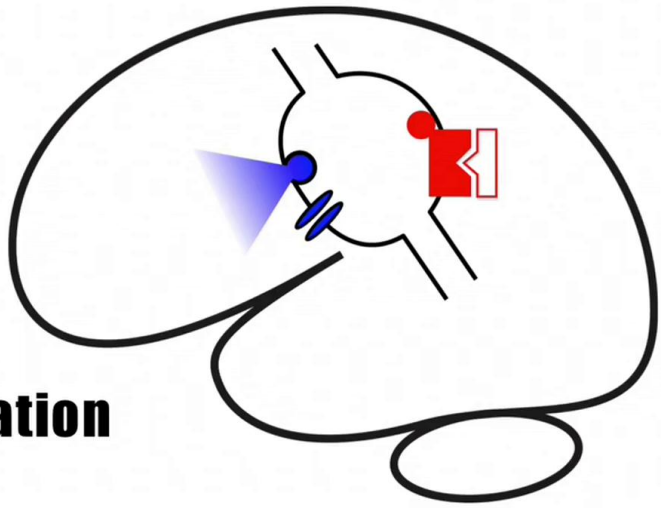
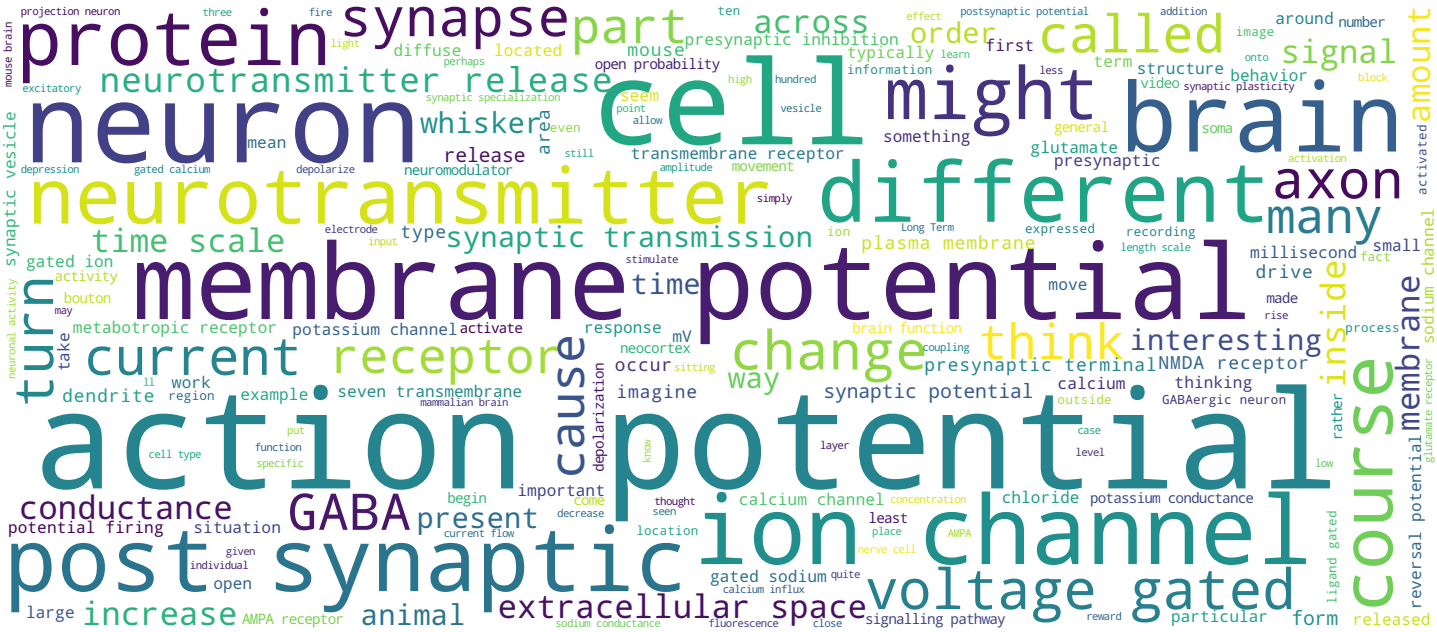


3.4 Presynaptic modulation

Cellular Mechanisms of Brain Function

Prof. Carl Petersen


action potential
membrane potential
neuron
cell
brain
protein
synapse
neurotransmitter
different
ion channel
post synaptic
voltage gated
current
receptor
change
think
interesting
course
cause
turn
time scale
neurotransmitter release
synaptic transmission
extracellular space
GABA
conductance
potential firing
calcium channel
chloride
potassium conductance
NMDA receptor
presynaptic terminal
synaptic potential
metabotropic receptor
potassium channel
dendrite
seven transmembrane
transmembrane receptor
whisker
axon
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order
signal
behavior
structure
glutamate
presynaptic
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membrane
sodium channel
reversal potential
ligand gated
extracellular space
increase
AMPA receptor
animal
gated sodium
calcium influx
signalling pathway
particular
form
released
reward
fluorescence
close
sodium conductance
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individual
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begin
important
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brain function
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bouton
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gated ion
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gated calcium
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general
soma
activation
activated
amount
around
number
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onto
block
addition
postsynaptic potential
effect
ten
light
diffuse
located
fire
three
projection neuron
mouse brain
excitatory
synaptic vesicle
neuronal activity
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video
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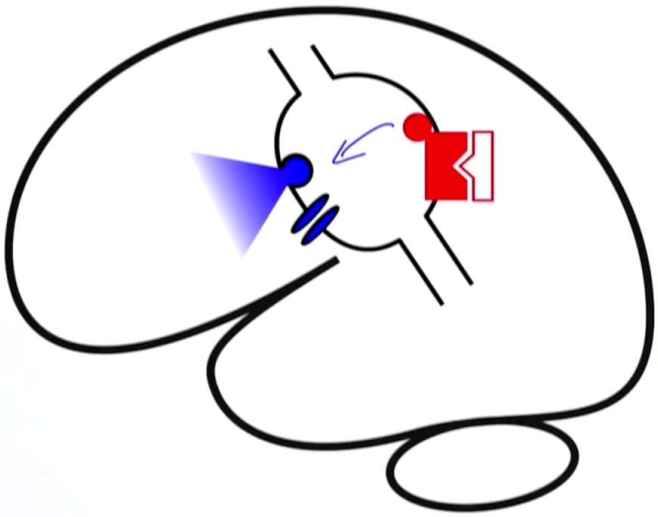
region
example
seven transmembrane

Presynaptic neuromodulation



Cellular Mechanisms of Brain Function

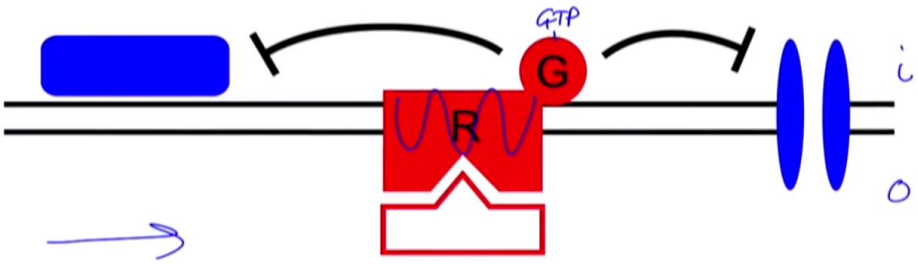
In the last lesson, we learned that there's a certain context-dependence to synaptic transmission. The effect of an action potential and its coupling to neurotransmitter release depends heavily upon the recent activity of that axon. Now in this lesson, we're going to learn that there's another form of context-dependence to neurotransmission: that of the neurotransmitter content of the extracellular space. It turns out that the brain is made of about 20 percent or so of extracellular space. And that, then, means that neurotransmitters released from one bouton can diffuse relatively long distances and impinge upon membranes that are relatively far from that synapse. Also, interestingly, there are receptors that are present on the presynaptic boutons so that neurotransmitters diffusing from other boutons can impinge upon these receptors, and that, then, can affect the release process at this synapse that we're considering. This process of presynaptic modulation, then, is what we'll be considering in this video.

Notes

Summary

0m 04s

Presynaptic metabotropic receptors



Most metabotropic receptors are seven-transmembrane receptors (R), activating GTP-binding proteins (G), which signal via diverse pathways, including ion channels, second messenger systems and gene regulation.

Cellular Mechanisms of Brain Function

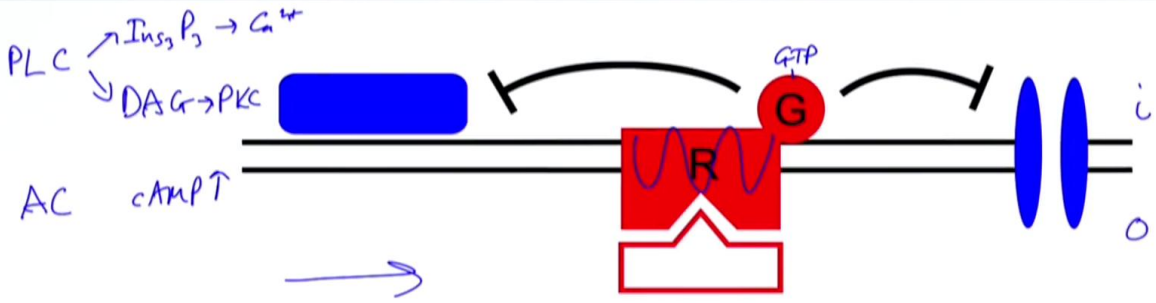
The receptors that are most relevant in terms of regulating presynaptic neurotransmitter release are the so-called *metabotropic receptors*. These are transmembrane proteins, so they have alpha helices just like the ion channels; but, rather than forming directly an ion channel, they signal through to other proteins that are located on the intercellular side. And so, if this is a piece of the plasma membrane, and this is the outside, and this is the inside, then here, in the extracellular space, we have neurotransmitters that are diffusing around. Some of these neurotransmitters might then bind to one of these seven-transmembrane receptors; and so, they have seven parts that cross the plasma membrane. These are the alpha helices. When an agonist binds to that receptor, the protein changes its conformational structure but rather than being an intrinsic ion channel, it then acts upon an intracellular protein, a so-called *GTP-binding* protein, or a G protein. The G protein, upon receptor activation, binds GTP; then, it becomes activated. It splits into two parts, an alpha and a beta/gamma part. They can then diffuse inside the cell and, in part, they might act directly upon ion channels.

Notes

Summary

1m 21s

Presynaptic metabotropic receptors



Most metabotropic receptors are seven-transmembrane receptors (R), activating GTP-binding proteins (G), which signal via diverse pathways, including ion channels, second messenger systems and gene regulation.

Cellular Mechanisms of Brain Function

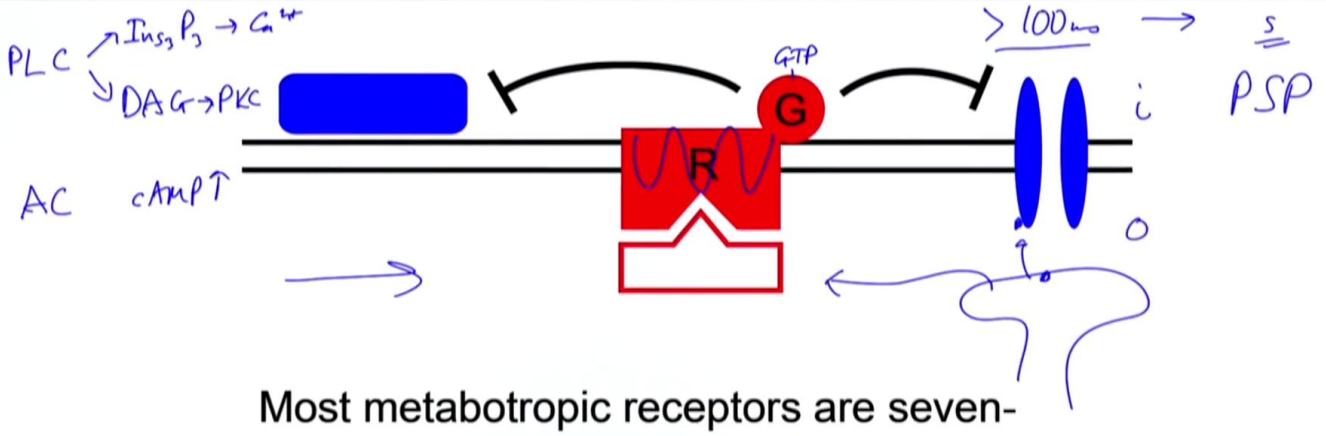
And in part, these G proteins might act upon other enzymes that are present inside the cell that then might activate downstream signalling cascades. And so, one of the enzymes that G proteins act upon is an enzyme called phospholipase C that splits into two parts: one part that releases inositol trisphosphate but then goes on to release calcium from intracellular calcium stores, and another part that releases diacylglycerol that then activates protein kinase C. Or, you might activate the enzyme adenylate cyclase, and that might increase the level of cyclic ANP. And there are many, many other signalling pathways giving rise to different second messenger systems that affect both the structure of nerve cells and can also even effect the gene expression patterns of these cells. And so, metabotropic receptors have very diverse functions inside neurons, and they can, therefore, be extremely useful. They do, however, operate on a slower timescale than our ligand-gated ion channels that we've been thinking about in terms of synaptic transmission up to now, where we'd have a presynaptic terminal releasing neurotransmitter, acting directly on ligand-gated ion channels to create post-synaptic potentials.

Notes

Summary

2m 50s

Presynaptic metabotropic receptors



Most metabotropic receptors are seven-transmembrane receptors (R), activating GTP-binding proteins (G), which signal via diverse pathways, including ion channels, second messenger systems and gene regulation.

Cellular Mechanisms of Brain Function

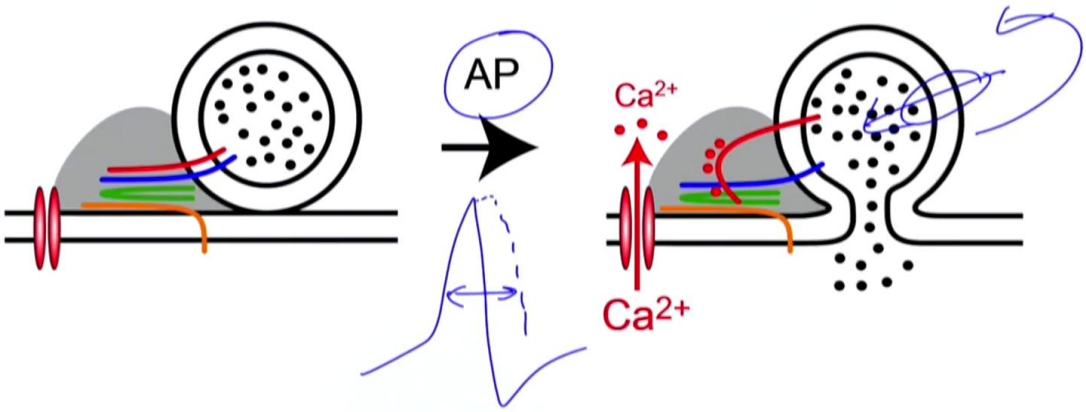
Now we're thinking about the diffusion of messengers that in itself is occurring on a longer length scale, but also on a longer time scale, because diffusion takes some time; and there's, then, multiple steps in the signalling process. First, we need to activate a receptor that then activates a G protein; the G protein needs to diffuse; and then it might activate secondary messenger signalling cascades. And so, the whole process downstream of metabotropic receptors probably requires at least some tens of milliseconds; -- probably, we're thinking, more than a hundred milliseconds, in most cases -- and the effects, then, can also be longer-lasting: they can last for many seconds and even, in some cases, hours. So, the metabotropic receptor signalling pathways are extremely useful, very diverse. They couple to many different signalling pathways, and they operate on longer length scales, because the diffusion, messengers to these receptors, and also on longer time scales, because of the greater complexity of the intracellular signalling machinery that's been activated.

Notes

Summary

4m 17s

Presynaptic modulation of synaptic transmission



Many targets for modulating synaptic transmission:

AP, Ca^{2+}, Synaptotagmin, Synaptobrevin, SNAP-25, Syntaxin, Rab3/27, NSF, MUNC13/18, RIM/RIM-BP, Complexin, Vesicular transporters ...

Cellular Mechanisms of Brain Function

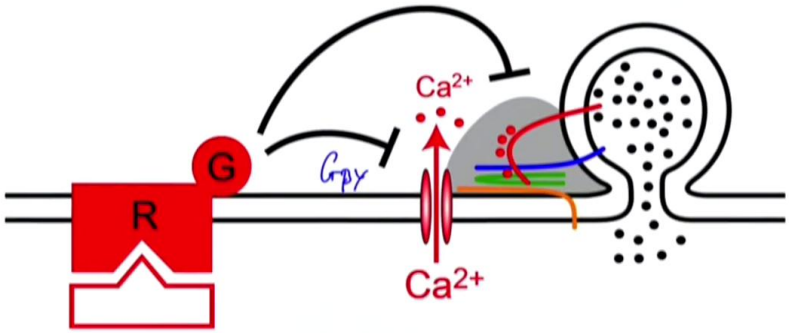
There are, of course, a large number of targets that we've already begun to think about in terms of the coupling of the action potential to neurotransmitter release. So, if we imagine this metabotropic signalling pathway from the seven-transmembrane receptor, activating a G protein, activating other enzymatic cascades, one place where it could interact with is with the action potential waveform itself. We can imagine a fast sodium spike, and the G protein might inactivate potassium conductances, thus giving rise to a broader action potential and more calcium influx, and thus enhancing neurotransmitter release. Or, the G protein might directly act on the calcium channel and thus alter the amount of calcium that enters in the presynaptic terminal; or, it might affect the release machinery, or other parts that influence how much neurotransmitter's being taken up, or the recycling, and docking, and replenishment of the readily-releasable pool. So, we've already identified many potential targets for modulating synaptic transmission through such metabotropic pathways; and of course, it's interesting to see which of these actually occur in a major way in the brain.

Notes

Summary

5m 26s

Presynaptic inhibition



Neuromodulators can presynaptically inhibit neurotransmitter release, through seven-transmembrane receptors (R) activating GTP-binding proteins (G), which act to reduce calcium influx and inhibit release machinery.

Cellular Mechanisms of Brain Function

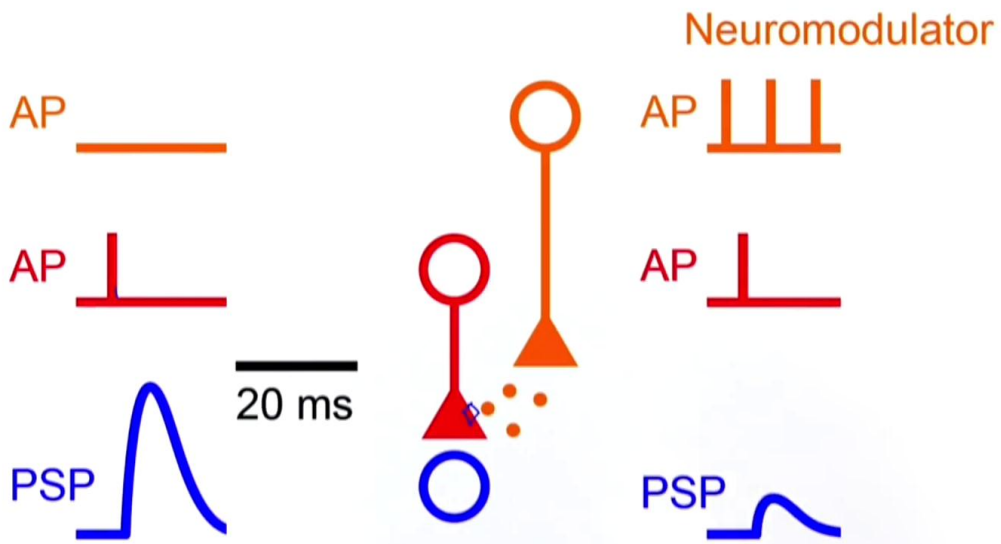
And one major form of presynaptic modulation is called presynaptic inhibition. And this occurs at almost all synapses in the brain. Near to the release site, but not at the actual active zone, there are typically seven-transmembrane receptors that couple to G proteins. Upon activation by an agonist of the receptor, the G protein splits; the beta/gamma subunit can go and block the entry of calcium through voltage-gated calcium channels; so that's a direct interaction of the G protein with voltage-gated calcium channels to inhibit calcium influx. And the other place where presynaptic inhibition has been noted in a major way is through directly impinging upon the release machinery. And so, it inhibits the release of synaptic vesicles in response to calcium. So, there are at least two independent ways of regulating neurotransmitter release through presynaptic inhibition. One is reduction of calcium entry, and the other is reduction in release rates in response to calcium rises.

Notes

Summary

6m 44s

Presynaptic inhibition



Cellular Mechanisms of Brain Function

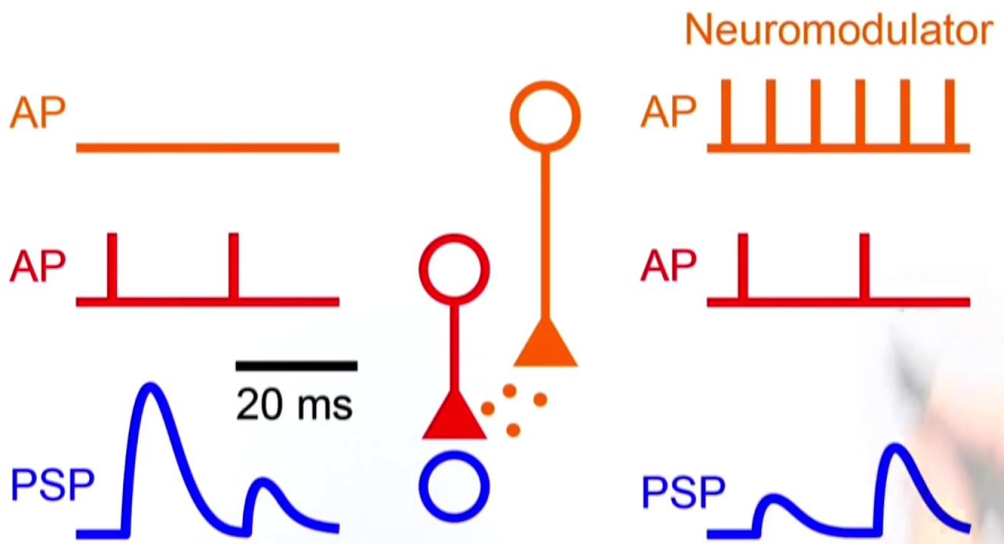
So, if we now think about how presynaptic inhibition might work in the brain, we can imagine a situation where the neuromodulator, the axon, is turned off; and that we have a presynaptic action potential in our red cell. It propagates down its axon, induces a calcium rise in the presynaptic terminal, and that, then, in turn, induces release of neurotransmitter on to the blue cell, driving a post-synaptic potential. Now we turn the neuromodulator on: so, there's action potential firing in this neuromodulatory axon; and that axon, the bouton that releases a neuromodulator, is typically not immediately next to the presynaptic terminal, but it might be spaced some five micrometers away. The neurotransmitter is then released; diffuses in the extracellular space -- so we've got about 20 percent or so extracellular space -- can then bind onto the receptors here at the presynaptic terminal; and then cause a decrease in the amount of neurotransmitter release in response to the action potential. So, here's the action potential; here's the postsynaptic potential; and that's clearly smaller than when there was no neuromodulator present. And so this is, then, presynaptic inhibition.

Notes

Summary

7m 55s

Presynaptic inhibition affects dynamics



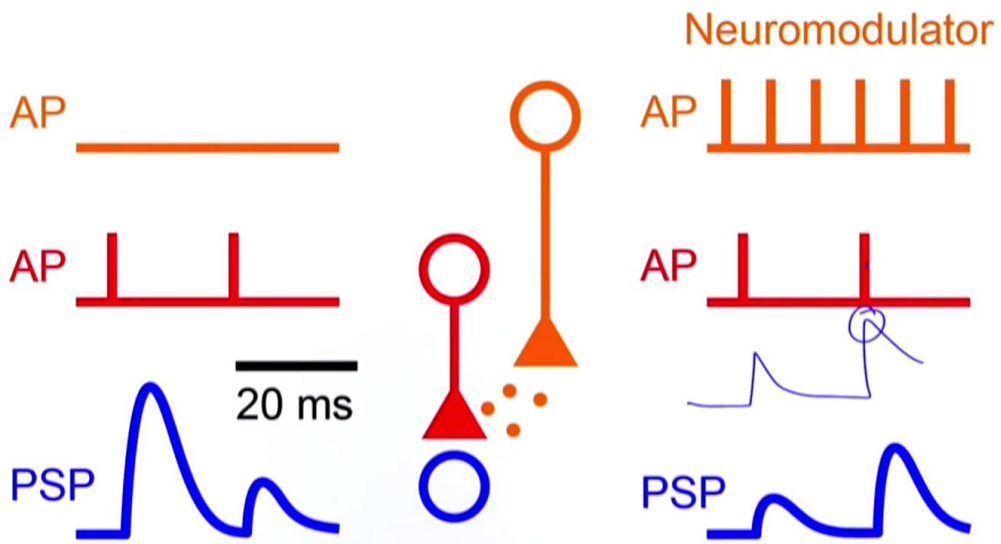
The neuromodulator has caused a decrease in the amount of neurotransmitter released in response to the action potential. So, this is a simple view of presynaptic inhibition. The neuromodulator comes on, and that simply decreases the amount of neurotransmitter that's released. However, the situation is not quite so simple, because we also have to think about short-term synaptic plasticity that we discussed in the last lesson. And one common form of short-term synaptic plasticity is depression, where a second action potential induces a smaller post-synaptic potential because of a depletion in the amount of readily-releasable pool in the presynaptic terminal. Now, in the presence of a neuromodulator, we've decreased the amount of neurotransmitter released. We've decreased the release probability; and so this action potential that here caused a major depletion of the presynaptic terminal now fails to do so. There's only been a small amount released. The neuromodulator decreased the release probability. That, then, means, in response to the second action potential, that we can get a facilitation; we can get an increase in the amount of neurotransmitter released.

Notes

Summary

9m 08s

Presynaptic inhibition affects dynamics



Cellular Mechanisms of Brain Function

The calcium is probably peaking at a higher level, and the first action potential didn't deplete the synaptic vesicles, so they're still all present, all these: many of them are still present. And that, then, allows the second action potential, now, to become facilitating rather than depressing. And so, there's an interesting interaction between presynaptic inhibition and presynaptic neuromodulation in general and short-term plasticity, where presynaptic inhibition causes a change from depression to facilitating kinetics in general at the presynaptic terminal.

Notes

Summary

10m 19s

Neuromodulatory transmitters

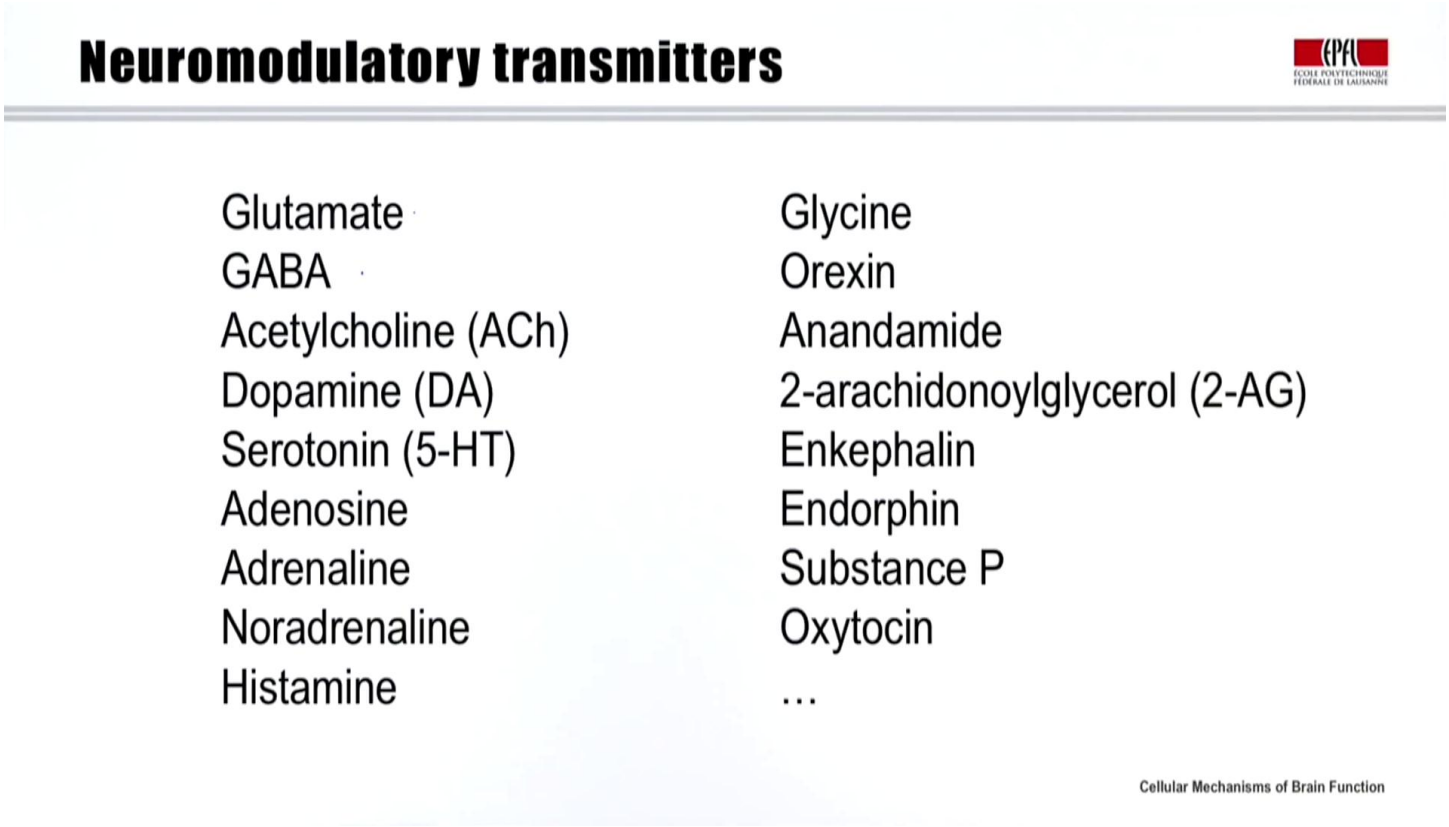
Glutamate	Glycine
GABA	Orexin
Acetylcholine (ACh)	Anandamide
Dopamine (DA)	2-arachidonoylglycerol (2-AG)
Serotonin (5-HT)	Enkephalin
Adenosine	Endorphin
Adrenaline	Substance P
Noradrenaline	Oxytocin
Histamine	…

There are, of course, very many neurotransmitters that act as presynaptic neuromodulators. Glutamate and GABA are two of the most important ones. These are also the main synaptic neurotransmitters, so they release glutamate directly onto ionotropic glutamate receptors; and GABA releases... GABAergic synapses release GABA directly onto GABA ionotropic receptors, and that's a direct, local, point-to-point neurotransmission that occurs on that hundred-nanometer length scale. However, the glutamate and the GABA released at these synapses also diffuse out into the extra-synaptic space. And there, they can diffuse for long distances, and indeed, in general, it's thought that the extracellular space has relatively high concentrations of glutamate and GABA that, presumably, are escaping from their synaptic release sites. And certainly, presynaptic receptors, metabotropic glutamate receptors, metabotropic GABA receptors, are equally important in terms of modulating brain function as many of the other metabotropic receptors, and they form an important complement to the ionotropic glutamate and GABA transmitters that are working on the millisecond time scale, whereas the metabotropic receptors are working on the hundreds-of-milliseconds or second time scale.

Notes

Summary

10m 58s



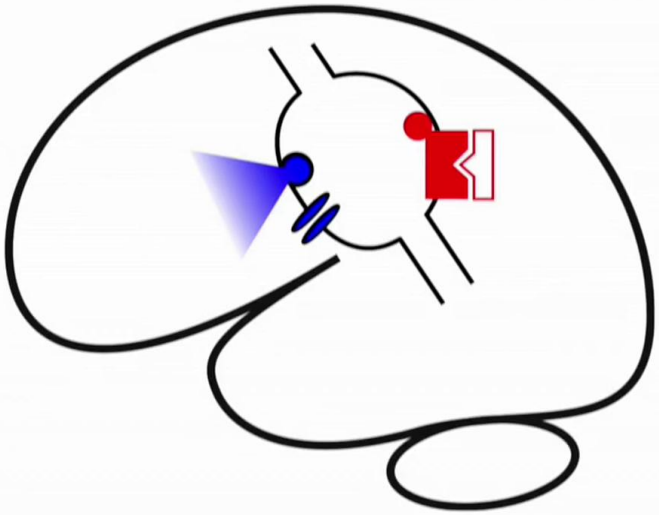
So, glutamate and GABA, in addition to the fast ionotropic action driving post-synaptic potentials, also drive much slower neuromodulatory events, including presynaptic inhibition. Similarly, there are axons for acetylcholine, dopamine, serotonin, and many other neurotransmitters that travel long distances and can traverse long and large parts of the brain. So, a single axon from a cholinergic neuron can innervate a large expanse of, for example, neocortical territory, and there, the boutons diffusely release neurotransmitter into the extracellular space. Very often, for the neuromodulatory neurotransmitters, there is no post-synaptic specialization, and the neurotransmitter is simply released into the extra-cellular space, where it diffuses and adds up to a volume transmission of neurotransmitter. And so, acetylcholine, dopamine, serotonin, and these other neurotransmitters that you see listed here are all typically working in a volume-like manner. So, this means that they don't have the point-to-point specificity of the direct synaptic transmission, but rather they act on a longer length scale, and also on a longer time scale, to affect presynaptic release and other components of the synaptic transmission process.

Notes

Summary

12m 22s

Presynaptic modulation by neurotransmitters



Cellular Mechanisms of Brain Function

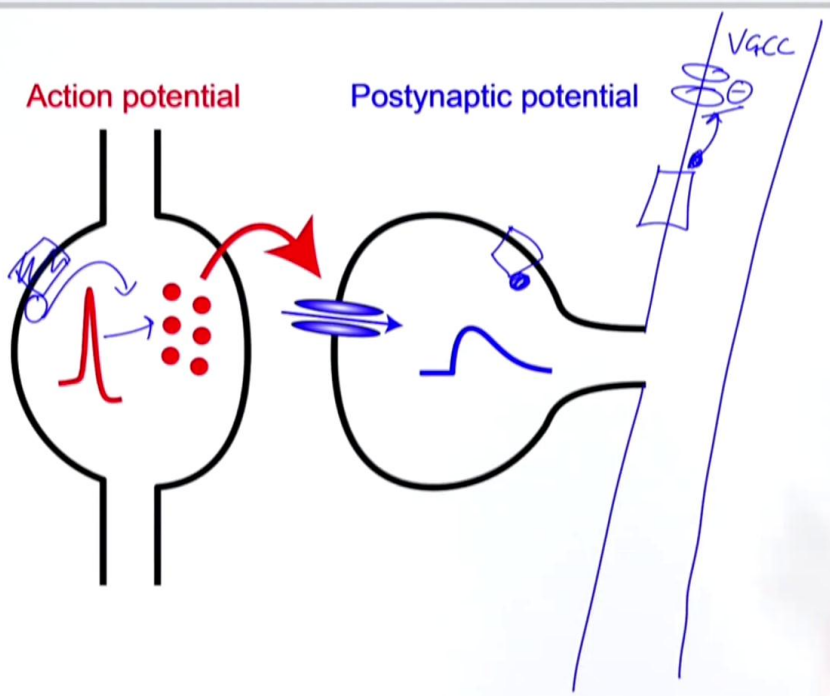
So, the synaptic transmission, the output of an axon, is modulated in a number of important ways. We learned previously about the temporal modulation in terms of the action potential firing pattern of that neuron. That can make a big difference in terms of facilitation or depression of neurotransmitter release. Here, we now see that the neurotransmitter concentrations in the extracellular space can also affect neurotransmitter release in an important way; and so, during different behavioral conditions, acetylcholine, serotonin, dopamine levels will increase or fall in different parts of the brain, depending upon the behavioral context; and, depending on where the receptors for these neuromodulators are expressed, this will have different and cell-type-specific effects upon the downstream brain structures and the synaptic transmission at different synapses between different specific cells in the brain.

Notes

Summary

13m 53s

Postsynaptic neuromodulation



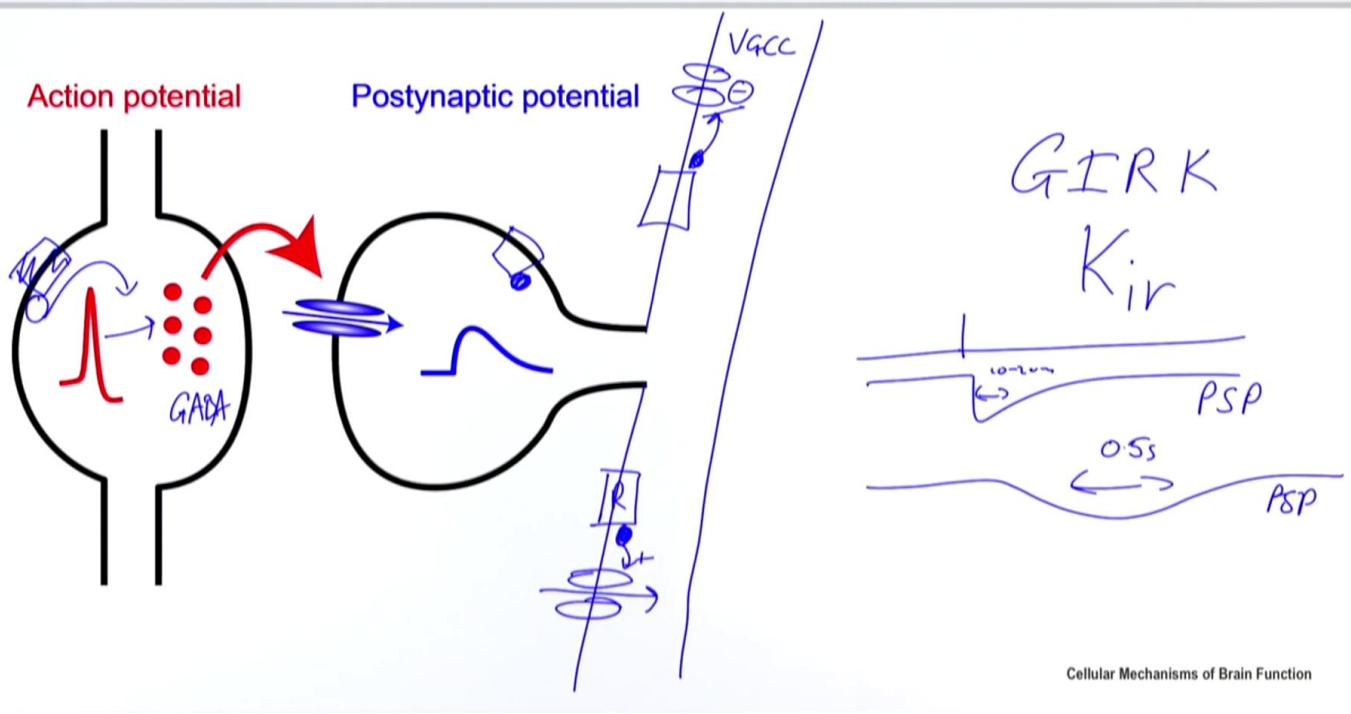
So, we've considered the situation where presynaptic metabotropic receptors on the bouton will affect the coupling of the action potential to the neurotransmitter release process, and a prominent feature here is presynaptic inhibition. Now, these metabotropic receptors are not just present on presynaptic membranes, but are also present post-synaptically. And so, here, if we think about a post-synaptic specialization, and a dendrite that will hook up to the soma of a cell, there will also be receptors, seven-transmembrane receptors, decorating the post-synaptic membrane. And so, we can imagine having a seven-transmembrane receptor here, coupling to a G protein; and that, then, might affect several cellular processes here, in the post-synaptic neuron. In part, it might affect similar things post-synaptically as presynaptically. In fact, we also have voltage-gated calcium channels here on the post-synaptic membrane, and seven-transmembrane receptors, via G proteins, have been shown, also, to block voltage-gated calcium channels on the post-synaptic dendrites. And so, that's one similarity about the signalling processes and the presynaptic and the post-synaptic specializations.

Notes

Summary

14m 56s

Postsynaptic neuromodulation



Also, on post-synaptic membranes, there are other interesting potassium channels that are strongly regulated by seven-transmembrane receptors. So again, via G proteins, they can affect potassium channels. In particular there's a family of potassium channels called the *G protein inwardly-rectifying potassium channels*, or the K_ir channels, that are strongly affected by G protein coupling here; and they're activated by receptor activation. And this, then, can give rise to so-called slow post-synaptic potentials where we can imagine, say, from a GABAergic release of neurotransmitter that can then cause an inhibitory post-synaptic potential that's fast via the standard ionotropic receptors. This is the spike in the presynaptic cell, and it can cause a slow post-synaptic potential through activating potassium channels via this G protein signalling pathway; and this might be something that takes place on the half-second time scale: so, much slower than the ten- to twenty-millisecond post-synaptic potential via the ionotropic receptors. So, there are both presynaptic and post-synaptic effects of neuromodulation, and both of them contribute equally importantly to the neuromodulation of brain function.

Notes

Summary

16m 20s

Clinical relevance of neuromodulation

Examples

Depression: Fluoxetine / Sertraline – selective serotonin reuptake blockers

Antipsychotic: Risperidone – blocker of specific DA, 5HT, adrenergic receptors

Cellular Mechanisms of Brain Function

One of the exciting features about neuromodulation is its clinical relevance. The location of where receptors are expressed to the different neurotransmitters turns out to be highly specific. So, some cells express one type of dopamine receptor; others will express another type of dopamine receptor; and similary for serotonin receptors, adrenergic receptors, oxitocyn receptors, you name it: the seven-transmembrane receptors are expressed in highly specific manners, in terms of which cells express those receptor subtypes, and also where in the nerve cell those receptors are located. So, some will be located on presynaptic specializations, others on post-synaptic specializations, and some will only be located on a presynaptic specialization that contacts a specific post-synaptic cell type. And so, where the neuromodulators gain their specificity from is really where the receptors are expressed. The neurotransmitter itself is, of course, also released with some temporal and spacial specificity, but that's much less so than the standard, fast synaptic transmitters we've been thinking of.

Notes

Summary

17m 46s

Clinical relevance of neuromodulation

Examples

Depression: Fluoxetine / Sertraline – selective serotonin reuptake blockers

Antipsychotic: Risperidone – blocker of specific DA, 5HT, adrenergic receptors

Cellular Mechanisms of Brain Function

And that means that they're relatively amenable to neuropharmacology, which, of course, we can influence the receptors and the neuromodulatory transmitters on long time scales, and without much spatial specificity. And there, there's some match between what we can do pharmacologically and what is physiologically involved in the neuromodulatory process. And here, I'd just like to highlight two types of drugs that are in common usage for different brain disorders. One is the fluoxetine / sertraline type of drug that works against depression; and the way that they work is as a selective serotonin re-uptake blocker. And so, we have our serotonin nerve terminals, our boutons that release serotonin. Serotonin is also called 5-hydroxytryptamine, 5HT. And so, these serotonergic axons release serotonin into the extracellular space. There's no post-synaptic specialization for these axons, and the amount of neurotransmitter that's released, and the distance they can diffuse, depends upon how it's degraded and taken up from the extracellular space. And it turns out that there are specific serotonin transporters that suck up the serotonin from the extracellular space.

Notes

Summary

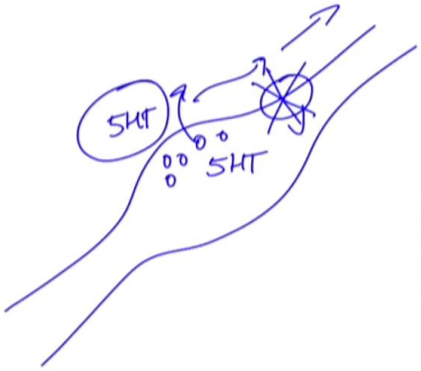
19m 00s

Clinical relevance of neuromodulation

Examples

Depression: Fluoxetine / Sertraline – selective serotonin reuptake blockers

Antipsychotic: Risperidone – blocker of specific DA, 5HT, adrenergic receptors



mAChR

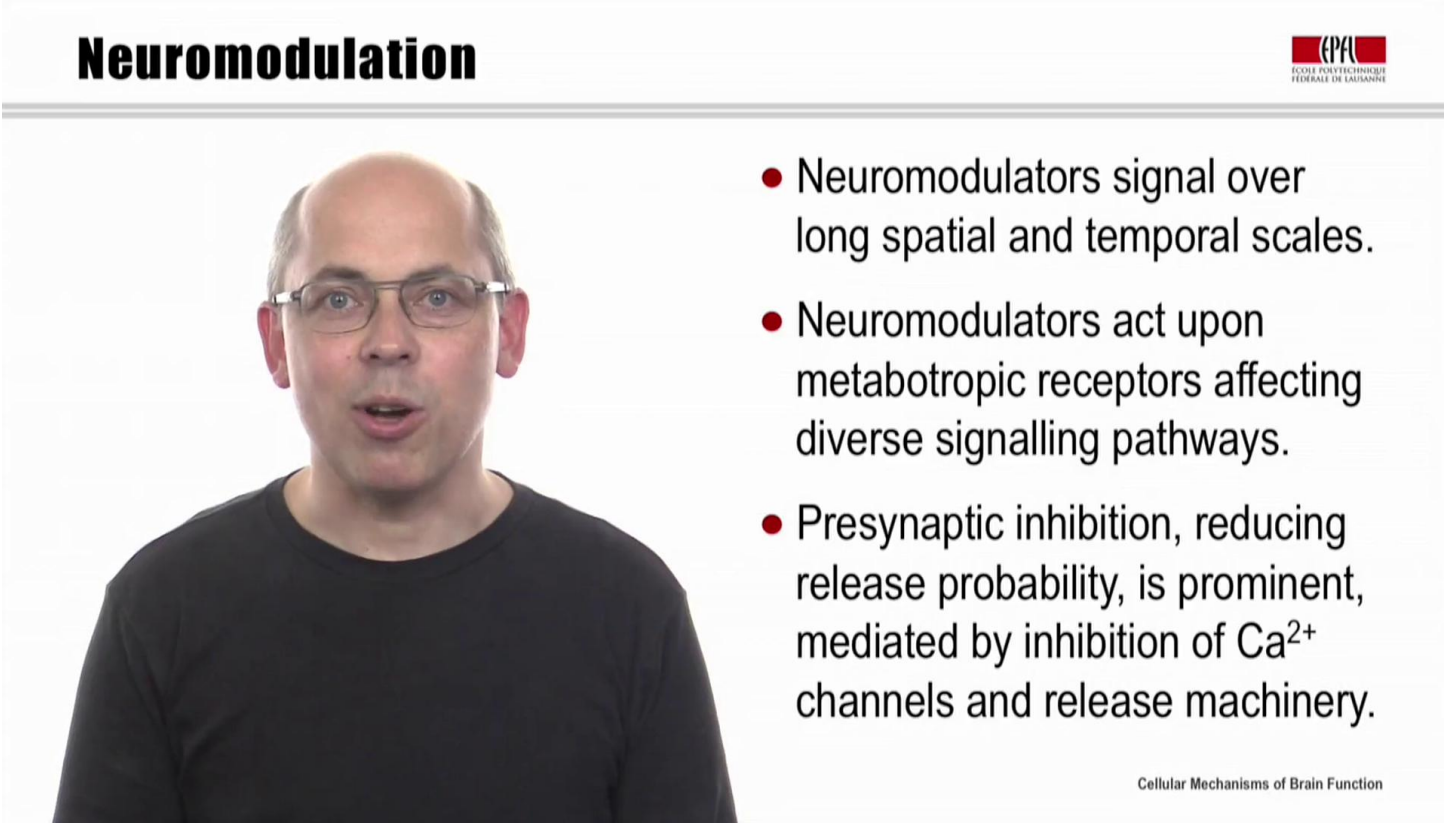
Cellular Mechanisms of Brain Function

And that's one of the major ways in which the extracellular 5HT concentration is regulated, is by the so-called *serotonin re-uptake proteins*. And what fluoxetine and sertraline do is that they block that re-uptake machinery; and that, then, allows the 5HT to diffuse further, and reach higher concentrations. And so, fluoxetine has its major way of action to increase serotonin in the extracellular space by blocking the re-uptake blockers; and it turns out that the fluoxetine has been very successful in countering depression and anxiety. Another drug, risperidone, acts by blocking specific subtypes of dopamine receptors, of serotonin receptors, and adrenergic receptors; and, interestingly, it seems to derive some degree of specificity from not binding to muscarinic acetylcholine receptors. So it targets many of these other systems, but seems to have more than a thousand-fold less binding to muscarinic acetylcholine receptors. And so another drug, this Risperidone, acts at a whole bunch of different neuromodulatory receptors, and it seems to have an interesting and useful effect as an anti-psychotic that can help treat patients with schizophrenia.

Notes

Summary

20m 31s



The neuromodulators bind to seven-transmembrane receptors that activate G proteins; they bind GTP; they diffuse and activate, then, downstream signalling pathways; and there's really a large variety of signalling pathways that are open to seven-transmembrane receptors. In particular, they act to presynaptically inhibit neurotransmitter release, by down-regulating calcium influx and by decreasing the efficacy of neurotransmitter release; and that, then, also impacts synaptic dynamics in the presynaptic terminal. The neuromodulators are also particularly interesting: because they act on this long time scale and in a more diffuse way, they're also amenable to pharmacological interventions, and there, there's a great deal of interest in trying to specify which receptors are responsible for which types of neuromodulation, and how that interacts with different brain diseases, which is an area of intense research in neuropharmacology.

Notes

Summary

21m 54s