

# Neuro 80 Lecture 11: Synaptic Modulation

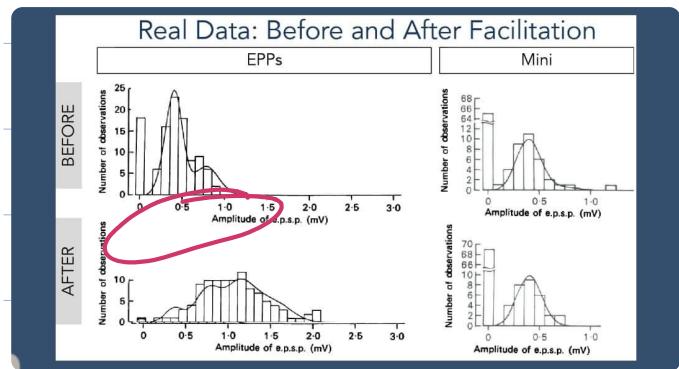
In a typical excitatory response

Glutamate binds to and opens AMPA receptors

Facilitation is pre or post synaptic change?

• Pre-synaptic, no change in quantal / mini size

• EPP histogram left-shifted



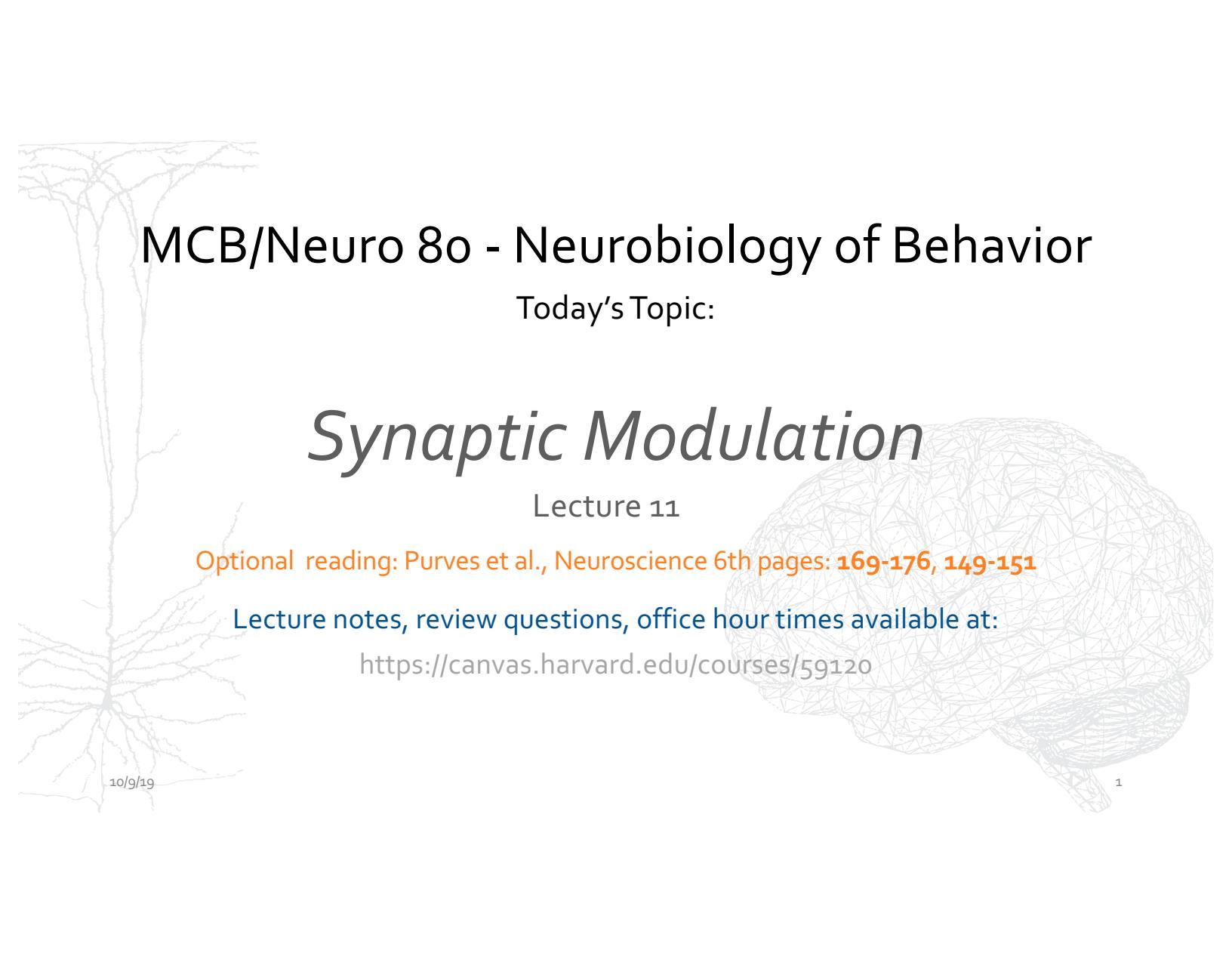
If you look at a neuron at rest, membrane would

depolarize (increase closer to grad).

If you block endorphin release, pain levels increase

which would not lead to privilege remain

- 0 Increasing conductance of voltage-gated Ca channels
- 0 Increasing postpotassium conductances
- 0 Increasing the calcium affinity of synaptotagmin
- 0 Increasing the time before the voltage-gated sodium channel inactivates



# MCB/Neuro 8o - Neurobiology of Behavior

Today's Topic:

## *Synaptic Modulation*

Lecture 11

Optional reading: Purves et al., Neuroscience 6th pages: **169-176, 149-151**

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

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

## Mt. Potential

Postsynaptic properties

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

Presynaptic properties

## Synaptic Potential

## Action Potential

## Resting Potential

# Synapses are dynamic – can be modulated

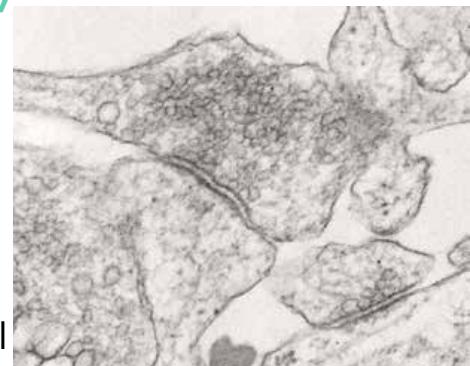
## What causes synaptic strength to change?

- Diseases (myasthenia gravis, startle disease...)
- Drugs (therapeutic, recreational...)
- Prior or ongoing activity (experience...learning?)

Experience shapes our thoughts and actions by altering synaptic function

## What mechanisms lead to altered synaptic strength?

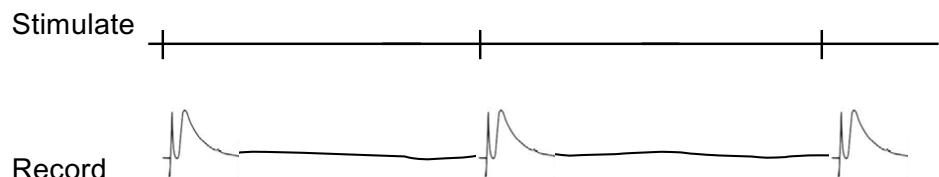
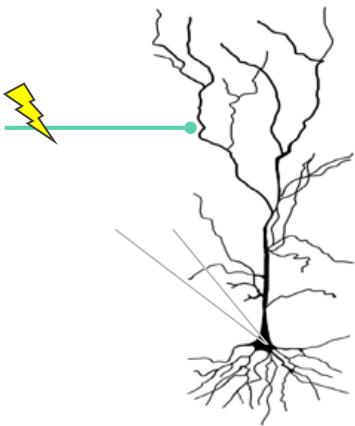
- Addition or loss of synapses
- Growth or shrinkage of synapse
- Rapid change in synaptic efficacy with no structural change



# A fast change in neural state

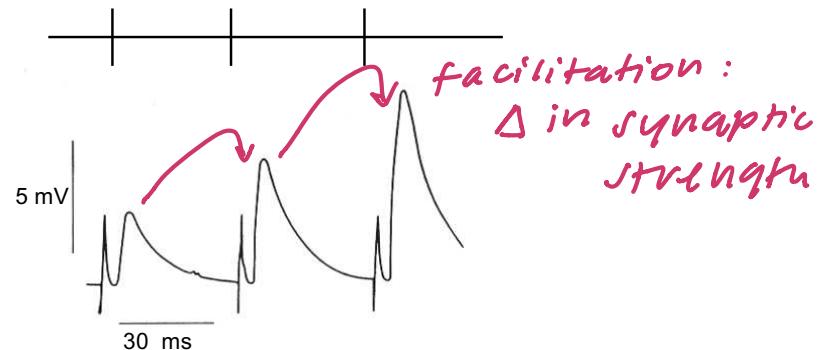
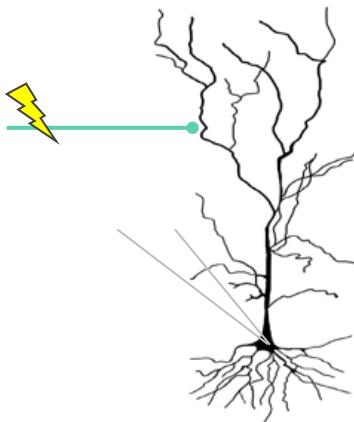
- Your boy/girlfriend says,
- "Since the MCB8o midterm is coming up next week, how about coming over to my room after dinner so we can study together."
- "**I think we really need to start seeing other people, but since the MCB8o midterm is coming up next week, how about coming over to my room after dinner so we can study together.**"

# Synapses can be modulated by prior activity



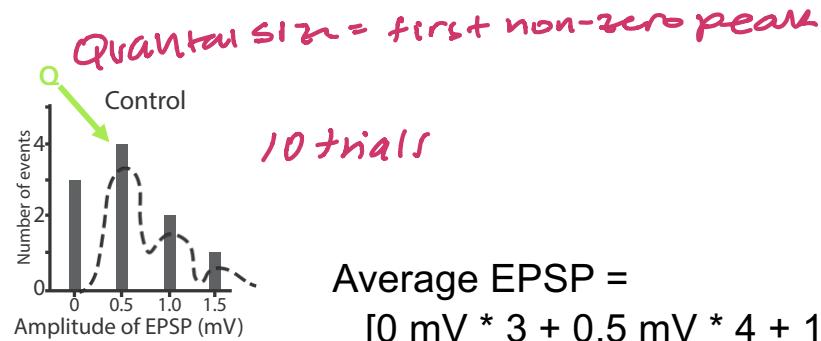
- Stimulate at a low frequency (1 Hz)
  - Consistent response
  - No change in postsynaptic potential

# Facilitation - Second of two closely timed EPSPs bigger than the first



- Stimulate very quickly (25 Hz)
- Change in **synaptic strength** could be due to either more neurotransmitter released (vesicles, presynaptic) or increased sensitivity to neurotransmitter (postsynaptic)

# Quantal analysis of Facilitation

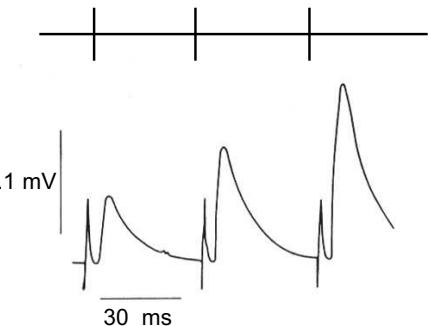


Average EPSP =

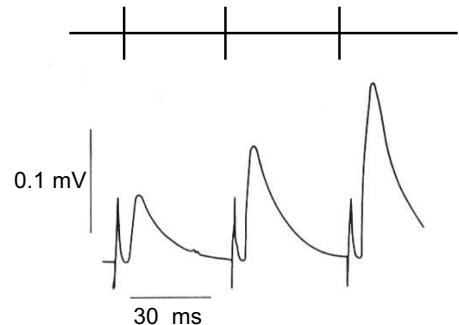
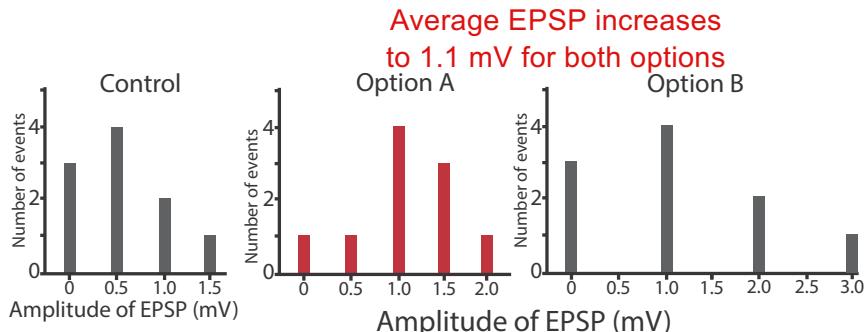
$$[0 \text{ mV} * 3 + 0.5 \text{ mV} * 4 + 1.0 \text{ mV} * 2 + 1.5 \text{ mV} * 1] / 10 \\ = 0.55 \text{ mV}$$

Q (Quantal size) = 0.5 mV

M (Quantal content) =  $0.55 \text{ mV} / 0.5 \text{ mV} = 1.1 \text{ quanta}$



# Quantal analysis of Facilitation



- In facilitation, EPSP increases:
  - If M (quantal content) increases -> presynaptic
  - If Q (quantal size) increases -> postsynaptic

	Presynaptic Alteration	Postsynaptic Alteration
EPP size	Increase	Increase
Mini size (Q)	No change	Increase
EPP/mini (M)	Increase	No change

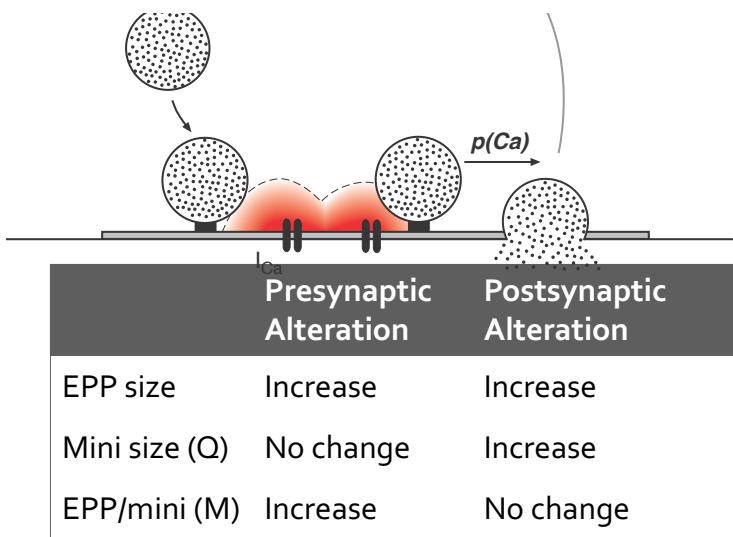
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↑  
more receptors  
channels open longer  
channels pass more voltage

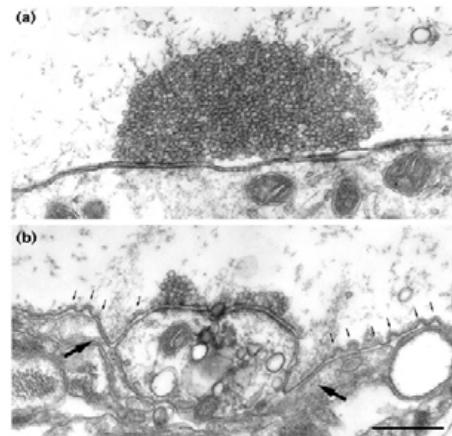
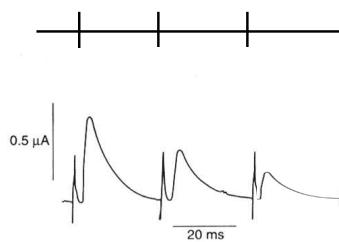
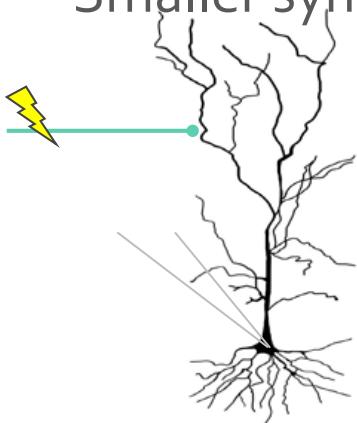
*→ short-term plasticity changes*

## Facilitation – why does quantal content increase?



- “Residual calcium” hypothesis:  $\text{Ca}^{++}$  enters to trigger transmitter release, then is removed.
- When second stimulus is soon after the first, “new”  $\text{Ca}^{++}$  enters before the initial pulse is fully removed.
- Why does a little bit make a big difference?  $m$  (quantal content) proportional to  $[\text{Ca}^{++}]^4$ . (20%  $\text{Ca}^{++} \uparrow$  leads to 100%  $\uparrow$  release.)

## Short term Depression: Smaller synaptic potentials with repetitive stimulation

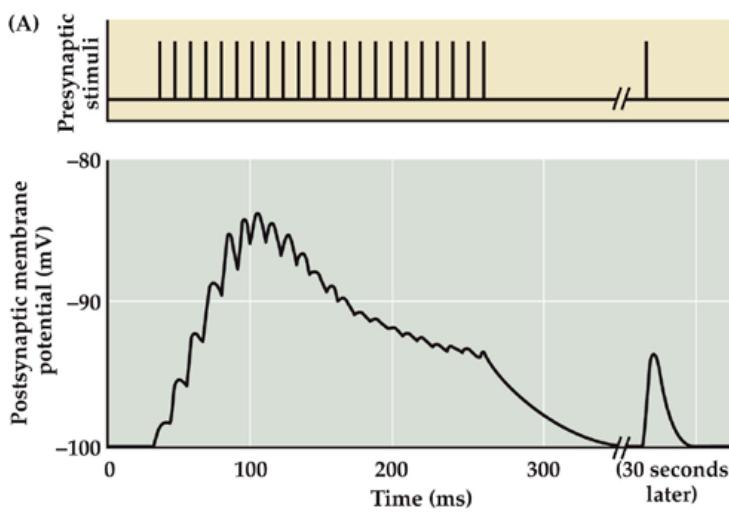


### Also Presynaptic mechanism:

- Vesicles close to the nerve terminal membrane, are “next in line” for release.
- Depression results from depletion of these readily releasable vesicles.

# of vesicles is reduced

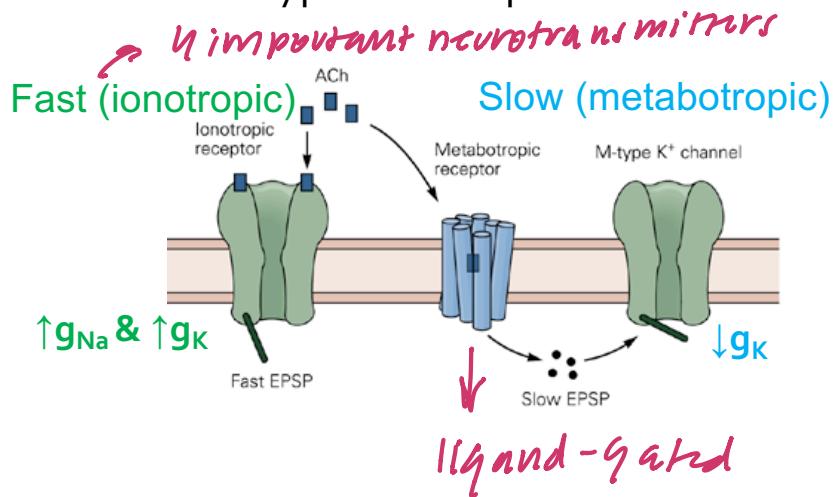
# Presynaptic changes are rapid, usually short-lived



- Changes in the presynaptic release (not impacting receptors) are usually rapid and short-lived
- Each cell can have different short term responses – depends on vesicle pools, channels, etc.
- Can combine facilitation and depression for complex responses

# Postsynaptic responses – fast and slow

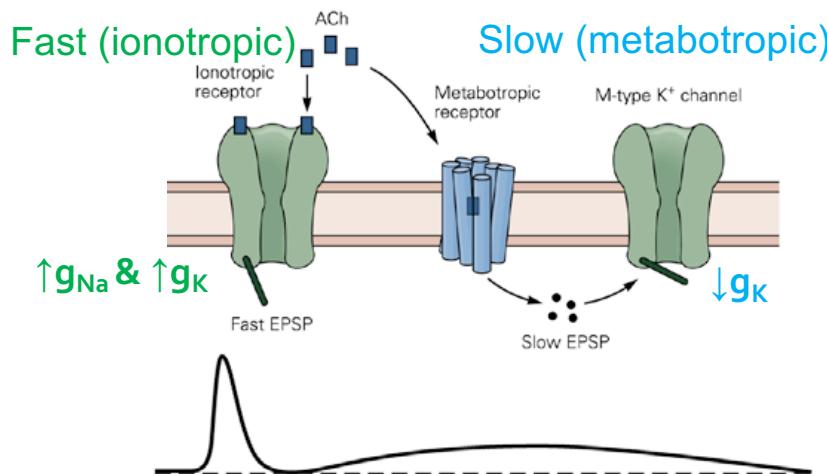
Large variety of neurotransmitters, but even more types of receptors



- Synaptic speed determined by receptor, not transmitter
- Ionotropic receptors - receptors themselves are ion channels
  - Can be either excitatory or inhibitory
- Metabotropic receptors activate protein intermediates (takes time), which have many targets.
  - Typically have a **modulatory** effect.

# Postsynaptic responses – fast and slow

Large variety of neurotransmitters, but even more types of receptors

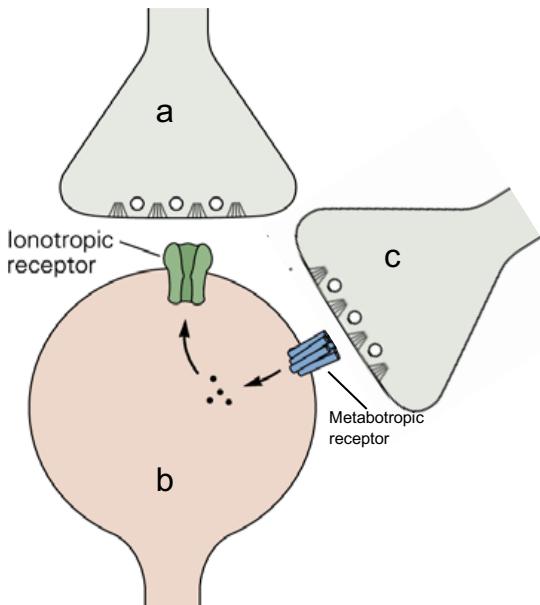


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# Some synapses are “modulatory”

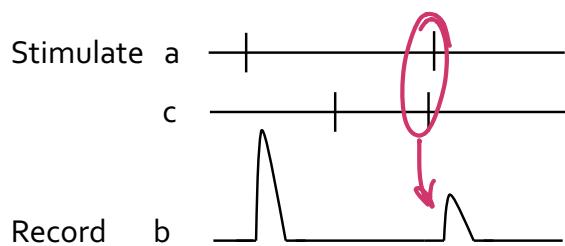
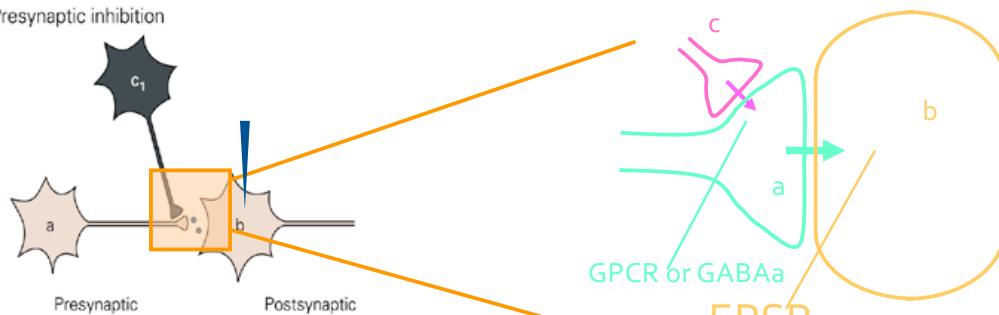


- Don't cause spiking
- Increase or decrease the cell's excitability over longer period of time
  - (1) Modulator is released from "c"
  - (2) It activates a metabotropic receptor, leading to formation of second messengers, which
  - (3) Changes the sensitivity of the ionotropic receptor to transmitter released from nerve terminal "a."
- ...but unless "a" releases a transmitter, "c" has no effect on signaling!

*Most modulatory synapses are metabotropic, but not all metabotropic synapses are modulatory.*

# Presynaptic inhibition is modulatory

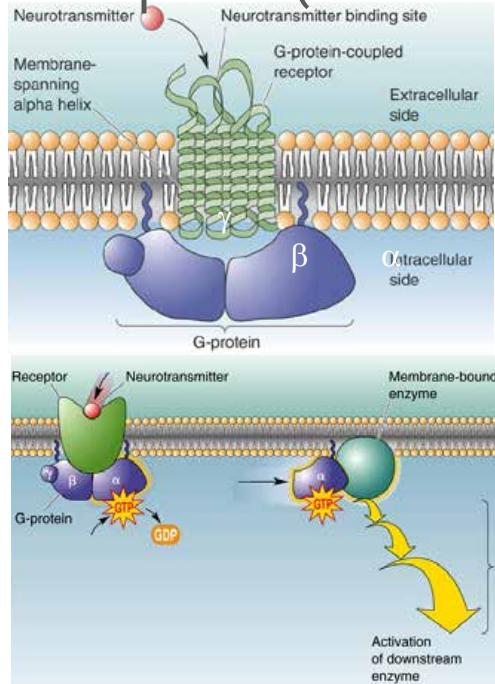
A Presynaptic inhibition



- Inhibitory transmitter released from "c," an axoaxonic synapse
- Receptor activated (could be ionotropic or GPCR)
- $g_{Ca} \downarrow$  in nerve terminal of "a"
- Quantal content (M)  $\downarrow$

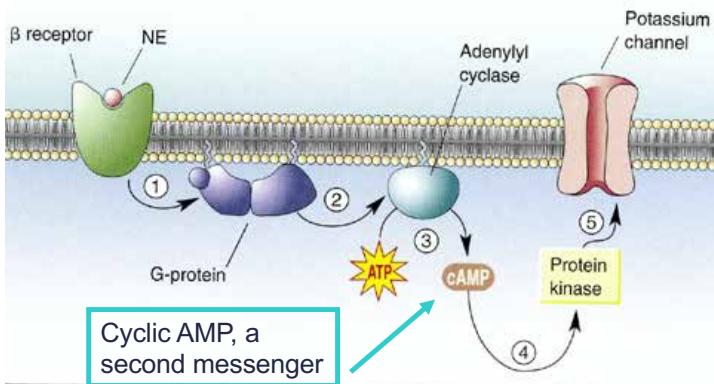
*ATC = smaller activation*  
• EPSP  $\downarrow$  in "b"

# Metabotropic receptors are G protein-coupled receptors (GPCRs)



- Huge family of genes (~2000)
- Diverse group of receptors - small neurotransmitters, catecholamines, peptides, etc.
- Intracellular domain binds a set of three proteins -  $\alpha$ ,  $\beta$ , and  $\gamma$ - together called G proteins because they bind GTP
- Three steps in transmission
  1. Binding of the neurotransmitter to the extracellular receptor protein
  2. Activation of G-proteins
  3. Activation of effector systems

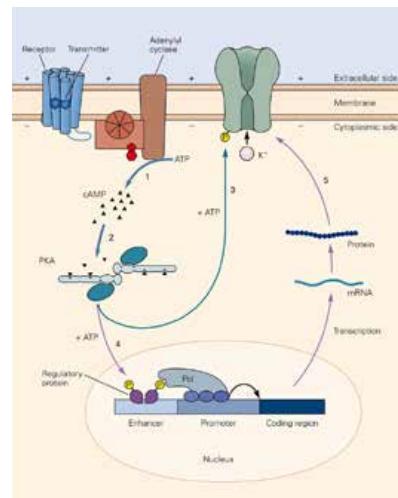
# Second messengers



- Frequently, the activated proteins are enzymes, which generate small molecules that affect channels (or something else). These molecules are called "second messengers."
  - e.g., cyclic AMP (cAMP) is generated from ATP by adenyl cyclase
  - cAMP activates protein kinase A (PKA), which can activate many proteins, including channels, receptors, etc.
- 3 general second messenger systems that interact with specific G-proteins
  - Increase cAMP ( $G_s$ )
  - Decreases cAMP ( $G_i/G_o$ )
  - Stimulates phospholipase C, DAG, IP<sub>3</sub> and PKC ( $G_q$ )

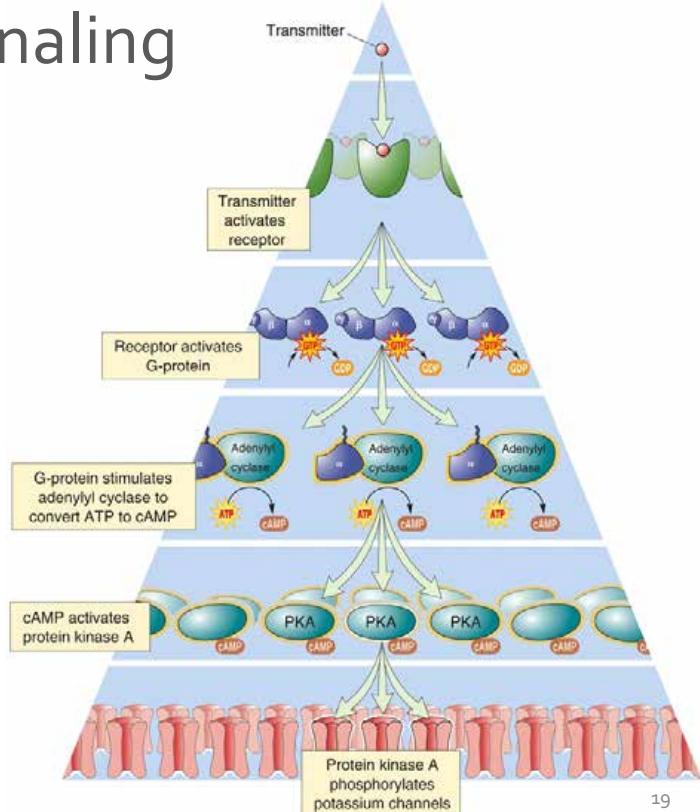
## Versatility of GPCR signaling

- A. Amplification A few molecules of transmitter can exert a big effect.
- B. Multiple effects on a single target. Different GPCRs exert different effects on the same enzyme.
- C. Multiple targets. Messengers can affect channels in the membrane, metabolites in the cytoplasm. They can also affect gene expression in the nucleus, leading to long-lasting changes (like memory???)



# Versatility of GPCR signaling

- A. **Amplification:** A few molecules of transmitter can exert a big effect.

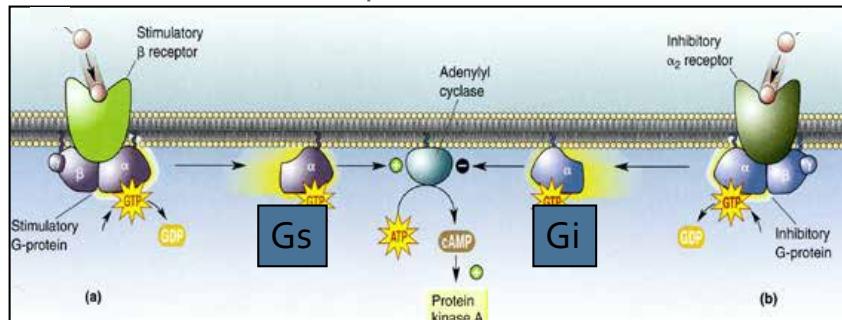


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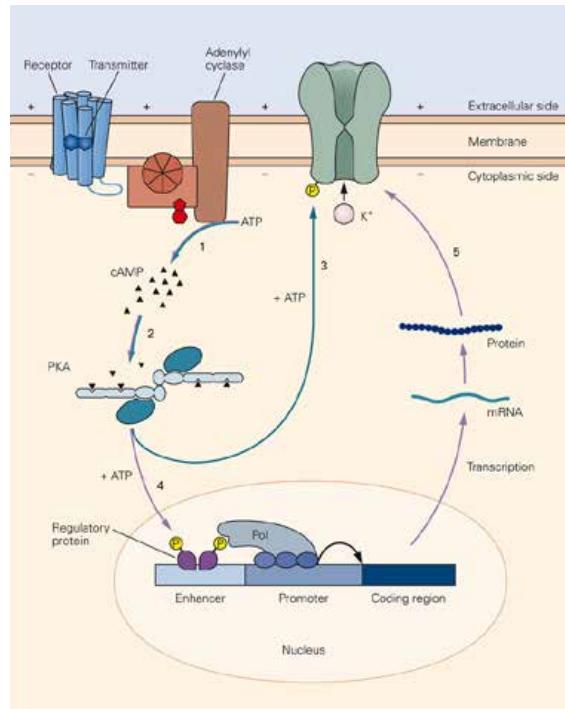
sympathetic  $\leftrightarrow$  parasympathetic  
act on GPCR

Used in the autonomic system...allows norepinephrine and acetylcholine to exert opposite effects ("fight or flight" and "rest and digest" respectively) on the same processes.



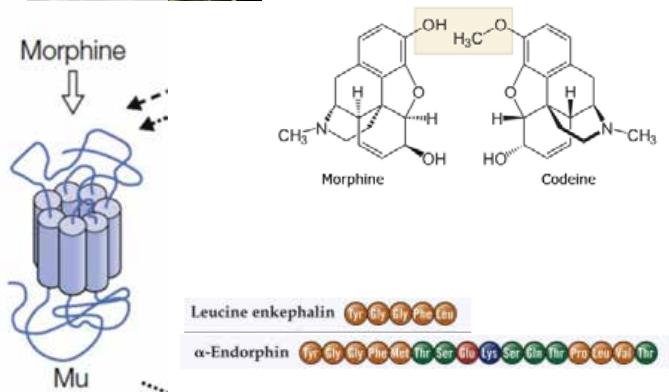
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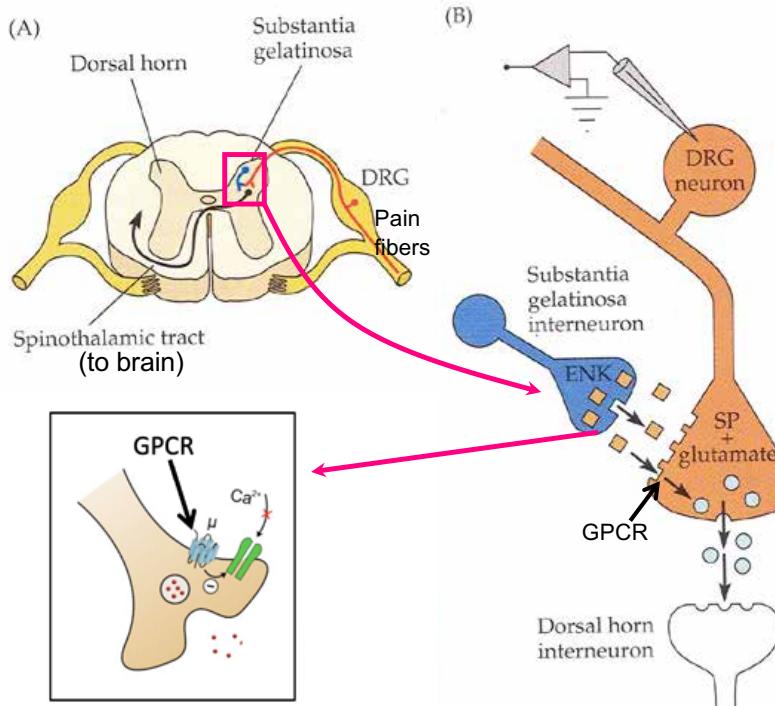


# Opiate Receptors and their Ligands

- Many opiates are structurally similar. This led to the idea that they interact with common receptors. A search for such receptors was undertaken.
- The opiate receptors turned out to be GPCRs. This led to the idea that the receptors must have natural (endogenous) ligands. A search for such ligands was undertaken.
- The ligands turned out to be small peptides, which were named enkephalins and endorphins. Like morphine, they are analgesic (decrease pain) and can be very pleasant (runner's high).

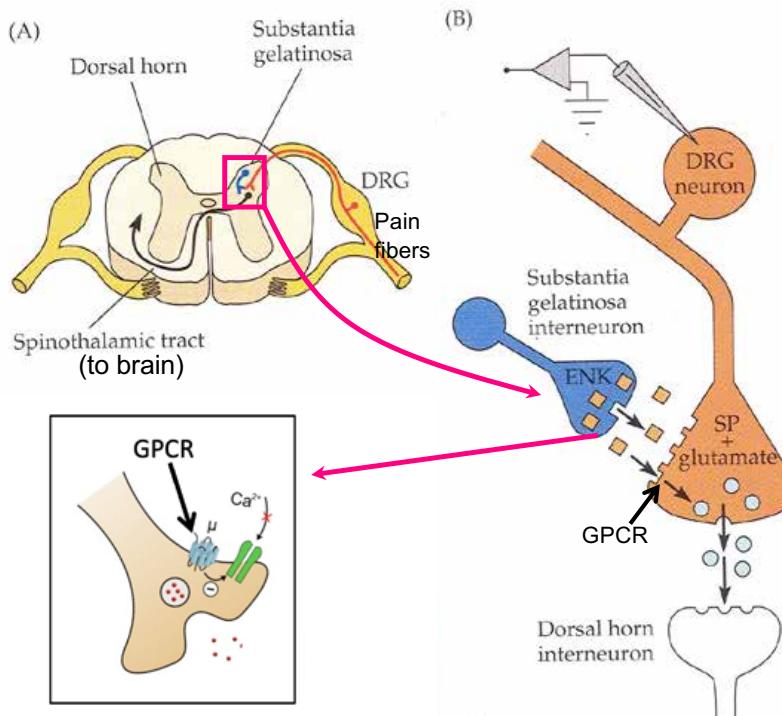


# Pain modulation by opioid receptors



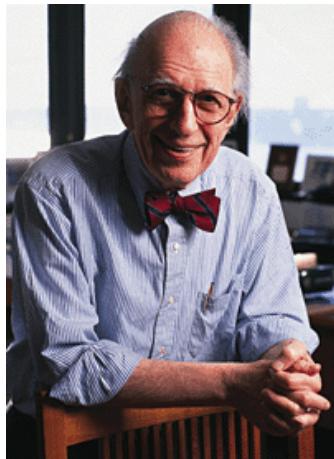
- Dorsal root ganglion cells sense pain, interneuron releases enkephalin
- Enkephalin binds GPCR
- G-protein ( $\text{G}_\alpha$ ) inhibits VG Ca channel
- Less neurotransmitter release when activated

# Pain modulation by opioid receptors



- Dorsal root ganglion cells sense pain, interneuron releases enkephalin
  - Enkephalin binds GPCR
  - G-protein ( $G\alpha$ ) inhibits VG Ca channel
  - Less neurotransmitter release when activated
- Weaker pain signal

# How synaptic alterations alter behavior - Aplysia



Eric Kandel,  
Nobel Prize 2000



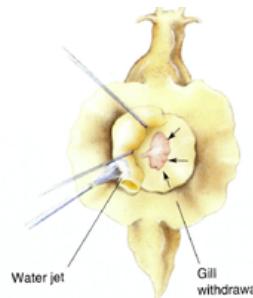
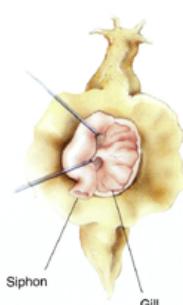
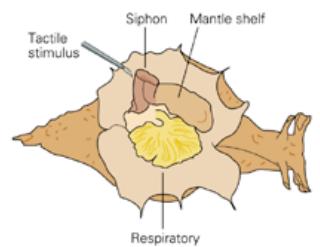
...a giant sea slug

## Aplysia "Sea slug"

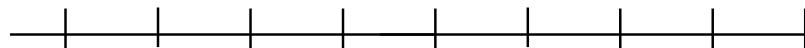
- Ugly
- Simple nervous system
- Large neurons
- Stereotyped behaviors
- Habituation
  - ignore stimulus over time
- Sensitization
  - intensify response to second stimulus

# Habituation: repetitive stimulation leads to decreased response

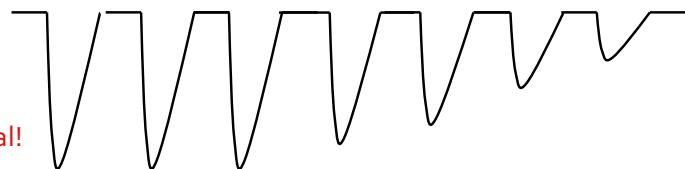
A Experimental setup



Stimulate  
siphon

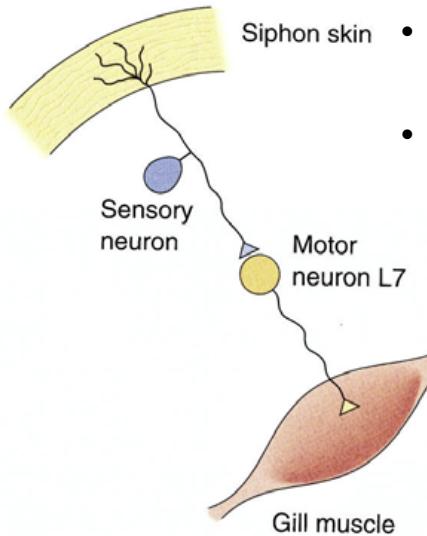


Contraction  
of gill  
**NOT electric signal!**  
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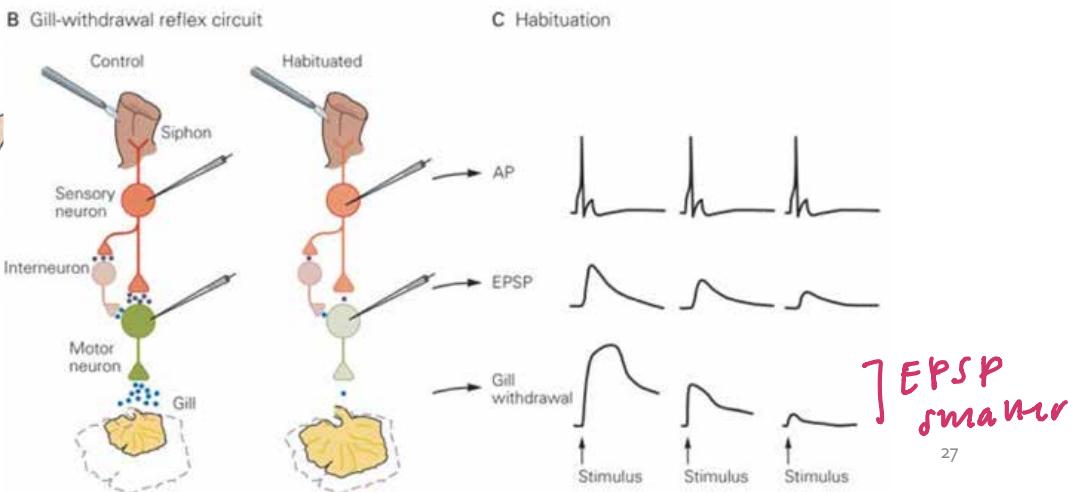


- Siphon sucks water into gills (respiration)
- Protective Reflex: Touch 'siphon', gill retracts
  - Less and less retraction with repeated touch

# Habituation due to synaptic depression

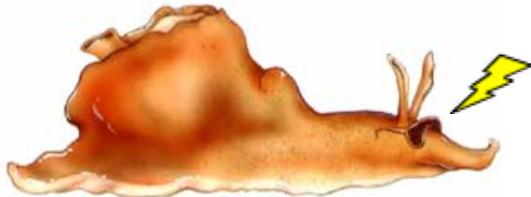


- Repeated stimulus leads to smaller EPSP in the gill muscle motor neuron
- Quantal analysis shows decreased M (quantal content)
  - Short-term depression
  - Simple form of plasticity underlies behavior

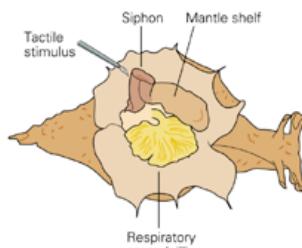


*Opposite of Habituation*

Sensitization: intensify response after (harmful) stimulus

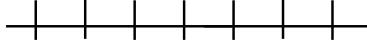


A Experimental setup



<https://www.youtube.com/watch?v=P7Qjjl-CN4U>

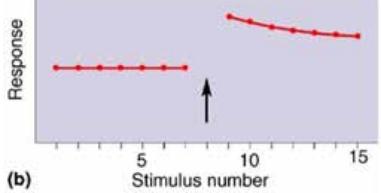
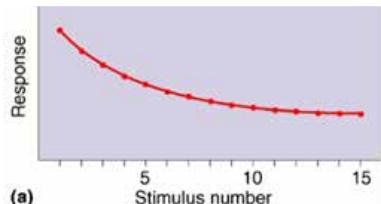
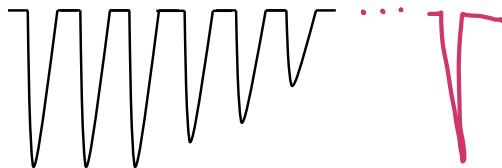
Siphon



Head

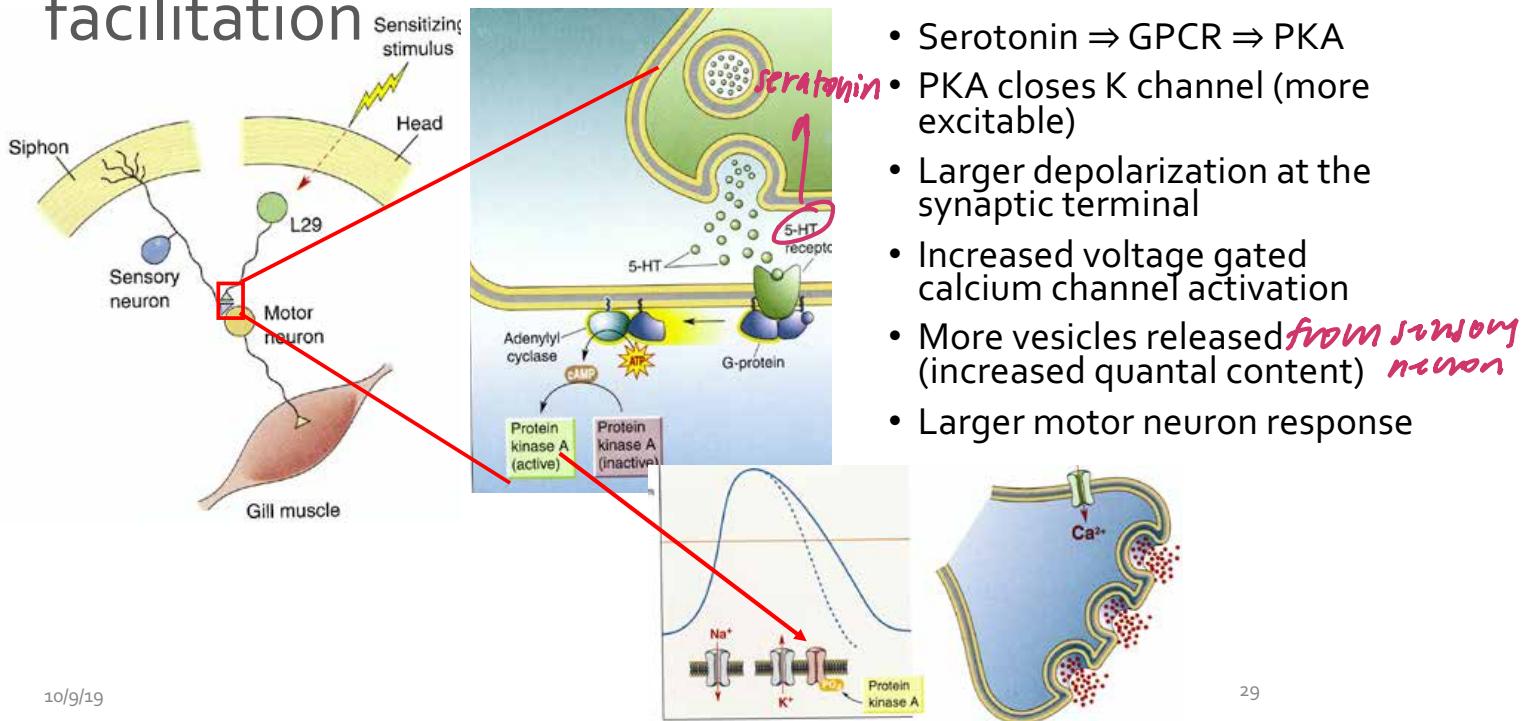


Contraction  
of gill



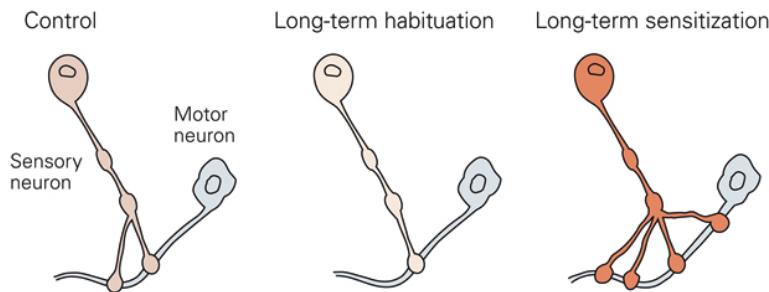
*response = function (# of shocks)*

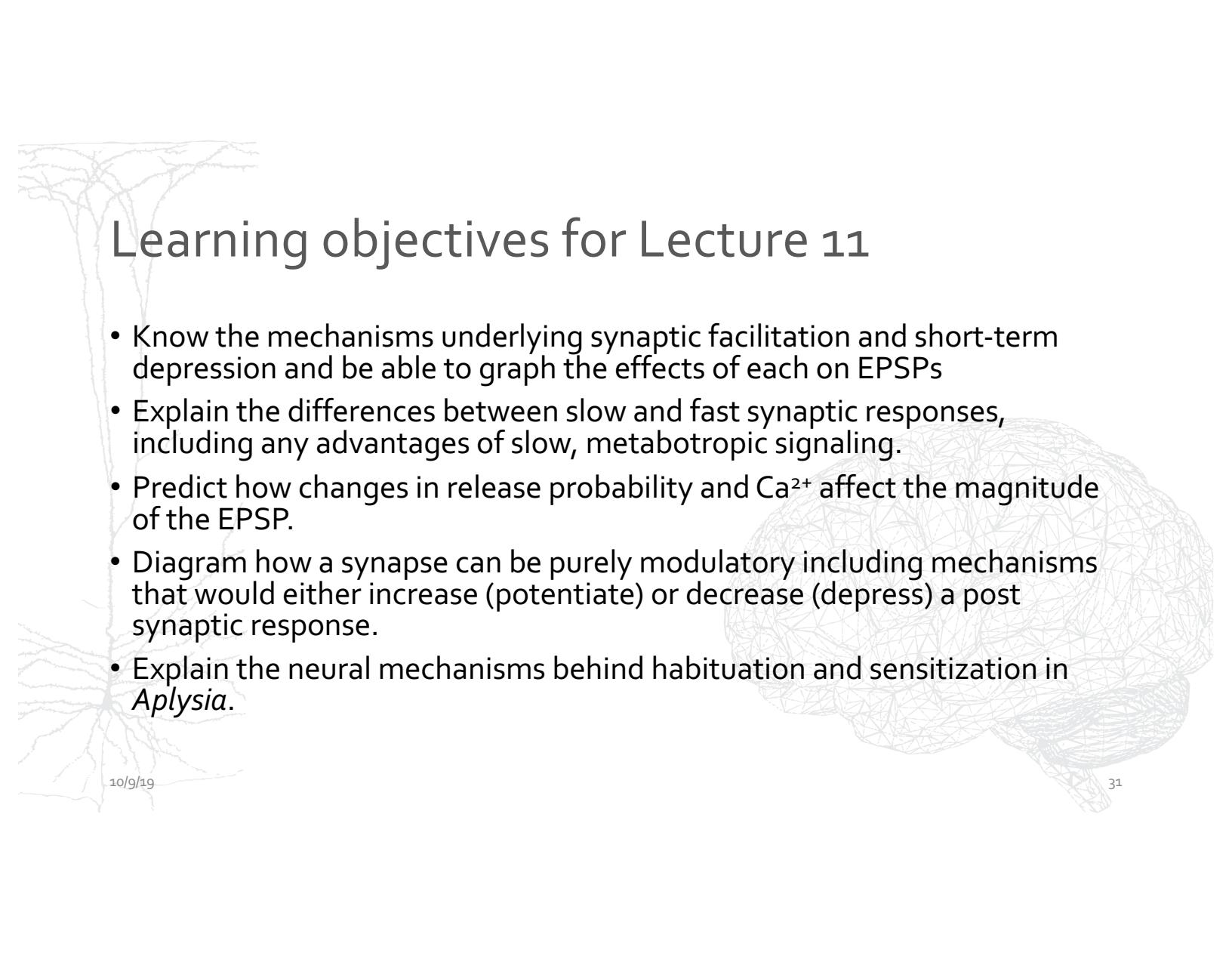
# Sensitization due to heterosynaptic facilitation



# Repeated/Long-term habituation & sensitization involve structural changes

- Repeated shocks lead changes in gene expression and long term sensitization
- Long term changes in synapses lead to long term changes in neuronal structure/number of branches





# Learning objectives for Lecture 11

- Know the mechanisms underlying synaptic facilitation and short-term depression and be able to graph the effects of each on EPSPs
- Explain the differences between slow and fast synaptic responses, including any advantages of slow, metabotropic signaling.
- Predict how changes in release probability and  $\text{Ca}^{2+}$  affect the magnitude of the EPSP.
- Diagram how a synapse can be purely modulatory including mechanisms that would either increase (potentiate) or decrease (depress) a post synaptic response.
- Explain the neural mechanisms behind habituation and sensitization in *Aplysia*.

## Lecture 11 - Short-term synaptic plasticity and modulation

Pre-class notes for October 9<sup>th</sup>, 2019

Reading: Neuroscience by Purves et al., pages 169-176, 149-151

**Synaptic Strength** - the average change in membrane potential of~ a postsynaptic neuron elicited by a presynaptic action potential.

**Synaptic modulation** - changes in strength or efficacy of neuronal connections. Can be caused by a variety of physiologic and signaling mechanisms at time scales that vary from ms to days or longer.

**Short-term plasticity** - a change in synaptic strength (time scale of milliseconds to seconds) caused by *presynaptic* mechanisms which alter the quantal content (average # of vesicles released by one presynaptic action potential ).

**Facilitation** - increased synaptic strength (EPSP amplitude) apparent after two or more presynaptic action potentials. Caused by elevation of residual  $\text{Ca}^{2+}$  in the *presynaptic* terminal.

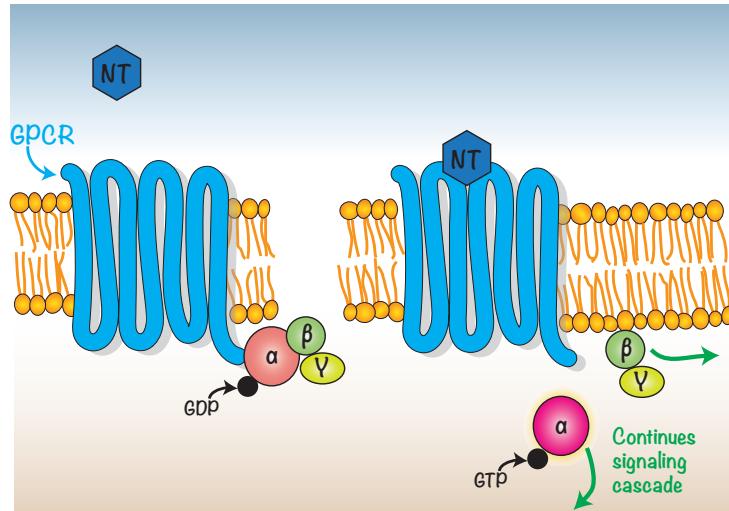
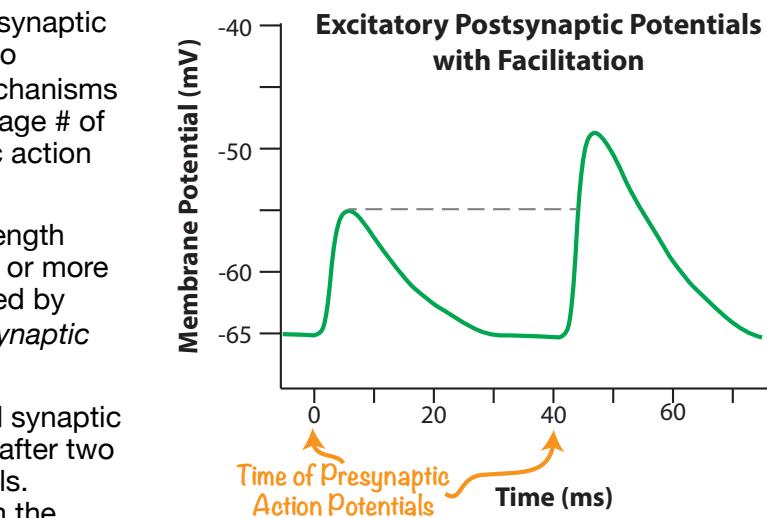
**Short-term depression** - decreased synaptic strength (EPSP amplitude) apparent after two or more pre-synaptic action potentials. Caused by depletion of vesicles from the *presynaptic* terminal.

**Ionotropic receptor** - a neurotransmitter-gated ion channel which directly leads to changes in membrane potential.

**Metabotropic receptor** - a neurotransmitter receptor that effects neuron excitability or membrane potential indirectly through intracellular signaling cascades.

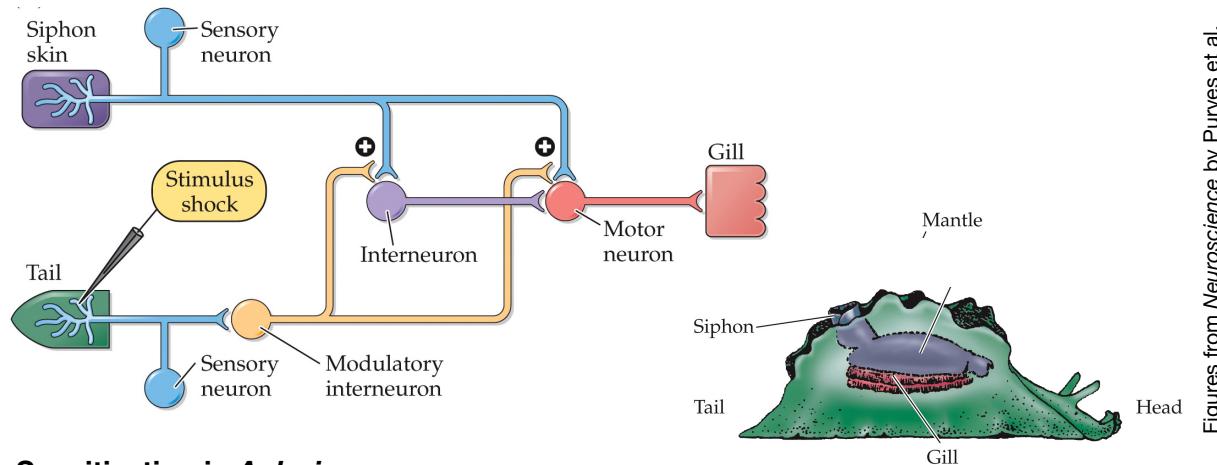
**Neuropeptides** - large classification of neurotransmitter molecules that are made up of a short polypeptide chain. Neuropeptides active GPCRs (see below) for diverse effects on varying timescales.

**G-protein coupled receptor (GPCR)** - Type of metabotropic receptor with 7 transmembrane domains that interacts with G proteins. GPCRs are a diverse group with each subtype activated by one of a variety of ligands (light, specific neuropeptides, sugars, or lipids).

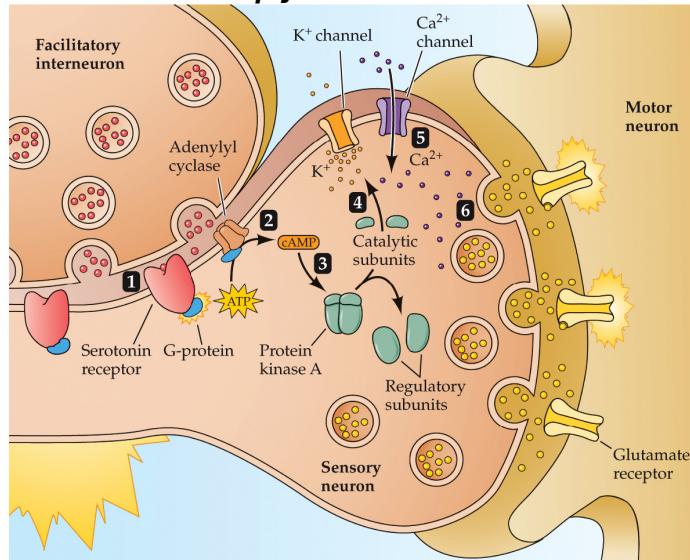


**Second messenger** - one of the intracellular signaling molecules that is activated by an extracellular signal (i.e. activation of GPCR) and triggers a signaling cascade to alter a neuron's excitability or physiology.

**Aplysia** - a type of sea slug used as an experimental animal to study the molecular underpinnings of behavioral learning or plasticity. A relatively simple circuit causes a reflexive retraction of the gills when the animal's siphon is touched. This response and the underlying synaptic strengths can be modulated.



### Sensitization in Aplysia



**Habituation** - a decrease in the magnitude of behavioral responses to repeated stimuli. In *Aplysia*, repeated stimulation of the siphon causes a reduced gill retraction after multiple stimulations. This is due in part to a decrease in the synaptic strength between the sensory and motor neurons.

**Sensitization** - an increase in the magnitude of a behavioral response to a stimulus after a separate, often noxious stimulus has been applied. In *Aplysia*, pairing a shock to the tail with stimulation of the siphon, causes a increase in gill retraction when then stimulating the siphon alone.

**Heterosynaptic plasticity** - when synaptic strength between two neurons maybe be regulated by a third neuron/synapse. (e.g. sensitization in *Aplysia*)

**Learning Objectives:** (By the end of Lecture 11 you should be able answer the following)

1. Know the mechanisms underlying synaptic facilitation and short-term depression and be able to graph the effects of each on EPSPs
2. Explain the differences between slow and fast synaptic responses, including any advantages of slow, metabotropic signaling.
3. Predict how changes in release probability and Ca<sup>2+</sup> affect the magnitude of the EPSP.
4. Diagram how a synapse can be purely modulatory including mechanisms that would either increase (potentiate) or decrease (depress) a post synaptic response.
5. Explain the neural mechanisms behind habituation and sensitization in *Aplysia*.

Figures from Neuroscience by Purves et al.