

# Lecture 14. Introduction to Plasticity

*Dr. Shelby Dietz*

## Required Reading

Be able to explain the following figures from Bear et al.: p. 113 Fig. 5.2; p. 123, Fig. 5.12; p.162, Fig. 6.17

## Learning Objectives

1. To start to understand the importance of synaptic plasticity for computation
2. To explain how the kinetics of calcium sequestration and vesicle recycling can lead to short-term forms of synaptic plasticity
3. Learn pre-synaptic and post-synaptic mechanisms by which neuromodulators or activity can change the strength of a glutamatergic or GABAergic synapse.

## Lecture Outline

1. Plasticity, the capacity of the brain to change, is at the core of how we respond to our environment and learn from our past experiences. The major advantage of chemical synaptic transmission is its plasticity—changes in synaptic strength.
  - Synaptic strength can vary as a function of its previous history of activity at a synapse
  - Synaptic strength can be altered by neuromodulation
  - Long term changes in synaptic strength will be covered in upcoming lectures
2. Rapid intrinsic modulation of synaptic strength, over periods up to a second
  - Synaptic facilitation: strengthening of synapses when fired in rapid succession, or with a train of action potentials, due in part to accumulation of calcium in the pre-synaptic nerve terminal
  - Synaptic depression: weakening of synapses during rapid stimulation due to exhaustion of the readily releasable pool of vesicles.
  - Receptor desensitization: phosphorylation of receptors to reduce their response to ligands
  - Receptor saturation: all available receptors occupied by ligand
3. Many additional methods of short-term alteration of synaptic strength
  - Neuromodulator-induced synaptic modulation
  - Co-transmission of multiple transmitters and modulators
  - Binding of retrograde transmitters to presynaptic receptors
4. Change in synaptic strength can be limited at synapses at which stability is important

## Study Questions

1. You have discovered a drug that slows the rate at which calcium is sequestered by mitochondria and endoplasmic reticulum in pre-synaptic nerve terminals. What would this drug do to: a) the postsynaptic response to a single pre-synaptic action potential; b) the postsynaptic response to a train of pre-synaptic action potentials. Explain your answer.
  
2. Describe 5 mechanisms by which a neuromodulator can alter the strength of another synapse. Think of ion channels and other proteins as possible targets of the signal transduction cascade activated by the neuromodulator.



EYES ON YOU

Z+

CU

My

R.F.

NRE

PK SA

More For Me



## Lecture 14: Plasticity

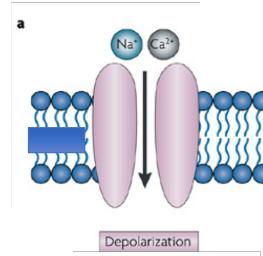
Learning goals:

1. To start to understand the importance of synaptic plasticity for computation.
2. To explain how changes in calcium concentration, vesicle recycling, and receptor availability can lead to short-term forms of synaptic plasticity
3. Learn pre-synaptic and post-synaptic mechanisms by which neuromodulators or activity can change the strength of a glutamatergic or GABAergic synapse.

# Three types of chemical synapses

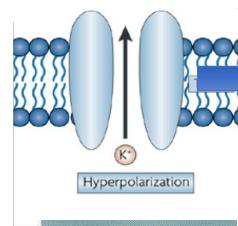
## Excitatory

Push the cell toward threshold for firing action potentials



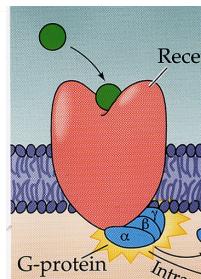
## Inhibitory

Hold the cell below threshold for action potentials



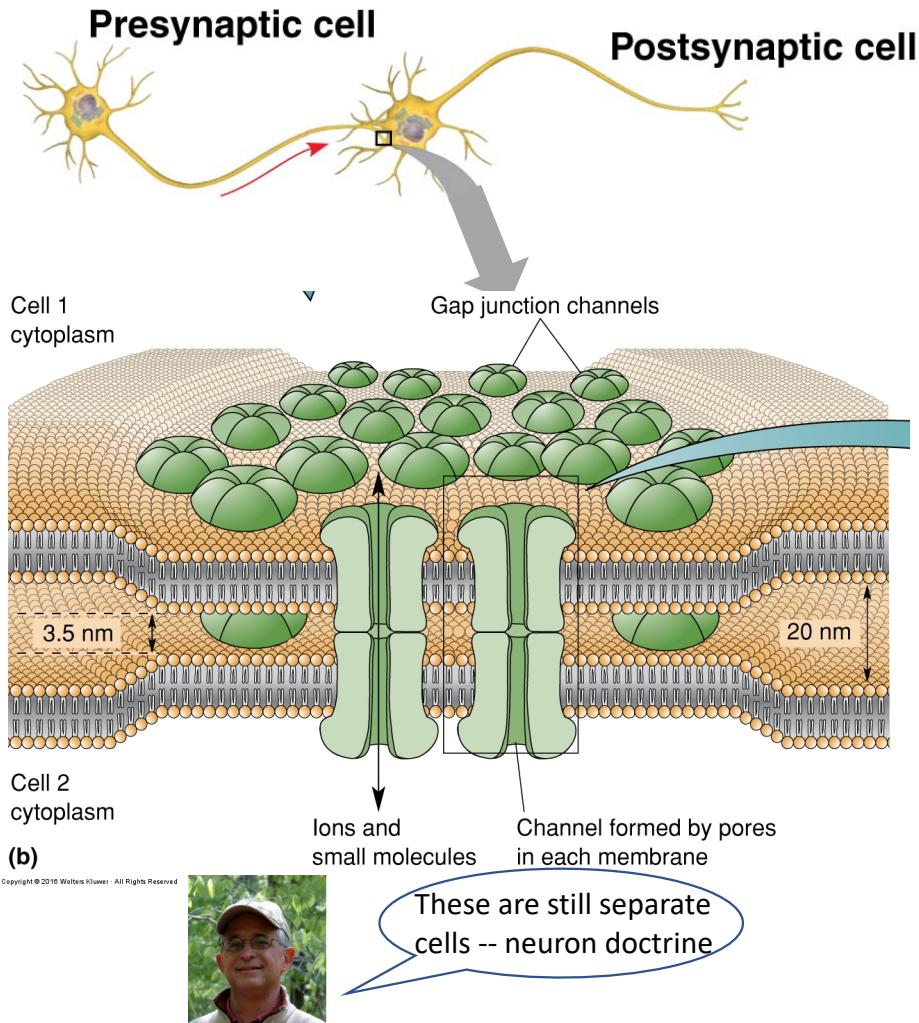
## Modulatory

Often has little effect alone, but can greatly modify the effects of other transmitters that are simultaneously active.



*But not all synapses are chemical*

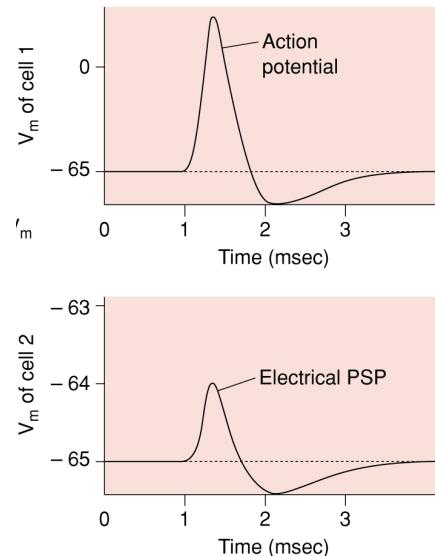
# Some synapses are a direct electrical connection



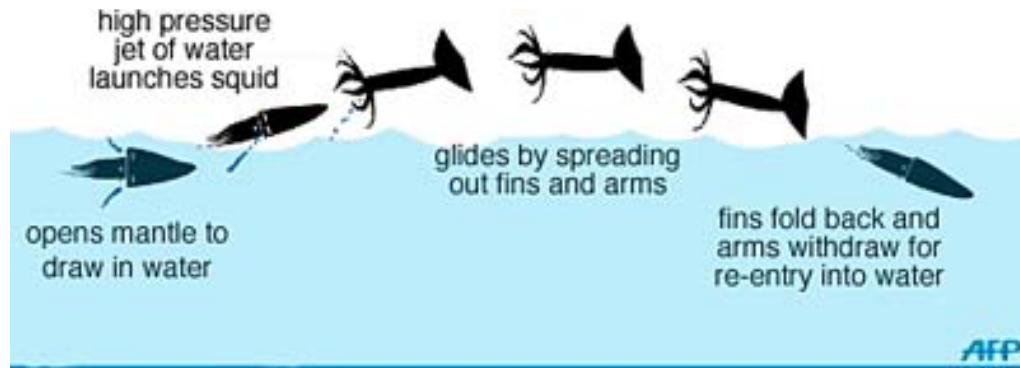
## Gap junctions

-- fast (~0.2 ms), usually act bidirectionally

-- high fidelity



# Gap junctions provide speed and reliability in circuits



Escape response

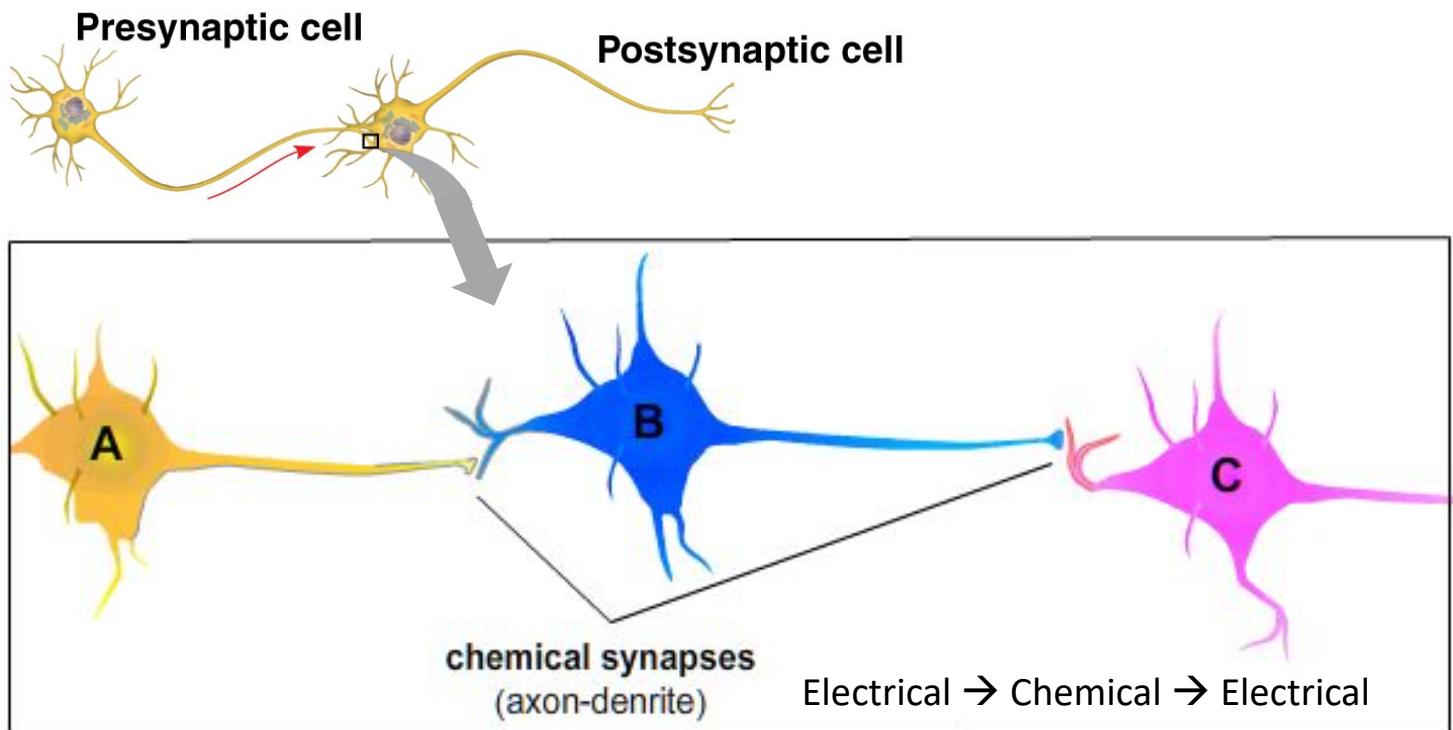
If you want highly coordinated activity, gap junctions can be useful ...

Many of the sensory and motor systems we will learn about in upcoming lectures use gap junctions.



So if electrical synapses are so useful ...

# So why do we have so many chemical synapses?



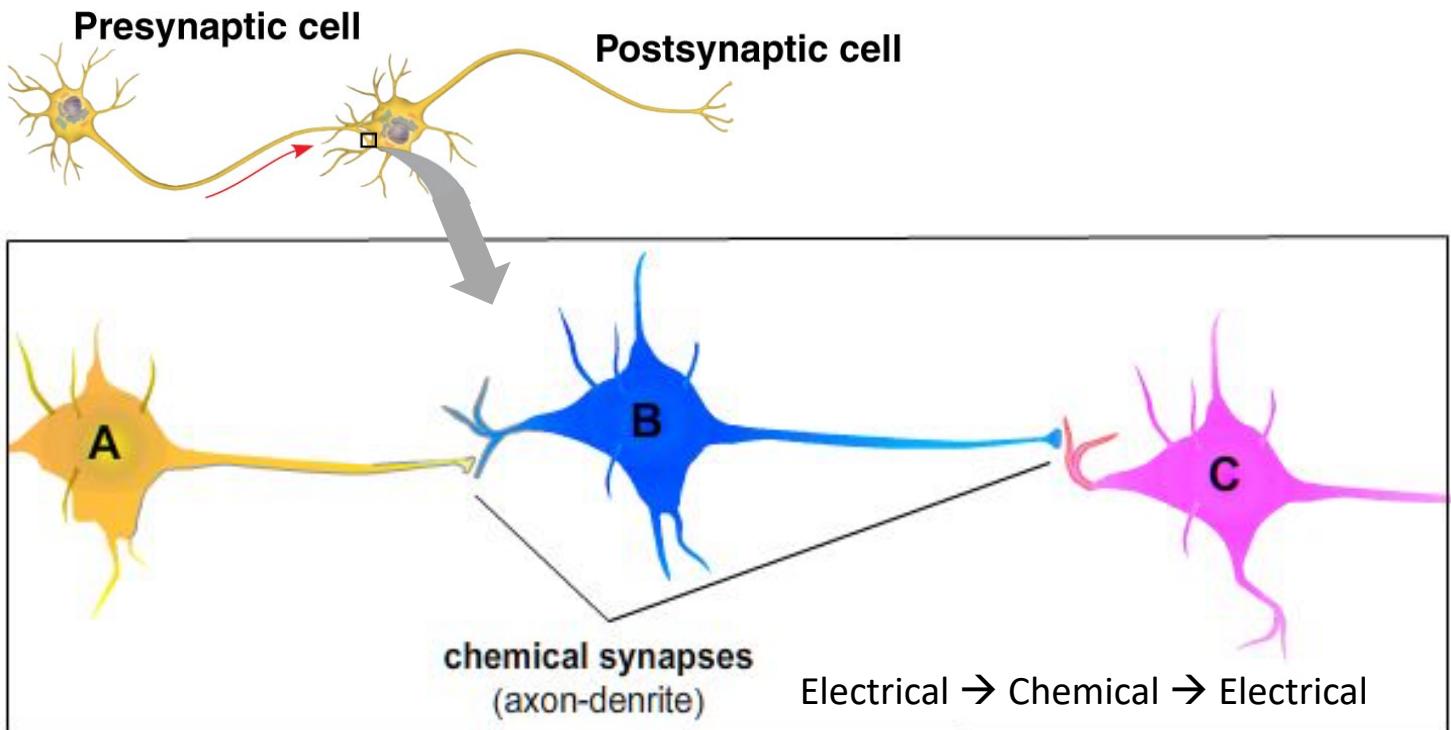
## Discussion question

What about chemical synaptic transmission makes it worth the cost? Discuss with a neighbor:

Student responses:

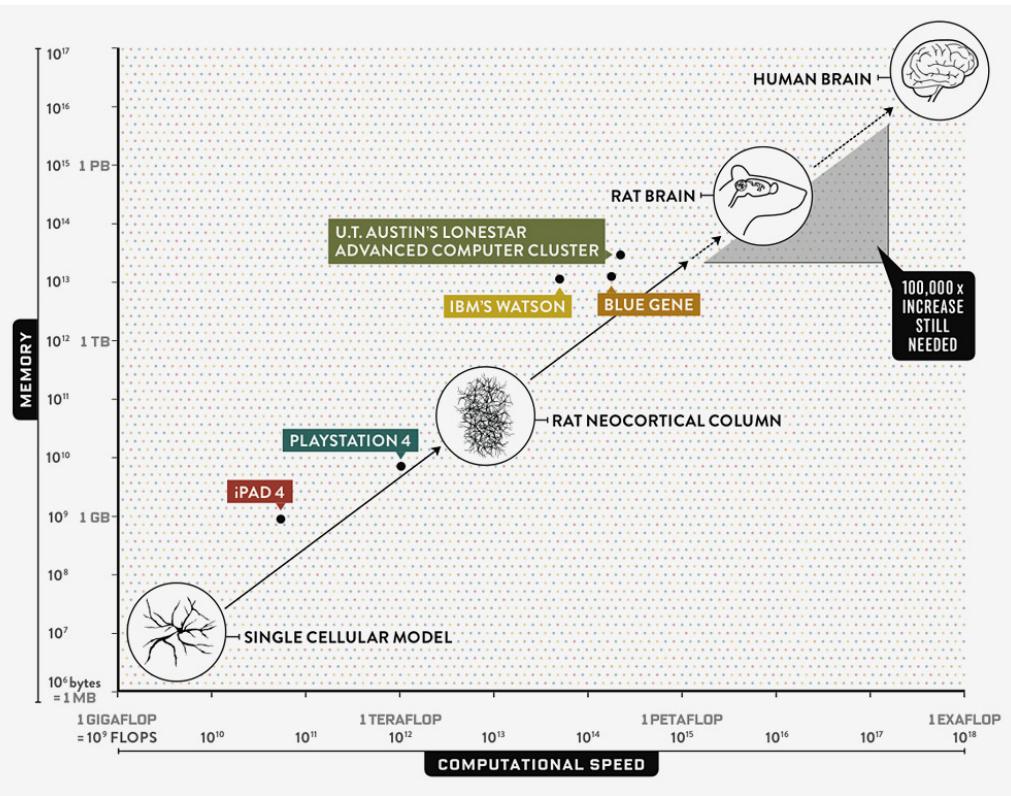
- Chemical reactions can be long-lasting
- Allow fine control
- Allow modification

# Why is the time and energy cost of chemical synaptic transmission worth it?



A synapse is a **choice point**, at which a signal can be passed, withheld, sign reversed, strengthened, weakened, amplified, extended in time ...

Counting the number of synapses between neurons is a first step in estimating the information storage capacity of the brain



BUT just counting  
synapses  
underestimates the  
capacity of the brain

...

Possibility of change  
in synaptic strength  
vastly increases the  
information storage  
capacity of the brain

<https://www.wired.com/2013/05/neurologist-markam-human-brain/>

## Changes in synaptic strength allow for remodeling of the information flow

Existing synapses can change their strength

→ new ways to respond to a changing environment → learning?



Even gap junctions can change their strength-- it's everywhere!

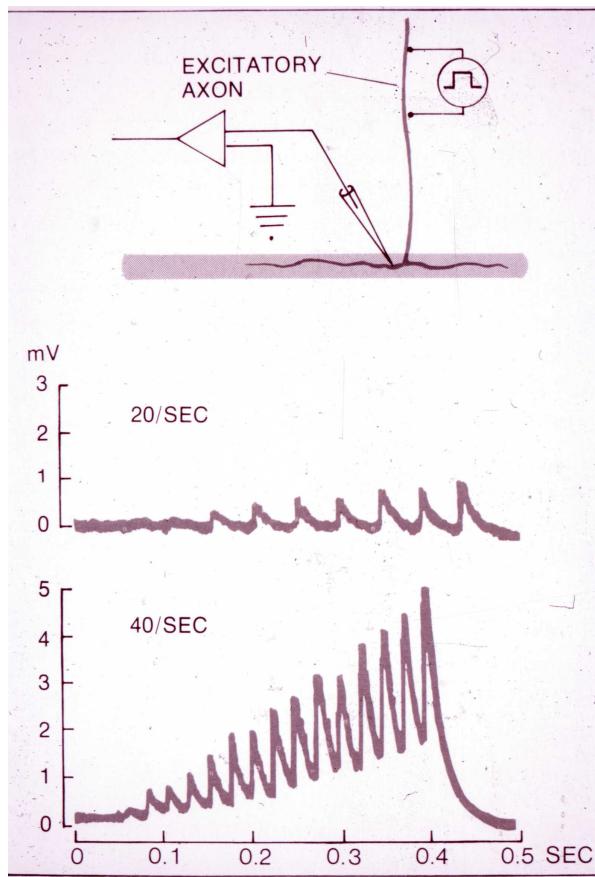
# Synaptic plasticity allows for remodeling of the information flow

**Plasticity:** changes in the strength of a synapse as a function of ...

... neuromodulatory actions

... or its *own* previous history (beginning of memory)

Can be SHORT TERM (returns to previous strength quickly) or LONG TERM



## Habituation is reduced response to a repeated stimulus



Habituation can be the result of decreases OR increases in synaptic strength, depending in where they occur in a complex circuit

To start studying behavioral changes, we will begin with the building blocks: the simplest forms of synaptic change

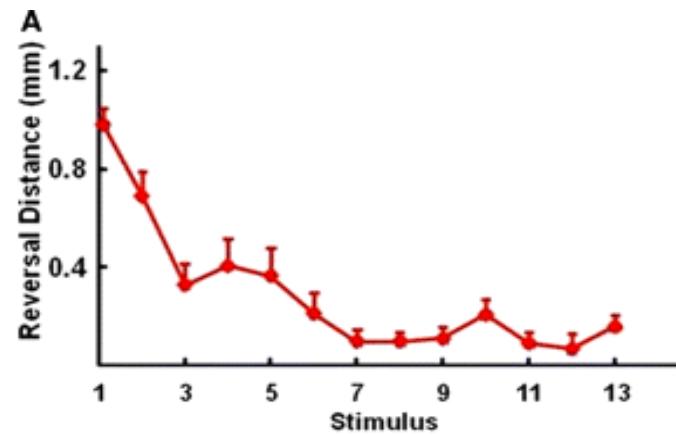
We can start studying habituation at the cellular level with the simplest animals and the simplest behaviors we can find ...



*C. Elegans*

1. Simple nervous system using many of the same cellular and molecular mechanisms as in humans
2. Anatomy is well characterized
3. *Displays behaviors including habituation*

C. Elegans can respond to recent events in its environment by changing its behavior ...



This tiny animal can learn!

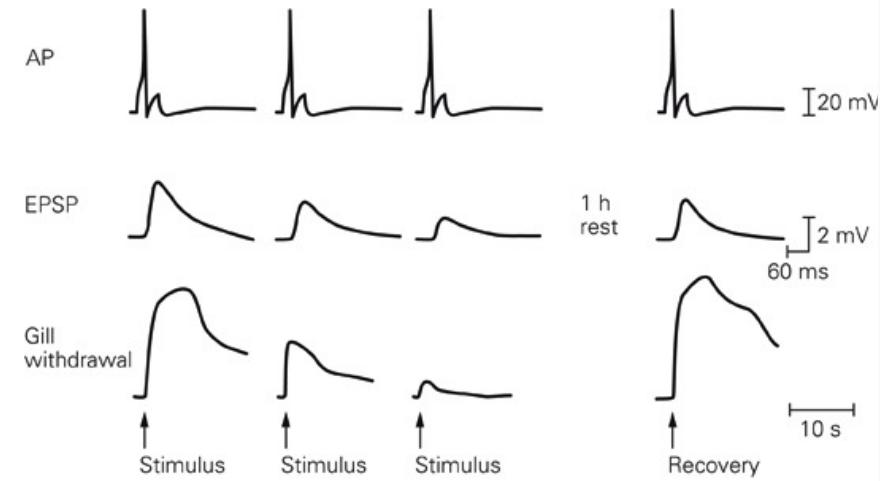
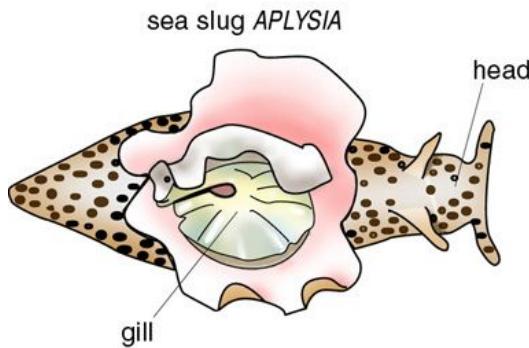
Ardiel and Rankin 2010

# *Aplysia* as a model system for the study of the neurobiological basis of learning and memory



*Aplysia californica*

# *Aplysia* gill-withdrawal reflex can habituate with repeated stimulation



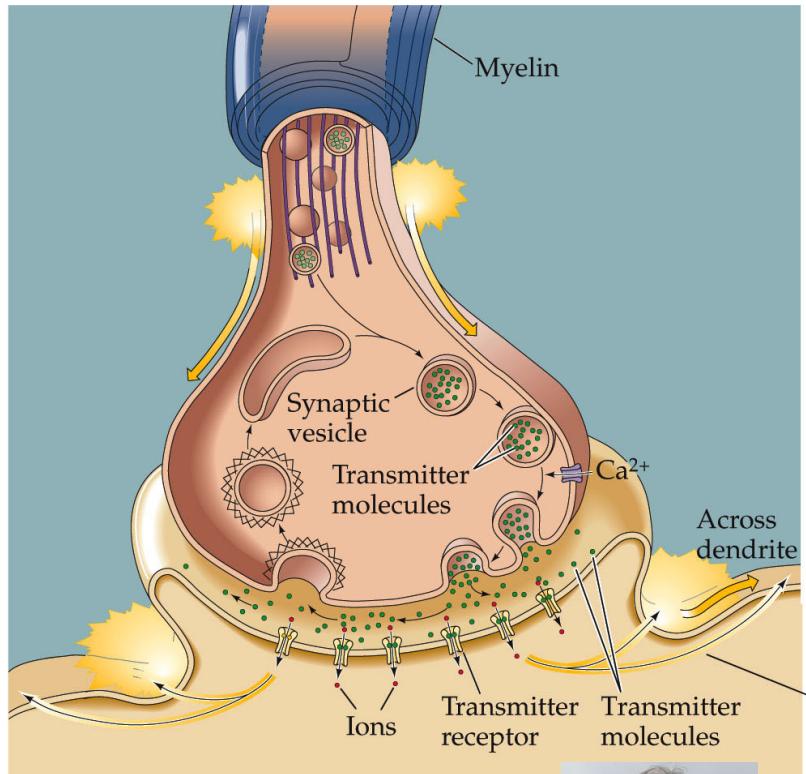
Not permanent

- Habituation results in a decline in the size of the muscle PSPs
- No change in the response of the sensory neuron
- What could be the molecular basis of habituation?

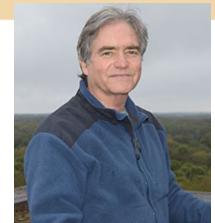
Altering any step in the transmission pathway can induce short-term plasticity

1. Synthesis
2. Packaging into vesicles
3. Release
4. Postsynaptic receptor activation
5. Reuptake

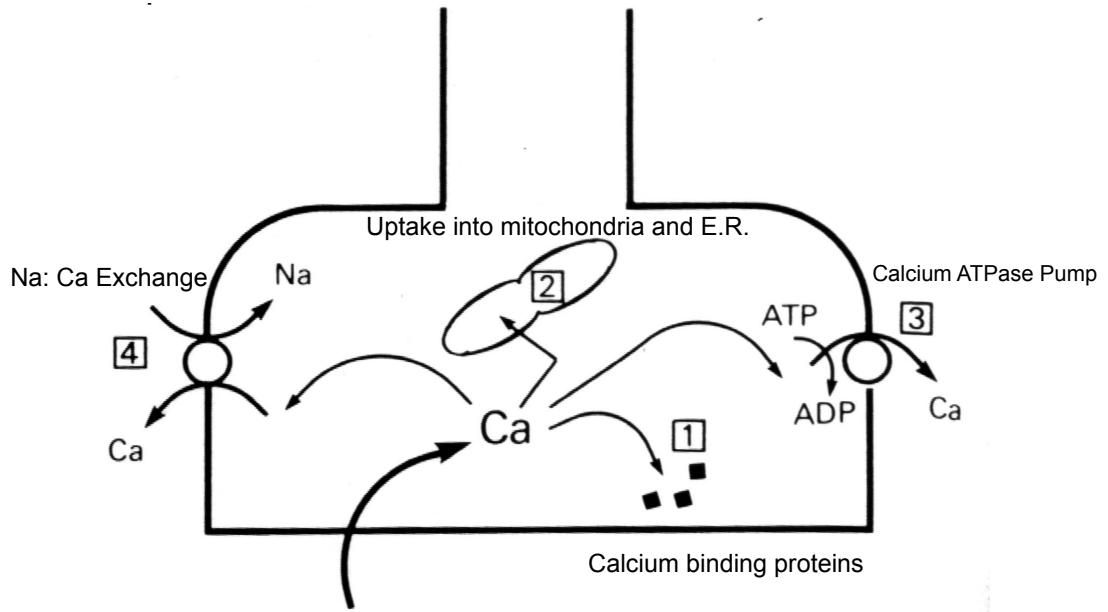
*Each of these steps can be modulated by drugs, and dysfunction at any step can cause disease*



*NEUROSCIENCE, Fourth Edition, Figure 5.3*



**Facilitation** is due to buildup of calcium in the presynaptic terminal during a series of APs

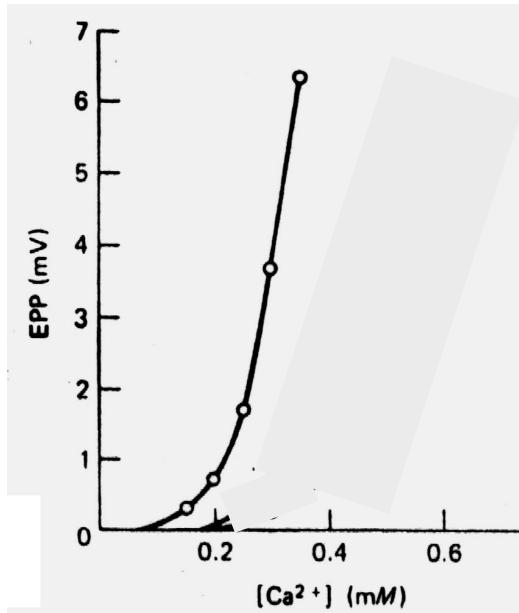


Takes 100-500 msec to bring calcium levels to normal after an A.P.

Calcium sequestration is pretty slow

**Facilitation** is due to buildup of calcium in the presynaptic terminal during a series of APs

$$\text{Release} = k \times [\text{Ca}^{++}]^4$$



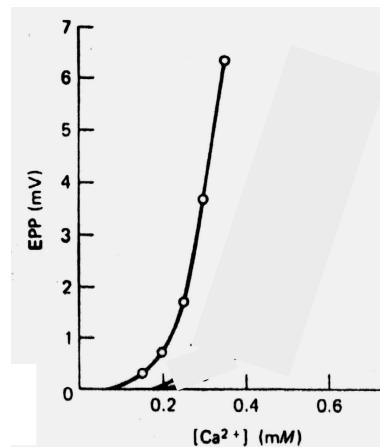
The probability of release goes up nonlinearly with the calcium concentration— a relatively small Ca increase has a huge impact.

## Clicker question

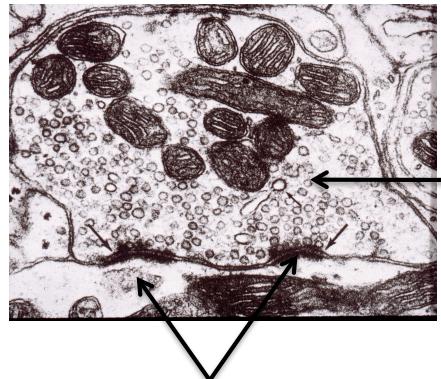
BAPTA is a calcium chelator, a compound which quickly binds calcium to prevent its levels from changing. You inject BAPTA into a pre-synaptic terminal. What effect will this have on the degree of synaptic facilitation in response to a train of action potentials?

- a) Increase facilitation
- b) Decrease facilitation
- c) No effect

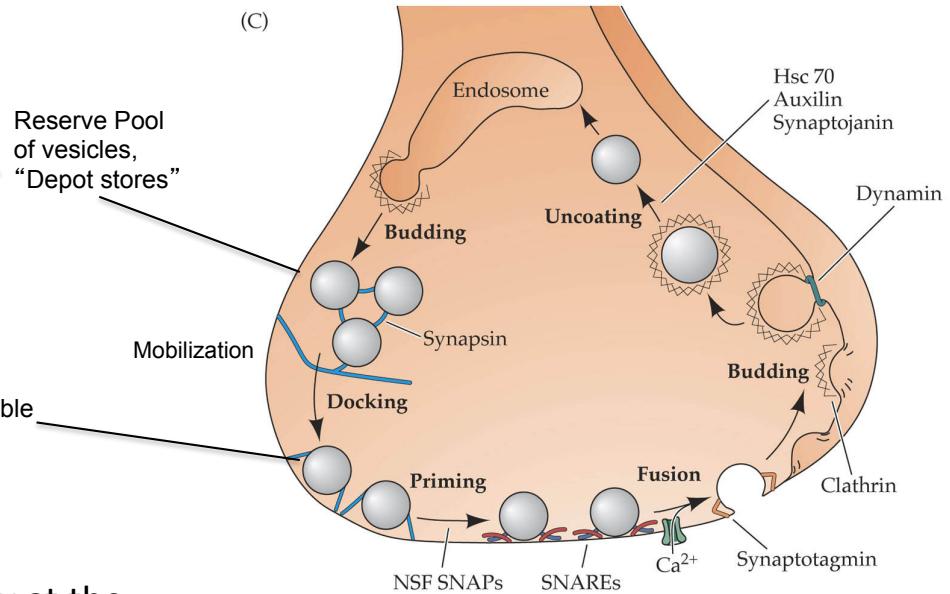
$$\text{Release} = k \times [\text{Ca}^{++}]^4$$



## Depression is due to depletion of available vesicles after a series of APs



Docked, readily releasable pool of vesicles



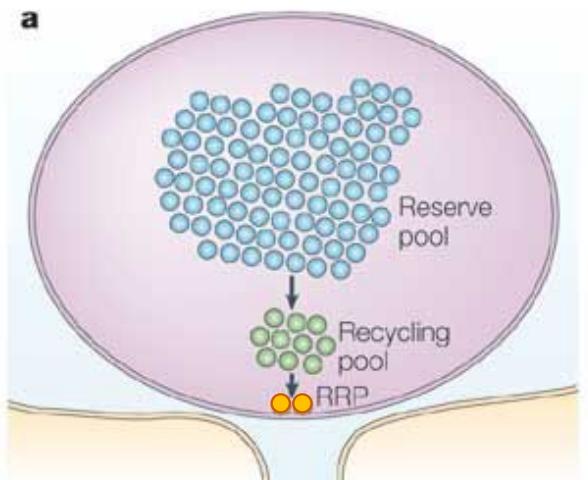
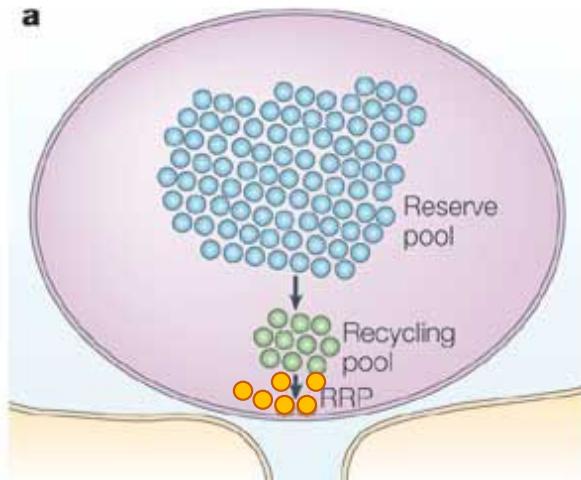
Only docked vesicles already at the membrane (the “**readily releasable pool**”) can be released by an AP, and they can run low.

## Clicker question

You discover a drug that **reduces** the number of vesicles in the readily releasable pool. What effect will this have on short-term depression?

- a) Increase depression
- b) Decrease depression
- c) No effect

If you have fewer vesicles ready to release, you run out on the first few AP

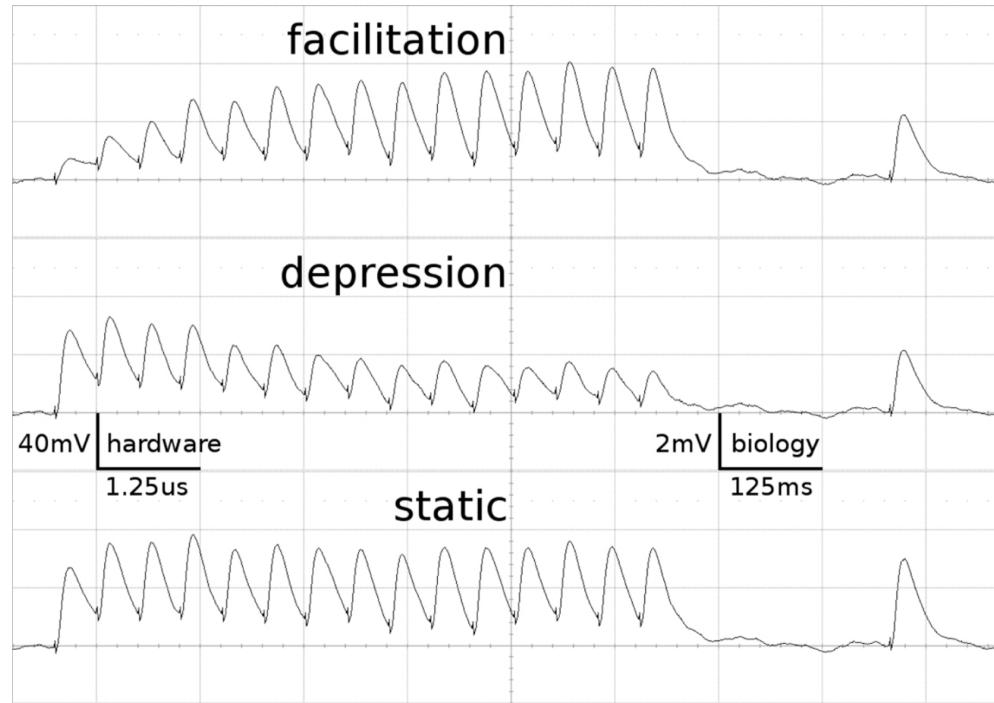


## Discussion question

You trigger a series of APs in a presynaptic neuron and measure the size of the EPSPs in the post-synaptic neuron. Which will predominate, facilitation or depression?

- a) Facilitation
- b) Depression
- c) They will cancel each other out exactly and there will be no effect
- d) You can't tell without more information

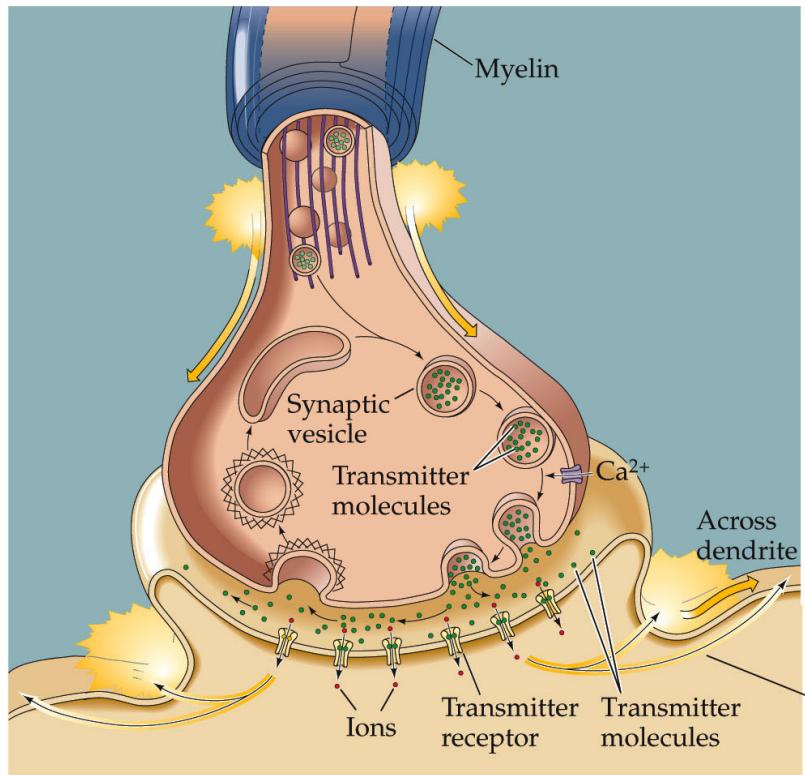
A particular synapse can show **facilitation**, **depression** or no change in synaptic strength during a bout of activity



Which pattern will a synapse show? Depends on balance, very individual to each cell type, each synapse type within a cell type. You can't know until you test that particular synapse!

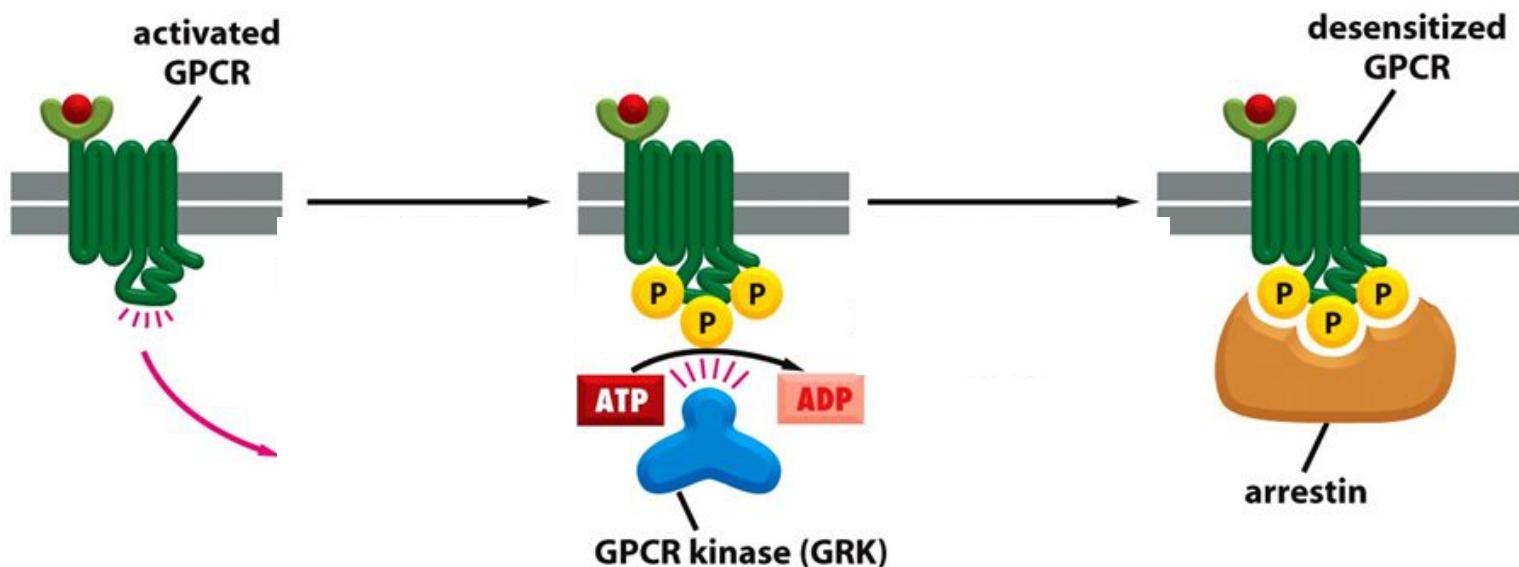
Altering any step in the transmission pathway can induce short-term plasticity

1. Synthesis
2. Packaging into vesicles
3. Release
4. Postsynaptic receptor activation
5. Reuptake

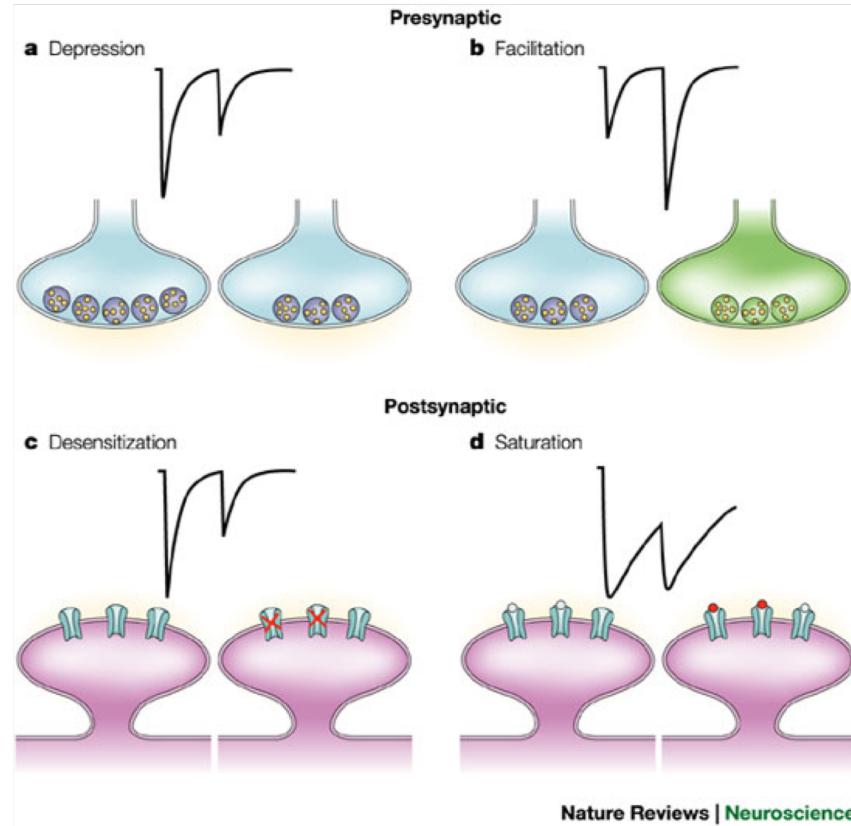


*NEUROSCIENCE, Fourth Edition, Figure 5.3*

Prolonged exposure to transmitters can cause receptor **desensitization**

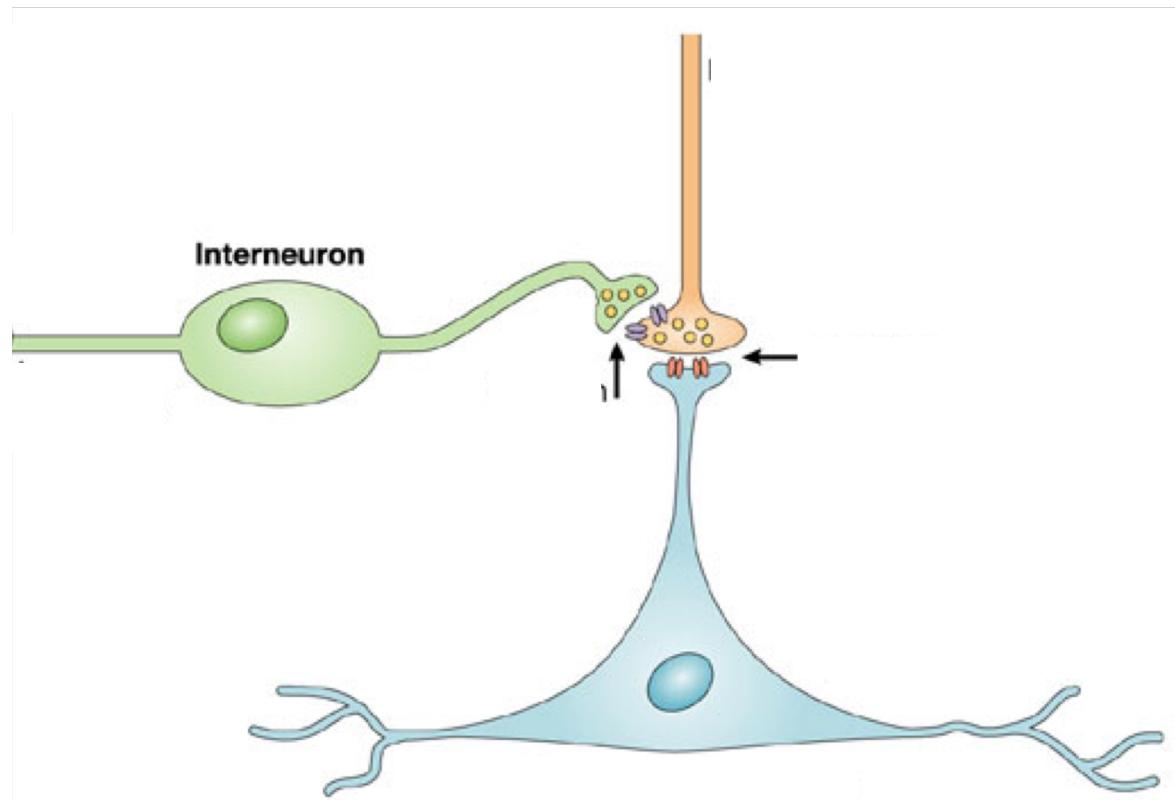


Both pre- and post-synaptic short-term plasticity can be **activity-dependent**



Comes not from signals from other cells like modulation, but as a record of the recent activity of that particular synapse

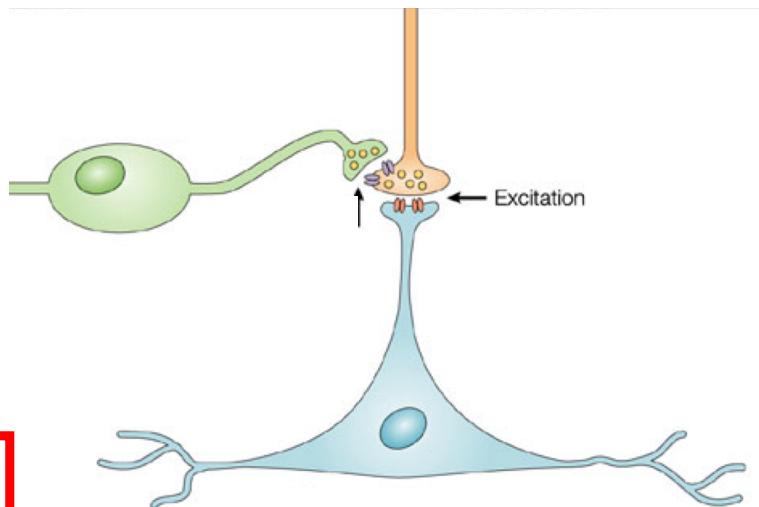
Synapses can form onto other synapses to regulate them presynaptically



## Clicker question

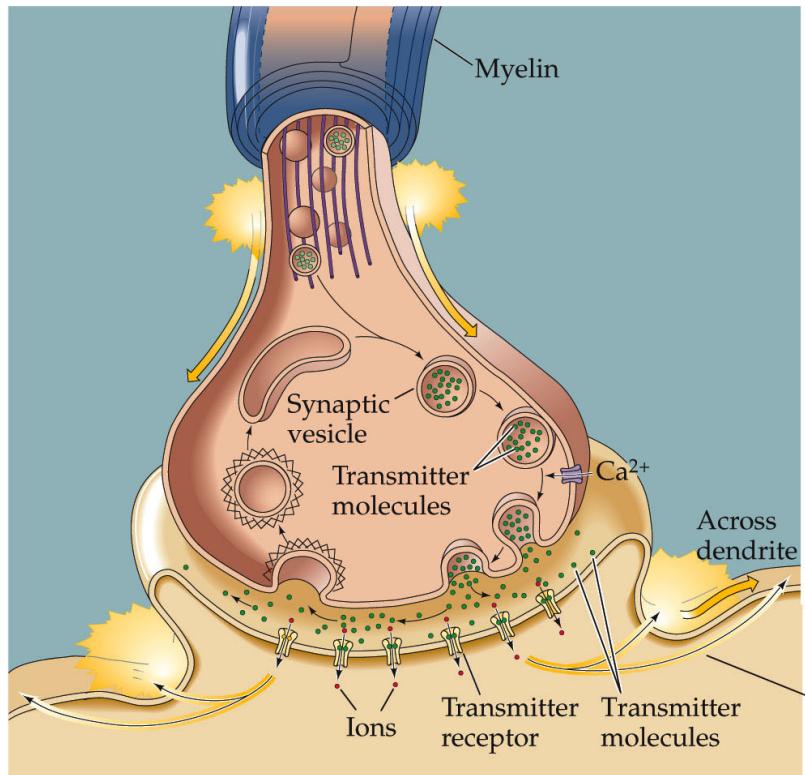
What mechanism could a pre-synaptic synapse (green) use to **strengthen** the glutamate EPSP in the target neuron (blue) by enhancing the release of glutamate?

- A. Decrease the rate of opening of voltage-dependent  $\text{Ca}^{2+}$  channels
- B. Increase the number of open  $\text{Cl}^-$  channels
- C. Increase the number of open  $\text{K}^+$  channels
- D. All of these would strengthen the synapse
- E. None of these would strengthen the synapse



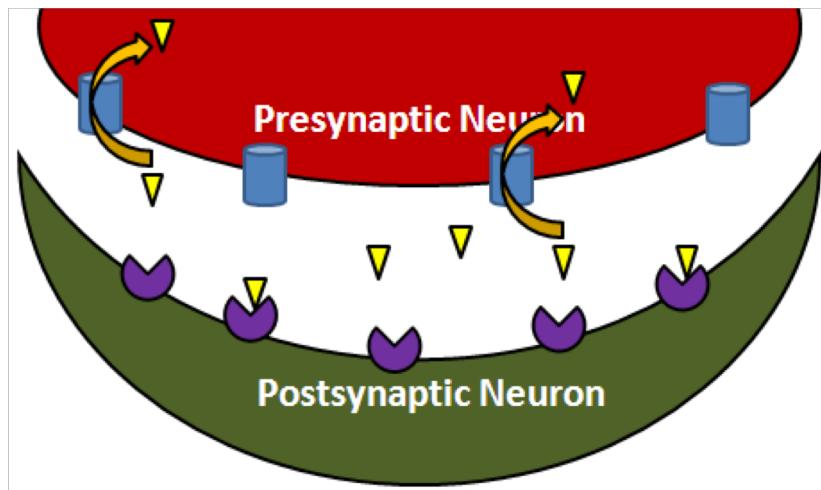
Altering any step in the transmission pathway can induce short-term plasticity

1. Synthesis
2. Packaging into vesicles
3. Release
4. Postsynaptic receptor activation
5. Reuptake



*NEUROSCIENCE, Fourth Edition, Figure 5.3*

# Transmitter reuptake is a crucial final step in transmission



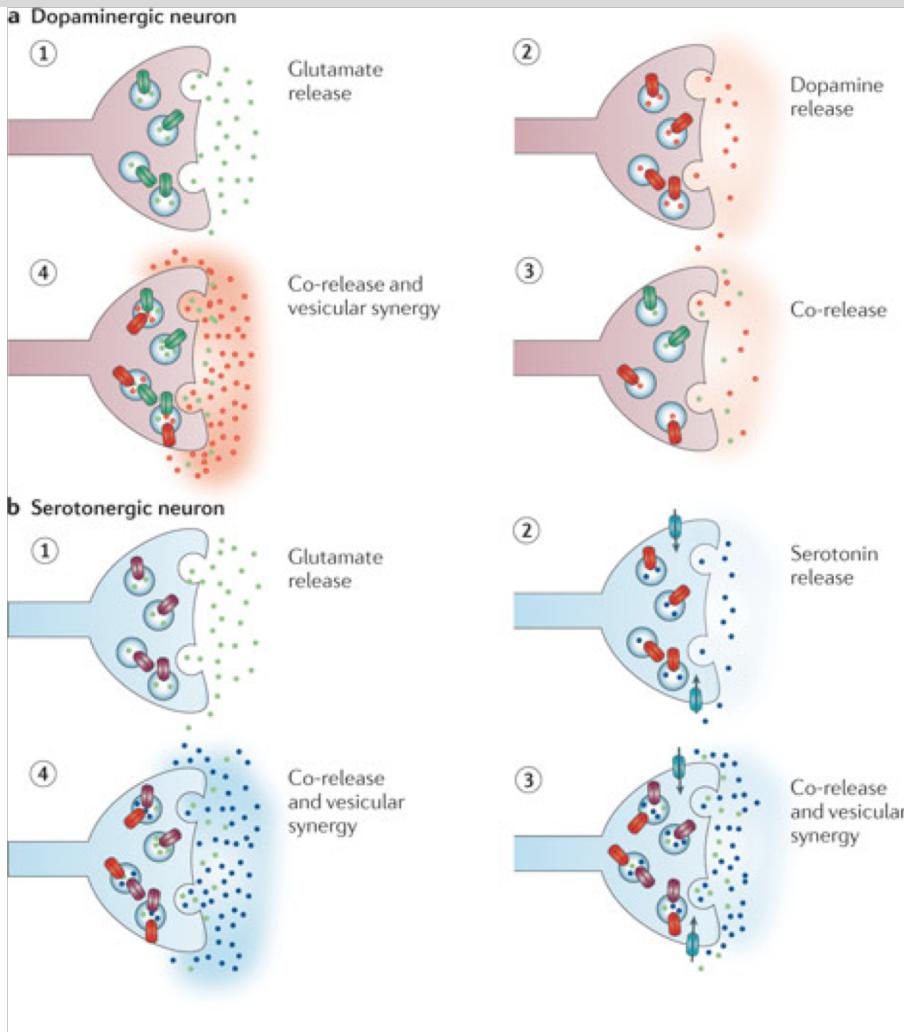
Transmitters will keep activating receptors, prolonging signal, as long as they're present

Active removal by transporters less an endogenous mechanism of short-term plasticity than an extremely important drug target

Cocaine, amphetamine block DA reuptake  
SSRI antidepressants (Prozac, Zoloft, etc.) block 5-HT (and other catecholamine) reuptake



# Co-transmission: multiple transmitters released from a single nerve terminal

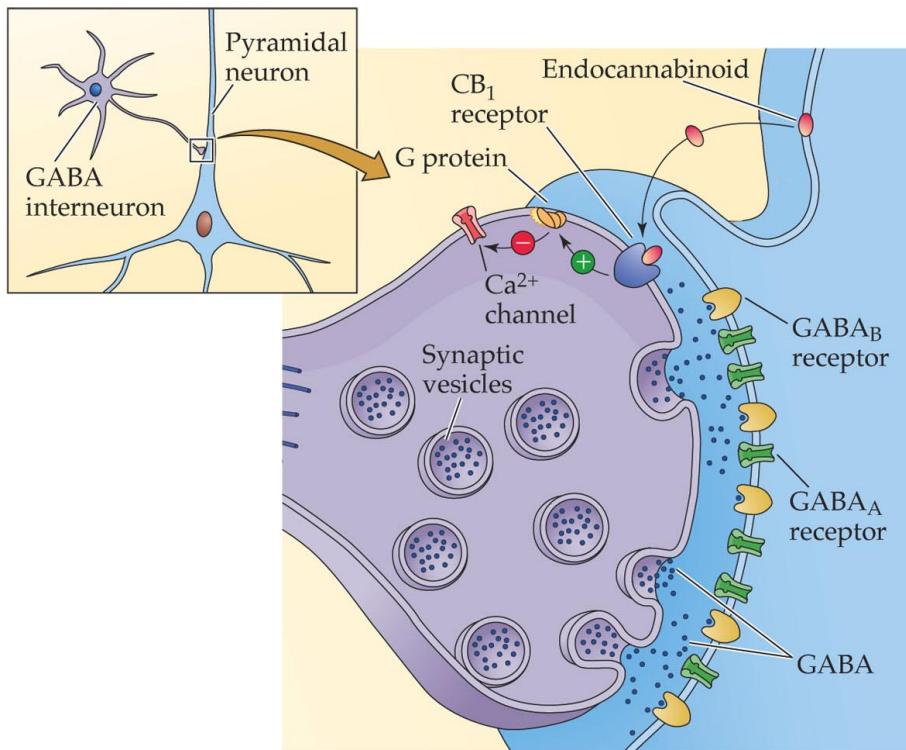


Why would synapses send signals for excitation and depression in parallel?

Synapses can self-regulate, always guarding against overexcitation.

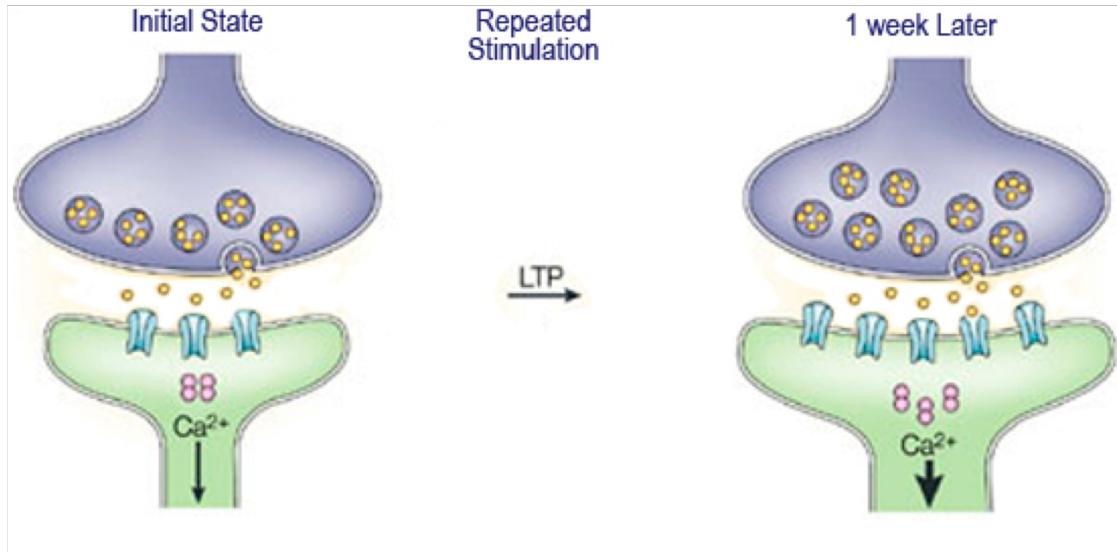
Recurring theme: **opposing forces to maintain balance.**

# Retrograde transmission: transmitters going backward from the postsynaptic to presynaptic cell



1. Transmitters include endocannabinoids
2. Activity dependent, synthesized in the post-synaptic neuron in response to synaptic activation
3. Why? Again, opposing forces to maintain balance.

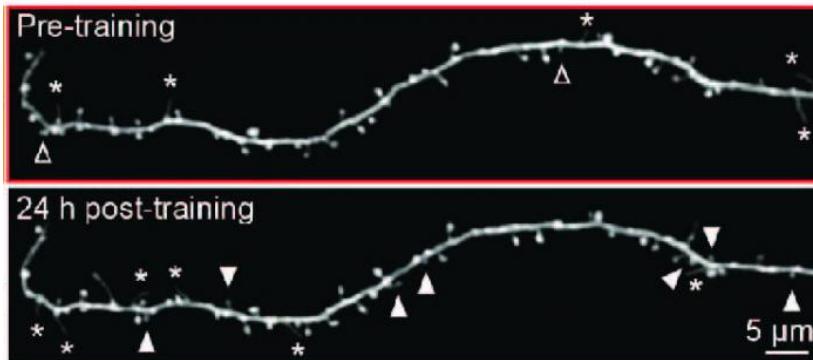
# What about long-term changes to synaptic strength?



Existing synapses can change their strength → **learning?**

# Information flow can be modified by changing the strength of existing cells ... or by forming new ones

New synapses can form between previously unconnected cells → learning?

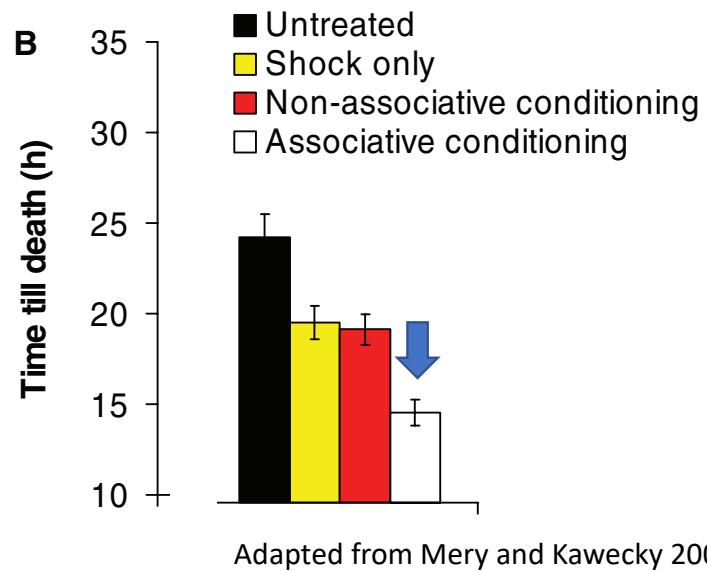


Yang et al, 2014

Next lecture: how new cells are born and synapses formed during **development**

# When is the energy cost of synaptic plasticity worth it?

The energy cost of learning (white bar) was associated with earlier death in this *Drosophila* experiment.



*Natural selection will not favor the capacity for learning unless it increases fitness.*

*Go and rest your brain... have a great break!*

