular volume transmission. But it is an important regulator of brain function and, indeed, the extracellular concentration of neurotransmitters is likely to have important roles.

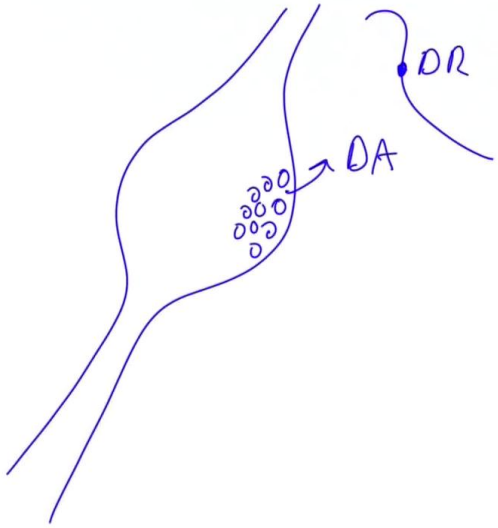
Notes

Summary

20m 31s

Volume transmission





Cellular Mechanisms of Brain Function

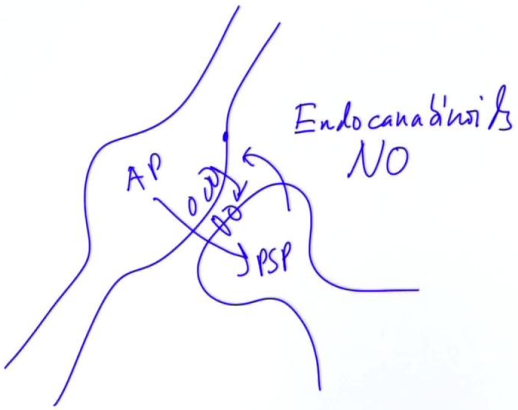
So, for glutamate and GABA, the two main fast synaptic transmitters in the mammalian nervous system, they have this fast one-to-one component; and then, in addition, there's glutamate and GABA that's present in the extracellular space, and that binds to different types of receptors than are present in the synapse. For yet other neurotransmitters, their only way of function is through volume transmission. And, so for example, at a dopaminergic synapse or presynaptic bouton, there's no postsynaptic specialization, at all. And here, the dopamine is simply being released into the extracellular space, where it can bind to different dopamine receptors that are present on a variety of different membranes. And so there are different forms of synaptic transmission: fast, point-to-point chemical synaptic transmission, driving the opening of ligand-gated ion channels; and a more diffuse volume transmission that typically operates through other, slower biochemical signaling cascades.

Notes

Summary

21m 49s

Dendritic release of neurotransmitters



Cellular Mechanisms of Brain Function

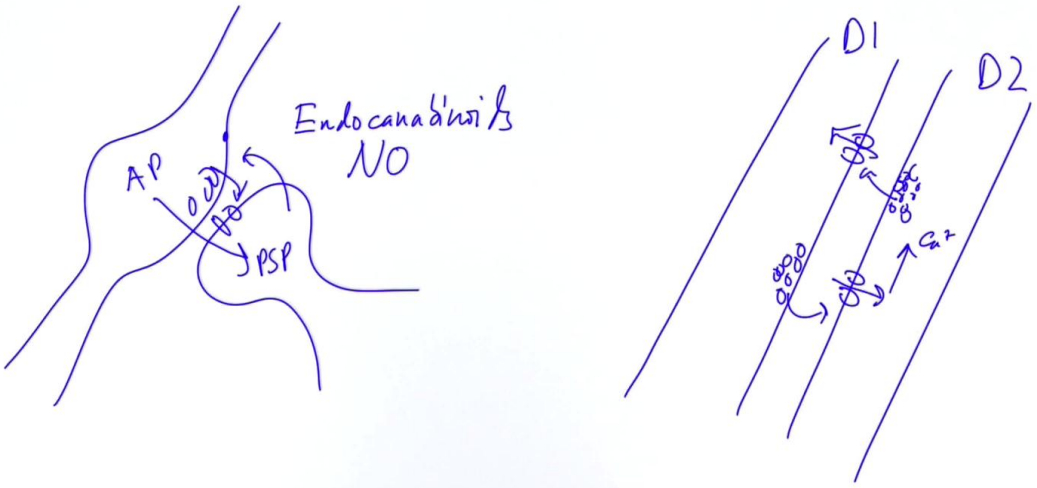
As a final point, I would like to make a note that synaptic transmission, although largely unidirectional -- that is, from the presynaptic bouton, on to the postsynaptic membrane; and so there's a one direction, the normal direction, from action potential to postsynaptic potential -- is, by far, the most important form of neurotransmission and synaptic transmission; but there is also a retrograde signaling that has been discovered over the last decades and that's likely to form an important regulatory role. And so dendrites and postsynaptic compartments can release neurotransmitters, such as the endocannabinoids, and other transmitters such as nitric oxide. And so it seems that the synapse is actually bidirectional communication, where the main direction is from the bouton, releasing synaptic vesicles' neurotransmitter onto ligand-gated ion channels, causing postsynaptic potentials; but retrograde signals are also important; and they act on other receptors and regulate the forward direction of synaptic transmission. In still other more specialized systems, for example in part of the olfactory bulb, there's actually the situation where two different dendrites, dendrite one and dendrite two, can communicate directly with each other through synaptic transmission.

Notes

Summary

22m 56s

Dendritic release of neurotransmitters



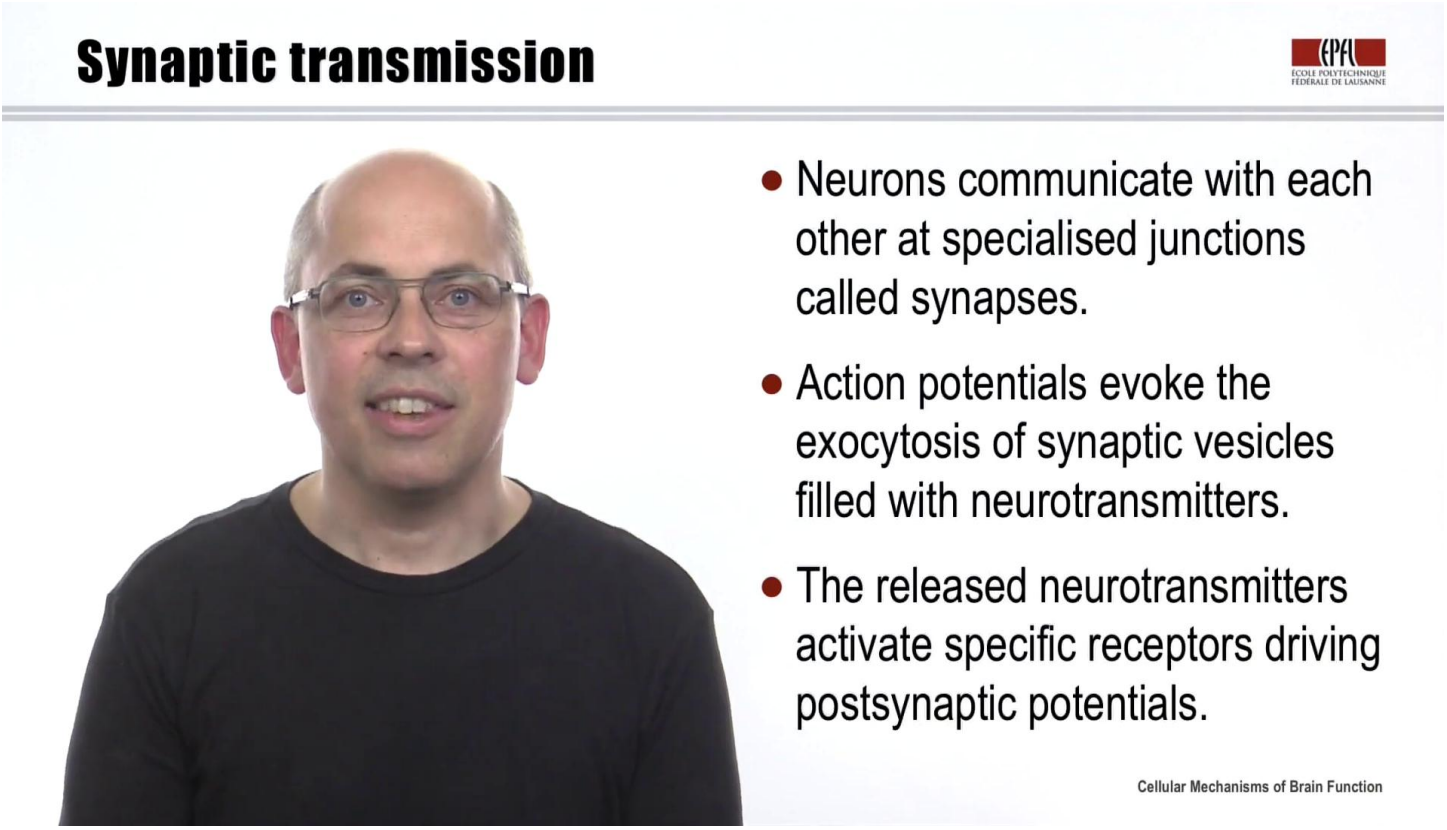
Cellular Mechanisms of Brain Function

And so, some dendrites actually have synaptic vesicles that can be released, act upon neurotransmitter receptors in the postsynaptic dendrite; that in turn causes calcium increases; and here, again, synaptic vesicles clustered here can then be released and act as a retrograde signal back onto the same dendrite. And so dendrodendritic release is also possible. And so there's a number of different ways in which synaptic transmission differs from its standard form; but these are specializations, and the most important thing is the standard, unidirectional synaptic transmission from presynaptic to postsynaptic neuron.

Notes

Summary

24m 27s

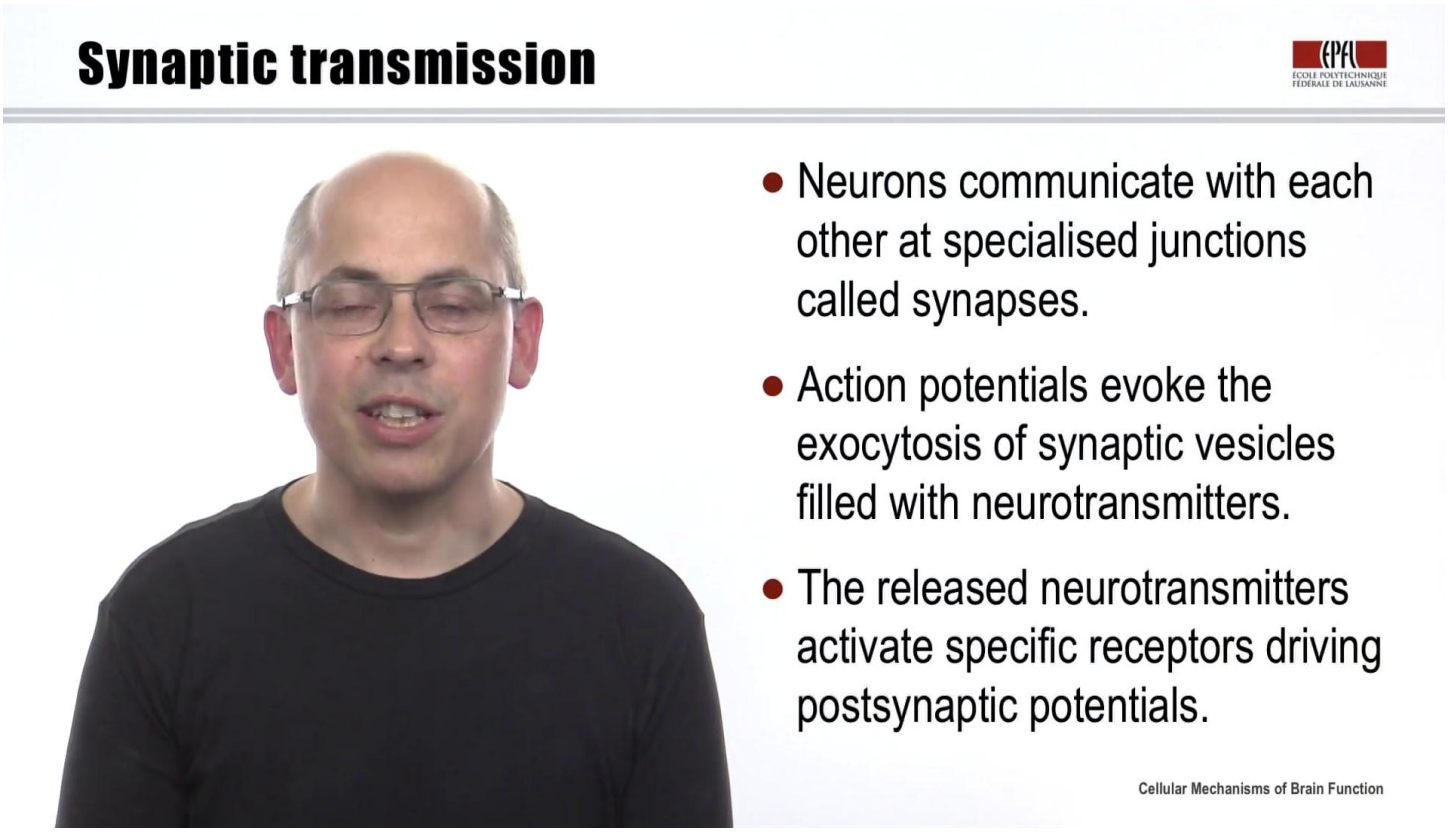


And so, in this lesson, we've seen interesting aspects of synaptic transmission, how two neurons talk to each other. Typically, in chemical fast synaptic transmission, the action potential invades the presynaptic bouton, causes an increase in the calcium concentration, and that rising calcium concentration causes the exocytosis of synaptic vesicles. Small, lipid-bound vesicles that contain high concentrations of neurotransmitter: they're released into the synaptic cleft, and they then bind rapidly onto ionotropic ligand-gated receptors that form ion channels that increase their open probability in response to the neurotransmitter, causing, in turn, a change in the postsynaptic membrane potential. We then have excitatory postsynaptic potentials that tend to increase the firing of the postsynaptic cell, and inhibitory postsynaptic potentials that tend to hyperpolarize the postsynaptic cell and reduce action potential firing. Neurons receive excitatory and inhibitory synapses all across their dendrites, and they need to integrate that and decide whether to fire an action potential themselves. That action potential is then transmitted down the axon of that nerve cell, and the nerve cell releases one type of neurotransmitter from its presynaptic specializations.

Notes

Summary

25m 11s



It might release glutamate, if it's an excitatory cell; or GABA, if it's an inhibitory cell; or, if it's another type of cell, it might release more specialized neurotransmitters such as dopamine, acetylcholine, norepinephrine, or any of a large plethora of neurotransmitters that are available for the mammalian brain. In the next lessons, we'll learn more about the molecular details of neurotransmission.

Notes

Summary

26m 40s