

Nervous System Lecture 10

Tuesday Review Session for Midterm

- Which ions are culprit for inhibitory conduction?

K^+ and Cl^- are hyperpolarizing

- If you blocked Ach degradative enzymes and stimulate NMJ, what happens to quantal size?

increase then decrease

- If $E_A = -65 \text{ mV}$ and $V_{rest} = -65 \text{ mV}$, what is shape of IPSP mediated by GABA A receptors?

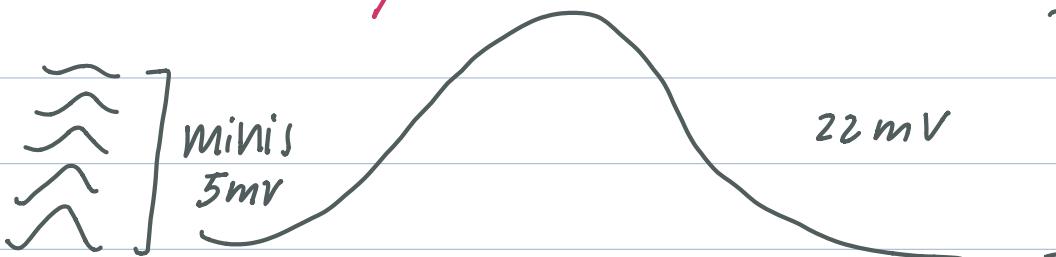
no change in membrane potential (driving force = 0)

- Does presynaptic inhibition change quantal size, content, or neither

quantal content: reduction in # of vesicles released (hyperpolarization \rightarrow less Ca^{2+} channel activation)

- Quantal content measured in quantal

- Nonlinear summation would have what effect on quantal content when measured by dividing EPSP amplitude by mini amplitude?



suggests
quantal content
is smaller
than it
actually is

if each decreases, more minis \rightarrow EPSPs



MCB/Neuro 80 - Neurobiology of Behavior

Today's Topic:

Synapses: Inhibition and Integration

Lecture 10

Optional reading: Purves et al., Neuroscience 6th pages:

Lecture notes, review questions, office hour times available at:

<https://canvas.harvard.edu/courses/59120>



Mt. Potential

Postsynaptic properties

- {
 - Integrating signals
 - IPSPs
 - EPSPs
 - Reversal Potential
 - LGICs

Presynaptic properties

- {
 - Snare hypothesis
 - Ca^{++} Hypothesis
 - Vesicle Hypothesis
 - Quantal Hypothesis

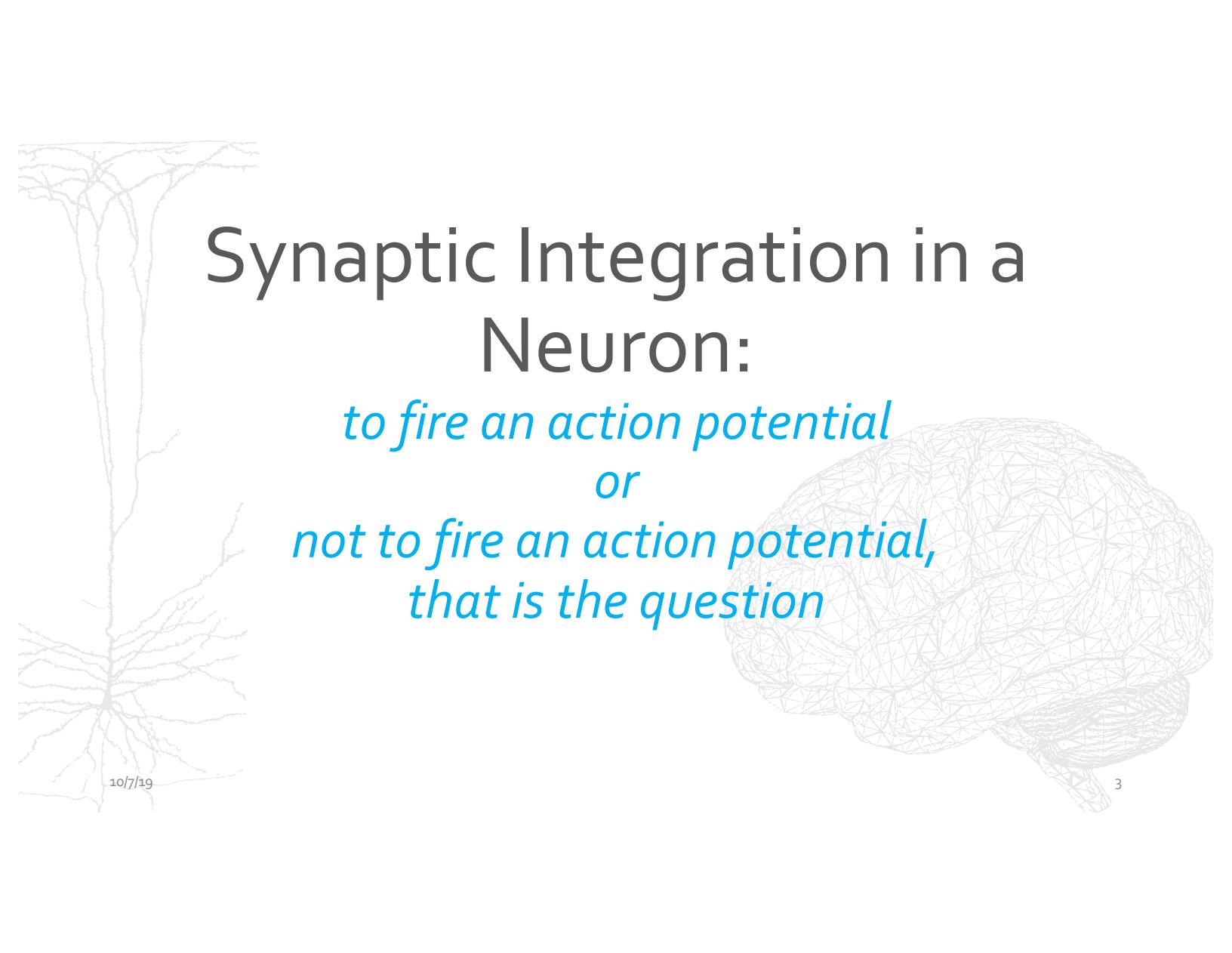
- Myelin
- Cable Properties
- Conduction
- VGICs
- Ohm's Law

- Na K Pump
- GHK Equation
- Nernst Equation
- Impermeable anions and cation selective channels

Synaptic Potential

Action Potential

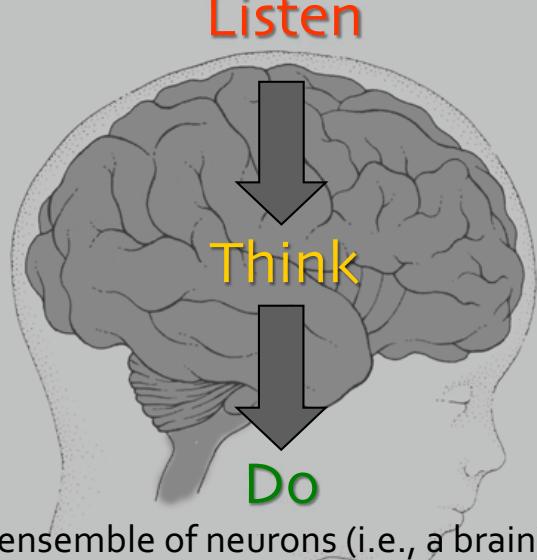
Resting Potential



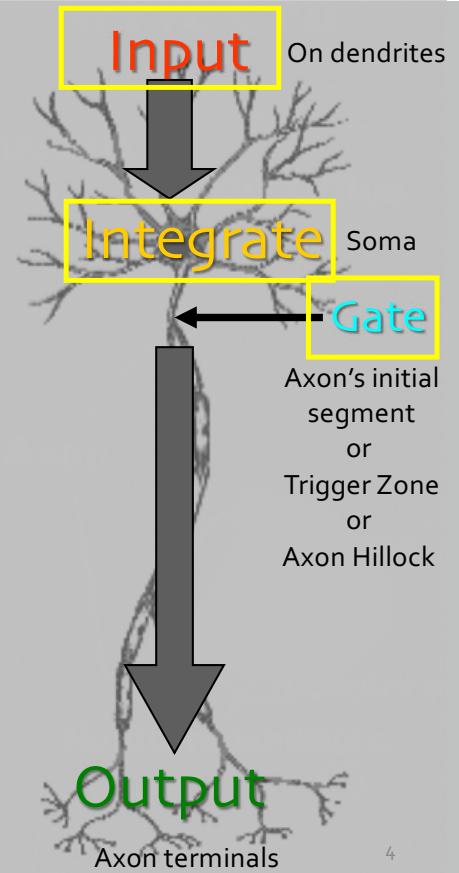
Synaptic Integration in a Neuron:

*to fire an action potential
or*

*not to fire an action potential,
that is the question*



An ensemble of neurons (i.e., a brain) does something very similar to what each individual neuron does: it integrates input before taking action



high quantal content:
↑ within neuron

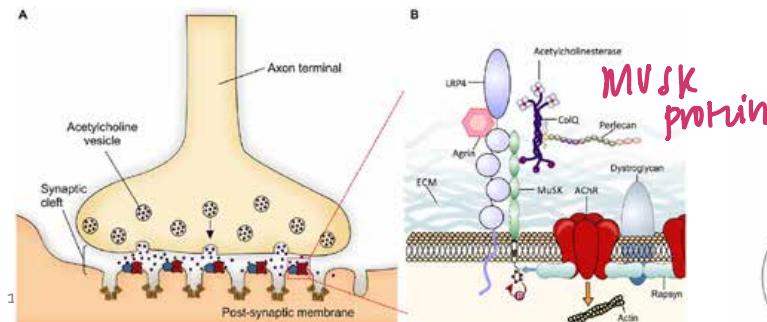
Excitatory ligand-gated ion channels

Neuromuscular junction (NMJ)

- Acetylcholine (ACh) [$M = 50+$]
- Very high quantal content
- nicotinic acetylcholine receptor (nAChR)
 - $g_{Na} = g_K$
 - desensitizes

ionotropic:
new transmitter binds and it opens

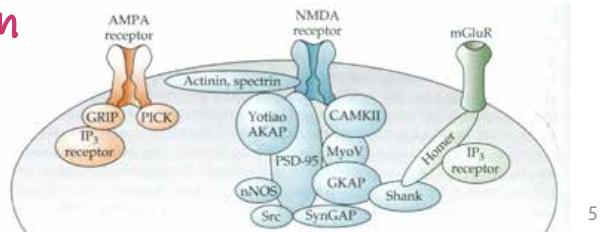
Lots of proteins anchor receptors at the synapse



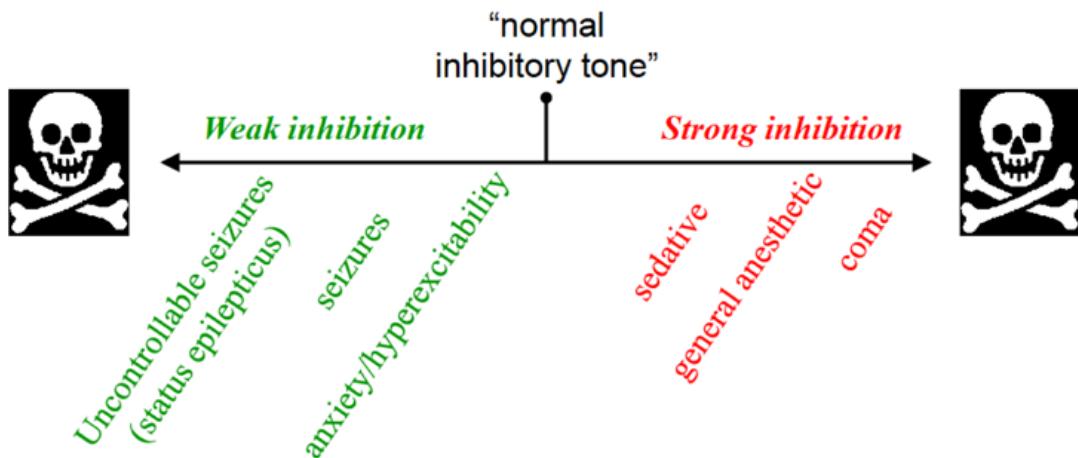
*reversal potential: avg of
E_{Na} and E_K*

Central nervous system (brain)

- Glutamate – lower quantal content [$M = 1-10$]
- AMPA
 - $g_{Na} = g_K$
 - desensitizes
- NMDA *active when other channels open*
 - g_{Na}, g_K and g_{Ca}
 - Ligand-gated and voltage-gated
 - does not desensitize *permable to Ca²⁺*

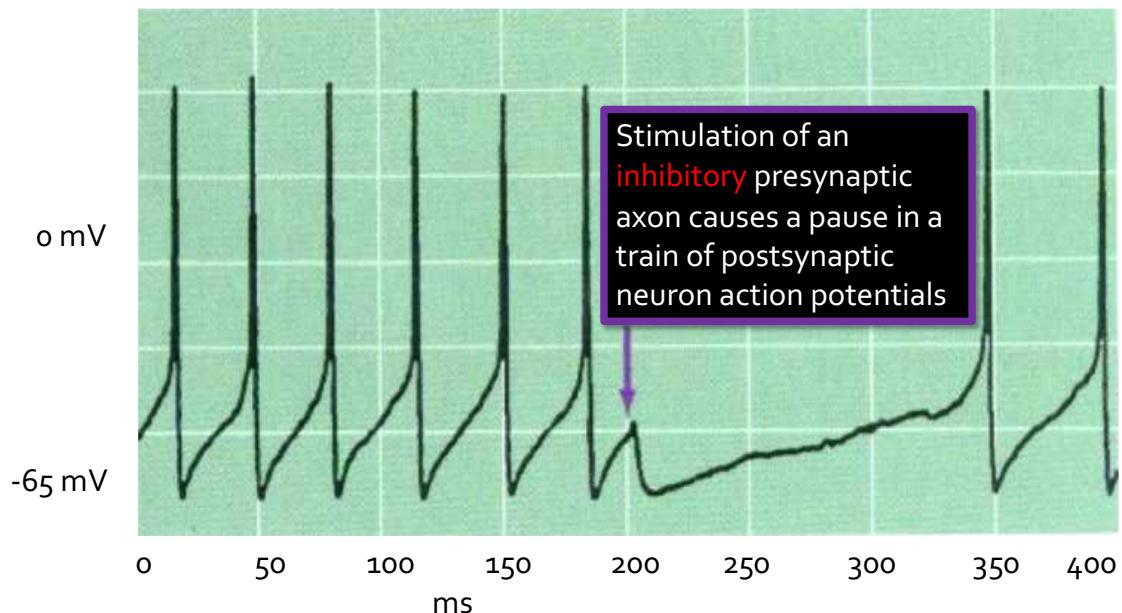


Balance of neuronal activity is critical



Most neurons receive both excitatory and inhibitory input

Inhibitory synapse activation decreases likelihood of action potentials in postsynaptic cells



Two NTs for Ionotropic Inhibition

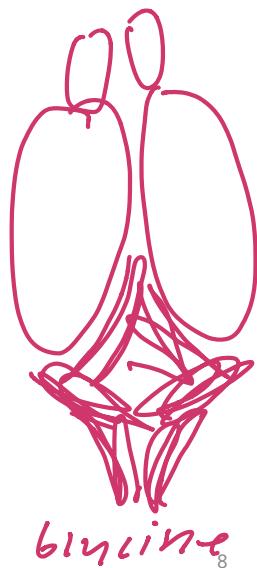
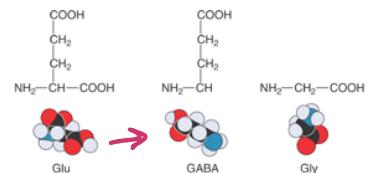
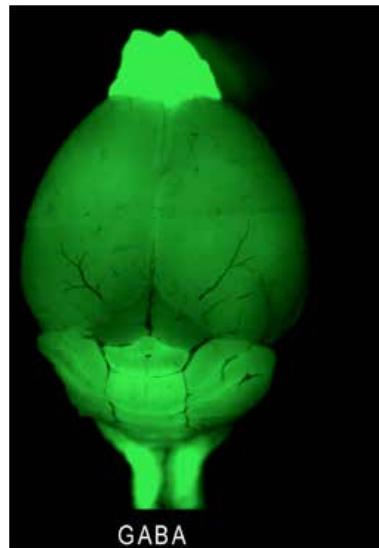
GABA-A (ionotropic)

1. GABA - (short for γ -aminobutyric acid)

- **Everywhere** (Cortex, midbrain, etc)
- Most important inhibitory NT in Brain
- Ionotropic receptor: GABA "A" receptor

2. Glycine – an amino acid

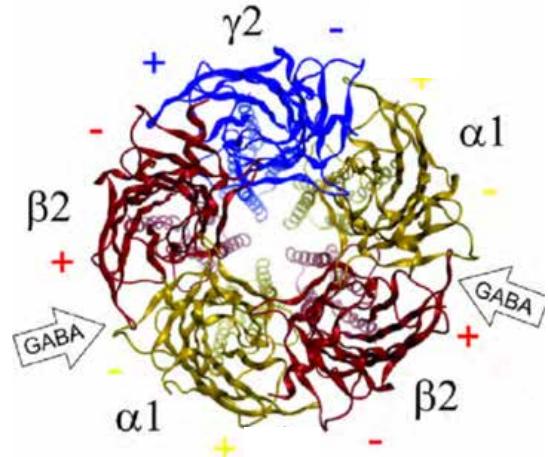
- **Spinal cord, brainstem** (evolutionarily older)
- Also in the retina (50:50 with GABA)
- Low levels in other areas
- Ionotropic receptor: GlycineR



Ionotropic GABA and glycine receptors: ligand-gated chloride channels

- Analogous to AChR (same gene family), similar in structure except:
 - affinity for different neurotransmitters
 - the channel pore (lined by the M2 membrane spanning domains -) is lined by positively charged amino acids, as opposed to negative charges in the AChR.
- These ligand-gated ion channels are anionic. When neurotransmitter binds, g_{Cl^-} increases
- Effect is to keep V_m near E_{Cl^-} which is below threshold ($E_{rev} = E_{Cl^-}$ for GABA/glycine receptors)
- This is in contrast to excitatory neurotransmitters that are trying to depolarize the cell to above threshold ($E_{rev} = -10mV$)

made of 5 subunits



$$\text{reversal potential for GABA} = Cl^- \text{ Eq potential}$$

because only
permable to Cl^-

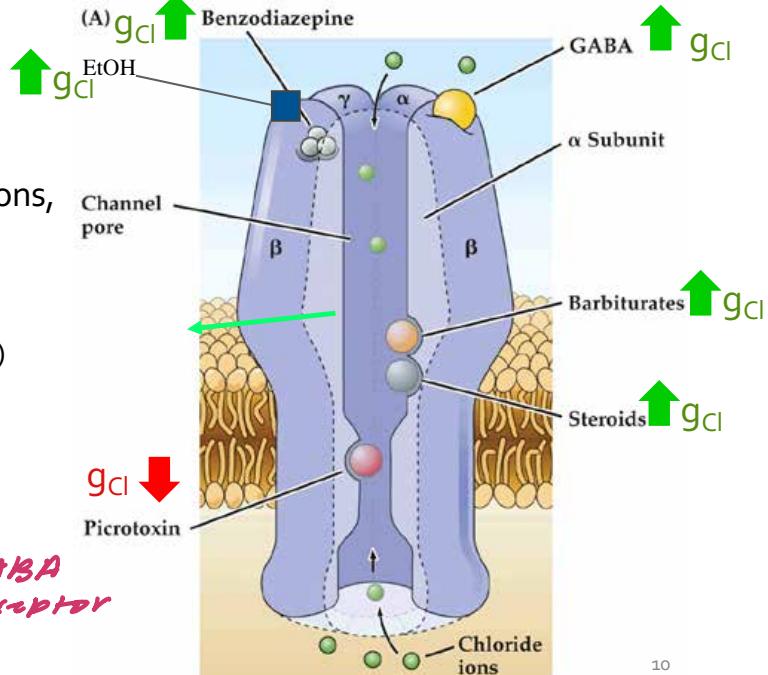
* Cl^- flows in

Inhibitory ligand-gated chloride channel has binding sites for the many factors that affect its chloride conductance

- Blockers decrease g_{Cl} :
 - Strychnine (glycine R),
 - picrotoxin (GABA A)
 - Both from plants cause rigidity, convulsions, seizures
- Agonists increase g_{Cl} :
 - Benzodiazepines
 - Anti-anxiety or Anxiolytics (Valium, Xanax)
 - Sleep aids, antiseizure (Klonopin, Atavan)
 - Barbiturates
 - Anti-convulsant (phenobarbital)
 - "Truth" serum (sodium amytal)
 - Capital punishment (sodium thiopental)
 - Alcohol (*Etanol*) interacts w/ GABA receptor
 - Neurosteroids - antianxiety
 - General anesthetics

10/7/19

*increase conductance,
depress Nervous system*



* *most agonists are not competitive*

Diseases of inhibitory systems

- Probably many psychiatric illnesses, sleep disorders, some types of epilepsy are related to disorders in inhibitory transmission.
- Startle Diseases “Hyperekplexia” (exaggerated responses to stimuli like noise)-small single amino acid mutations in the glycine R make it less able to open



ligand-gated ion channel

The physiologic role of each LGIC (neurotransmitter receptors) is determined by its ion conductivity

Cation selective: *excitatory*

AChRs (acetylcholine receptors): Na^+ & K^+

AMPA (glutamate receptors): Na^+ & K^+

NMDA (glutamate receptors): Ca^{++} mostly



EPSP

Excitatory post-synaptic potential

10/7/19

Anion selective: *inhibitory*

GABA & Glycine receptors: Cl^-



but often they look like this:



IPSP

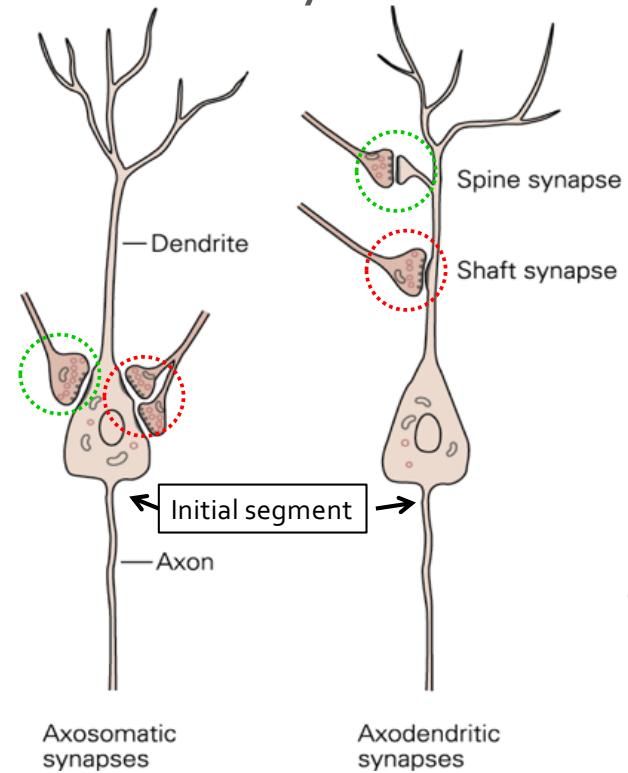
Inhibitory post-synaptic potential

12

shunting inhibition

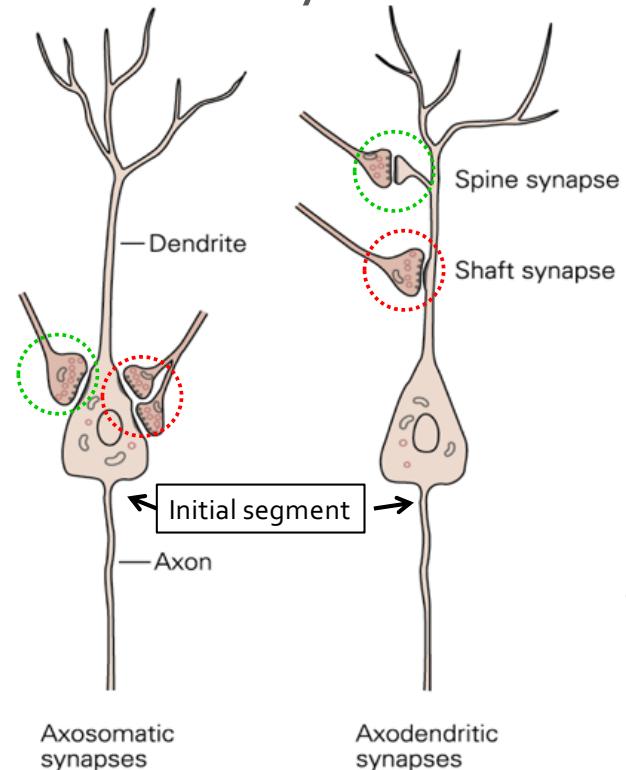
Most neurons receive both inhibitory and excitatory synaptic input

- Excitatory synapses generally occur on dendritic shafts or spines
 - If spines exist, they are excitatory synapse
- Inhibitory synapses generally found on dendritic shafts, soma, the initial segment of axon, and even the presynaptic terminal



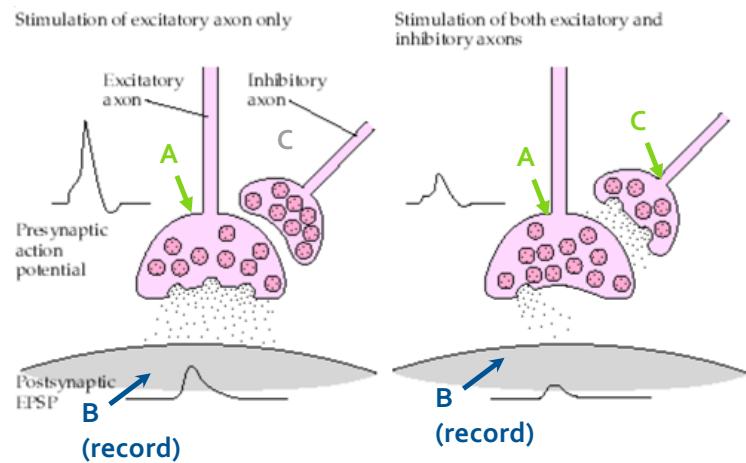
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- **Excitatory** synapses generally occur on dendritic shafts or spines
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- **Inhibitory** synapses generally found on dendritic shafts, soma, the initial segment of axon, and even the presynaptic terminal
- Initial segment is the “Trigger Zone” (aka axon hillock)
 - Highest density of voltage-gated Na^+ channels
 - Lowest threshold for action potential
 - Site of action potential initiation
- There are **5** critical factors that regulate the effectiveness of synapses



Presynaptic inhibition can be incredibly specific

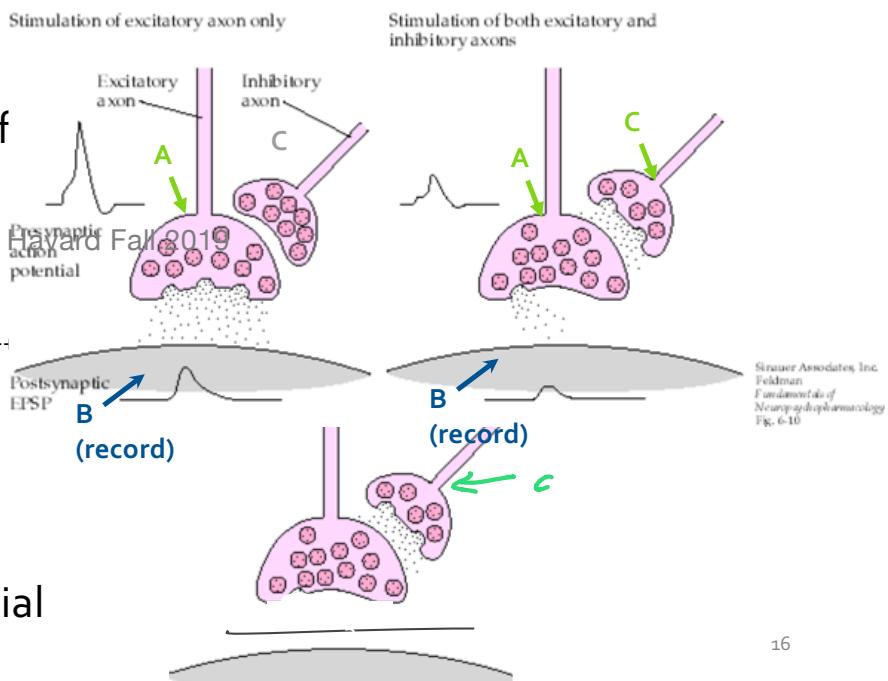
- A synapse on a synapse



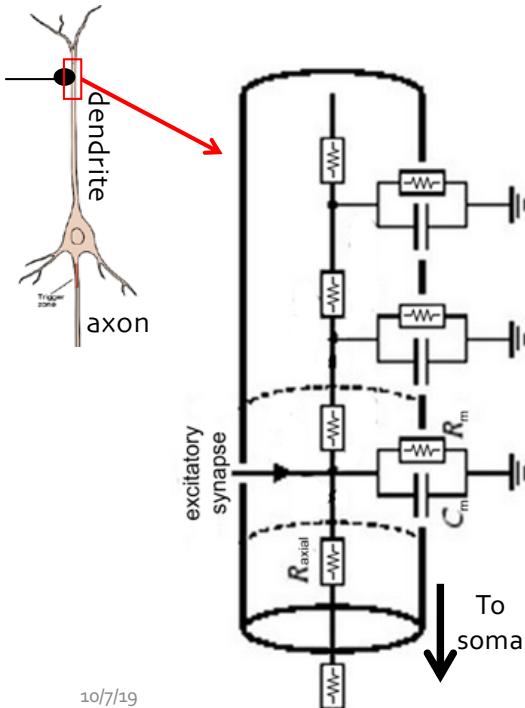
Strauer Associates, Inc.
Feldman
*Fundamentals of
Neuropharmacology*
Fig. 6-10

Presynaptic inhibition can be very specific

- A synapse on a synapse
- Decreases the probability of release.
- Hyperpolarize/shunting at terminal
 - Less likely to activate VG Ca⁺ channel
 - Therefore fewer vesicles released
 - Reduced quantal content
- What is the synaptic potential if we just stimulate C?

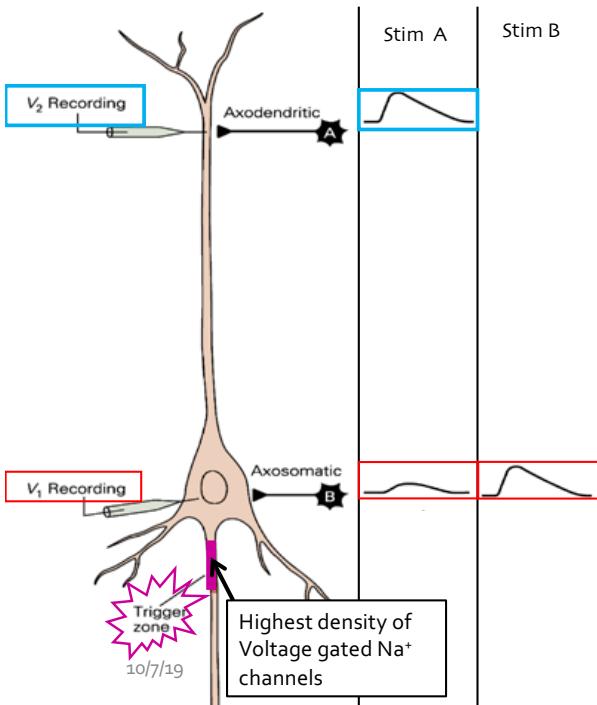


Factor #1: The farther an excitatory synapse is from the initial segment (trigger zone) the less powerful it is



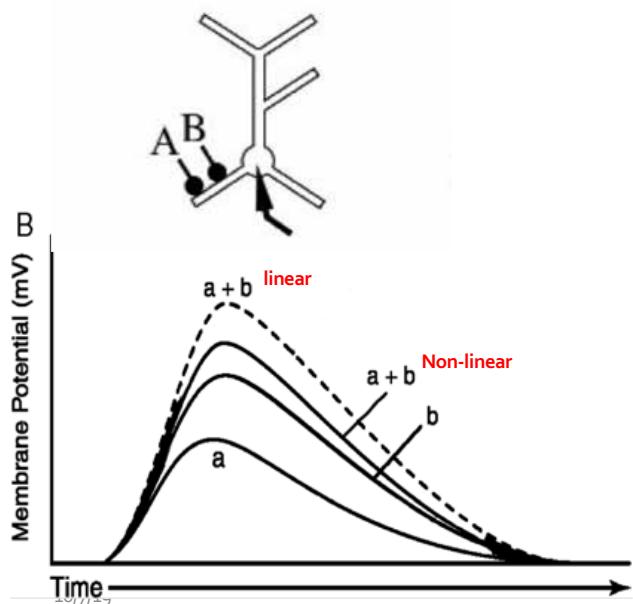
- Dendrites are “leaky cables” with low membrane resistance (resting K permeability) and high capacitance (not myelinated) and large axial resistance,
 τ very thin = \uparrow resistance
- EPSPs will attenuate (decrease) in amplitude with distance
- Remember a synaptic potential is a local potential
gradual potential

Factor #1: The farther an excitatory synapse is from the initial segment (trigger zone) the less powerful it is



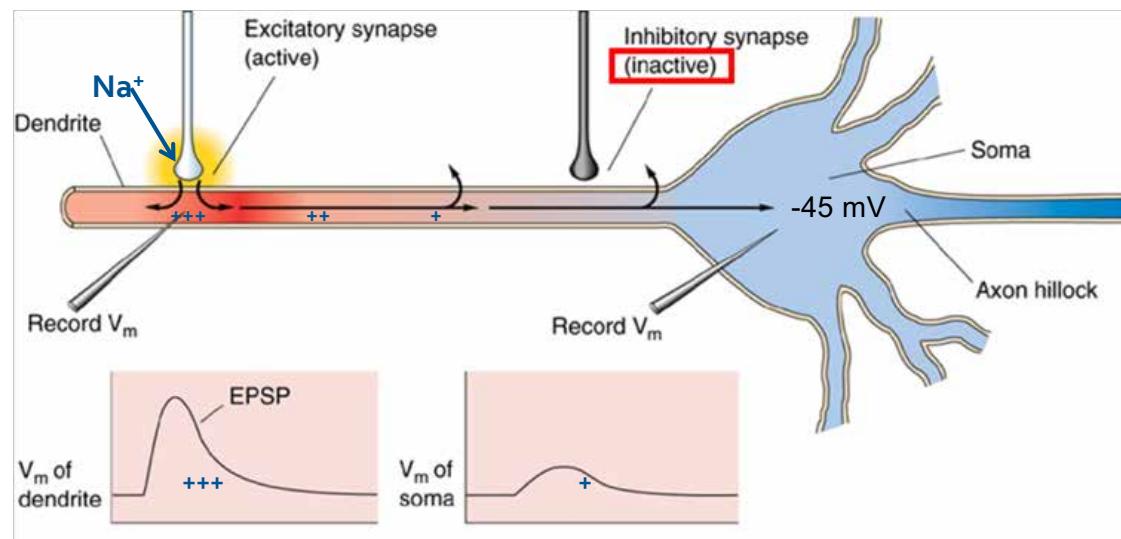
- Dendrites are “leaky cables” with low membrane resistance (resting K permeability) and high capacitance (not myelinated) and large axial resistance ,
- EPSPs will **attenuate** (decrease) in amplitude with distance
- Remember a synaptic potential is a local potential
- Same synaptic potential looks very different at the soma

Critical factor #2: Synaptic potentials of different axons sum but in a non-linear way



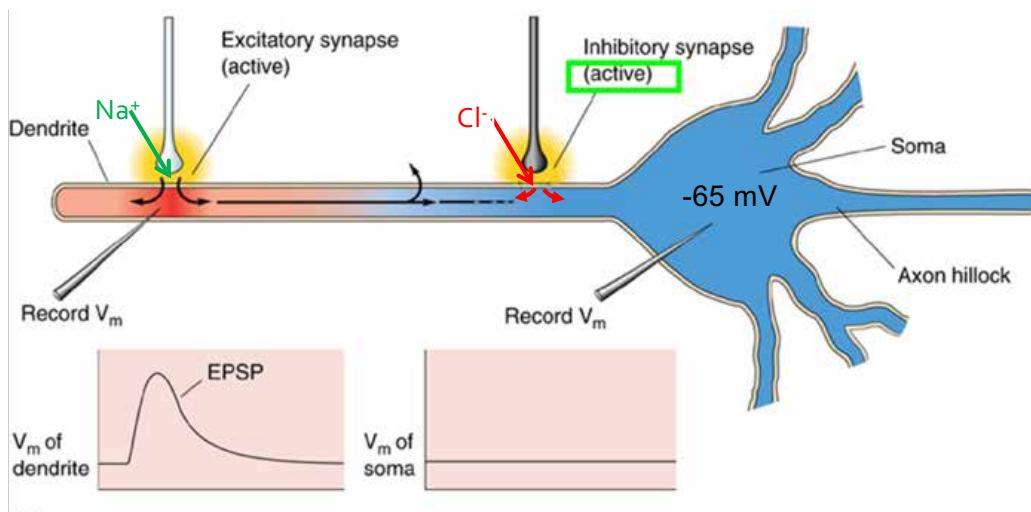
- Dendrites allow addition of the excitatory synaptic contributions of many inputs to sum at the soma
- Summation of potentials is “non-linear” -- Not the arithmetic sum of each of the synaptic potential amplitudes
- As the membrane potential gets more positive, the driving force on Na^+ gets smaller (and the driving force on K^+ gets larger)
- A synapse can't depolarize the membrane beyond the reversal potential
 - So adding many synapses together can only approach -10mV and each additional input has less effect

Critical factor #3: IPSPs interposed between an EPSP and the initial segment **counteracts depolarization**



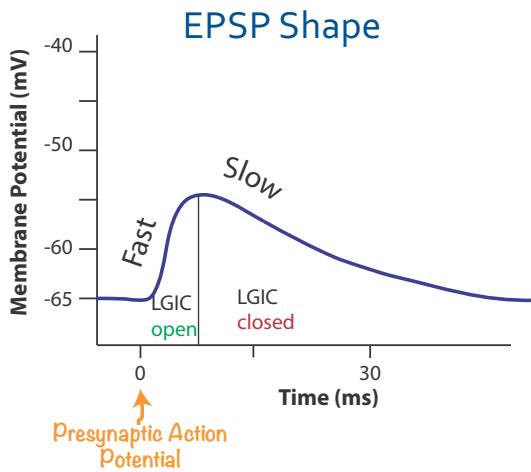
- Passive spread weakens synapses far from the axon hillock
 - Inhibitory synapse between excitatory synapse and soma can 'shunt' EPSP

Critical factor #3: IPSPs interposed between an EPSP and the initial segment block the EPSP from reaching threshold



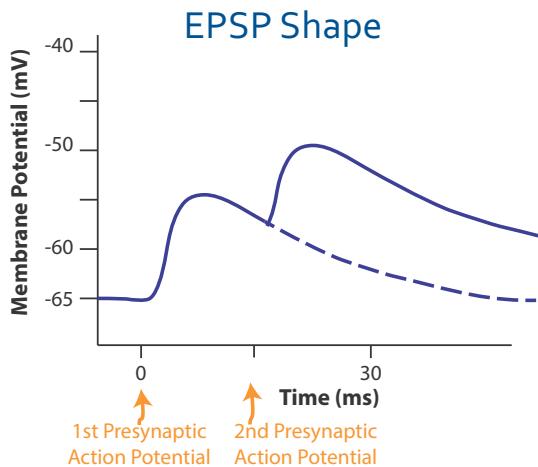
- Chloride flows in as EPSP moves down membrane
- Counteracts depolarizing excitatory potential
- Works even when $E_{\text{Cl}} = V_{\text{rest}}$
 - Cl^- will move in to keep membrane potential at E_{Cl}

Critical factor #4: Temporal Summation allows one EPSP to “piggy back” on another



- EPSP shape has a fast rise and slow fall
- During the rise, LGICs are open so R_{mem} is low and charge passes through quickly.
- During the fall, LGICs are closed, so R_{mem} is higher and it takes longer time to remove the added positive charge

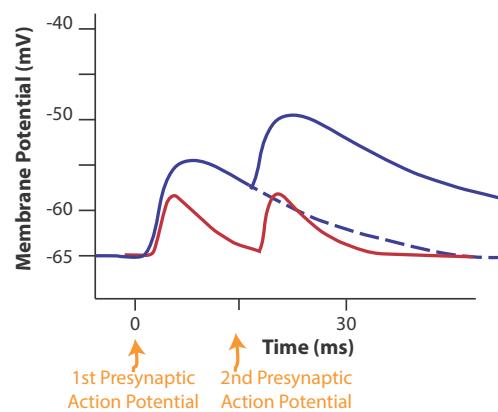
Critical factor #4: Temporal Summation allows one EPSP to “piggy back” on another



- EPSP shape has a fast rise and slow fall
- During the rise, LGICs are open so R_{mem} is low and charge passes through quickly.
- During the fall, LGICs are closed, so R_{mem} is higher and it takes longer time to remove the added positive charge
- When a presynaptic terminal is activated at high frequency the postsynaptic amplitude sums because each EPSP sits on the falling phase of the previous potential

may happen non-linearly bc
reduced driving force

Critical factor #5: Inhibition changes shape of EPSP preventing temporal summation

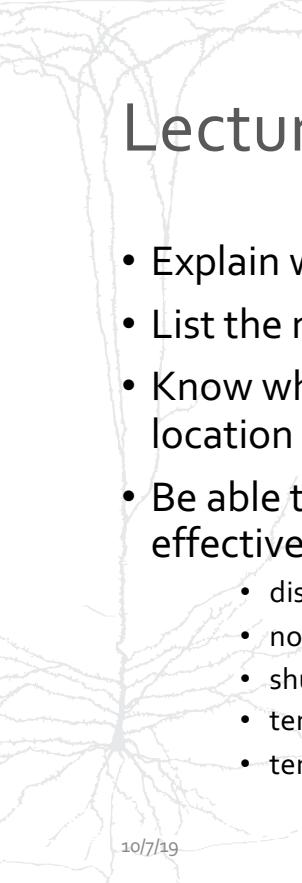


- Concurrent inhibition decreases the membrane resistance allows the falling phase to return to the resting potential more quickly (via Cl^- entry) so summation is less likely to occur

* inhibition don't deactivate

To summarize...

1. **Distance matters:** The **farther** an excitatory synapse is from the initial segment (trigger zone) **the less powerful** it is.
2. **Things don't add up right:** Synaptic potentials of different axons sum in a ***non-linear way***
3. **A little bit of g_{Cl^-} goes a long way:** IPSPs interposed between EPSPs and the initial segment **block** the EPSPs from reaching **threshold**
4. Piggy-back  : Temporal Summation
5. No Piggy-back  : Inhibition changes shape of EPSP preventing temporal summation



Lecture 10 – Learning objectives

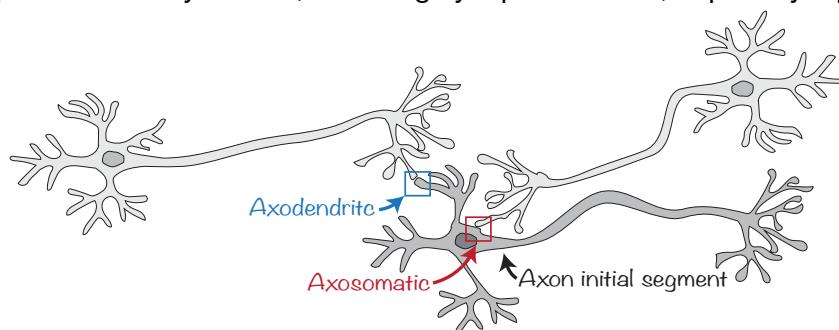
- Explain what makes a synapse inhibitory and the ionic basis of inhibition.
- List the most common inhibitory neurotransmitters in the CNS and PNS.
- Know where inhibitory synapses are located on the neuron and how their location and receptor properties (and E_{Cl}) relate to the IPSP shape.
- Be able to describe and apply the following factors that regulate the effectiveness of synapses:
 - distance from initial segment of an axon
 - non-linear summation
 - shunting IPSPs
 - temporal summation
 - temporal summation with concurrent inhibition

Lecture 10 - Synapses: Inhibition and Integration

Pre-class notes for October 7th, 2019

Reading: *Neuroscience* by Purves et al., pages 126-131, 107-109

A neuron in the brain may receive synaptic input from thousands of different neurons. Most of the inputs are very small, so how do all of these inputs, both excitatory and inhibitory integrate together to decide whether a neuron fires an action potential or not? This decision depends on the voltage at the **initial segment of the axon** (*axon hillock*). The **excitatory synapses**, are increasing the likelihood that the neuron fires, while the **inhibitory synapse** are synapses where the release of neurotransmitter decreases the likelihood that the *postsynaptic* neuron fires an action potential. Many factors, including synapse location, impact synaptic integration.



Axodendritic synapse - a presynaptic axon that establishes a synapses onto a dendrite or spine of the postsynaptic cell. Synapses onto spines and distal axodendritic synapses are typically excitatory.

Axosomatic synapse - a presynaptic axon that establishes a synapses onto the soma (cell body) of the postsynaptic cell. Axosomatic synapses are often inhibitory.

Axoaxonic synapse - a presynaptic axon that establishes a synapses onto the axon or an axon terminal of another cell. These synapses are often inhibitory and can prevent the other presynaptic neuron from releasing vesicles.

There are two main inhibitory neurotransmitters: **GABA** (short for g-aminobutyric acid) found at brain/central nervous system inhibitory synapses and **Glycine** (an amino acid) found in spinal cord inhibitory synapses.

Receptors on postsynaptic cells for these neurotransmitter molecules are the **GABA "A" receptor** and **GlycineR** respectively. They are similar in structure to the acetylcholine receptor (nAChR) except: 1. An affinity for different neurotransmitters (GABA or Glycine as opposed to ACh) and 2. The channel pore (the M2 membrane spanning domains) is lined by positively charged amino acids, as opposed to negative charges in the AChR. This means the channels are selective for anions, specifically Cl⁻.

Effect of the inhibitory ligand-gated ion channels is to keep the membrane potential near E_{Cl} (i.e., its reversal potential is -65mV, near resting potential). This is below threshold, in contrast to excitatory neurotransmitters that are trying to depolarize the cell to above threshold (AChR/ AMPA E_{rev}= -10mV). This inhibition mechanism is called **shunting** inhibition.

Shunting inhibition - even though the reversal potential (E_{Cl}) for inhibitory synapses is approximately the resting membrane potential, the opening of GABA channels is very effective in preventing the postsynaptic neuron from reaching threshold. This inhibition essentially allows Cl⁻ entry anytime the membrane potential is depolarized. This *shunts* the excitatory synaptic current.

Presynaptic inhibition - when an inhibitory neuron makes a synapse on the presynaptic terminal of another neuron. The inhibitory synapse causes a reduction in the conductance of voltage-gated Ca⁺⁺ channels, and a decrease in synaptic release.

Synaptic integration, is the manner in which multiple spatially or temporally distributed synaptic potentials sum. The **axon initial segment**, also known as the “trigger zone” determines if a neuron fires an action potential or not. The axon initial segment has the highest density of voltage-gated Na⁺ channels and therefore the lowest threshold value. Typical membrane potentials for threshold (V_{thresh}) are between -30 - -45 mV depending on channel density, cell morphology, and which subtypes of voltage-gated channels are expressed.

Subthreshold potential - a synaptic potential (or summation of potentials) that does not cause depolarization above threshold above action potential potential.

Suprathreshold potential- a synaptic potential (or summation of potentials) that does elicit an action potential.

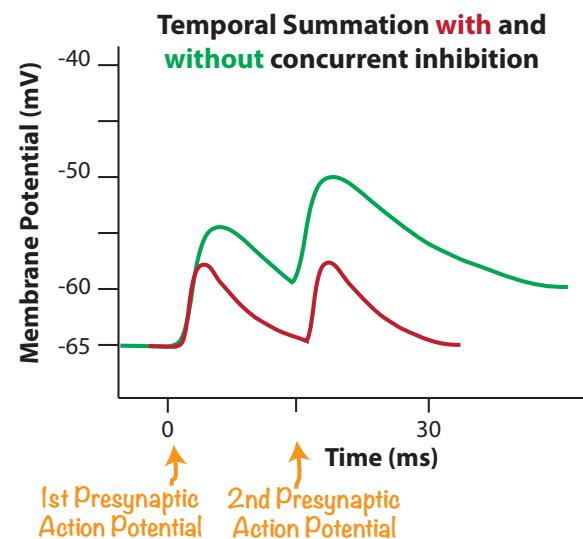
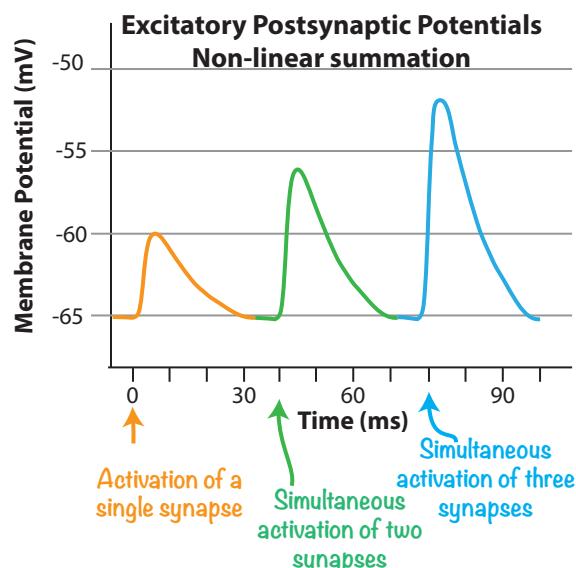
Several factors regulate the effectiveness of a synapse/integration, including:

Synaptic Attenuation - EPSPs in dendrites obey cable properties and their amplitudes will decrease along the length of the dendrite. (See lecture 6 for cable properties.) Thus a synapse on a distal branch will cause a smaller depolarization at the soma or initial segment than a similar size synapse on a proximal dendrite (close to the soma).

Non-linear synaptic summation - multiple EPSPs will not linearly summate (i.e. the final amplitude is less than the sum of individual amplitudes) because the synaptic potential cannot exceed the reversal potential and gets progressively smaller the closer the membrane potential gets to the reversal potential.

Temporal summation - the long decay time course of an EPSP allows for multiple EPSPs at a single synapse to “piggyback” or summate over time.

Concurrent Inhibition during temporal summation - inhibition occurring at the same time activation of excitatory synapses can prevent temporal summation as inhibition not only the decreases EPSP amplitude, but also reduces membrane resistance (opens additional channels which ions can flow through) which shortens the decay time course of the EPSP.



Learning Objectives: (By the end of Lecture 10 you should be able answer the following)

1. Explain what makes a synapse inhibitory and the ionic basis of inhibition.
2. List the most common inhibitory neurotransmitters in the CNS and PNS.
3. Know where inhibitory synapses are located on the neuron and how their location and receptor properties (including E_{Cl}) relate to the IPSP shape.
4. Be able to describe and apply the following factors that regulate the effectiveness of synapses:
 - distance from initial segment of an axon
 - non-linear summation
 - shunting IPSPs
 - temporal summation
 - temporal summation with concurrent inhibition