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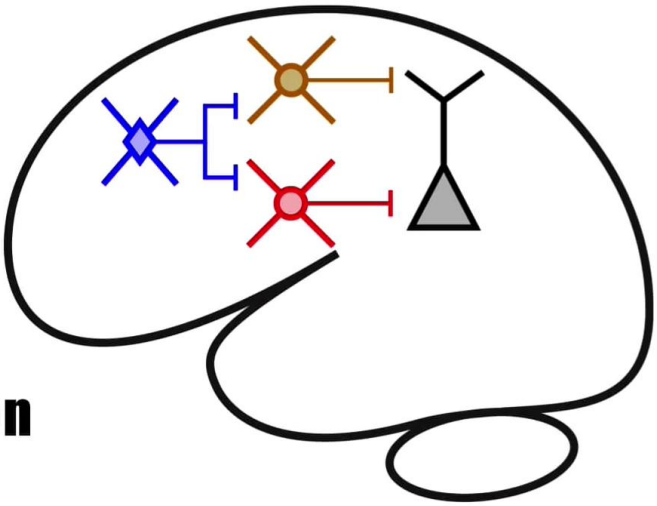
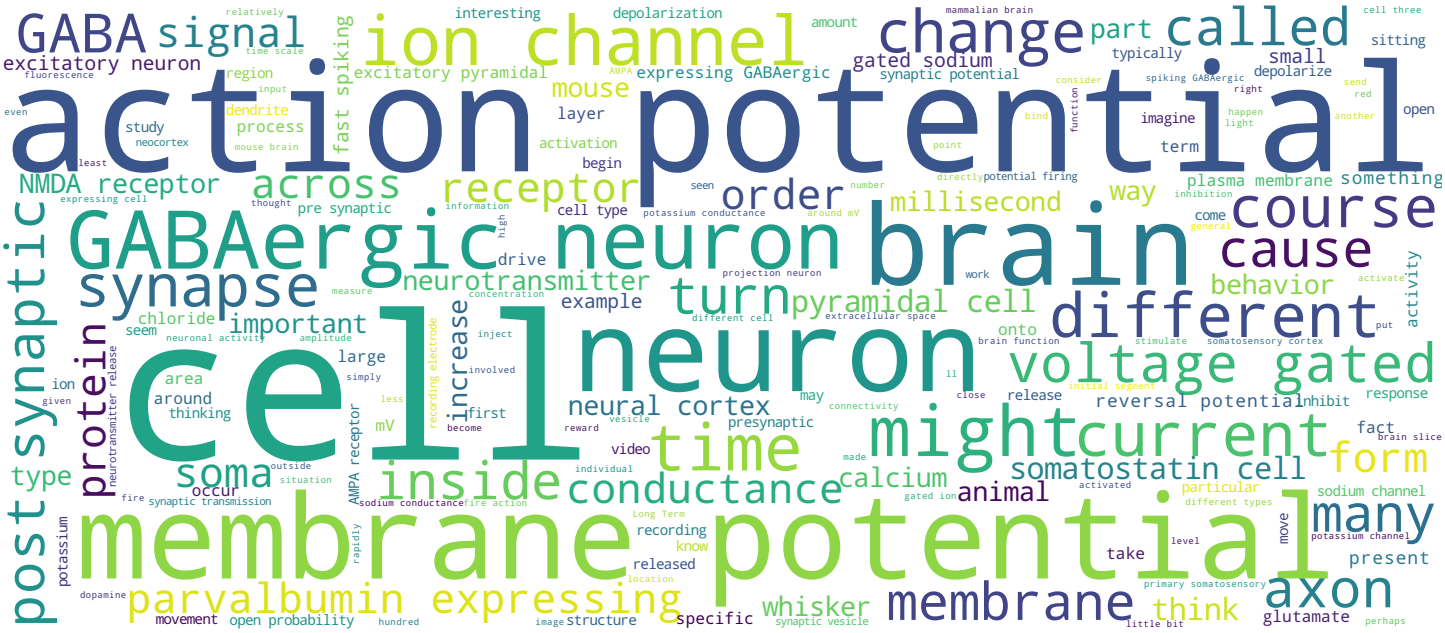


5.5 Neocortical inhibition

Cellular Mechanisms of Brain Function

Prof. Carl Petersen



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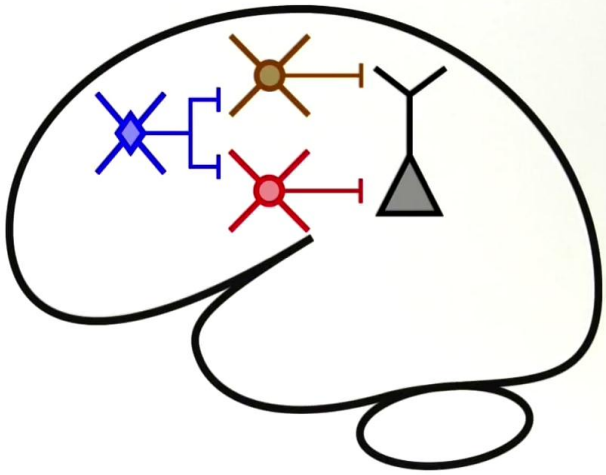
Video

EPFL

Inhibitory GABAergic neurons of the neocortex



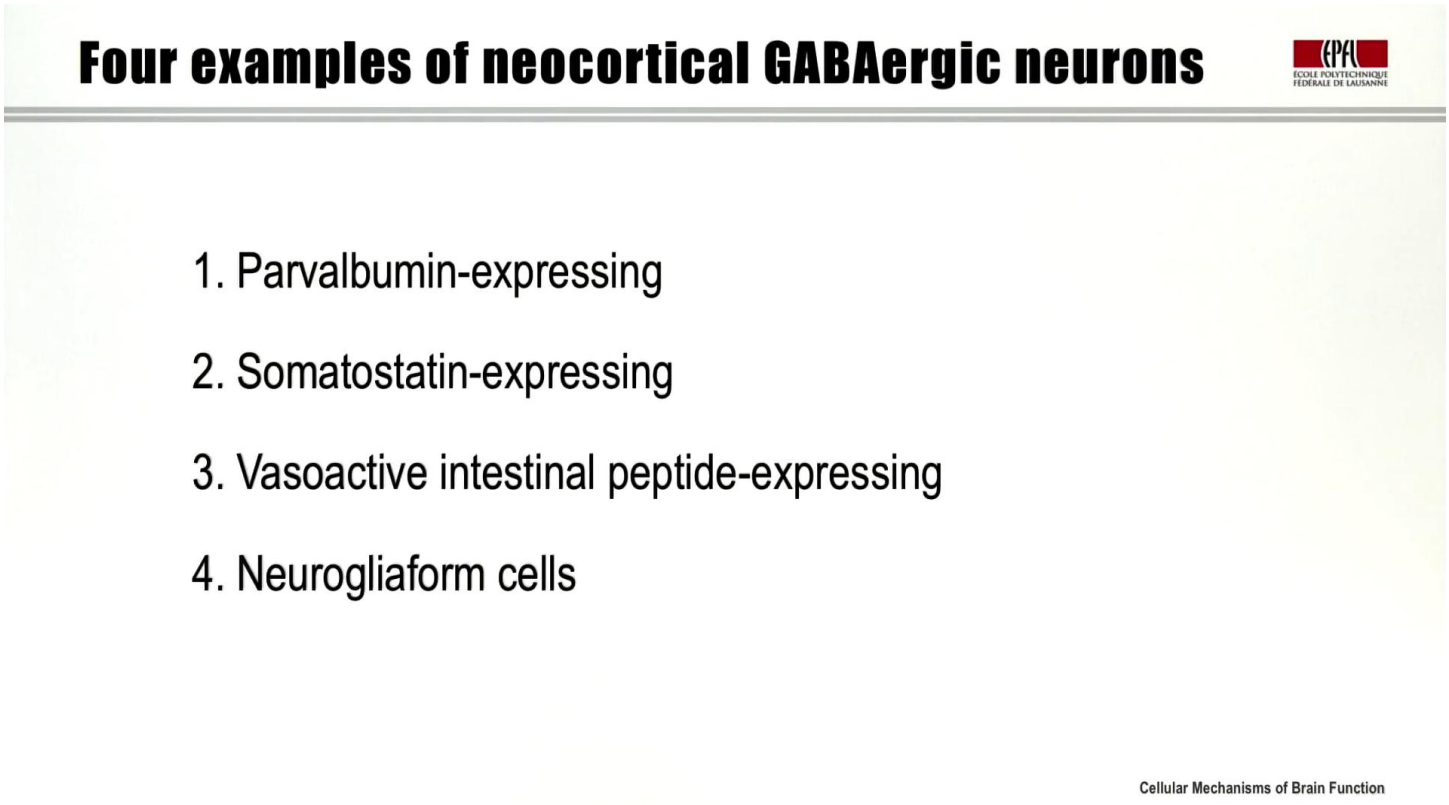
Cellular Mechanisms of Brain Function

In contrast to the long range GABAergic projection neurons that we considered in the last video, many GABAergic neurons in the brain don't have long range axonal projections, they have local axons that maybe stretch some hundreds of microns and they're often termed GABAergic interneurons for that reason. They regulate the activity of the local microcircuits in which they are imbedded. The inhibitory neurons of the neural cortex are such local interneurons and in general, they don't have long-range axonal projections. The GABAergic neurons of the neural cortex are a small fraction of the total number of neurons in the neural cortex. 85% if the neurons in the neural cortex are excitatory glutamatergic neurons and that leaves about 15% of the cells as GABAergic local inhibitory neurons. Despite the fact that there's not so many of them, they show a striking diversity in almost any feature that you care to analyze. The morphology of the cells is different, their electric physiological properties are different, their synaptic connectivity, and perhaps, most importantly in terms of characterizing the cell types, their molecular expression patterns are distinct and diverse.

Notes

Summary

0m 05s

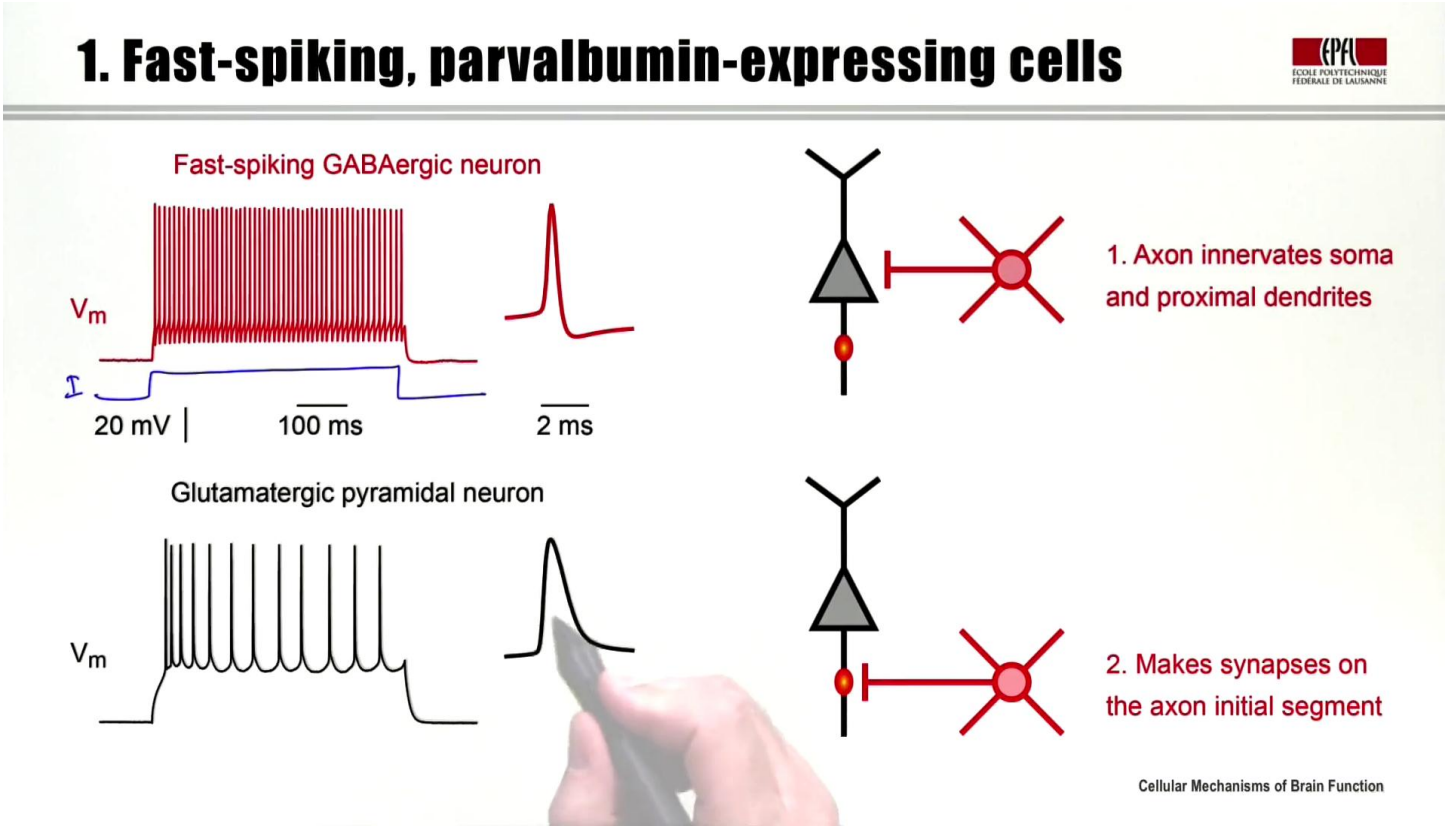


In this video we're going to consider four different types of GABAergic neocortical neurons. We'll think about three types of GABAergic neurons that are defined through their expression of different marker genes, so we'll discuss GABAergic neurons that express parvalbumin; we'll discuss others that express somatostatin; and others that express vasoactive intestinal peptide. These are non-overlapping expression patterns, at least largely, so they're different classes of neurons that don't overlap with each other. Then finally, we'll talk about neuroglialform cells that at this time don't have a good molecular marker for them.

Notes

Summary

1m 31s

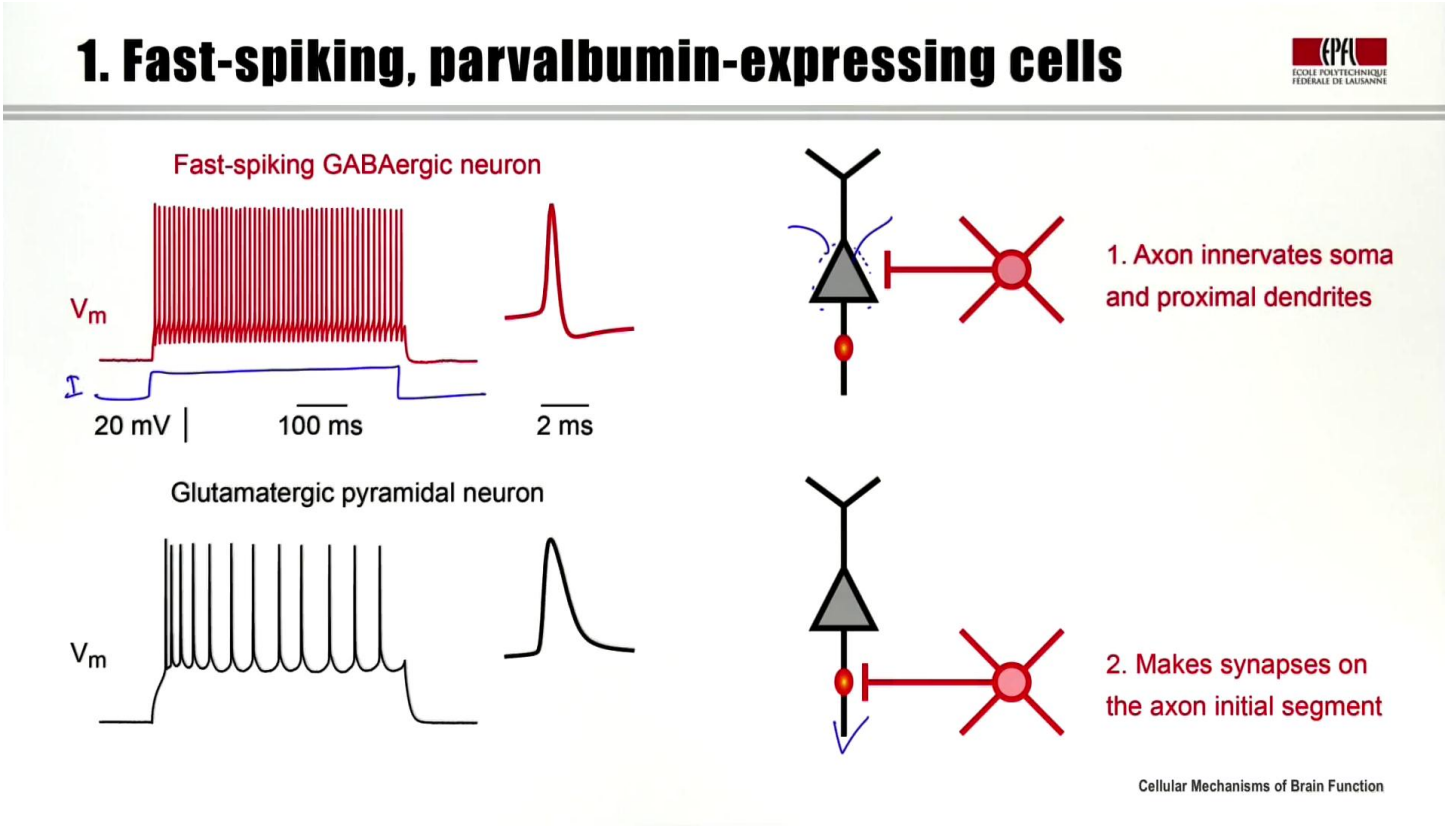


We'll begin by talking about parvalbumin expressing GABAergic neurons. In fact, we've already discussed these briefly in previous lectures, when we were thinking about the action potential waveform. The parvalbumin expressing cells have fast-spiking intrinsic electric physiological properties so if you have one of these cells on your recording electrode in a brain slice and you inject some depolarizing current into that cell, it'll depolarize and fire action potentials, and if you inject a lot of current into it, it'll fire action potentials at a very high rate, some hundreds of Hertz are the maximum firing rates of the fast-spiking GABAergic neurons. If we zoom in on each individual action potential, we'll see that they have fast waveforms, and the A-P half width is something like 300 microseconds. That contrasts with the glutamatergic excitatory pyramidal cells where if you inject depolarizing current into them, they certainly fire action potentials, but the maximum firing rates are much lower than the fast-spiking parvalbumin-expressing GABAergic neurons, about an order of magnitude lower. Each individual action potential in the glutamatergic cells has a broad waveform lasting more than a millisecond.

Notes

Summary

2m 15s



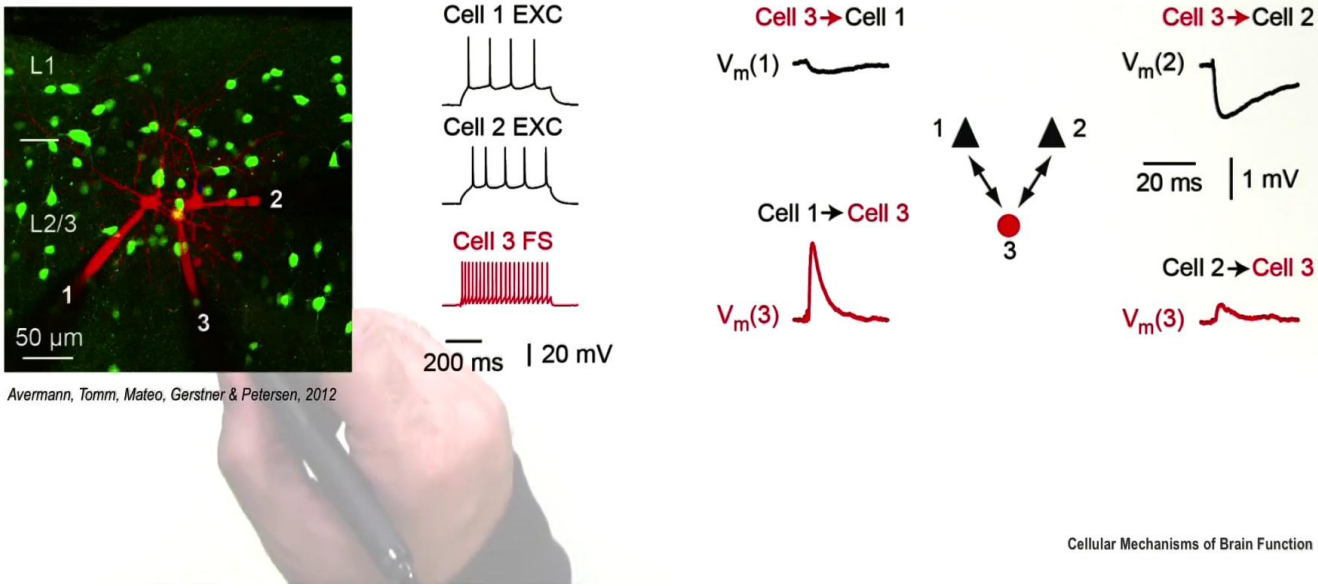
The axonal output of the fast-spiking parvalbumin-expressing GABAergic cells comes in two different flavors, and there are two different types of PV, parvalbumin, expressing cells. The major one, the so-called parvalbumin expressing basket cell, sends its axon close to soma, and often it'll decorate the soma with a basket-shape around the soma causing a fast hyperpolarizing IPSP mediated by GABA-A here at the soma, or on proximal dendrites. The other type of parvalbumin-expressing cell specifically sends its axon to the axon initial segment of the excitatory pyramidal cells. These axial, axonic cells or these chandelier cells, as they're also called, then target their inhibition to a very specific place of the pyramidal cell, the axon initial segment, where action potentials are typically thought to initiate. So, these cells specifically inhibit that area and it may be that they leave dendritic integration in their main dendrites and the soma of the cell largely untouched, and they specifically edit whether the cell is able to output an action potential or not. A very interesting type of cell. The parvalbumin-expressing GABAergic neurons, especially this type of soma and proximal dendrite targeting cell, form the largest family of the GABAergic neurons in the neural cortex.

Notes

Summary

3m 37s

Excitatory and inhibitory microcircuits



Cellular Mechanisms of Brain Function

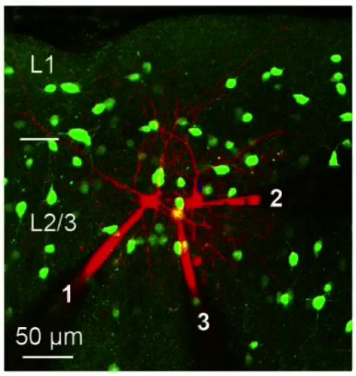
We can study the connectivity of these fast-spiking parvalbumin-expressing GABAergic neurons in brain slices, where we can record from different neurons simultaneously, and we can then initiate action potentials in different cells and study their synaptic connectivity. This brain slice is from a specific type of transgenic mouse that expresses green fluorescent protein in all the GABAergic neurons. So we have green GABAergic neurons, and excitatory pyramidal cells which form the majority of the cells here, are invisible, except when they're being recorded from where we have the red fluorescence from the recording electrode that fills the soma and dendritic operizations. And so, cell one and cell two are excitatory pyramidal cells, and you might be able to make out their dendritic operizations here. If we inject depolarizing current into these two cells, they fire action potentials with broad waveforms and at slow firing rates, typical of excitatory pyramidal cells. Recording electrode three is sitting on a cell here that's turned yellow. That's because it's a superposition of the red from the recording electrode, and the green from the green fluorescent protein of the mouse indicating that this is a GABAergic neuron and upon injecting current into it, we see that it's a parvalbumin and fast-spiking GABAergic neuron.

Notes

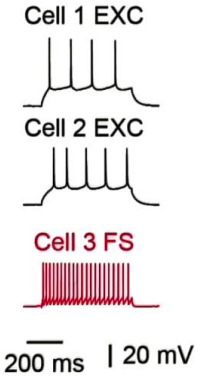
Summary

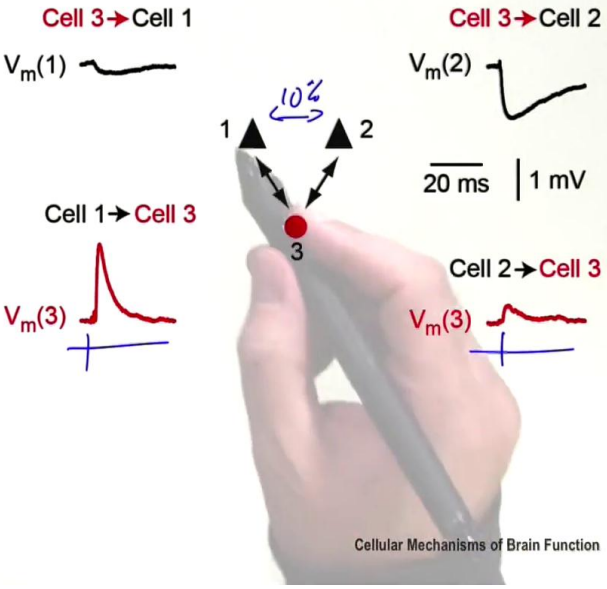
5m 19s

Excitatory and inhibitory microcircuits



Avermann, Tomm, Mateo, Gerstner & Petersen, 2012





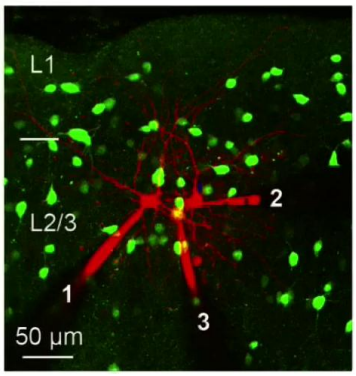
And so, we can study the synaptic connectivity between these three different cells by firing action potentials in each cell in turn. If we evoke an action potential in cell one, and we measure what happens in cell two and cell three, we see that there's an excitatory post-synaptic potential in our fast-spiking GABAergic neuron, so these are synaptically connected. Not shown is that there's no impact on cell two, so cell one connects to cell three, but not to cell two. We can find an action potential in cell two, and we see that also causes an excitatory post-synaptic potential in cell three. And so, both cell one and cell two are excitatory pyramidal cells, provide input into the fast-spiking parvalbumin GABAergic neuron. This type of connectivity is entirely typical. We saw in last week's lectures that excitatory neurons in the neural cortex connect to each other with something like a 10% connection probability. On average, excitatory neurons and fast-binding GABAergic neurons connect with something like 50% probability, so the connectivity of excitatory neurons is much higher onto these parvalbumin-expressing GABAergic neurons than it is onto other excitatory neurons.

Notes

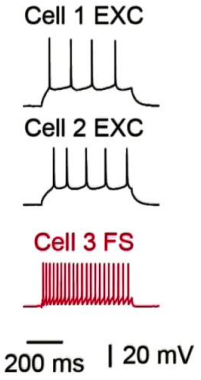
Summary

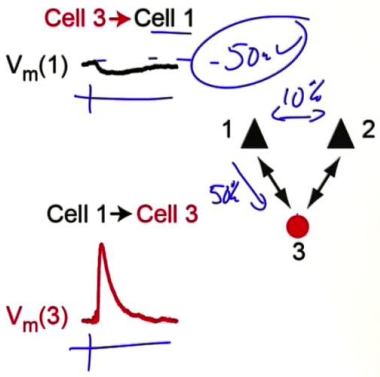
6m 43s

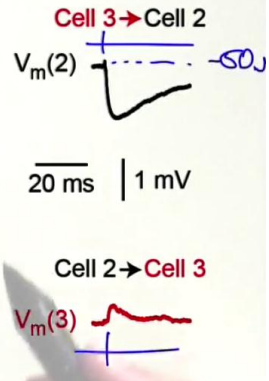
Excitatory and inhibitory microcircuits

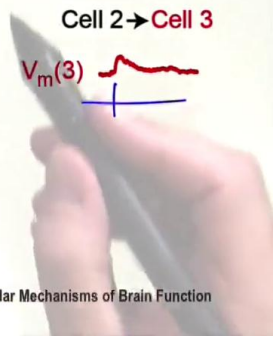


Avermann, Tomm, Mateo, Gerstner & Petersen, 2012









Cellular Mechanisms of Brain Function

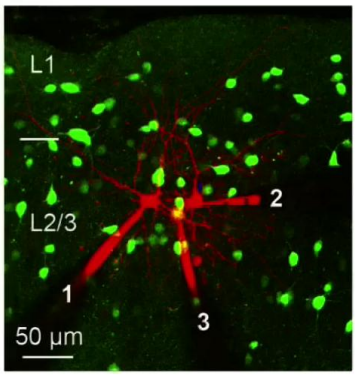
We can also evoke action potentials across any parvalbumin expressing neuron and see what happens in these inhibitory cells, and that's what we do here. An action potential is fired in cell three, a fast-spiking GABAergic neuron, and that causes an inhibitory post-synaptic potential in cell one. You can do the same here, fire an action potential in cell three, and that also causes an IPSP in cell two. So cell three inhibits both cell two and cell one, and so there are bidirectional synaptic connections here. In order to see these IPSP's we have to depolarize the post-synaptic cell and so here we're not at the resting membrane potential, but we're depolarized to -50 mV, and same here. We have to depolarize the cell to -50mV, and that's because of course, the chloride reversal potential of the GABA-A receptor is sitting at around -70 mV, so at resting membrane potential of cell one or cell two, you don't see that IPSP. It's just a conductance, and the hyperpolarization is only visible if you depolarize the cell. This type of connectivity where we have excitatory neurons that connect to other excitatory neurons with relatively low rates and very strong connectivity to the inhibitory GABAergic neuron, here we have about 50% connectivity, and equally the inhibitory connectivity which is also strong, we said this is a strong inhibitory loop.

Notes

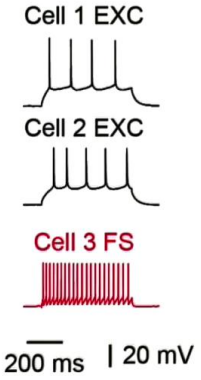
Summary

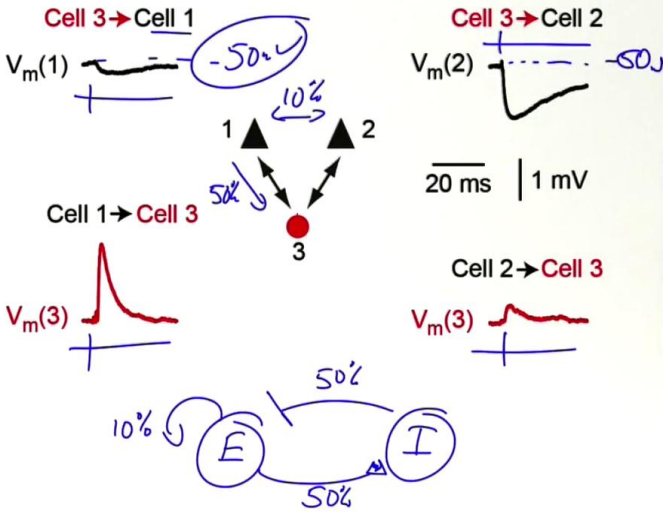
8m 04s

Excitatory and inhibitory microcircuits



Avermann, Tomm, Mateo, Gerstner & Petersen, 2012





Cellular Mechanisms of Brain Function

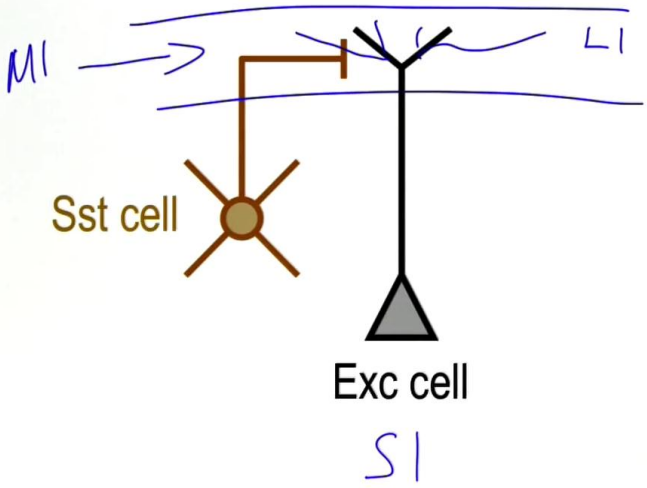
If there's more excitation and excitatory neurons that's rapidly going to be damped by this very strong inhibition, and in fact, the whole system here, at least in layer two / three, our primary somatosensory cortex, is strongly over-damped, so it's actually very difficult to get polysynaptic explosive excitation because of this very strong feedback inhibition loop from the local parvalbumin-expressing fast-spiking GABAergic neurons.

Notes

Summary

9m 37s

2. Somatostatin-expressing GABAergic neurons



Somatostatin-expressing (Sst) GABAergic neurons of the necortex strongly innervate distal dendrites of excitatory (Exc) pyramidal neurons.

Sst cells - distal dendritic inhibition

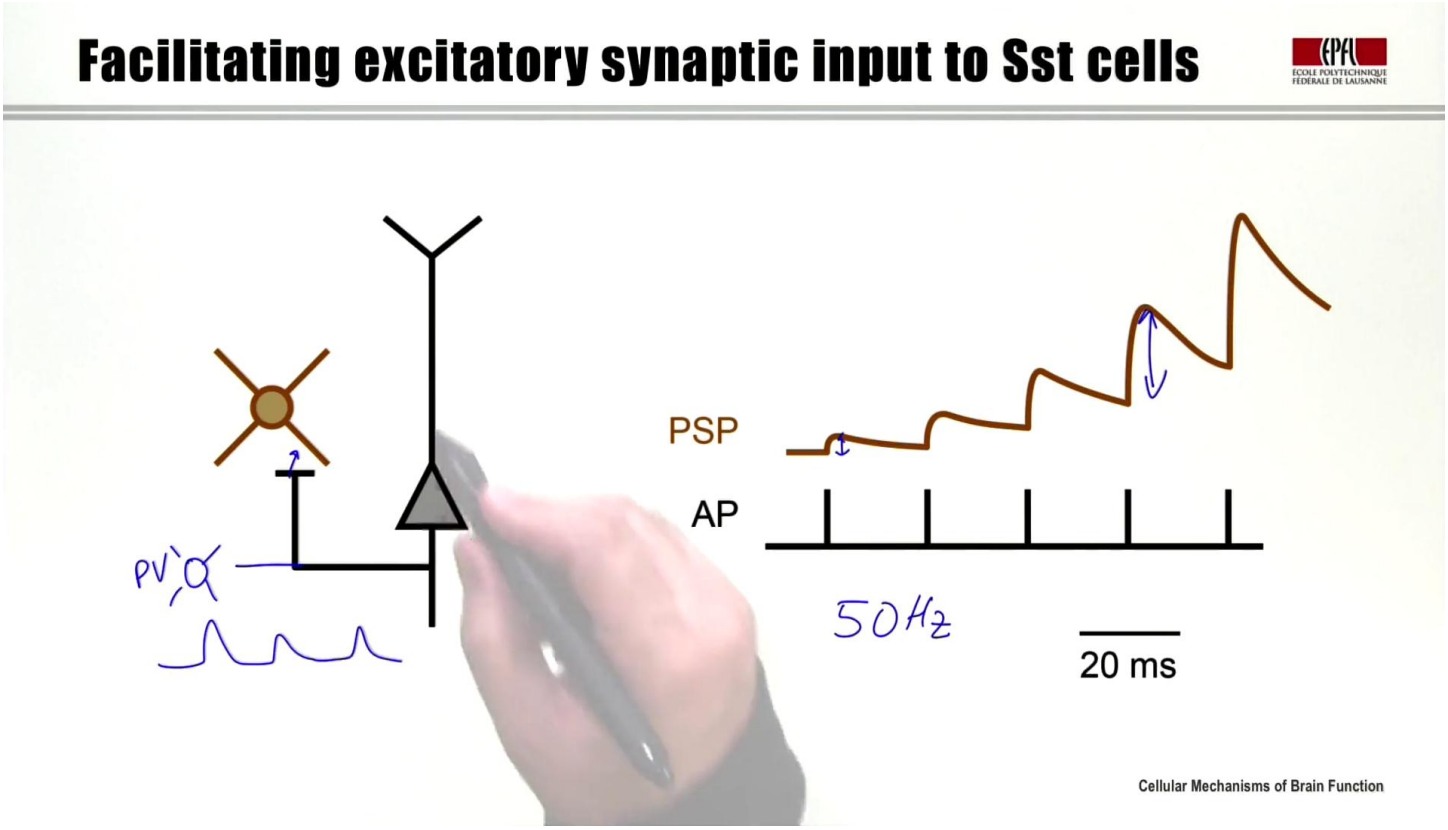
Cellular Mechanisms of Brain Function

The second type of GABAergic neuron that I'd like to consider are the so-called somatostatin-expressing GABAergic neurons. These neurons are particularly interesting because many of them send their axonal arborizations to a very specific region of the excitatory pyramidal cells. They target distal dendritic regions, and in particular, as we've seen in previous lectures, many of the excitatory pyramidal neurons have extensive arborizations here, right at the top of the brain. So this is the outside of the brain and this the surface of the brain here and there's sort of a layer of the brain called layer one that has GABAergic neurons in it, but very few excitatory cells, mainly just synapses, and this is where the pyramidal cells extend their dendritic tuft region here and that is a region that seems to be specifically targeted by the inhibition of the somatostatin-expressing neurons. There are very interesting inputs that arrive here in layer one. For example, if we're thinking about the primary somatosensory cortex of the mouse, then signals from the motor cortex arrive here specifically in layer one. So it may be that the somatostatin cells are specifically involved in gating the input of motor information into the primary somatosensory cortex. A very interesting role of this distal dendritic innovation that somatostatin cells might drive.

Notes

Summary

10m 04s



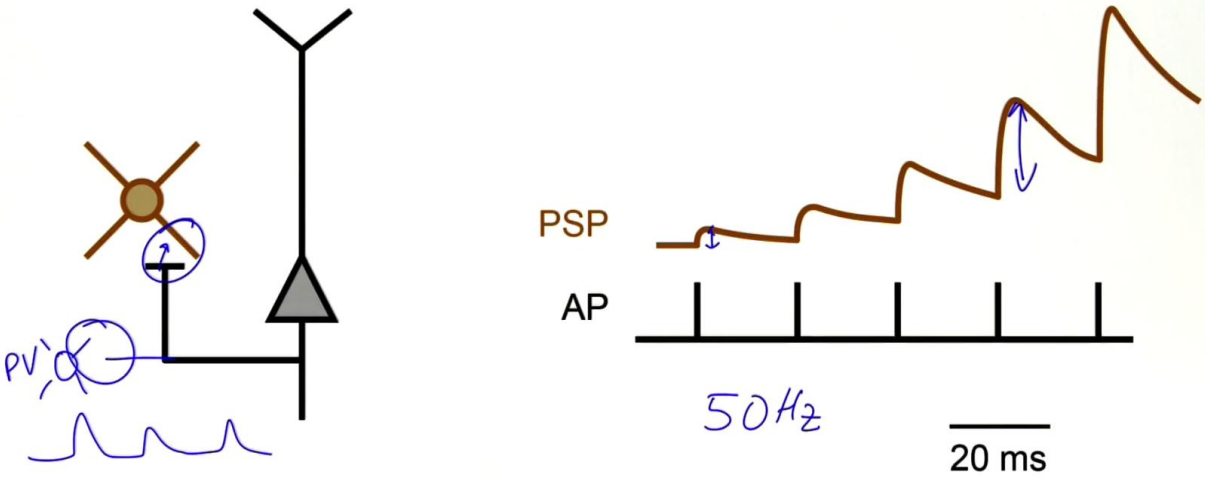
Another fascinating feature of the somatostatin cells is that they receive facilitating excitatory synaptic input from the nearby pyramidal cells. So, if this is a pyramidal cell that's somatically connected to a somatostatin cell, if we fire a single action potential, then the EPSP recorded here in the somatostatin cell is relatively small and variable in amplitude, but if we fire repetitive action potentials at high frequency, say at 50 Hertz as in this example, then the EPSP amplitude grows and it becomes much larger than it was on the first action potential. So this is typical of pre-synaptic facilitation: an increase in the neurotransmitter release probability that occurs at the pre-synaptic end of the specialization, and this facilitation is very specific onto the somatostatin cells. The same pre-synaptic neuron targeting a parvalbumin-expressing cell will not show facilitation. Rather, it will show something constant, or perhaps even something that's depressing. So there's something very specific about the synapses made here onto somatostatin cells as opposed to parvalbumin cells, even from the same axon of the same pre-synaptic neuron, that give it remarkably different properties in terms of what's sensed post-synaptically.

Notes

Summary

11m 28s

Facilitating excitatory synaptic input to Sst cells



Cellular Mechanisms of Brain Function

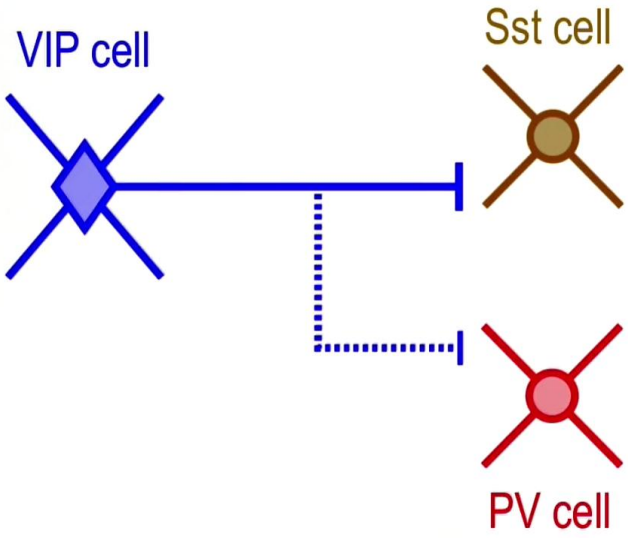
So there's something interesting occurring here in the somatostatin cells where they seem to be integrating bursts of action potentials from the pyramidal cells over longer periods of time when they can become strongly depolarized in response to trains of action potentials and that is unique to somatostatin cells. There's no other cells in the neural cortex that have such prominent synaptic facilitation.

Notes

Summary

12m 50s

3. VIP-expressing GABAergic neurons



Vasoactive intestinal peptide-expressing (VIP) GABAergic neurons inhibit other inhibitory neurons, especially Sst neurons.

VIP cells – dis-inhibition

Cellular Mechanisms of Brain Function

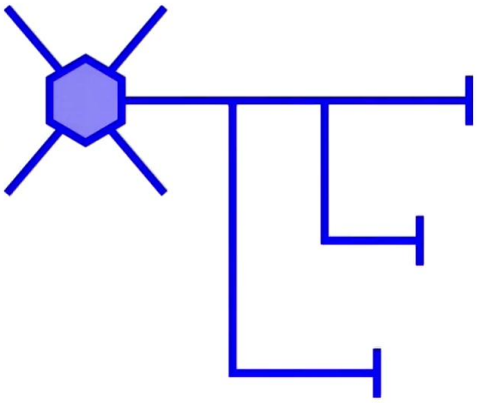
The VIP-expressing GABAergic neurons are also extremely interesting. VIP stands for vasoactive intestinal peptide, and we don't know what the functional role of VIP is in the neural cortex, but we can use it as a useful marker for our cell type in the brain. In the neural cortex, the VIP cells seem to have a specific role in inhibiting other GABAergic neurons so they release GABA here, they inhibit cells, and the cells that they inhibit are not the excitatory cells, but there are somatostatin cells, and a little bit less, the parvalbumin cells. And so, the VIP cells, rather than causing overall inhibition in the neocortical microcircuit, actually cause excitation, and they do that via disinhibition.

Notes

Summary

13m 16s

4. Neurogliaform GABAergic neurons



Neurogliaform cells release GABA into the extracellular space, thereby mediating volume transmission activating $GABA_B$Rs to drive slow IPSPs.

Cellular Mechanisms of Brain Function

The last type of neocortical GABAergic neuron that we'll consider is the so-called neurogliaform cell. These are small, compact cells which have an extremely dense axonal arborization close to the soma. What's specifically interesting about the neurogliaform cells is that along their axons they form, of course butons and they release GABA, but they don't have an obvious post-synaptic partner. So these cells seem to release GABA into the extracellular space, and they may then regulate the extracellular GABA concentrations, and they can signal via GABA-B receptors causing slow inhibitory post-synaptic potentials.

Notes

Summary

14m 04s

GABAergic neurons of the neocortex

- Most GABAergic neurons in the neocortex only have a local axon.
- PV neurons inhibit proximally
- Sst neurons inhibit distally
- VIP neurons dis-inhibit
- Neurogliaform cells inhibit via extrasynaptic $GABA_B$ receptors

Cellular Mechanisms of Brain Function

In this video we've seen that there are quite different types of GABAergic neurons in the neural cortex and they appear to serve quite different functions. Parvalbumin expressing GABAergic neurons can fire at extremely high rates, are highly connected to the excitatory neurons, and probably mediate some form of fast feedback inhibition. The somatostatin cells, on the other hand, target distal dendritic elements, and they receive facilitating input from the nearby excitatory neurons and they presumably respond to quite different patterns of activity in the neural cortex and furthermore, their inhibition is of a rather different element in the circuit than the parvalbumin cells. The parvalbumin cells inhibit proximal areas close to the soma. The soma itself acts on initial segment proximal dendrites, fast inhibition, whereas the somatostatin cells are inhibiting a slower form of inhibition at the distal dendrites. We also talked about VIP expressing cells that have an interesting role in disinhibition. They inhibit other inhibitory neurons. And finally, we mentioned neurogliaform cells that might be involved in controlling the extracellular space GABAergic concentrations, and mediate slower IPSP's via the GABA-B receptor.

Notes

Summary

14m 46s

GABAergic neurons of the neocortex

- Most GABAergic neurons in the neocortex only have a local axon.
- PV neurons inhibit proximally
- Sst neurons inhibit distally
- VIP neurons dis-inhibit
- Neurogliaform cells inhibit via extrasynaptic $GABA_B$ receptors

Cellular Mechanisms of Brain Function

So there's a whole diversity of GABAergic neurons and a challenge for the future is now to assemble these different cell types, these different mechanisms, and see how that functions in the living brain during behavior.

Notes

Summary

16m 09s