

Lecture 11. Synaptic Inhibition and Integration

Dr. Bruce Johnson

Recommended Reading

Watch Videos 11-1 “Synaptic inhibition” and 12-2 “Classic neuron integration”

Be able to describe and explain the following figures from Bear et al.: p.129, Fig. 5.16; p.134, Fig. 5.19; p.135, Fig. 5.20; p.138, Fig. 5.21.

Learning Objectives

1. To understand how inhibitory synapses reduce neuronal excitability.
2. To understand the dynamic and integrative interactions of EPSPs and IPSPs, and how IPSPs can shunt a simultaneous EPSP.
3. To understand how the principles of passive electrical flow apply to synaptic currents and their ability to influence the post-synaptic neuron's firing.

Lecture Outline

1. Ionic mechanisms of inhibitory synapses (Video)
 - Usually mediated by chloride and/or potassium flux
 - V_{Rev} is more hyperpolarized than the threshold for firing an action potential, but may be more depolarized than the resting potential
2. Major points about ionotropic synapses
 - V_{Rev} determined whether the synapse is excitatory or inhibitory
 - Many neurotransmitters can be excitatory or inhibitory
 - Each transmitter can bind to multiple types of receptors, with different properties
 - The response is dependent on the receptor types activated, not the neurotransmitter
3. Integration of multiple synaptic inputs to a neuron
 - Spatial summation
 - Temporal summation
4. Interaction of excitatory and inhibitory synapses
 - Linear or algebraic summation: when synapses are far apart and do not affect one another
 - Non-linear summation, or shunting: when the synapses are close together in space and time, or when the IPSP is along the path of the EPSP towards the soma
 - Shunting arises from rapid changes in driving force for the IPSP with smaller changes in driving force for the EPSP
5. Integration in traditional neurons, ex., spinal motoneurons (Video)
 - Synaptic inputs localized to dendrites and dendritic spines, which do not contain voltage-sensitive ionic channels
 - Synaptic output localized to end of the axon

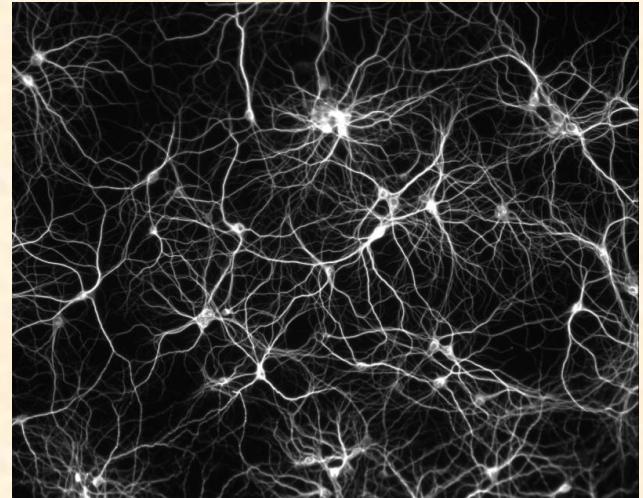
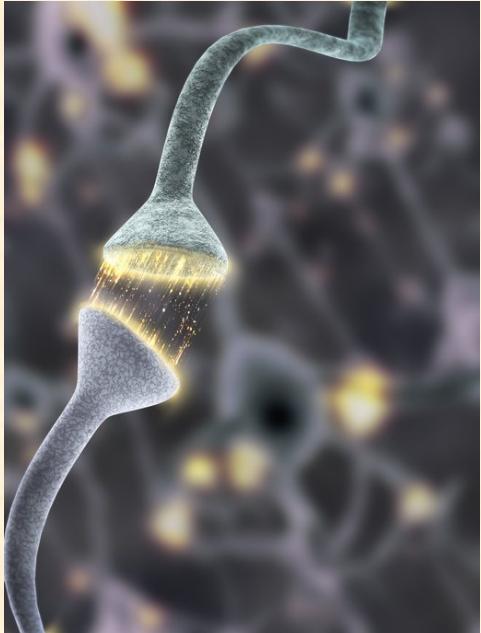
- Integration pointed at the spike-initiation zone (SIZ), region of lowest threshold for firing, which is typically in the initial segment of the axon next to the soma
 - Relative efficacy of a synapse depends on: 1) the distance from the SIZ; 2) the strength of the synapse; 3) the membrane resistance of the dendrites; 4) the complexity of the neuron
6. Integration in neurons with active dendrites, ex., cerebellar Purkinje neurons
 - Dendrites contain voltage-activated channels, and can fire action potentials
 - Distal dendritic synapses can reach the SIZ by triggering action potentials which summate as move towards the SIZ
 - Spikes can also flow retrogradely from the soma into the dendrites and contribute to synaptic plasticity
 7. Integration in non-spiking neurons, ex., thalamic local interneurons
 - Do not fire action potentials, due to low or absent levels of voltage-sensitive channels
 - Are typically very small
 - Have high membrane resistance to allow current to flow longer distances
 - Inputs and outputs are mingled in the processes, not segregated.

Study Questions

1. You are studying two different excitatory acetylcholine synapses on different dendrites on the same neuron. Synapse A leads to a 15 mV depolarization at the cell soma, and synapse B leads to a 5 mV depolarization at the cell soma. Both synapses release the same amount of transmitter, and activate the same number of acetylcholine receptors which pass an identical amount of depolarizing current into their respective dendrites, describe **two** different mechanisms which could produce the different responses at the cell soma.
2. Give two ways you could modulate a cell to make it more sensitive to synaptic input (i.e., more likely to fire in response to an EPSP).
3. If the V_{Rev} for a synapse is -55 mV, the resting potential of the neuron is -60 mV, and the threshold for spike generation is -45 mV, is the synapse excitatory or inhibitory? Explain your answer.

Lecture 11: Inhibition and Neuronal Integration

Bruce Johnson



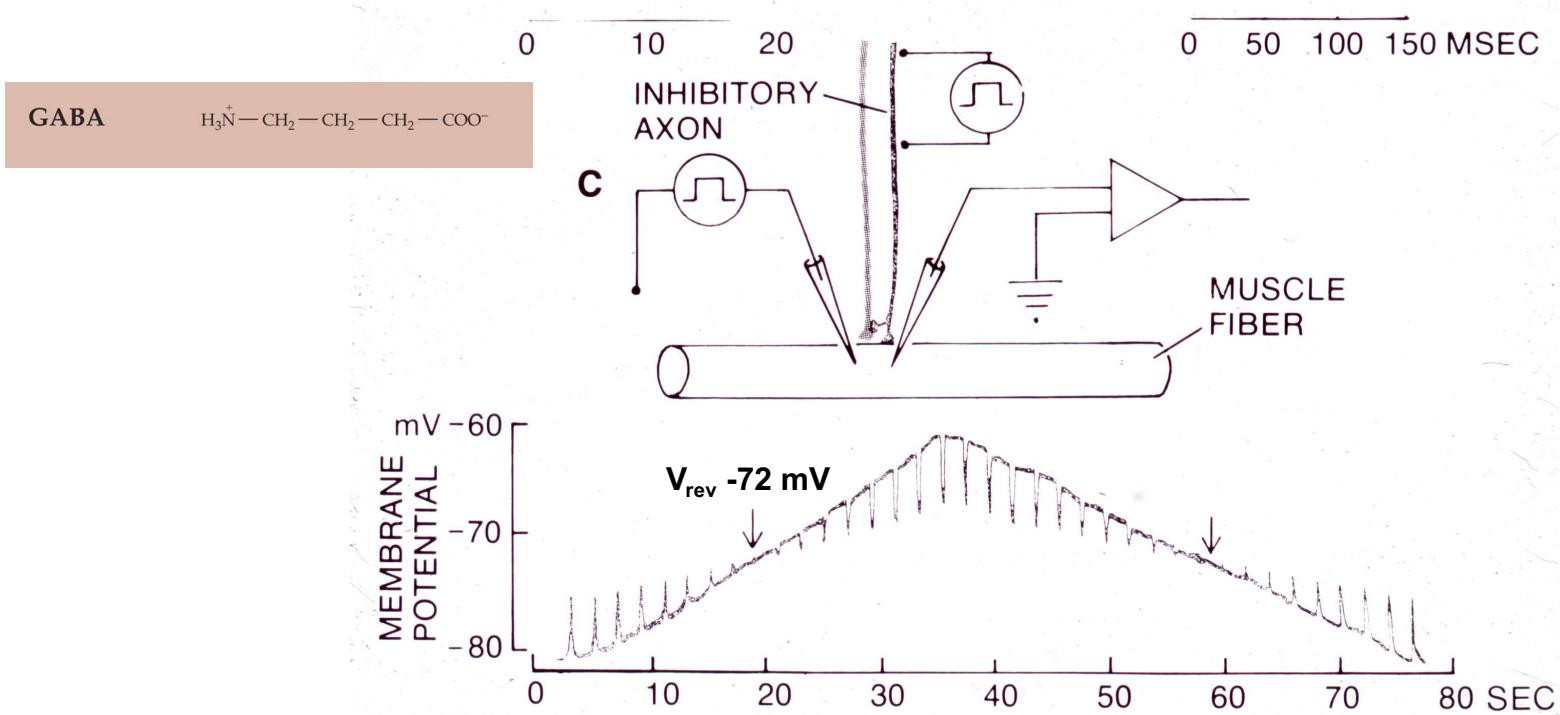
[https://www.youtube.com/watch?v=61irttlh
TyY](https://www.youtube.com/watch?v=61irttlhTyY)

Goals for Today

- Ionic mechanisms of synaptic inhibition
- Integration of excitatory and inhibitory synapses
- Dendritic integration in motoneurons, Purkinje cells and nonspiking neurons

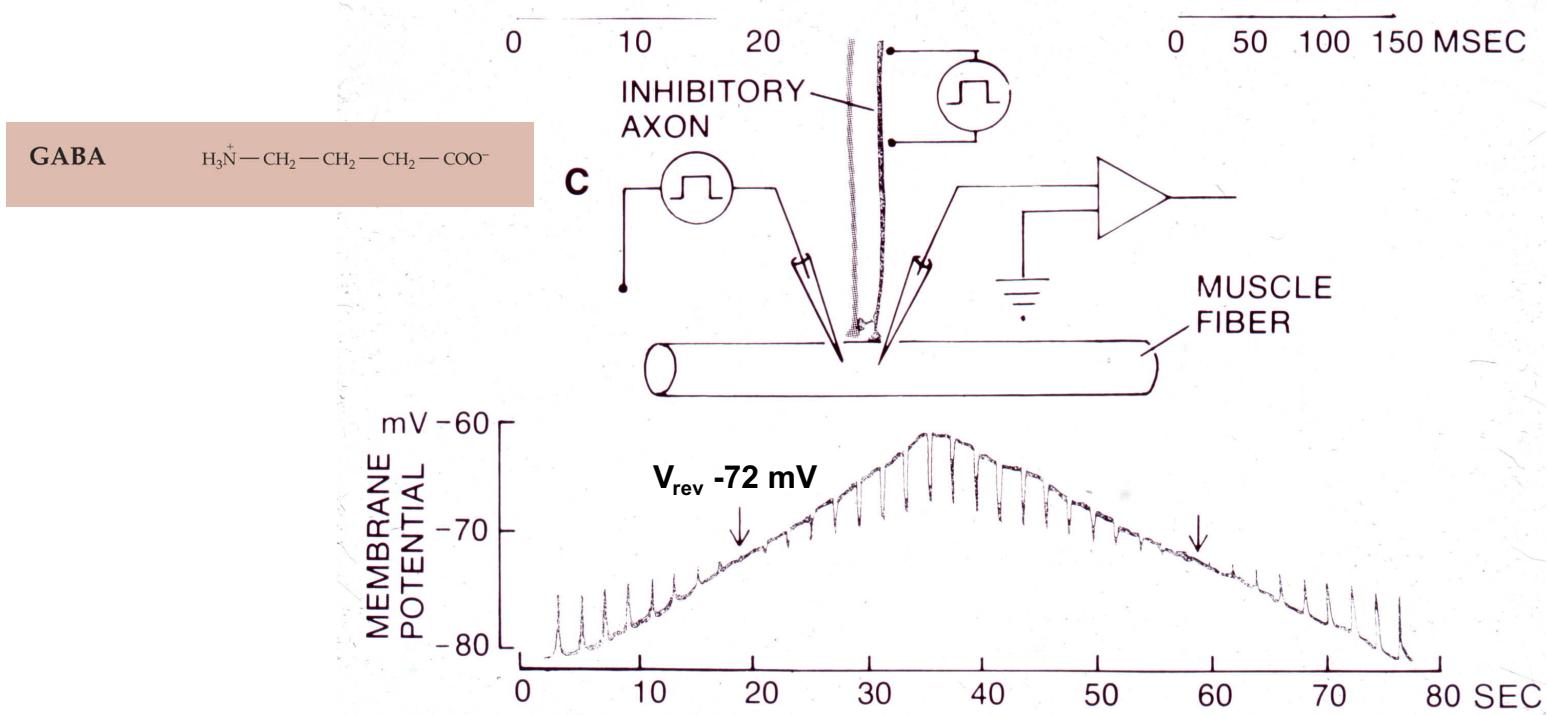
1. Ionic mechanisms of synaptic inhibition

Video: Determination of V_{Rev} at a GABAergic synapse



Two steps to show the GABA receptor is a Cl^- channel:

Video: Determination of V_{Rev} at a GABAergic synapse



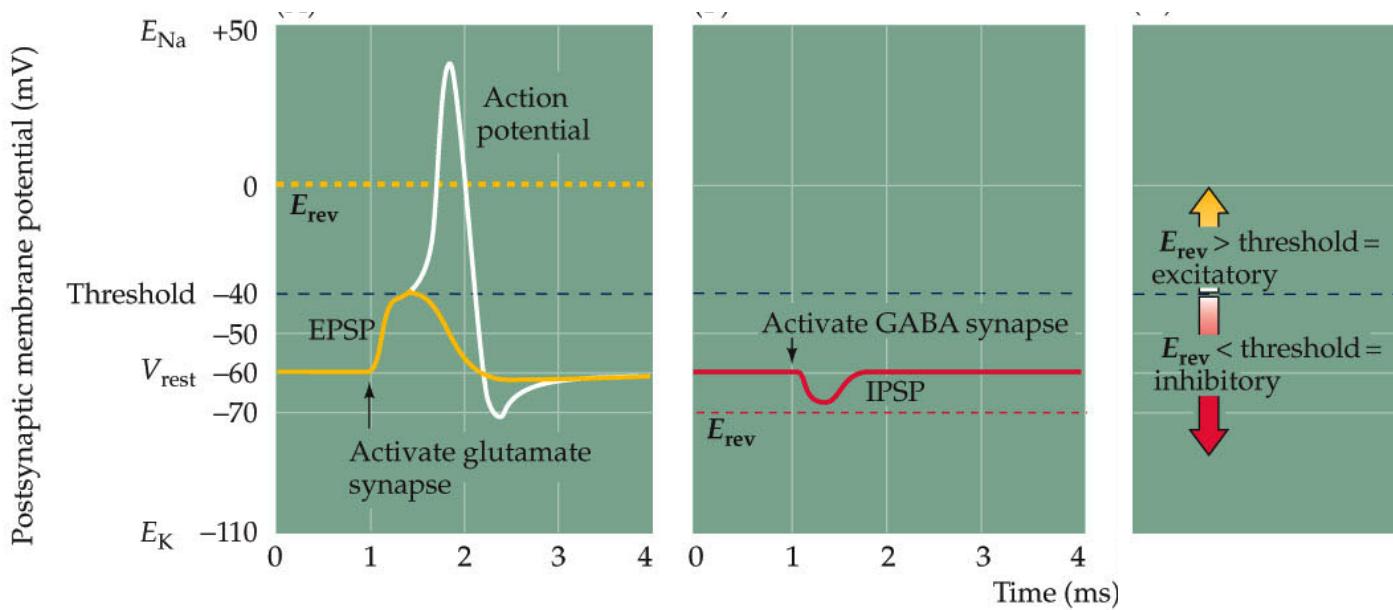
Two steps to show the GABA receptor is a Cl^- channel:

- 1) Determine V_{Rev}
- 2) Alter extracellular ion concentrations and see which alter V_{Rev}

The V_{rev} determines whether a synapse is excitatory or inhibitory for synaptic responses arising from channel opening:

Excitatory synapses have V_{rev} above AP threshold, try to evoke an AP

Inhibitory synapses have V_{rev} below AP threshold, try to prevent AP from firing



Clicker question

$E_{Na} = +50$ mV, $E_K = -80$ mV, $E_{Cl} = -65$ mV, Resting Potential (RP) = -50 mV

If a transmitter activates a ligand-gated chloride channel, the neuron will:

- A. Depolarize towards -10 mV
- B. Depolarize towards -60 mV
- C. Hyperpolarize towards -80 mV
- D. Not change, as chloride is not pumped strongly
- E. Hyperpolarize towards -65 mV

Clicker question

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- E. Hyperpolarize towards -65 mV

15 mV driving force into the cell

Clicker question

You mutate the GABA_A receptor so that it is only half as permeable to chloride as the normal receptor. How will this change the V_{rev} of the receptor channel?

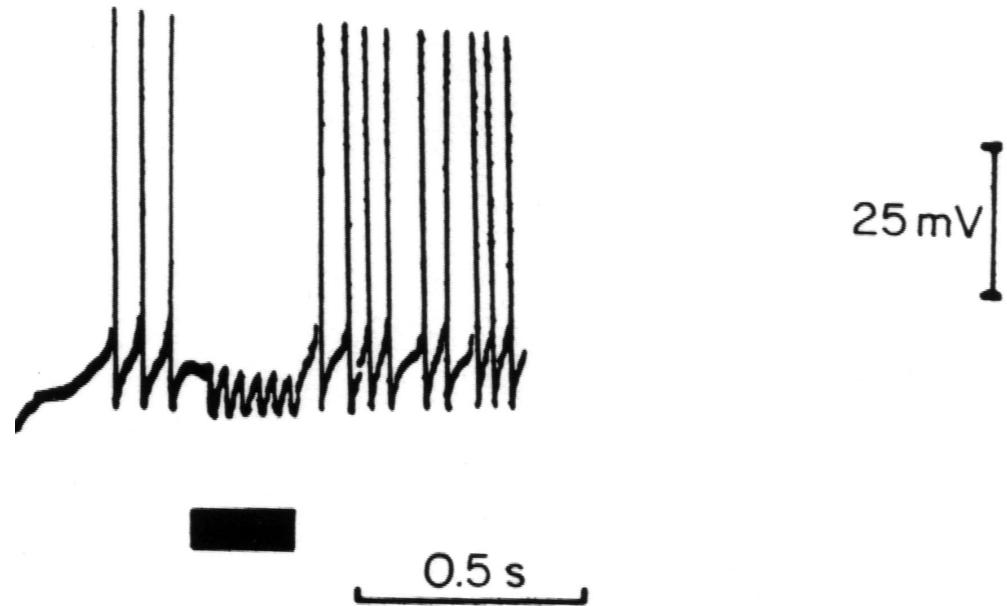
- A. It will be more hyperpolarized
- B. It will not change
- C. It will be more depolarized
- D. Cannot tell from this information

Clicker question

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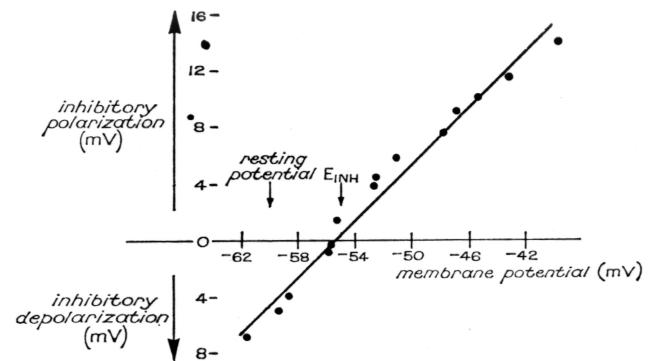
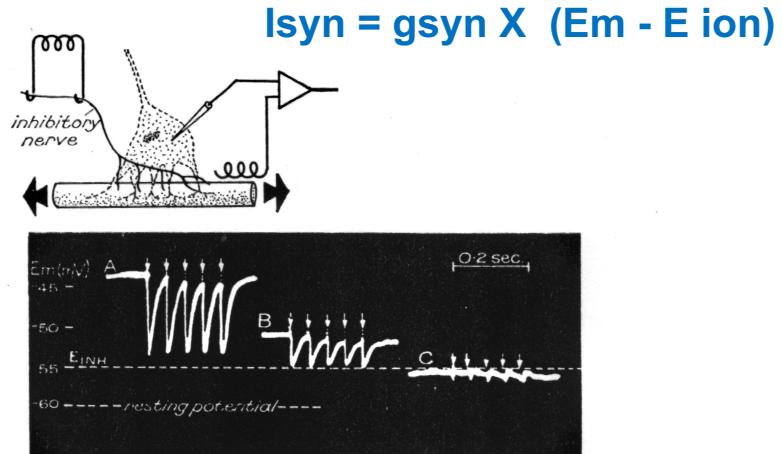
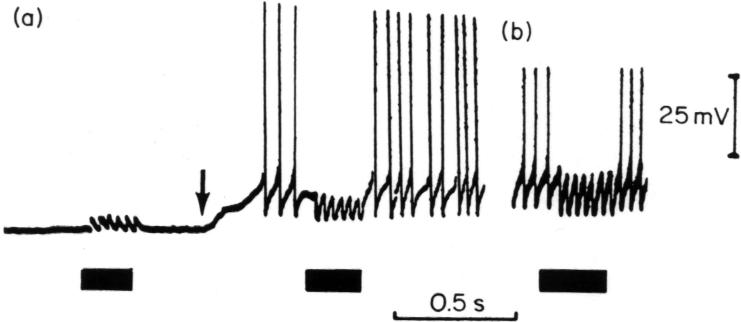
- A. It will be more hyperpolarized
- B. It will not change $E_{Cl} = -58 \text{ Log } [Cl]_{out}/[Cl]_{in}$
- C. It will be more depolarized
- D. Cannot tell from this information

IPSPs can block tonic spiking of a neuron



Stimulate inhibitory neuron

Inhibitory, conductance increase



Clicker question

For these questions, $E_{Na} = +50$ mV, $E_K = -80$ mV, $E_{Cl} = -65$ mV.
 $RP = -65$ mV. Threshold for AP generation = -40 mV

- A transmitter activates a receptor whose channel is selectively permeant to Cl^- . When the pre-synaptic neuron is stimulated, the post-synaptic neuron will:
- A. Depolarize
 - B. Hyperpolarize
 - C. Not change
 - D. Begin firing action potentials

Clicker question

For these questions, $E_{Na} = +50$ mV, $E_K = -80$ mV, $E_{Cl} = -65$ mV.
 $RP = -65$ mV. Threshold for AP generation = -40 mV

- A transmitter activates a receptor whose channel is selectively permeant to Cl^- . When the pre-synaptic neuron is stimulated, the post-synaptic neuron will:
- A. Depolarize
 - B. Hyperpolarize
 - C. Not change. No driving force
 - D. Begin firing action potentials

Clicker question

For these questions, $E_{Na} = +50$ mV, $E_K = -80$ mV, $E_{Cl} = -65$ mV.
 $RP = -65$ mV. Threshold for AP generation = -40 mV

A transmitter activates a receptor whose channel is selectively permeant to Cl^- . This synapse is:

- A. Excitatory
- B. Inhibitory
- C. Has no function
- D. Cannot tell

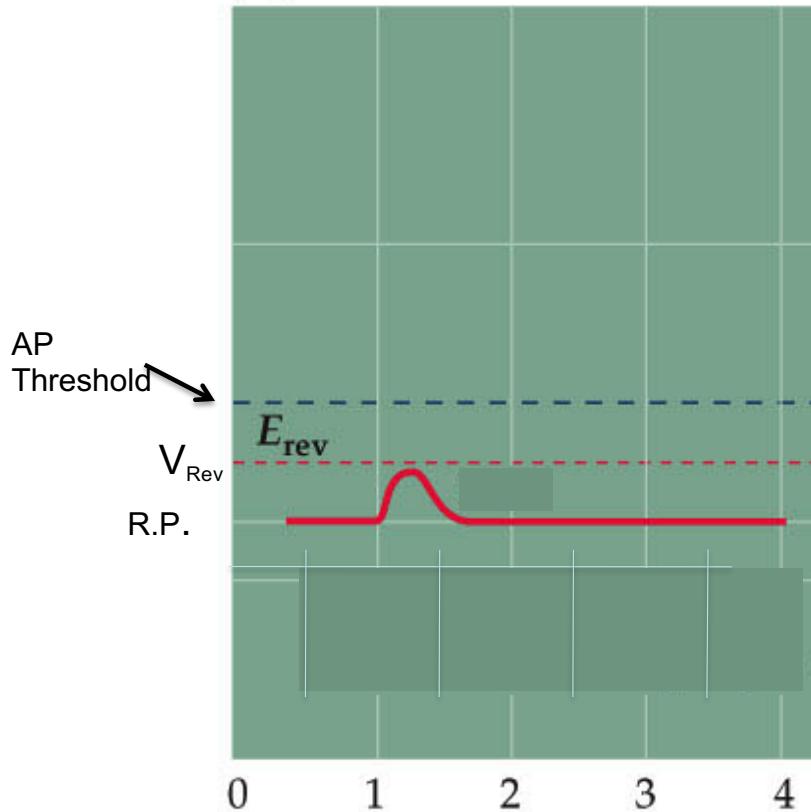
Clicker question

For these questions, $E_{Na} = +50$ mV, $E_K = -80$ mV, $E_{Cl} = -65$ mV.
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A transmitter activates a receptor whose channel is selectively permeant to Cl^- . This synapse is:

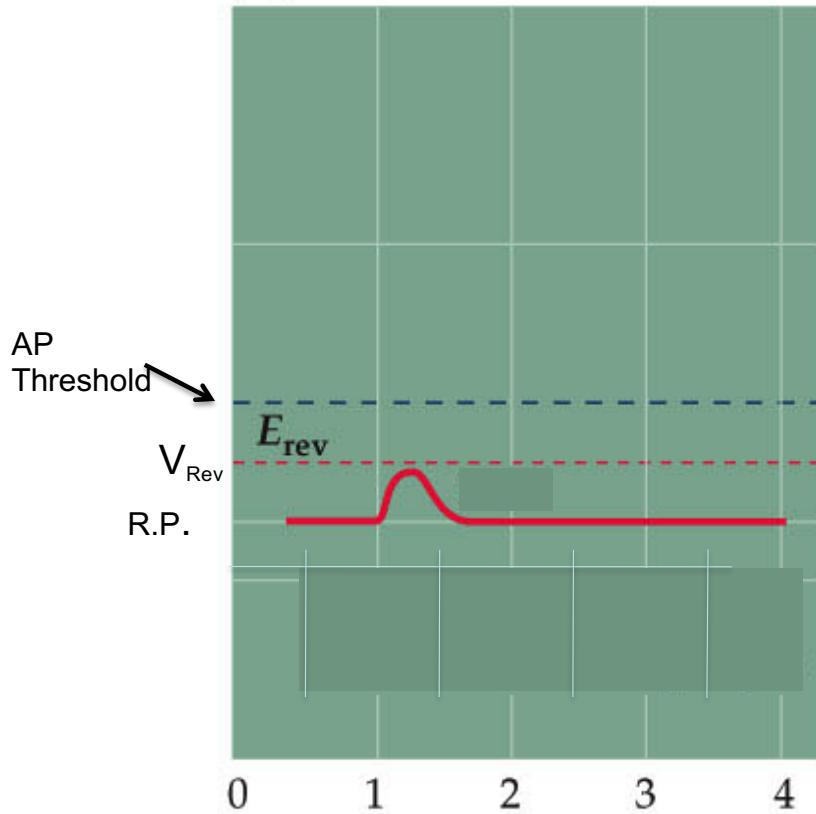
- A. Excitatory
- B. Inhibitory
- C. Has no function
- D. Cannot tell

Clicker question: Is the synapse below excitatory or inhibitory?



- A. Excitatory
- B. Inhibitory
- C. Cannot tell

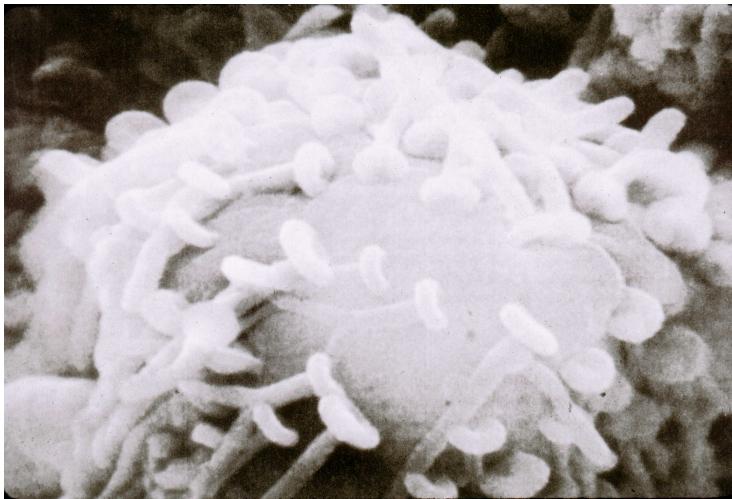
Clicker question: Is the synapse below excitatory or inhibitory?



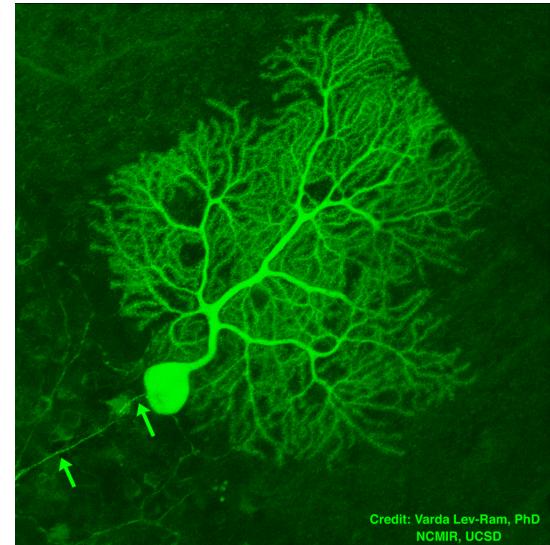
- A. Excitatory
- B. Inhibitory- membrane “clamped”
- C. Cannot tell

2. Synaptic integration:

How does a neuron integrate its thousands of synaptic inputs and decide whether or not to spike?



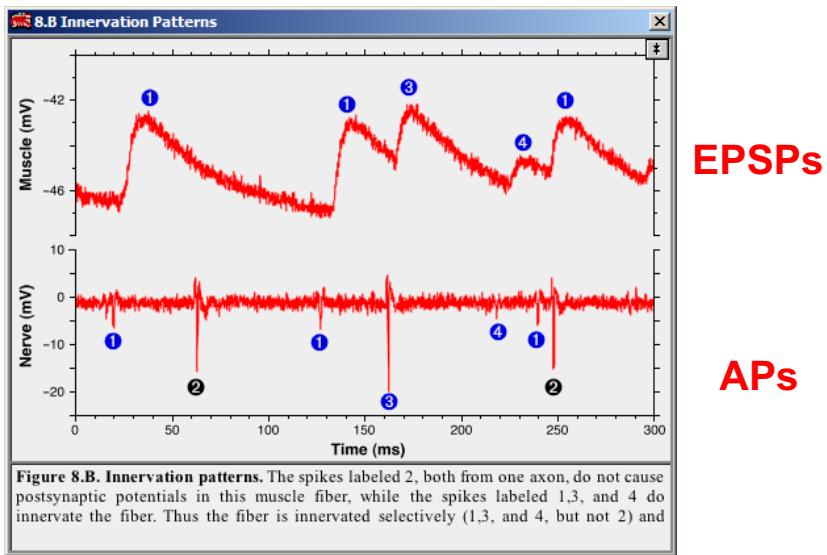
Scanning electron micrograph of Aplysia neuron



Cerebellar Purkinje neuron

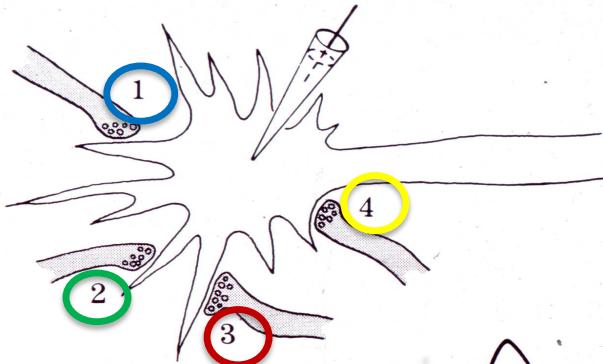
Credit: Varda Lev-Ram, PhD
NCMIR, UCSD

Synaptic integration example

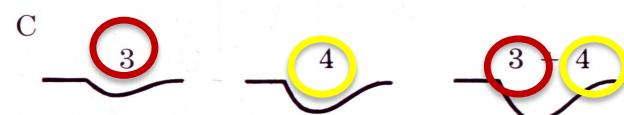


vid.5.3-PSP_Matching.mp4

Spatial and temporal summation



Spatial Summation
Depends on space cons

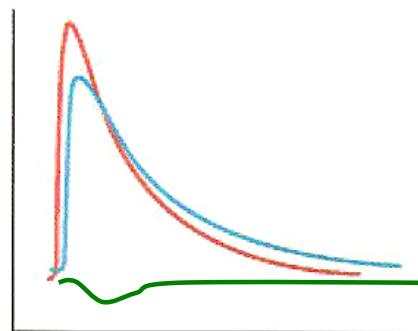
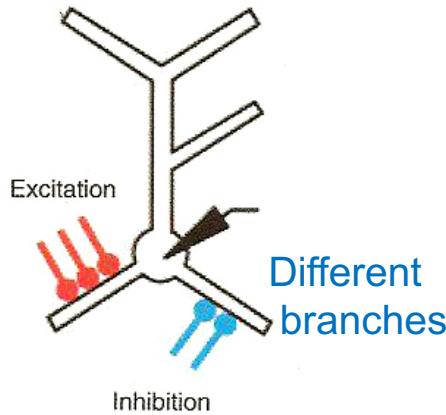


Temporal Summation
Depends on time cons

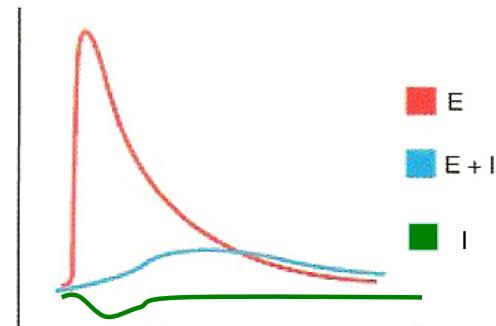
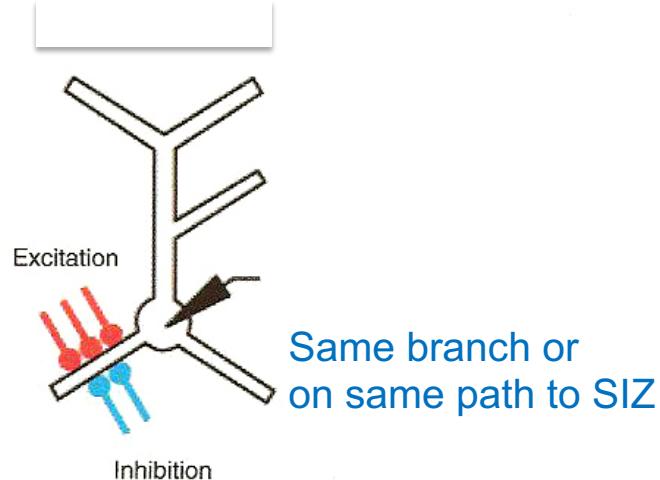
Linear and non-linear summation of EPSP and IPSP

Location, location, location

Linear: arithmetic summation



Non-linear: shunting

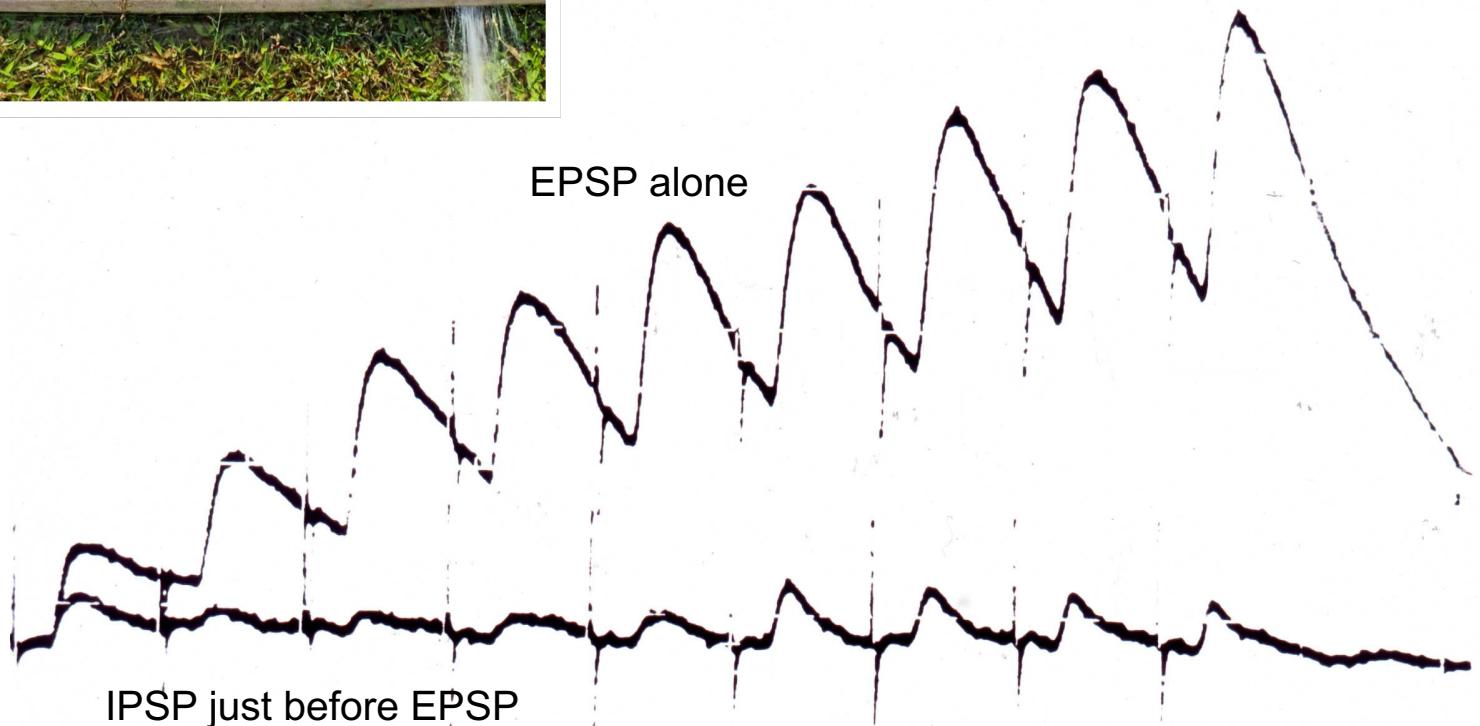


Non-linear: shunting

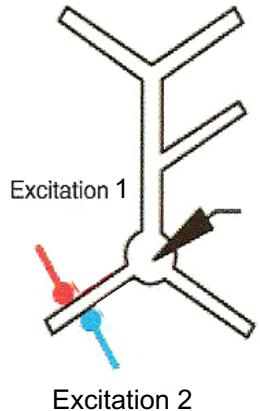


$$V = IR$$

EPSP alone



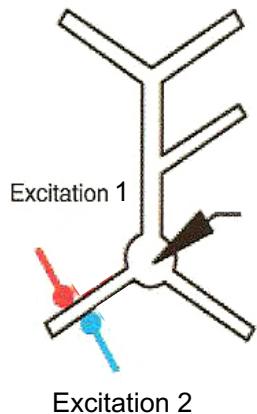
Clicker question



A neuron receives two **excitatory** synaptic inputs on the same process. Both EPSPs are 10 mV in amplitude. When both inputs are fired simultaneously, the resulting combined EPSP will be:

- A. 20 mV
- B. Less than 20 mV
- C. More than 20 mV
- D. Cannot tell

Clicker question



A neuron receives two **excitatory** synaptic inputs on the same process. Both EPSPs are 10 mV in amplitude. When both inputs are fired simultaneously, the resulting combined EPSP will be:

- A. 20 mV
- B. Less than 20 mV. (Reducing driving force for Na)
- C. More than 20 mV
- D. Cannot tell

Clicker question:

At a synapse, the m-EPSP (quantum) resulting from the fusion of one vesicle is 1 mV in amplitude.

An action potential arrives and evokes the simultaneous fusion of 15 vesicles. How large will the resulting EPSP be? (Assume it does not evoke an AP)

- A. 15 mV
- B. More than 15 mV
- C. Less than 15 mV
- D. 1 mV

Clicker question:

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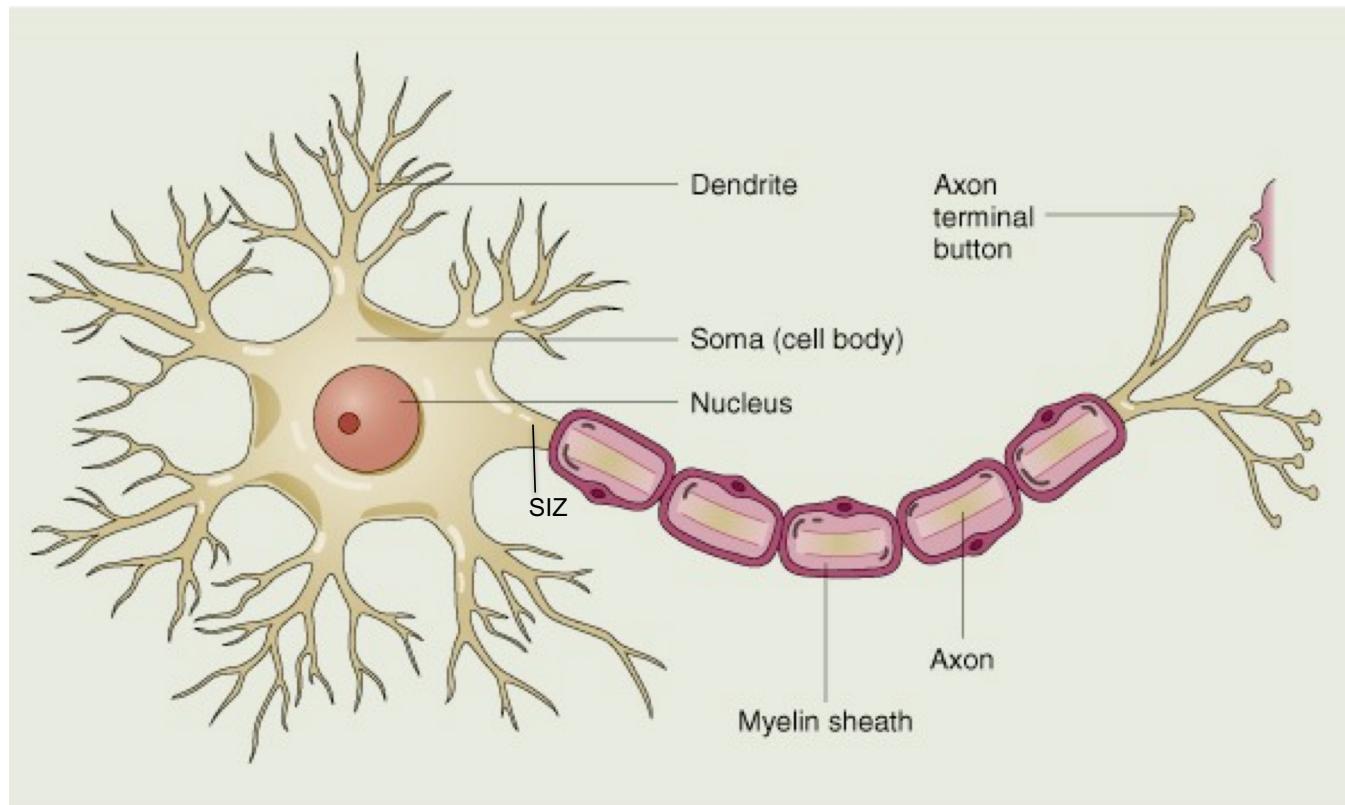
- A. 15 mV
- B. More than 15 mV
- C. Less than 15 mV (same as before)
- D. 1 mV

3. How does a neuron use synaptic integration to make the decision to spike or not?

1. Depends on where the decision to spike is located (SIZ: Spike Initiation Zone)
2. Depends on where the synapse is located relative to the SIZ

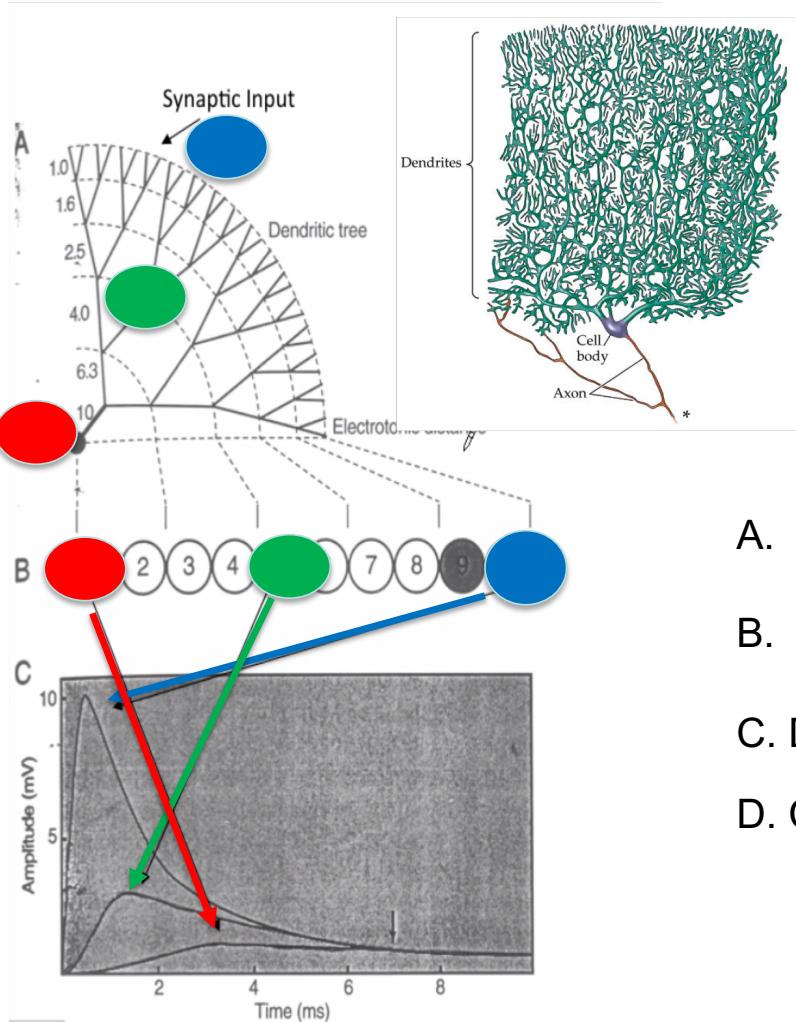
A spectrum of solutions for different neurons

Video: Classic neuron with passive dendrites



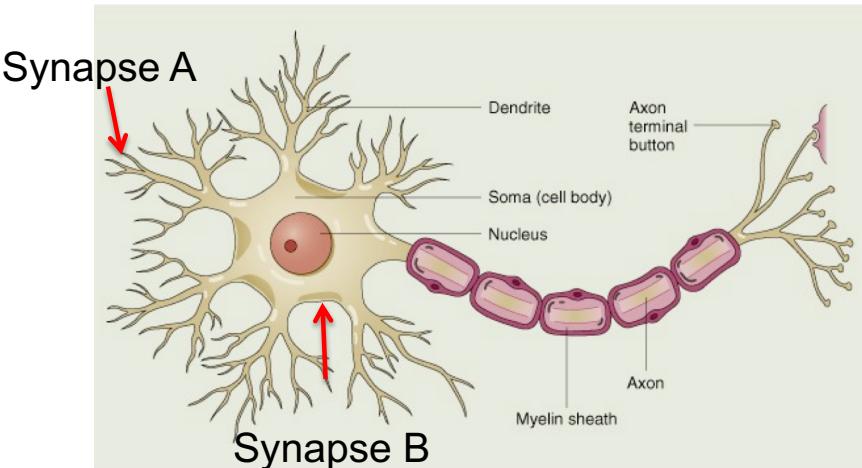
1. Physical separation of input (dendrites and soma) and output (axon terminal) sites
2. Dendrites do not express voltage-sensitive channels, cannot fire AP
3. One point, the Spike Initiation Zone (SIZ) at the axon hillock, has the lowest threshold for AP generation: this is where the decision is made.

Parameters that affect relative strength of a synapse: classic neuron



- A. Initial strength: current injected
- B. Dendrite membrane resistance, R_m
- C. Distance from the SIZ
- D. Complexity of dendritic arborization

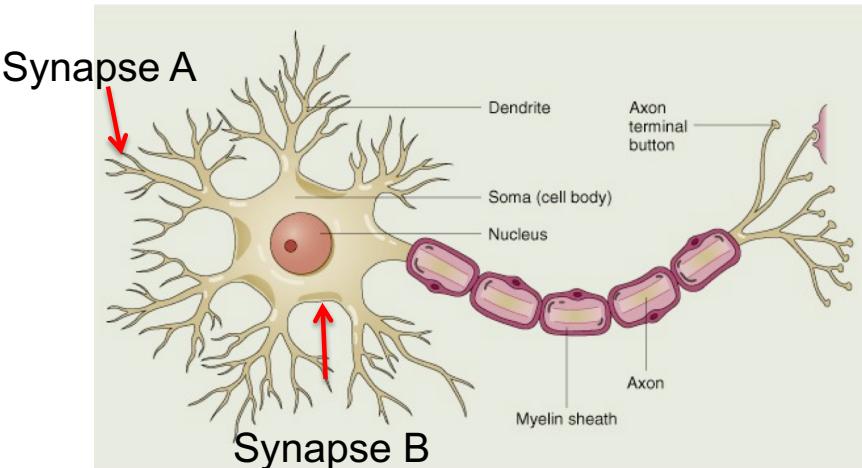
Clicker question



Which synapse will have a stronger effect on this classic neuron's decision to spike or not?

- A. Synapse A
- B. Synapse B
- C. They will both be equal

Clicker question



Which synapse will have a stronger effect on this classic neuron's decision to spike or not?

- A. Synapse A
- B. **Synapse B**
- C. They will both be equal

Clicker question

You add a drug that blocks half of the leak channels in a neuron, but does not change the resting potential.

As a consequence, dendritic EPSPs recorded in the soma will be:

- A. Larger and faster to rise and fall
- B. Smaller and slower to rise and fall
- C. Larger but slower to rise and fall
- D. Smaller but faster to rise and fall
- E. Not changed

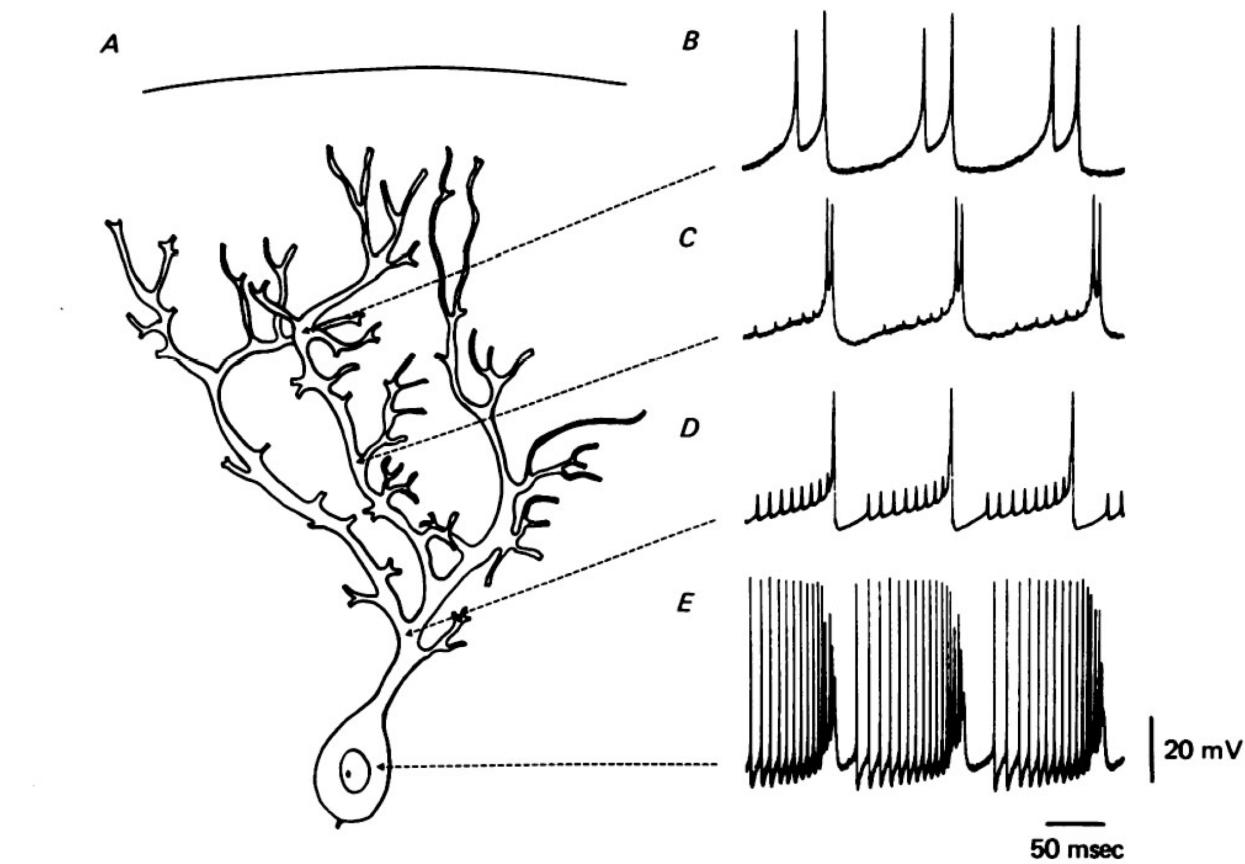
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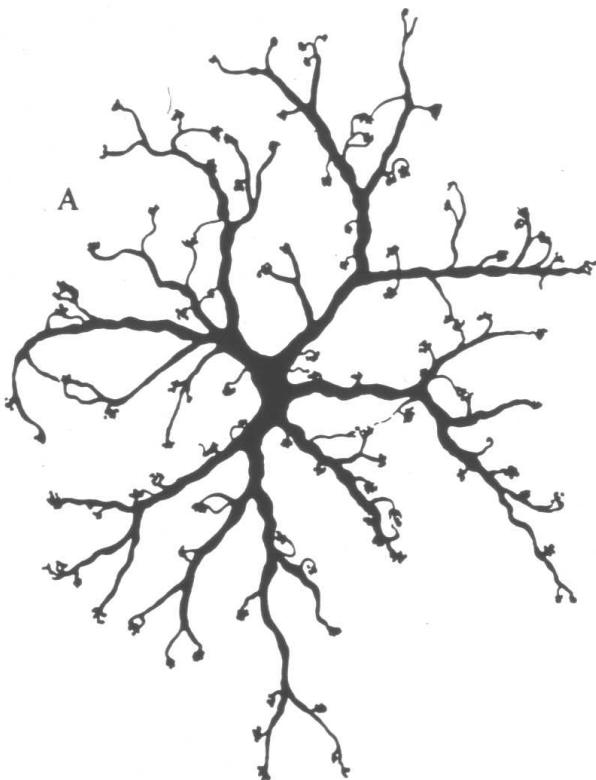
- A. Larger and faster to rise and fall
- B. Smaller and slower to rise and fall
- C. **Larger but slower to rise and fall**
- D. Smaller but faster to rise and fall
- E. Not changed

Action potentials recorded in Purkinje cell dendrites



Sugimori and Llinas, 1980

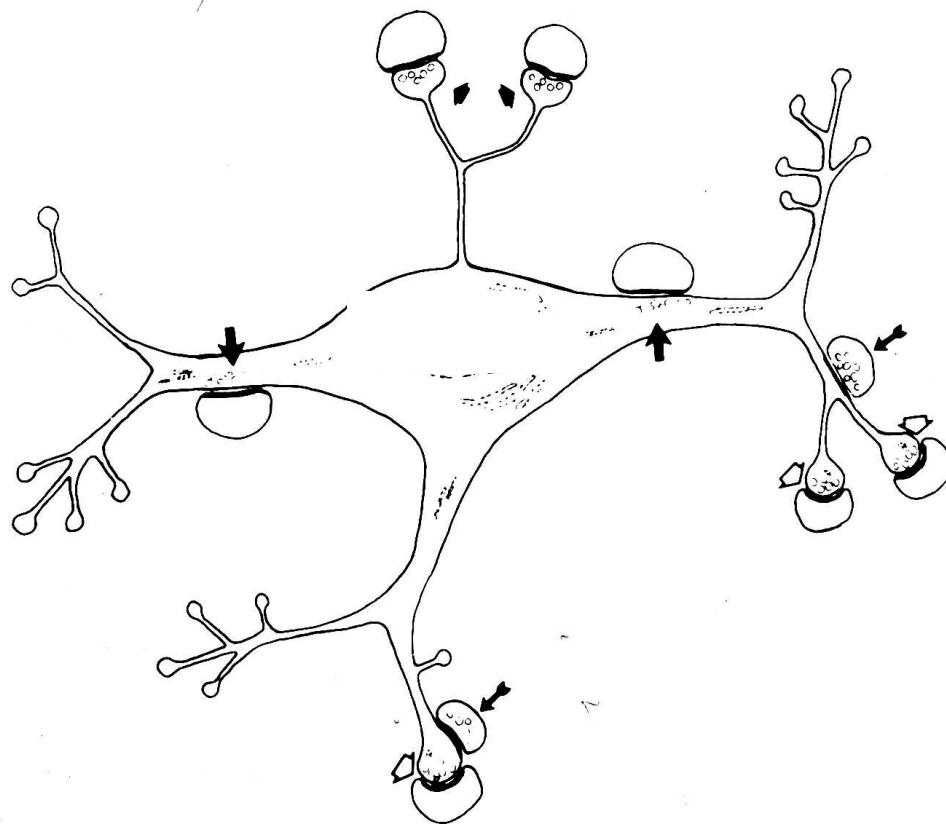
Non-spiking local interneurons: No action potentials



Retinal horizontal cell

1. Small neurons, limited processes
1. High membrane resistance, R_m
1. Mix input and output sites on processes

Mixing of input and output sites in a thalamic local interneuron



Conclusions

1. The decision to spike requires integration of excitatory and inhibitory inputs
2. Synaptic integration is often nonlinear (shunting)
3. Different neurons use different solutions to integration:
 - a. Classic neurons with passive dendrites
 - b. Neurons with voltage-activated channels in dendrites
 - c. Greater synaptic input at distant dendritic sites
 - d. Non-spiking neurons

Summary of main points about synapses so far

1. V_{rev} determines whether synapses are excitatory or inhibitory
2. Transmitters can be excitatory, inhibitory or modulatory (next!)
3. Each transmitter can bind to multiple types of receptors with different properties, different V_{rev} , etc.
4. The response to a transmitter is determined by the receptor, not the transmitter itself.
5. Synaptic integration can be linear or nonlinear with different strategies to ensure proper synaptic weight.