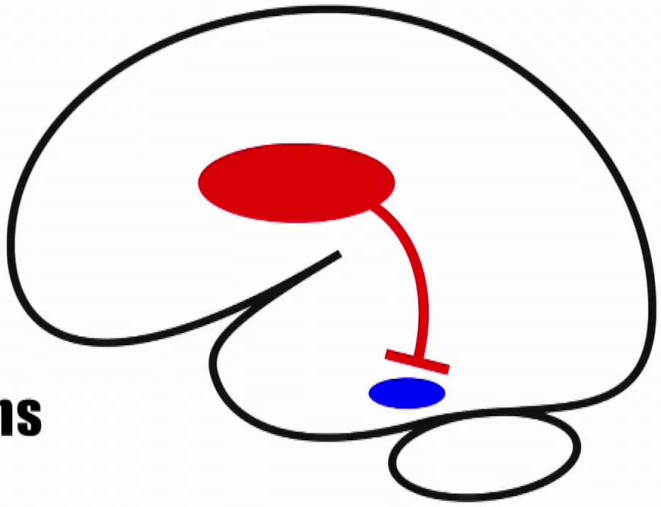
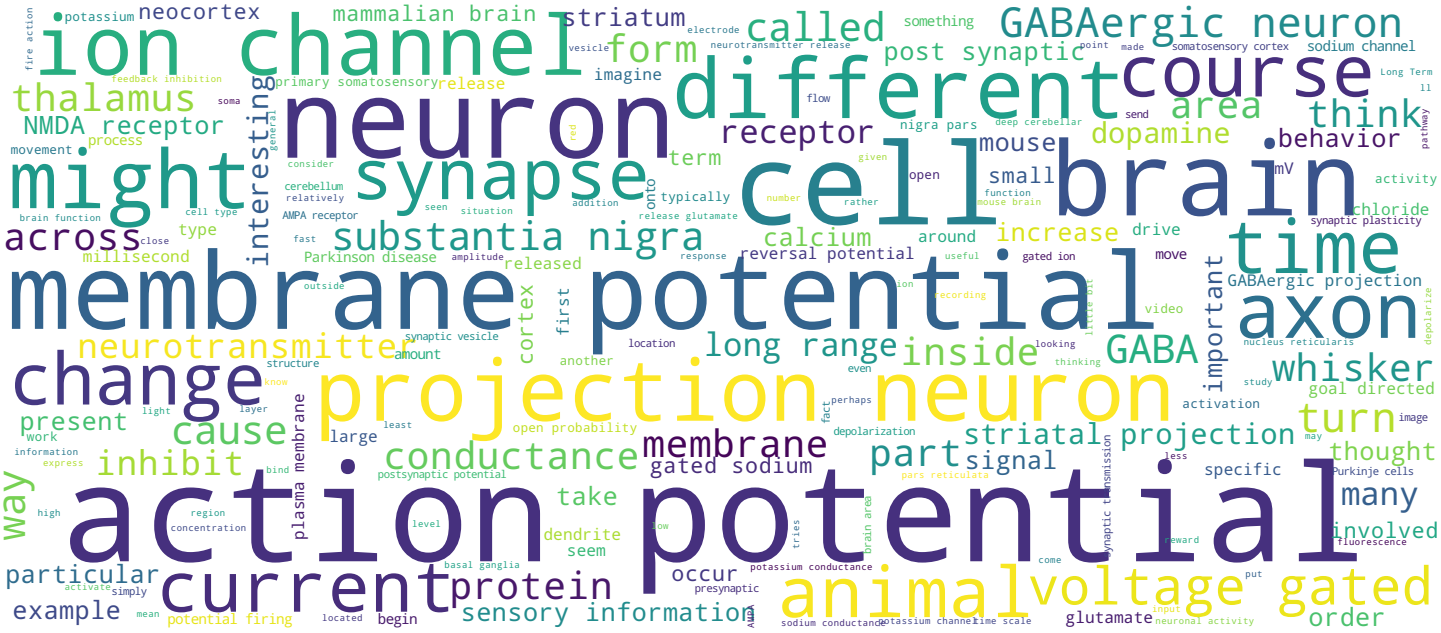


5.4 GABAergic projections

Cellular Mechanisms of Brain Function

Prof. Carl Petersen



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Video

EPFL

Long-range inhibition

Cellular Mechanisms of Brain Function

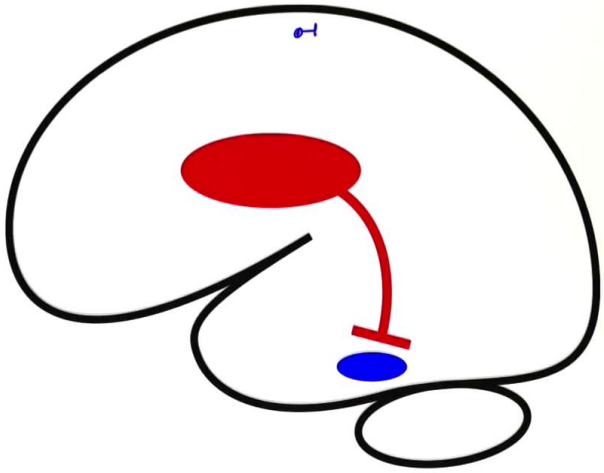
Last week we considered the importance of glutamatergic excitatory long-range projections. We thought a little bit about how sensory information came from the periphery and reached the neocortex where it's believed that sensory percepts are generated. The transmission of information turned out to depend upon glutamatergic synapses, and different brain areas were linked together by long-range axonal projections. So for example, there was an axon that went from the skin to the brain stem and would signal touch. And there was another set of cells in the retina that send long-range axonal projections that release glutamate in the thalamus. to signal sensory information. And so you can imagine an easy scenario where excitatory volleys of action potentials, and sequential brain areas become activated, fire action potentials in the downstream neurons, that then channel down axons and then release glutamate upon another downstream target. And that's easy to see how sequential steps of excitation are useful for propagating sensory information. It turns out that long-range GABAergic projections are equally important in the brain, and that's what we'll study in today's video.

Notes

Summary

0m 05s

GABAergic projections



Cellular Mechanisms of Brain Function

So some parts of the brain like the neocortex only have local GABAergic neurons, ones that have a short axon stretching maybe for a few hundred microns, at least, predominantly. However, other brain regions that also have GABAergic neurons in them send long-range axonal projections out of that brain area, and they then inhibit other nuclei in the brain, and that's what we'll be studying today, the long-range GABAergic projection neurons.

Notes

Summary

1m 27s

Three examples of GABAergic projection neurons

1. Neurons in the reticular nucleus of the thalamus
2. Striatal projection neurons of the basal ganglia
3. Purkinje cells of the cerebellum

Cellular Mechanisms of Brain Function

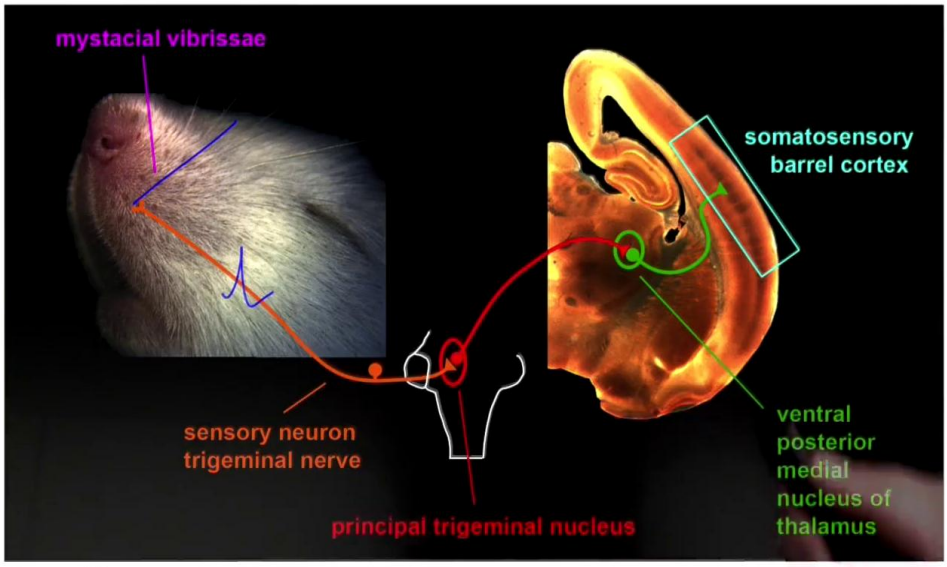
We're going to focus on three examples of GABAergic projection neurons that are present in the mammalian brain. We'll discuss the neurons in the reticular nucleus of the thalamus. They provide an interesting feedback inhibition to the main thalamus and presumably are involved in filtering sensory signals getting to the cortex. We'll also discuss striatal projection neurons, part of the basal ganglia, that are thought to be involved in goal-directed motor control. And finally, we'll discuss the GABAergic Purkinje cells the sole output of the cerebellum and how that's involved in sensory motor tuning.

Notes

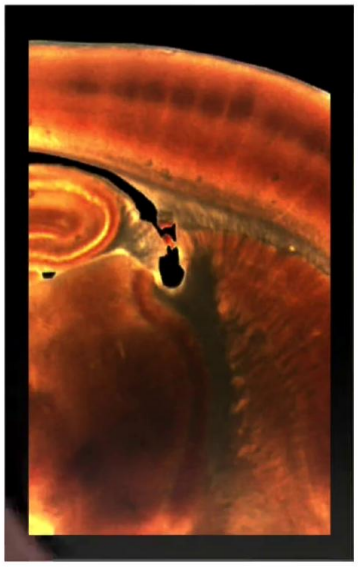
Summary

2m 00s

1. The reticular nucleus of the thalamus



Petersen, 2003



Cellular Mechanisms of Brain Function

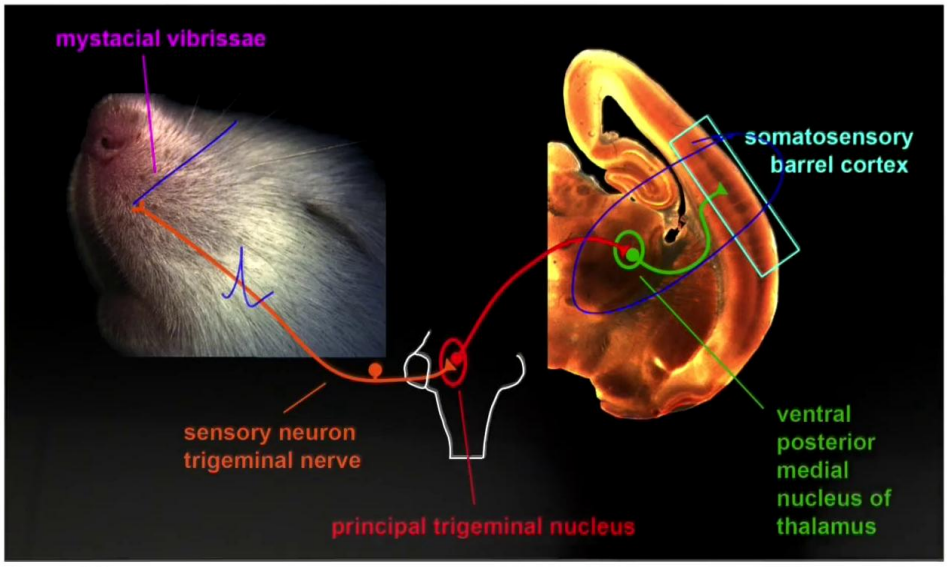
We'll begin by thinking about the reticular nucleus of the thalamus. And we'll consider it in the context of a sensory system that we've already discussed. The one that brings tactile information from the whisker hairs on the snout of a rodent, and bring it through to the somatosensory barrel cortex. So the signalling pathway begins at the periphery, we have whisker hairs that are embedded inside follicles, movement of one of these whiskers, activating mechano-gated ion channels causing an action potential to propagate down the sensory neurons of the trigeminal nerve. They release glutamate in the brain stem, in the principal trigeminal nucleus, some of these neurons will fire an action potential, that again, propagates down the axon and releases glutamate now in the thalamus. Some of the thalamic neurons then, will sense that glutamate, depolarize and then in turn, fire an action potential that then conveys the sensory information to the primary somatosensory cortex. This is where we have this nice organization of these dark stained structures here that correspond in a one to one mapping with the layout of the whiskers on the face of the animal.

Notes

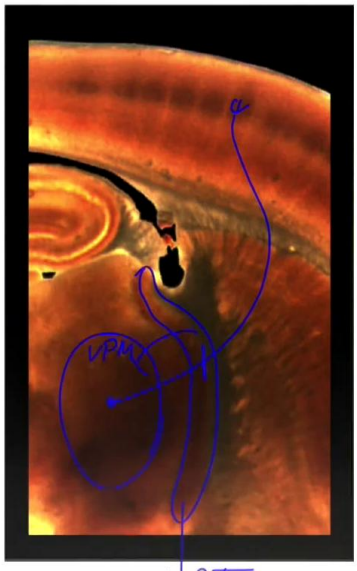
Summary

2m 41s

1. The reticular nucleus of the thalamus



Petersen, 2003



Cellular Mechanisms of Brain Function

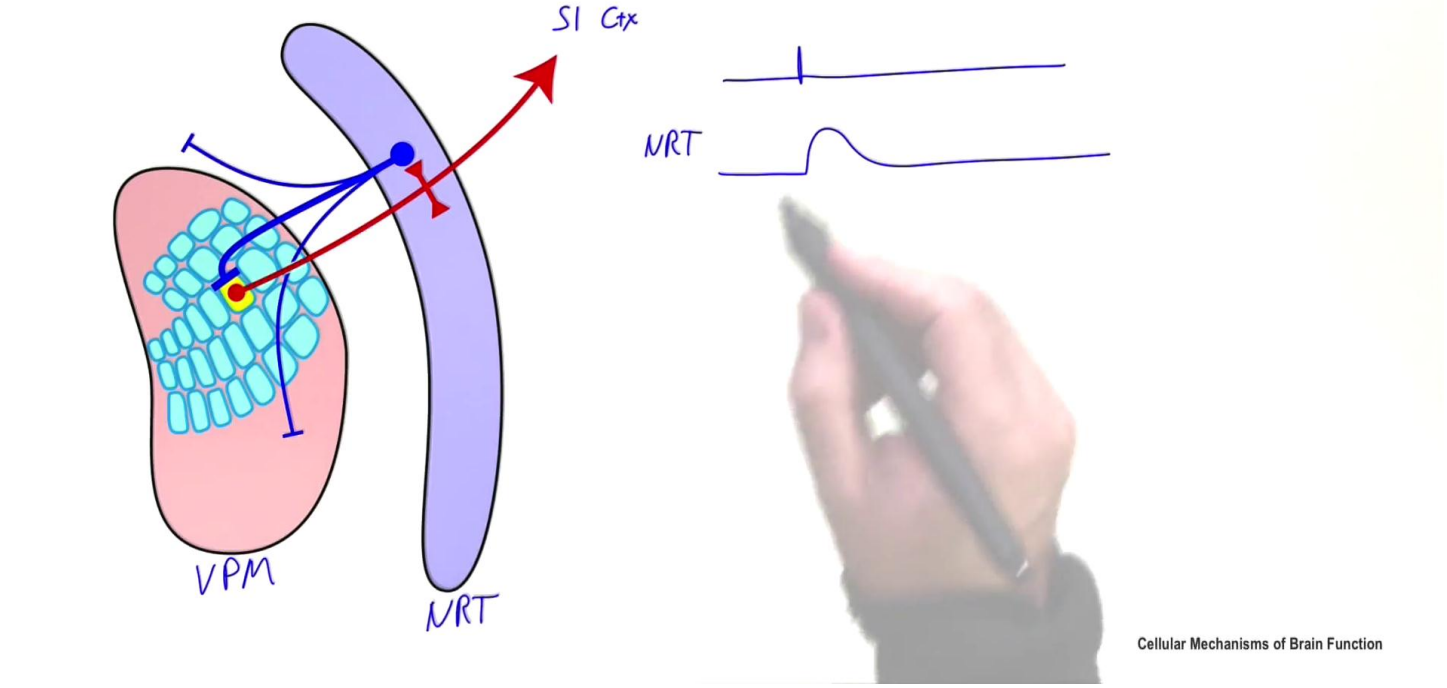
Now if we zoom in on this area in a little bit closer detail-- and that's what we see here, we see again, the thalamic nucleus here, the so called ventral posterior medial nucleus of the thalamus that sends the axons up here, and they then, innovate individual layers for barrels. On their way, these thalamic neurons send off collaterals. So the axon branches here, in a specific region here, a new area for us called the nucleus reticularis. And here, this is full of GABAergic neurons and these GABAergic neurons cause a feedback inhibition upon the thalamus.

Notes

Summary

3m 54s

Fast GABAergic feedback inhibition



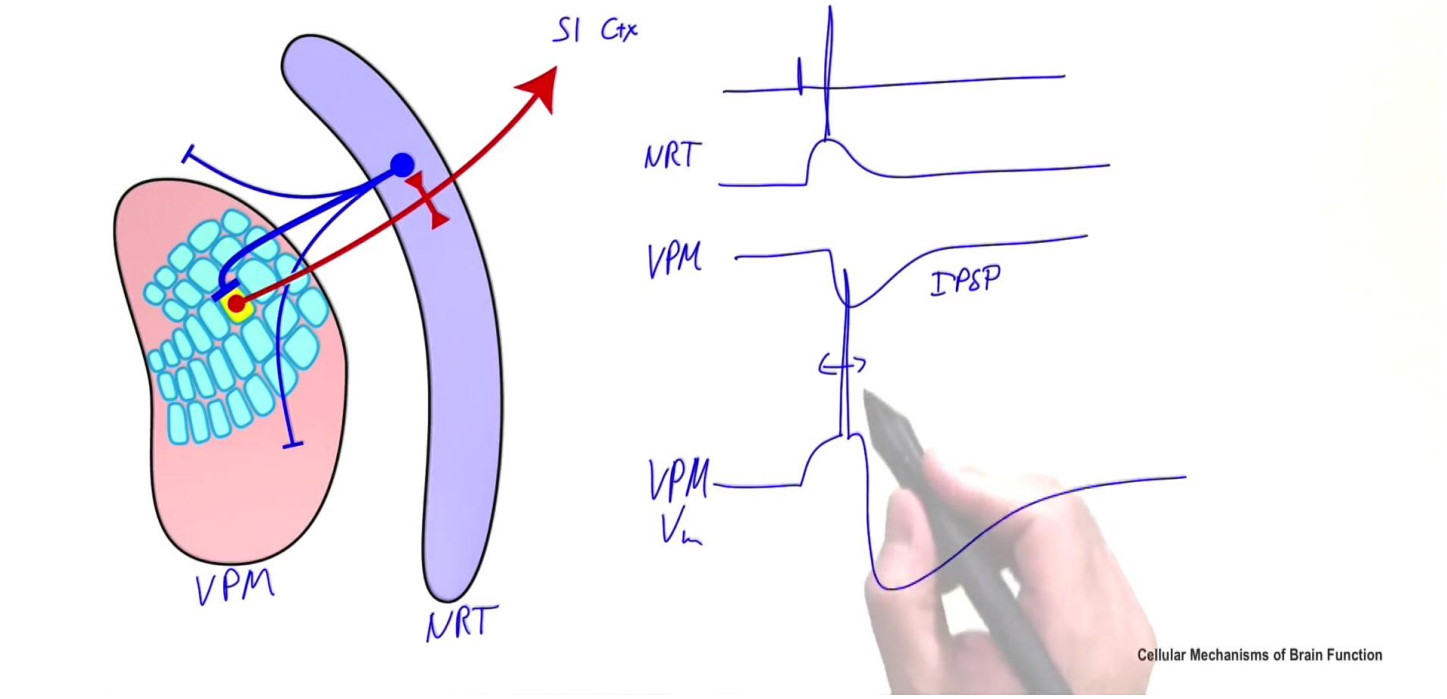
Let's take a closer look at how that works. We imagine the ventral posterior nucleus here, shaded in red. It contains a highly organized somatotopic map of the whiskers so in the same way that the neocortex has a map of the whiskers that is anatomically identifiable, the ventral posterior medial nucleus of the thalamus also has an anatomically identifiable whisker map. And so for example, our C2 whisker representation here, is found in the thalamus in the form of a C2 barreloid. So the deflection of the C2 whisker causes some neurons here in the ventral posterior nucleus to find action potential. That action potential propagates down the axon of the thalamocortical neuron towards the primary somatosensory cortex. And that's where sensory percepts are thought to be generated. On the way, it sends off axonal collaterals that also release glutamate, but now, onto the GABAergic neurons that are present inside the nucleus reticularis. So an NRT neuron here will receive a glutamatergic input when a VPM cell fires. If sufficient amount of excitation comes from the VPM the nuclear reticularis neurons, or at least some of them, will fire action potentials in turn.

Notes

Summary

4m 40s

Fast GABAergic feedback inhibition



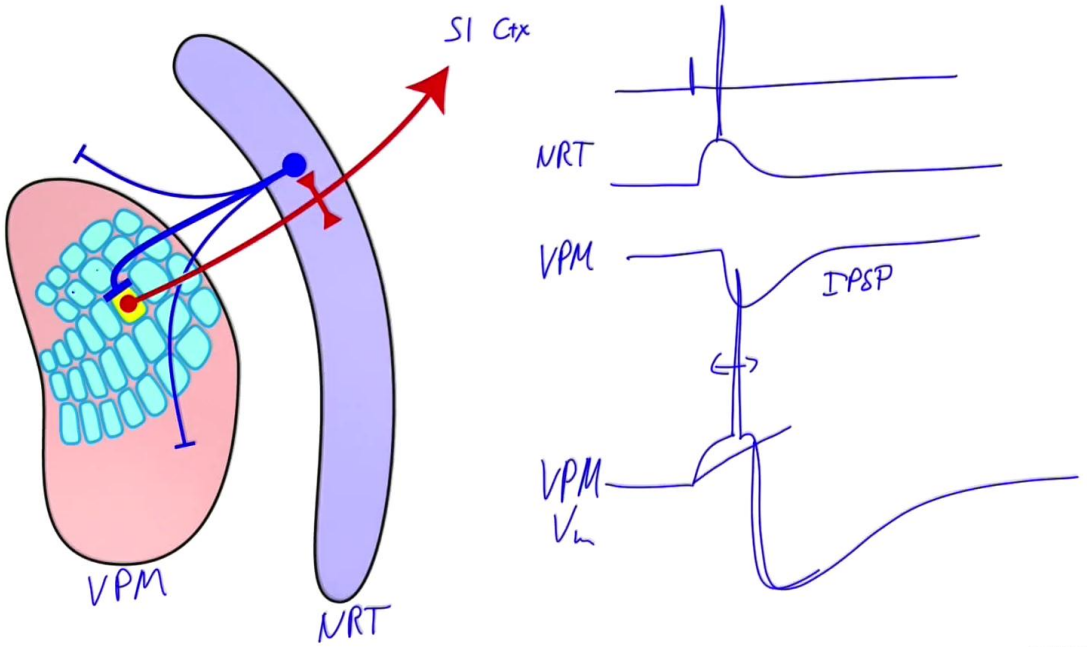
That then means that the axon of the nucleus reticularis neurons becomes relevant, and the axon comes back and in part, will innovate exactly the area from where it received excitation. And so there's a feedback inhibition right onto the cells that initially were excited. And so in the VPM, from this action potential, we'll see a hyperpolarizing IPSP. And it's a fast GABA(A) mediate inhibitory postsynaptic potential. And so for now, imagine what's happening, in general at the VPM in terms of a deflection here that a whisker sensory input that causes a depolarization action potential firing in the VPM cell. And then, we'll have the nucleus reticularis that then in turn, provides feedback inhibition so we'll get an inhibitory postsynaptic potential here from the VPM in terms of the membrane potential fluctuations. And what this inhibitory postsynaptic potential does is that it prevents action potential firing outside a very narrow time window. This IPSP very rapidly comes back and inhibits the main thalamic projection neurons. And that means that the timing of the action potentials coming out of the thalamus, have to occur with exquisite millisecond precision, presumably providing important temporal information for the primary somatosensory neocortex.

Notes

Summary

6m 01s

Fast GABAergic feedback inhibition



Cellular Mechanisms of Brain Function

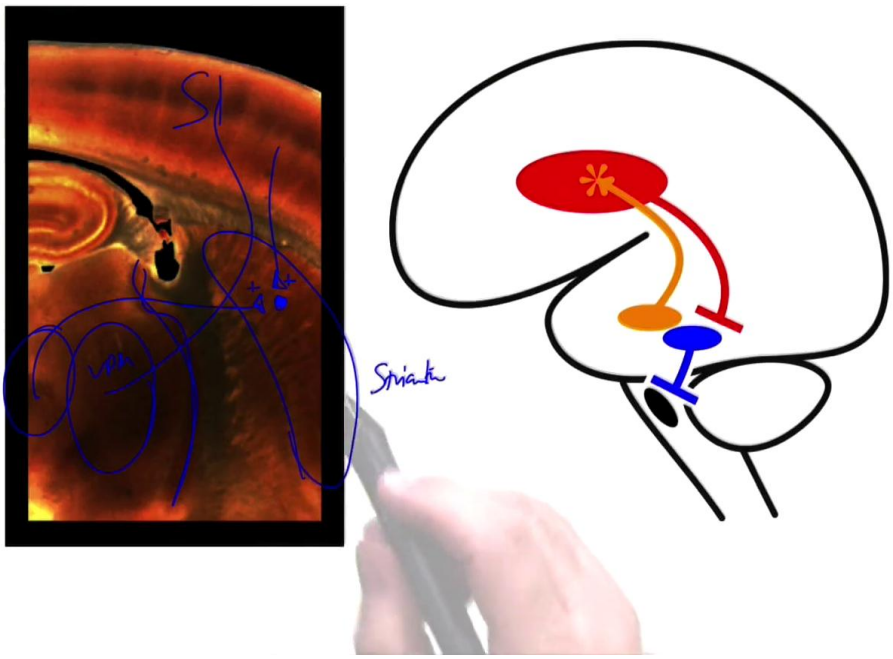
If this neuron was depolarizing more slowly, and was trying to get to threshold, it simply wouldn't make it. because the IPSP would come in and curtail it. And so only neurons that are strongly excited fire action potentials. And so there's a selection for the most active cells, to propagate action potentials to the cortex, and the ones that are less active, will be inhibited by the rapid GABAergic feedback inhibtion. In addition, the GABAergic neurons that are in the reticular nucleus don't just provide feedback inhibiton on to the location of where the excitation came from, but much more broadly. And so there's a surround inhibition that will then inhibit neurons both sitting nearby in other whisker representations but even in different thalamic nuclei. And so there's a competition as it were, for the flow of sensory information to the cortex that in part is regulated by the nucleus reticularis.

Notes

Summary

7m 26s

2. Striatum and substantia nigra



GABAergic striatal projection neurons inhibit tonically active GABAergic neurons in substantia nigra (SNr).

Dopaminergic neurons in a different part of the substantia nigra (SNc) project strongly to the striatum.

Cellular Mechanisms of Brain Function

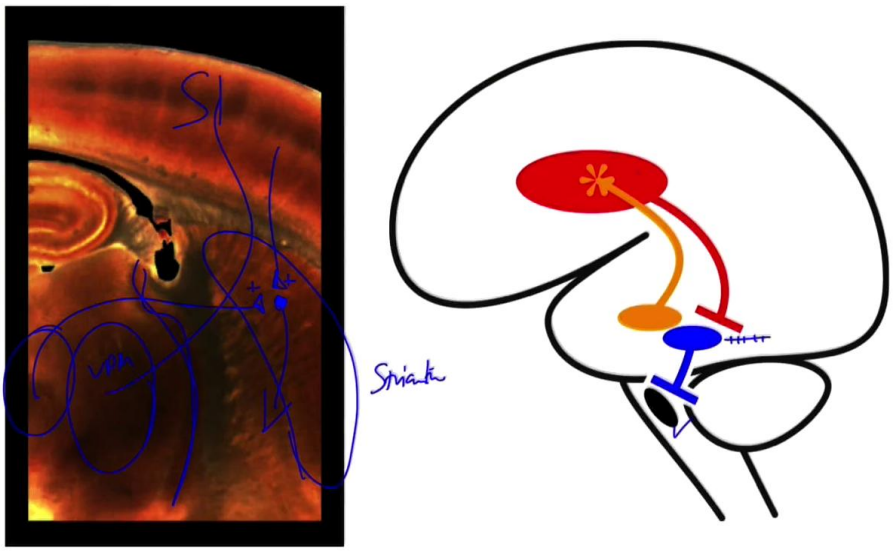
The second long-range GABAergic projection that we should consider, is from the basal ganglia. In particular, we'll consider the striatum and substantia nigra which are important components of the so called basal ganglia, an interconnected set of brain nuclei. And first, just to locate ourselves, where we are on the brain, we're going to look at the same slide as we were looking at before, where we have the somatosensory thalamus, we have the GABAergic reticular neurons, we have the primary somatosensory cortex, and of course, we have here, our axons that go from thalamus to cortex. In between, is a large area of the brain here called the striatum. And the striatum is full mainly of GABAergic projection neurons. These GABAergic projection neurons receive the inputs-- the excitatory inputs, from the cortex and also from higher thalamic areas. So they won't get it from the DPM nucleus of the thalamus, but from second order thalamic nuclei, they also provide excitation onto these striatal projection neurons. And so there are two major excitatory inputs that arrive onto these striatal projection neurons. The striatal projection neurons then project out of here-- by definition it's a projection neuron, and they're GABAergic.

Notes

Summary

8m 23s

2. Striatum and substantia nigra



GABAergic striatal projection neurons inhibit tonically active GABAergic neurons in substantia nigra (SNr).

Dopaminergic neurons in a different part of the substantia nigra (SNc) project strongly to the striatum.

Cellular Mechanisms of Brain Function

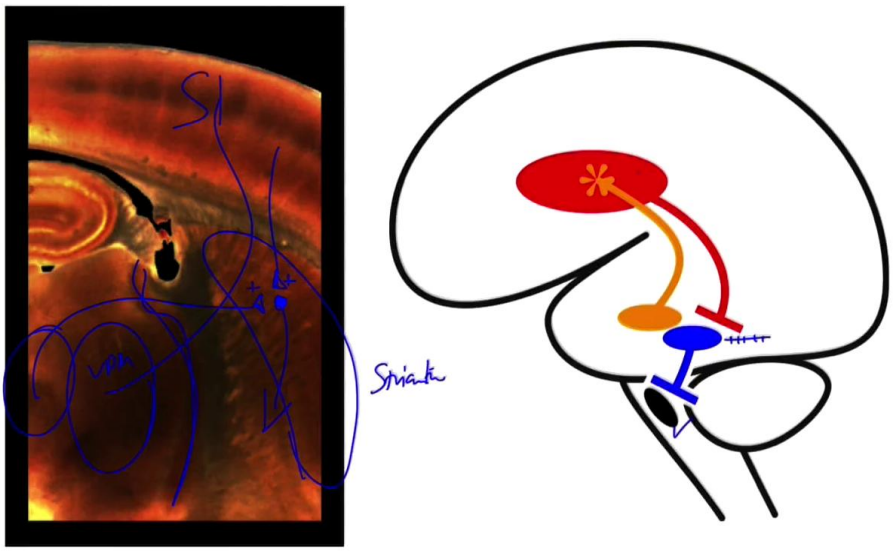
And this red blob here is suppose to indicate this area of the striatum that sends the axons out of the striatum and innovate an area of the brain called the substantia nigra. And in particular, they inhibit neurons in the substantia nigra pars reticulata. The substantia nigra pars reticulata also has GABAergic neurons in it and they're also GABAergic projection neurons. In fact, these neurons are tonicaly active, so at rest, these cell here, are firing action potentials at a high rate, and they're inhibiting brain stem motor areas, and so they prevent the animal from moving. If neurons in the striatum become active, these striatal projection neurons will inhibit the substantia nigra pars reticulata and then will allow these motor nuclei to become active and drive movement. And so there is a so called direct projection of these GABAergic neurons that inhibit substantia nigra and that in turn disinhibits motor neurons function and that then allows goal-directed behavior. The striatal projection neurons received one further very interesting input and that's the dopaminergic input also from the substantia nigra, but from a different part of the substantia nigra called substantia nigra pars compacta.

Notes

Summary

9m 50s

2. Striatum and substantia nigra



GABAergic striatal projection neurons inhibit tonically active GABAergic neurons in substantia nigra (SNr).

Dopaminergic neurons in a different part of the substantia nigra (SNc) project strongly to the striatum.

Cellular Mechanisms of Brain Function

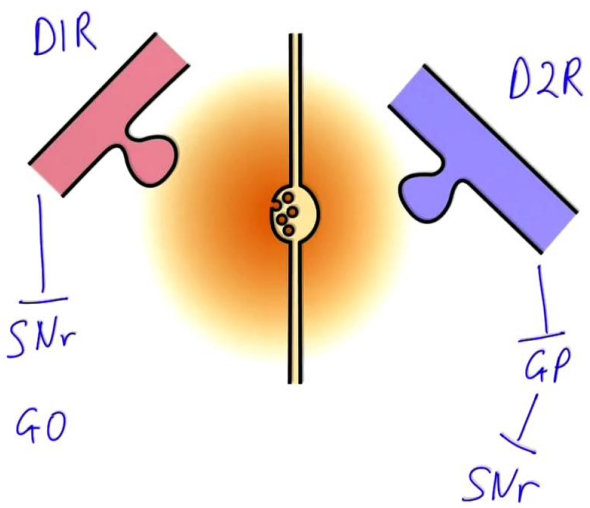
That's where the dopaminergic neurons of the midbrain are, and by far, the largest majority of the axons-- the dopaminergic axons, from the substantia nigra compacta innovate the striatum. So this is a hot spot for dopamine in the brain. And that dopamine is a very interesting signal it's involved in reward signaling, and motivating goal-directed behavior. And indeed, the major function supposedly, of the basal ganglia is to control goal-directed behavior.

Notes

Summary

11m 12s

Basal ganglia, dopamine and Parkinson's disease



In the striatum, dopamine acts at D1 and D2 receptors, which are expressed in different subtypes of GABA striatal projection neurons.

Dopamine may serve as an important reward signal, useful for learning and synaptic plasticity.

Degeneration of dopaminergic neurons is thought to underlie Parkinson's disease.

Cellular Mechanisms of Brain Function

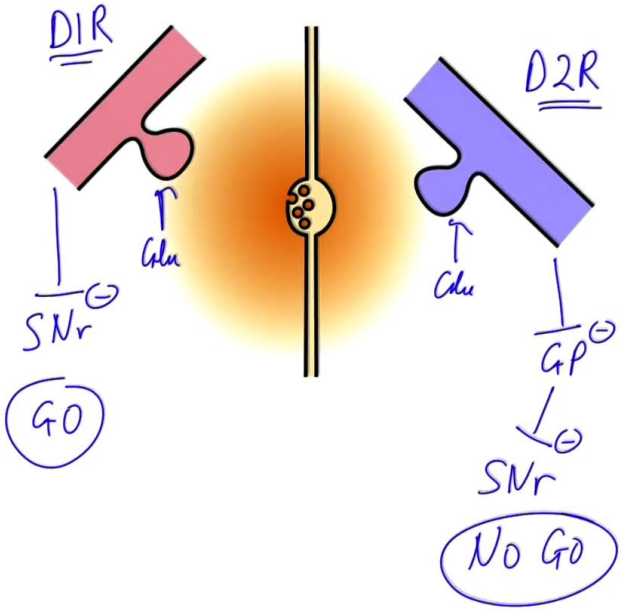
The dopaminergic innovation of the striatum occurs with volume transmission, so the swellings along the dopaminergic axons don't have tight postsynaptic appositions, but rather they release a dopamine into the extra cell space, the dopamine diffuses into the extra cellular space, and it targets two major sources of receptors, D1 receptors and D2 receptors. And these it turns out, are expressed on different types of neurons. So there are two different GABAergic striatal projection neurons, ones that express the D1 receptors, and these indeed turn out to be the so called direct path that inhibits the substantia nigra pars reticulata, and form the goal pathway that tries to drive action. The D2 spiny projection neurons, the ones that express the D2 receptors, form the so called indirect path, where they inhibit the globus pallidus, and the globus pallidus then in turn, inhibits the substantia nigra pars reticulata. And so here we've got two negative signs, here we have just one negative sign, and so this is a pathway that prevents movement, a so called no-go pathway, and so we have two different pathways, a D1 direct projection from the striatal projection neurons that enhances action, and we have a D2 pathway that tries to prevent movement of the animal.

Notes

Summary

11m 45s

Basal ganglia, dopamine and Parkinson's disease



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Cellular Mechanisms of Brain Function

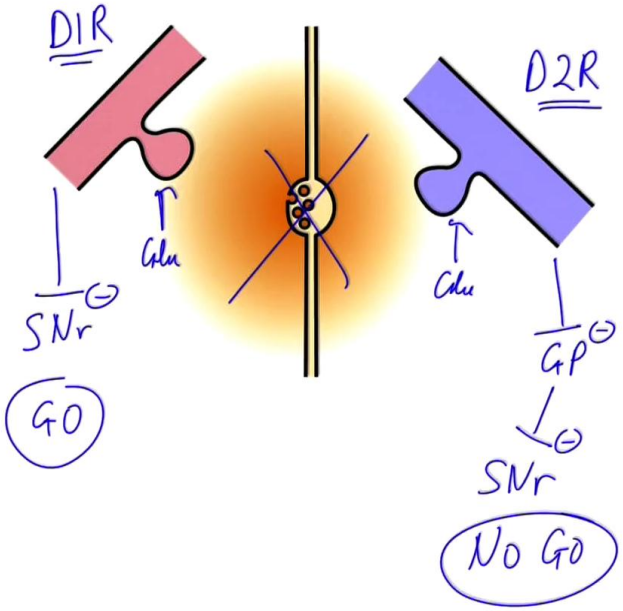
And what's interesting about the way that the dopamine signal works, upon the D1 and D2 receptors, is that it has different forms of synaptic plasticity. And so of course, the main inputs that these striatal projection neurons get, are glutamatergic inputs from the thalamus and cortex, that's true of both the D1 and the D2 spiny projection neurons. But the plasticity that occurs at these synapses is quite different comparing the D1 and the D2 expressing cells. Dopamine is released as a reward signal. So when the animal is expecting reward, then dopamine is released into the striatum and it is thought to act as a reinforcement signal that's useful for learning and synaptic plasticity. It tries to encourage the animal to do what it's doing because of this reward that's expected. And that then enhances plasticity here in the D1 goal pathway, and it seems to have the opposite effect on the D2 no-go pathway. And so there's an interesting way, in which dopamine seems to be involved as a rewards signal in terms of learning and synaptic plasticity and seems to be one that enhances the goal-directed actions of an animal that lead to reward. Obviously, a very interesting and useful learning signal.

Notes

Summary

13m 18s

Basal ganglia, dopamine and Parkinson's disease



In the striatum, dopamine acts at D1 and D2 receptors, which are expressed in different subtypes of GABA striatal projection neurons.

Dopamine may serve as an important reward signal, useful for learning and synaptic plasticity.

Degeneration of dopaminergic neurons is thought to underlie Parkinson's disease.

Cellular Mechanisms of Brain Function

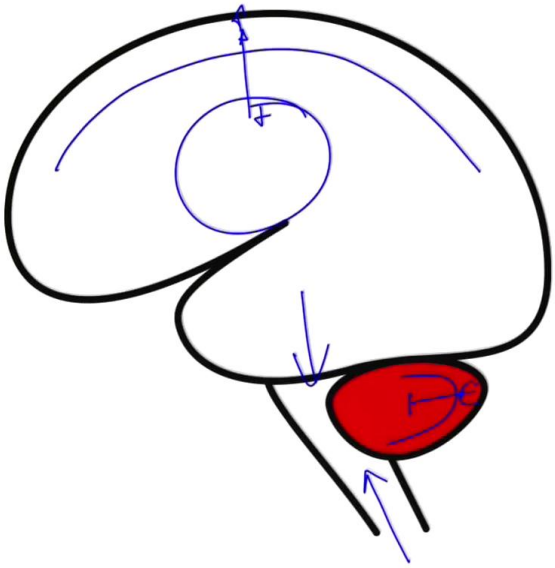
The other reason to be interested in dopamine, is that it has an important and major role in brain diseases. And in particular, in Parkinson's disease it seems to be the generation of the dopaminergic neurons that seem to be the major cause of the symptoms of Parkinson's disease. And the major symptoms of Parkinson's disease are things like bradykinesia, slowness of movement, and that might then be, because of a deficit here in the D1 go pathway where there's sort of a lack of self-motivated, goal-directed movements and that lack of dopamine might then be one of the causes of why bradykinesia comes about in Parkinson's disease, where the dopamine signal is missing.

Notes

Summary

14m 40s

3. The cerebellum



The cerebellum (‘*little brain*’) is thought to play an important role in sensorimotor learning and perhaps also in higher cognitive functions.

The cerebellum receives sensory information and uses it to fine tune motor output.

Cellular Mechanisms of Brain Function

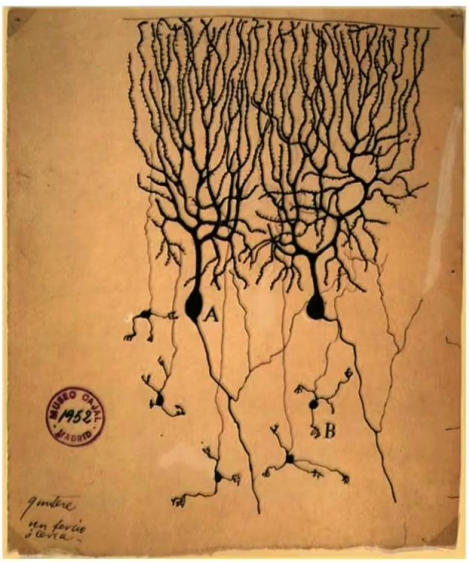
The third long-range projection neuron that we'll think about, are the Purkinje cells of the cerebellum. And the cerebellum, this area here shaded in red, in Latin cerebellum means "little brain", and in some respects, it really is a bit like a miniaturized version of the big, main brain. And so the cortex sitting around here, has projection neurons that are glutamatergic and they then project and excite, deep brain areas. In the cerebellum, there's also a cortical structure, the cerebellar cortex, that's where the Purkinje cells are located and these are GABAergic neurons and they inhibit the deep cerebellar nuclei. And so that's interesting that we have the main, big brain that has the cortex and cortical projection neurons that use glutamate to excite other areas, and we have the little brain, the cerebellum that uses GABA in terms of the GABAergic projection neurons that leaves us and inhibit deep cerebellar nuceli. And the cerebellum is thought to be involved in sensory motor learning, and also higher cognitive functions. It receives sensory information both from descending and ascending pathways, and it uses that sensory information to find true motor output.

Notes

Summary

15m 27s

Purkinje cells of the cerebellum



Santiago Ramón y Cajal 1899

The output neurons of the cerebellar cortex are the Purkinje cells.

Purkinje cells are GABAergic projection neurons, which inhibit deep cerebellar nuclei.

Cellular Mechanisms of Brain Function

The cerebellar Purkinje cells are among the most beautiful of the neurons in the mammalian brain. They have these elaborate dentritic arborizations here, you see in this drawing from over 100 years ago, by one the heroes of neuroanatomy, Santiago Ramon y Cajal, who used at that time, a new staining procedure invented by Golgi, and he studied many of the cell types of the mammalian brain in exquisite detail, and indeed predicted many of the circuit wiring diagrams of the brain about how information would flow from one brain area to another. And here, he's drawn two Purkinje cells next to each other with that elaborate dendritic arborizations so these are the largest dendrites that are present in the mammalian brain. Here's a descending axon from where it will project to the deep cerebellar nucei, and release GABA, and inhibit those deep cerebellar nucei. And these Purkinje cells seem to be useful integrators where they coordinate their sensory motor actions of the mammalian brain.

Notes

Summary

16m 46s

Long-range GABAergic projections

- Some GABAergic neurons have long-range axonal projections.
- Reticular nucleus of the thalamus drives fast feedback inhibition.
- Inhibitory basal ganglia circuits help drive goal-directed behavior.
- Purkinje cells inhibit deep nuclei helping fine sensorimotor skills.

Cellular Mechanisms of Brain Function

So in this video, we've seen that some GABAergic neurons have long-range axonal projections. And in particular, we've considered three types of long-range projection GABAergic neurons. We've thought about the thalamic reticular neurons, that have a role in feedback inhibition in the sensory thalamus, and they probably have an interesting role there in gating and filtering the sorts of sensory information that are relayed to the neocortex. We also discussed the GABAergic projection neurons of the basal ganglia, in particular the striatal projection neurons that inhibit the substantia nigra, and there, they're thought to have an interesting role in goal-directed motor control. And finally, we talked about the GABAergic Punkinje cells that form the sole output neurons of the cerebellum, where they inhibit the deep cerebellar nucei uninvolved in fine tuning motor action. And so, not only long-range excitatory neurons have important roles in brain function, but long-range GABAergic neurons also play a significant role in governing the action of the mammalian brain.

Notes

Summary

17m 55s