

Lecture 12. Neurochemistry and Neuromodulation

Summary:

The slow actions of neuromodulators allow neurons and their synapses to have variable properties and functional flexibility rather than fixed properties. This helps generate the behavioral flexibility in our everyday movements. Any neurotransmitter can act as a neuromodulator by binding to a modulatory receptor, which evokes effects that are slow, subtle, biochemically complex and use physiological mechanisms that are quite different from fast transmitter actions. The typical modulatory receptor is a G-protein-coupled receptor, called a metabotropic receptor: acting through the intermediary G proteins, they trigger a cascade of biochemical events in the neuron using second messenger molecules such as cAMP, phospholipid metabolites and calcium that last far longer and spread far wider through the neuron than a standard transmitter action. Physiologically, modulators can increase or decrease the strength of synapses mediated by other transmitters.

Neuromodulators can bind to receptors on the pre-synaptic terminal and alter the amount of neurotransmitter released in response to an action potential, or they can bind post-synaptically to alter the response to the neurotransmitter. Modulators can also change the firing properties of neurons, evoking oscillatory behavior, bistability, varied post-inhibitory rebound, etc. Neuromodulators evoke these changes by altering the activity of voltage-sensitive and leak ion channels, as well as by altering intracellular enzyme activity and even gene expression.

Learning Objectives

1. To know the main groups of neurotransmitters and modulators, their major functions, and the basic characteristics that distinguish neuromodulator action from neurotransmitter actions.
2. To understand the basics of signal transduction, the biochemical steps by which binding of the modulator to its receptor evokes broad and varied changes in enzyme and channel activity in the cell.
3. To understand the physiological mechanisms of modulator action, including their ability to affect the properties of voltage-dependent ion channels, and to act on leak channels.

Reading Assignment

Note: you DO NOT have to memorize all of the transmitters and their ligands, or all of the G protein second messenger pathways. See the lecture slides for details for what you need to remember for an exam.

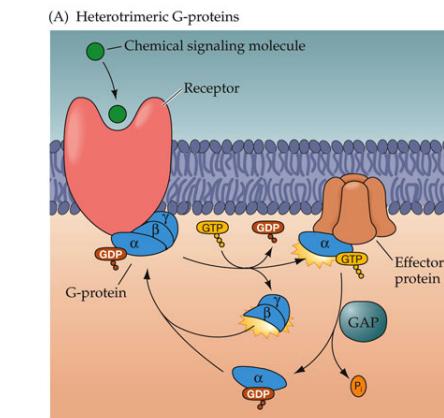
Bear et al., B:129, Fig 5.17; B:139, Fig. 5.22; B:171, Fig. 6.24; B:173, Fig. 6.27; B:175, Fig. 6.30; B:176, Fig. 6.31.

Lecture Outline

A. Neuromodulators

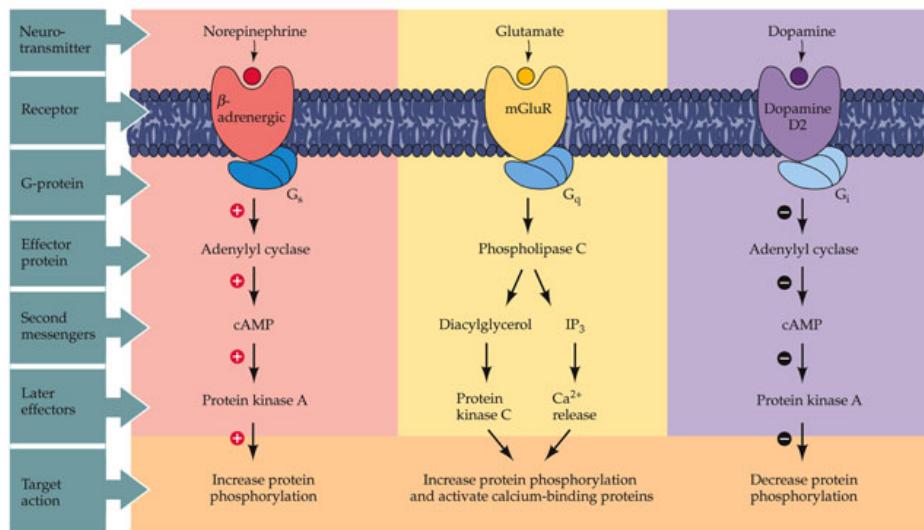
As usual, **the specificity of the response is a function of the receptor, not the compound.** Neuromodulatory synapses have a number of distinguishing features:

1. **Slow time course**—can last seconds, minutes, or hours.
2. Actions can be **subtle**.
3. They can act to **change the intrinsic properties of neurons.**
 - a. Can change the properties of voltage-sensitive ion channels
 - b. Can alter the number of ion channels in the membrane
4. They typically act via **complex biochemical mechanisms.**
 - a. Modulatory receptors are (almost) never ion channels themselves.
 - b. A cascade of biochemical steps called signal transduction leads from the modulator to the altered ion current
 - c. Intracellular binding domains that allow the receptor to bind and interact with a specialized signal-transducing protein called a **G protein**.
5. Neuromodulators act by a variety of **unusual physiological mechanisms.**
 - a. Some ion channels are direct targets of G protein subunits
 - b. In many cases, the G proteins activate enzymes that synthesize **second messengers**, small molecules that can diffuse throughout the cell carrying the signal of modulator activation. These include cAMP, cGMP, nitric oxide, calcium, lipids such as diacylglycerol, and phosphoinositides such as IP₃.
 - c. Second messenger systems can interact with each other.
 - d. If the cAMP level is high enough, it can activate new cascades of enzyme activity that can eventually lead to long term **changes in gene expression**.
6. There are several advantages of this biochemical cascade mechanism:
 - a. **it amplifies** the signal many thousand-fold
 - b. **it prolongs** the signal over seconds to hours
 - c. **it diffuses the signal spatially** so that regions of the cell that do not have modulator receptors can be affected.



NEUROSCIENCE, Fourth Edition, Figure 7.5 (Part 1)

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NEUROSCIENCE, Fourth Edition, Figure 7.6

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Study Questions:

1. Explain the differences between the action of a molecule (such as acetylcholine) when it is acting as a fast neurotransmitter and a slow neuromodulator. What are the advantages of each mechanism of action?
2. What are the advantages of the cascade of signal transduction events that occur in response to metabotropic receptor activation?
3. 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.
4. What is the reversal potential of a modulatory action that causes a conductance decrease in potassium channels? Explain your answer.
5. If a neuromodulator shifts the voltage dependence for the voltage-activated sodium channels by 10 mV in the hyperpolarizing direction, what consequences will this have for the firing activity of the neuron?

Lecture 12: Neurochemistry and neuromodulation

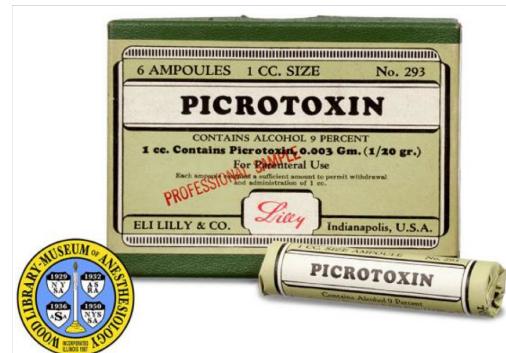
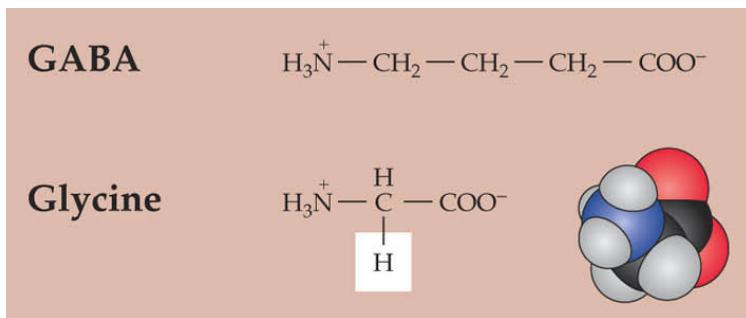
Learning goals:

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Clicker question

What effect would you expect if you give a human a drug that *blocks* GABA receptors?

- A. Cells are more excitable
- B. Cells are less excitable
- C. No change in excitability

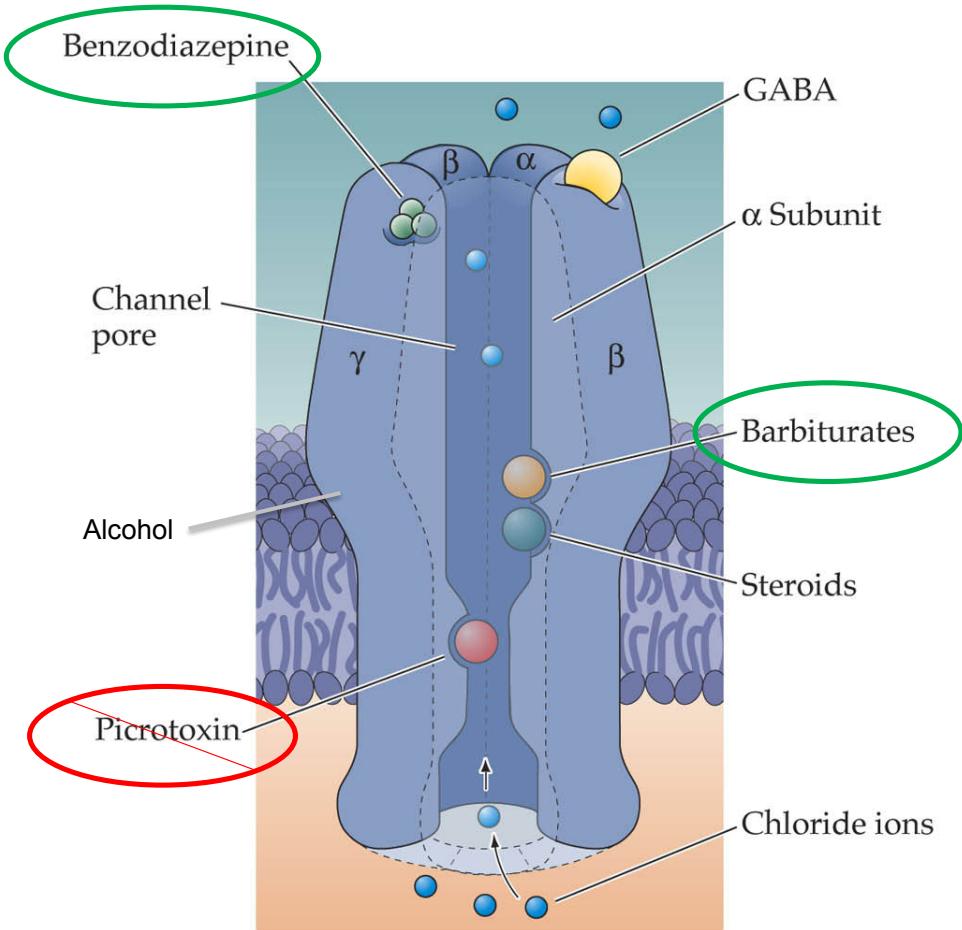


Convulsions and death!

Recap: what to remember from pre-lecture video on neurochemistry

1. In vertebrates, major fast excitatory transmitters in brain glutamate (and aspartate), at NMJ acetylcholine
2. In vertebrates, major fast inhibitory transmitters are GABA and glycine
3. Many other signaling molecules are also employed
4. Receptors can have both endogenous and exogenous agonists
5. The action of a ligand is determined by the receptor

Multiple ligands can act at on receptor simultaneously

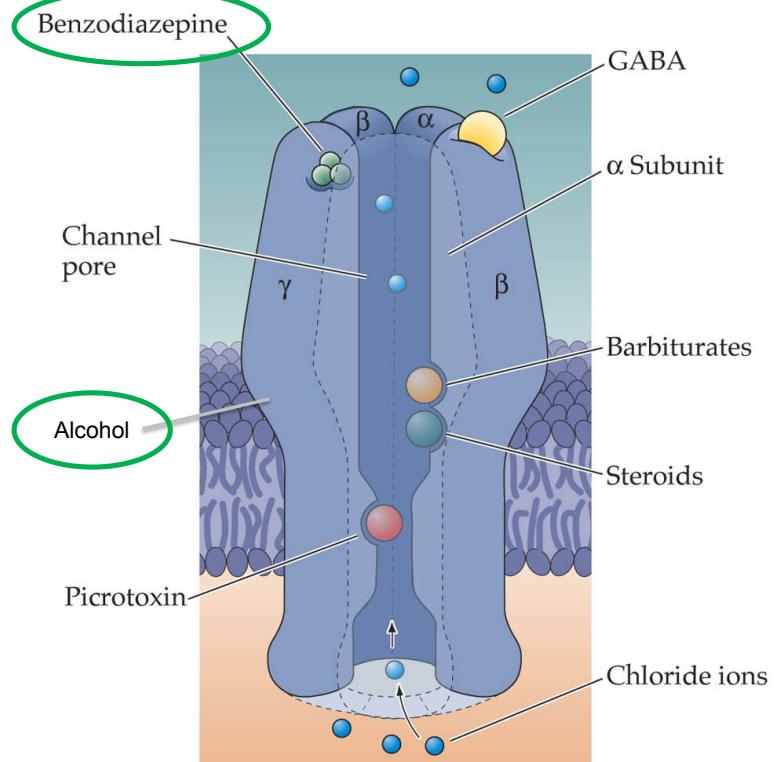


Clicker question

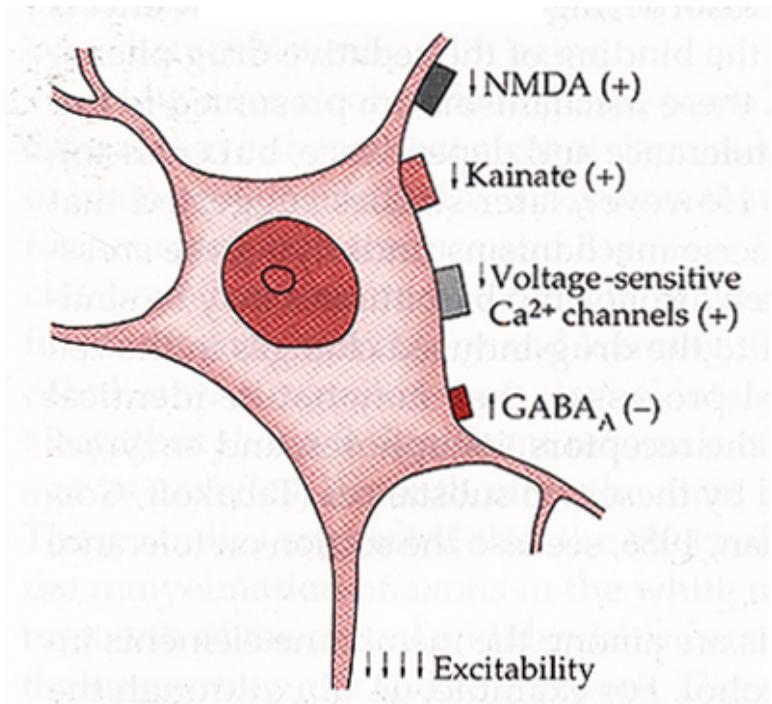
Which combination of drugs can you tell would be a terrible idea?

- A. Alcohol and valium
- B. Alcohol and Ritalin
- C. Valium and cocaine
- D. Barbiturates and nicotine

These are all pretty bad ideas, but alcohol and valium both potentiate the same channel (GABA), a combination with the strongest synergistic effect.



Many exogenous ligands act at multiple receptors



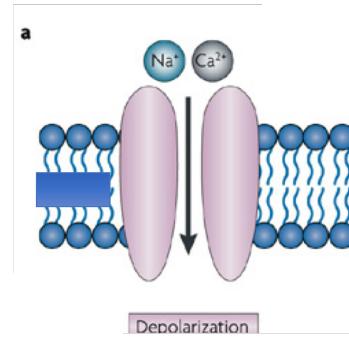
Some receptors require the presence of more than one transmitter to be activated

Some drugs enact their effects by binding to multiple receptors.

Three types of chemical synapses

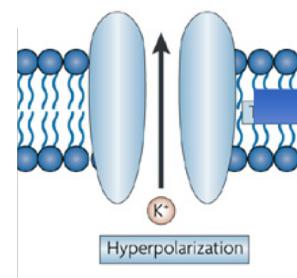
Excitatory

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.

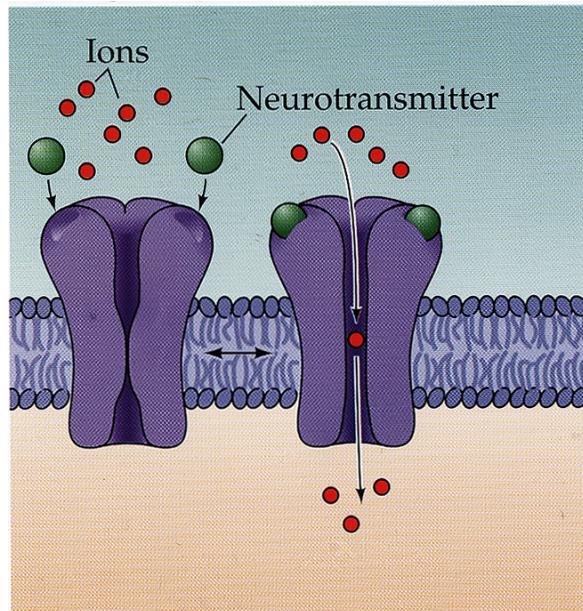


In mammals:
include glutamate,
aspartate,
acetylcholine

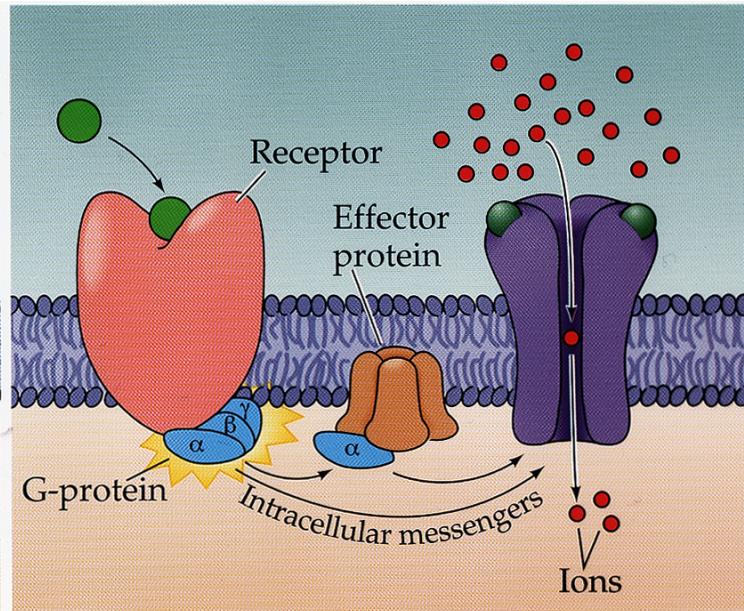
In mammals:
include GABA,
glycine

Many molecules (including transmitters) can be a neuromodulator

Ionotropic → Transmitter



Metabotropic → Modulator



Can be: any fast transmitter but glycine (so far), plus DA, NE, 5HT, all the peptides

Neuromodulation is SLOW ...

Takes 100s of milliseconds to start, can last seconds, minutes or hours

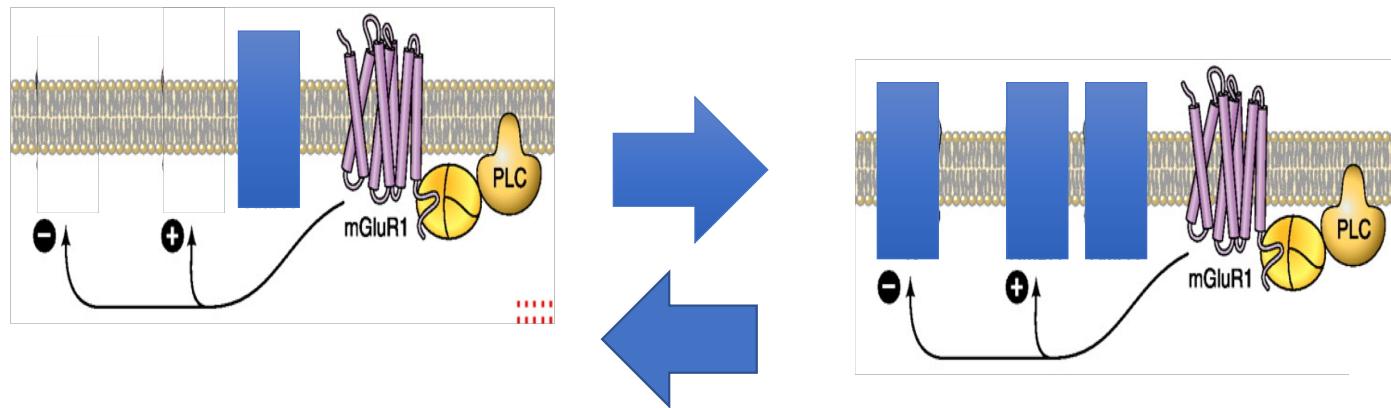
... and can be SUBTLE ...

Neuromodulators sometimes act almost invisibly by effects only measurable when the cell is in a particular voltage range, or when another synapse is active

... and can change many cellular and synaptic properties

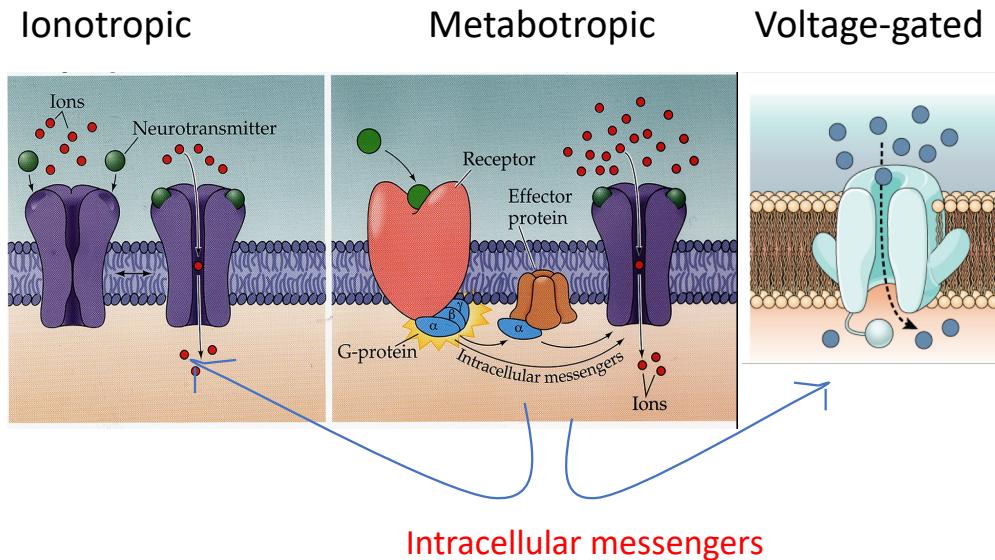
Modulation can alter synaptic strength or membrane excitability

1. Change number of activatable channels



Modulation can alter synaptic strength or membrane excitability

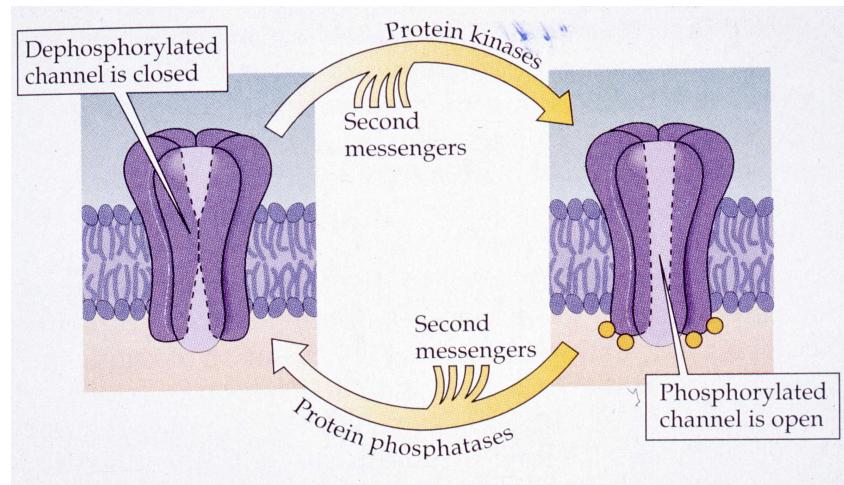
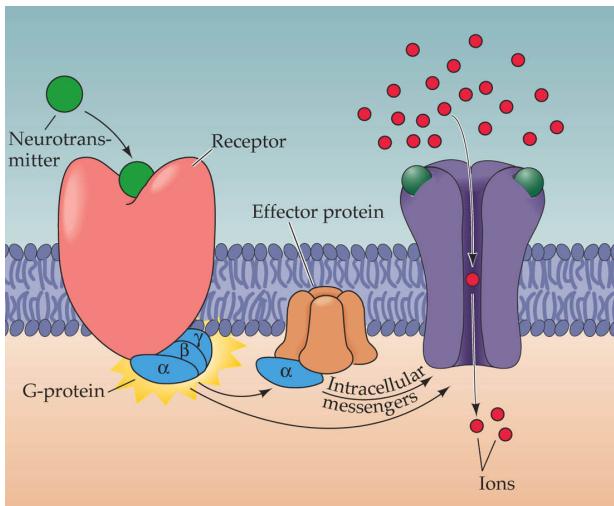
1. Change number of activatable channels
2. Change activation state, voltage dependence, kinetics, permeability, etc. of ion channels



Modulation can alter synaptic strength or membrane excitability

1. Change number of activatable channels
2. Change activation state, voltage dependence, kinetics, permeability, etc. of ion channels
3. Open or close ion channels via effector proteins

Any of these changes can take place on the presynaptic membrane, the postsynaptic membrane, or far away from synapses to change overall excitability of cell

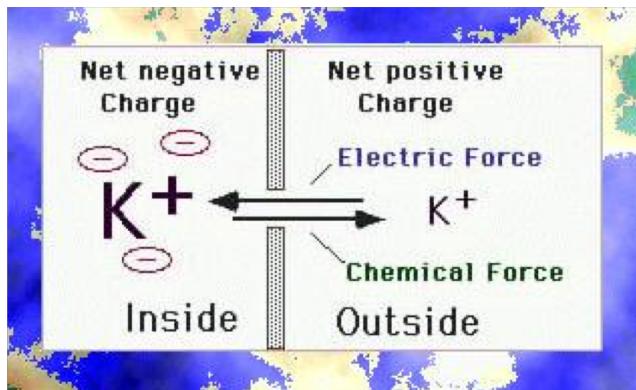


Clicker question

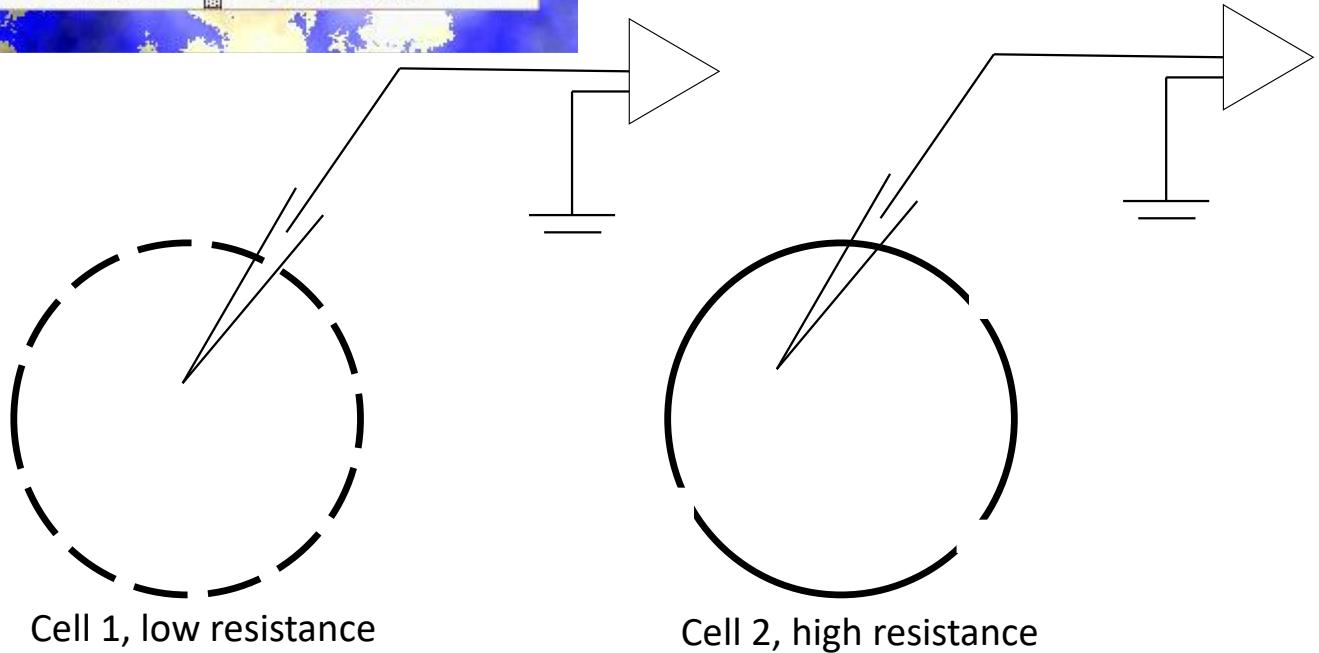
At one synapse, the neuromodulator serotonin (5-HT) acts to remove open leak potassium channels from the postsynaptic cell membrane. What effect would this have on the postsynaptic cell?

- A. Makes the cell more excitable
- B. Makes the cell less excitable
- C. No change in excitability

What effect would removing leak K channels have on membrane resistance?

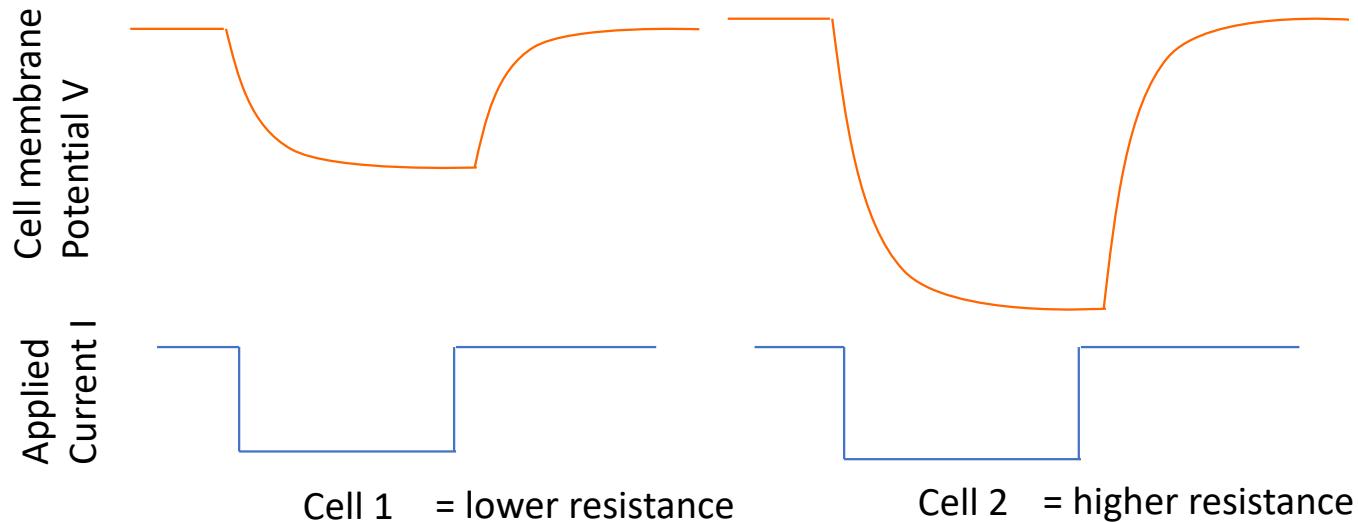


When any ion's permeability is high, it tends to keep the membrane potential near its reversal potential



Clicker question

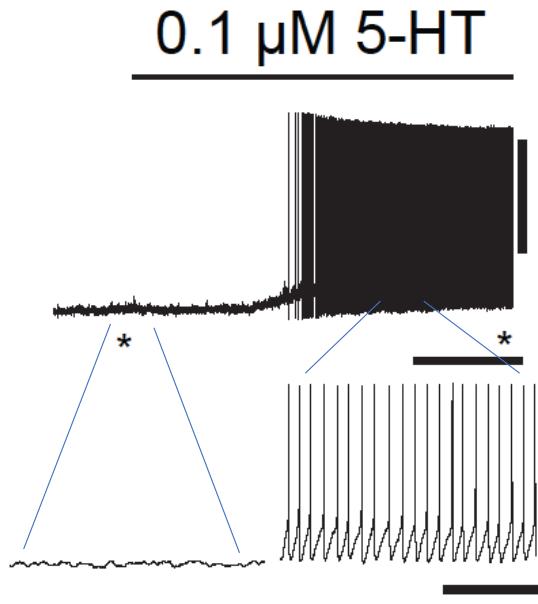
If you apply the same current and observe these voltage changes in two different cells, which cell has the *higher* resistance?



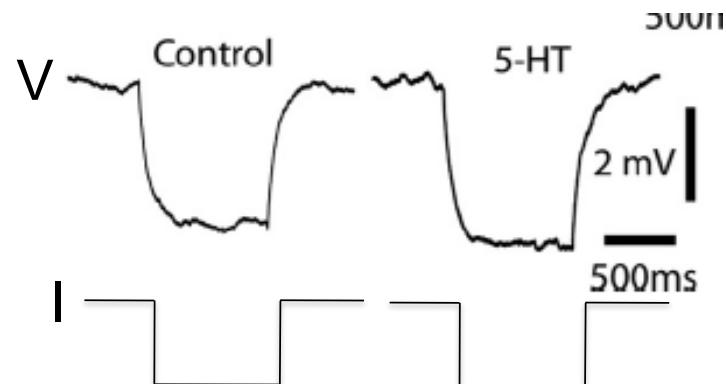
- A. Cell 1
- B. Cell 2

$$V = IR$$

What effect would removing leak K channels have on excitability?



Increased membrane resistance resulting from reduced number of open leak potassium channels



Zhong and Harris-Warrick, 2007

$$V = IR$$

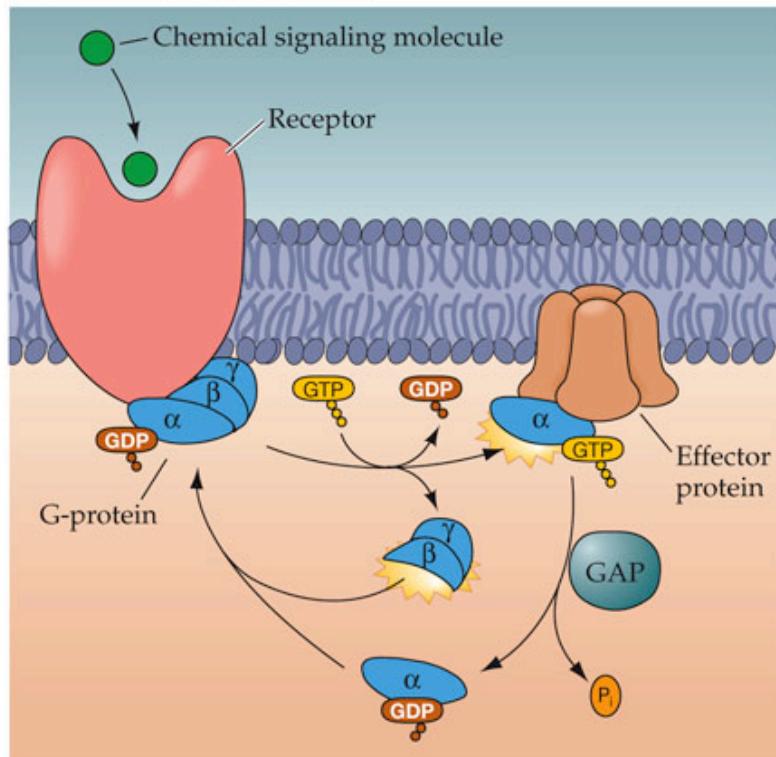
Clicker question

At one synapse, the neuromodulator serotonin (5-HT) acts to decrease the conductance of leak potassium channels in the postsynaptic cell membrane. What effect would this have on the EPSPs in the postsynaptic cell?

- A. Eliminate them
- B. Increase their amplitude
- C. Decrease their amplitude
- D. Reduce temporal summation to a train of pre-synaptic APs

Review: neuromodulation acts through G-protein-coupled receptors

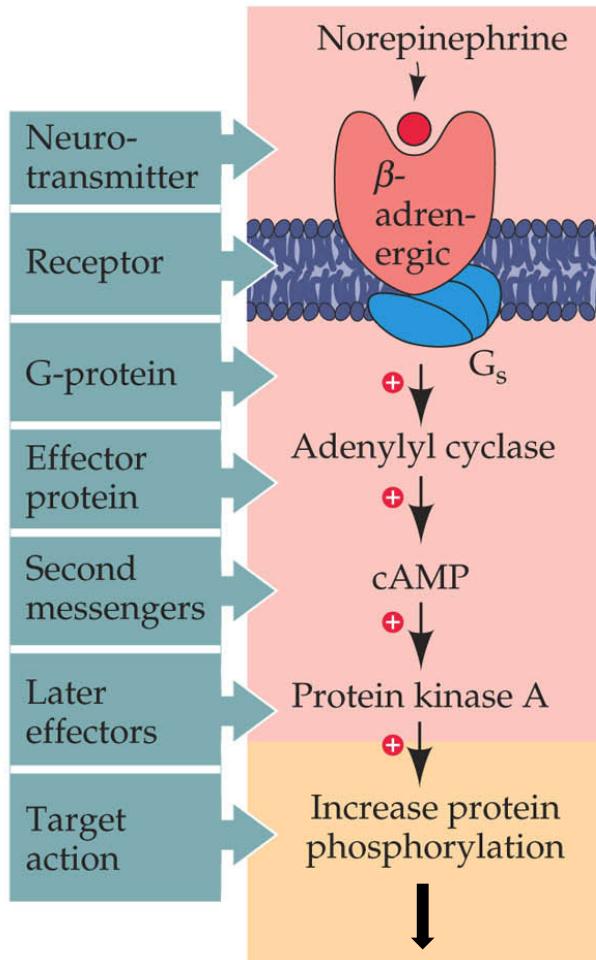
(A) Heterotrimeric G-proteins



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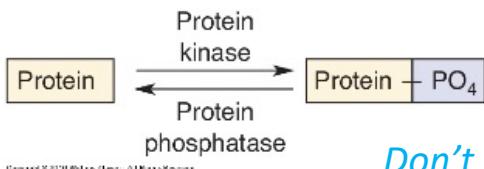
Neuromodulation acts through second messengers



-- Binding to receptor activates a chain of biochemical reactions in the cell, generating second messenger molecules

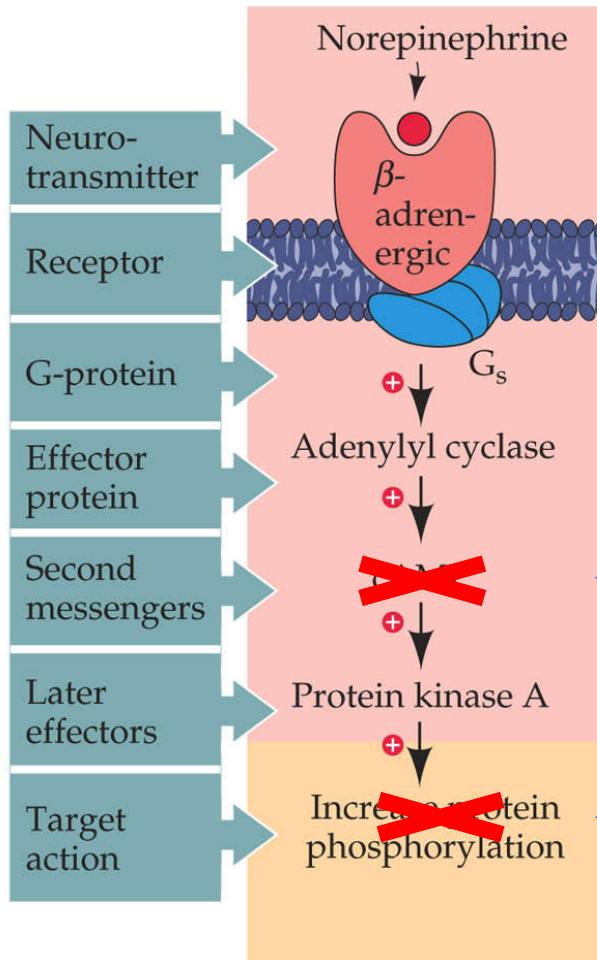
-- Most often, this involves activation of protein kinases which phosphorylate proteins

-- Phosphorylation can change the state of the cell (for example, by opening or closing an ion channel)



Don't memorize this pathway, but be ready to analyze the effects of changes to it.

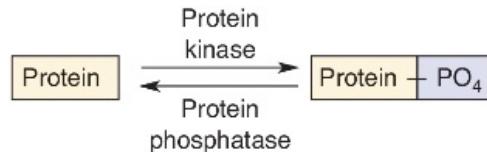
Neuromodulation acts through second messengers



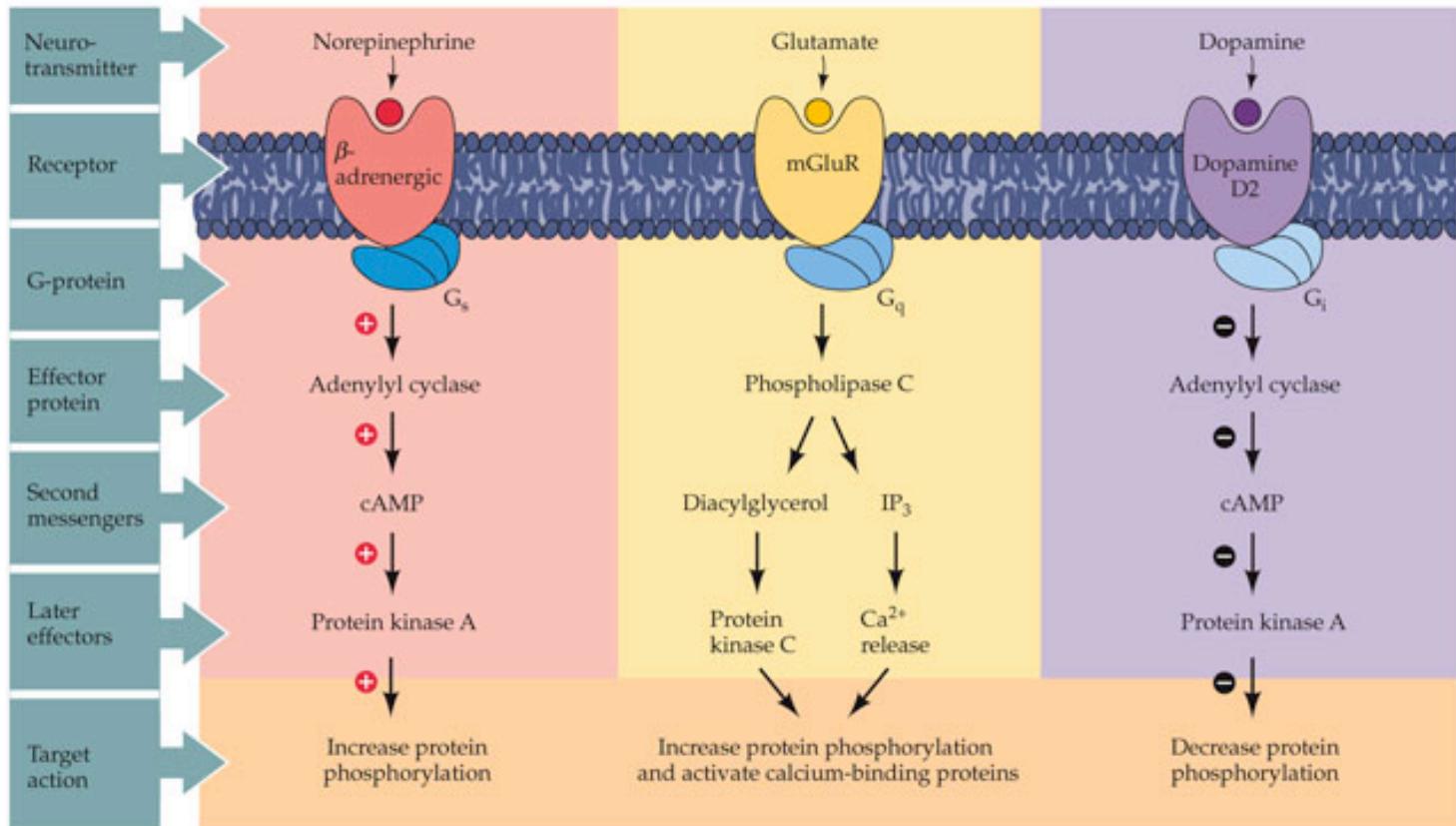
END modulatory signal by:

Phosphodiesterases: shut down cAMP

Phosphoprotein phosphatases:
remove phosphates from proteins

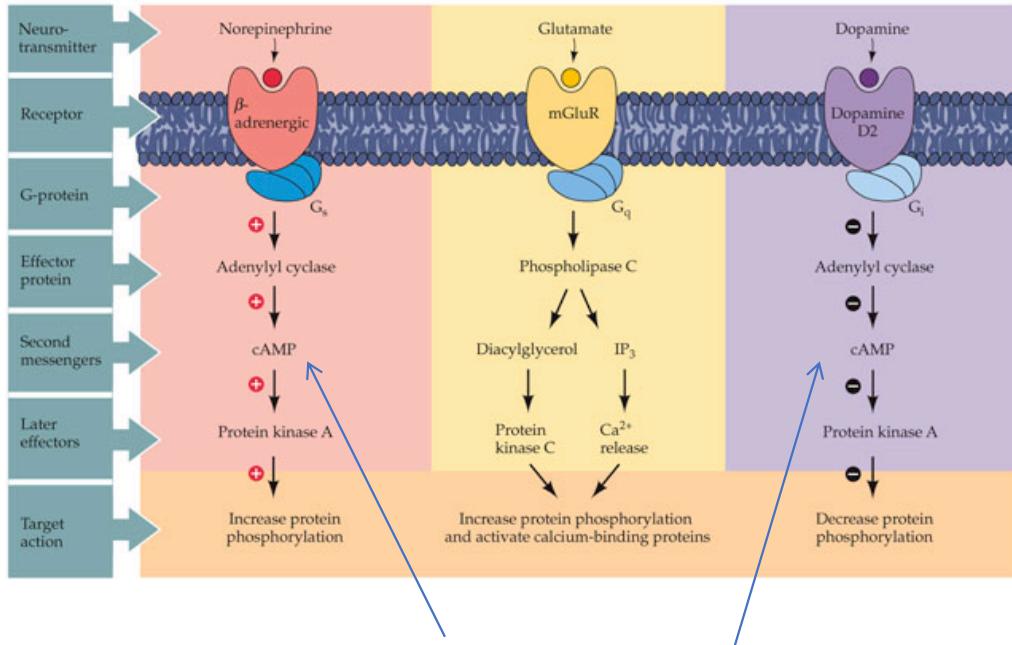


Neuromodulation uses common biochemical pathways, and simultaneously activated pathways can interact



Clicker question

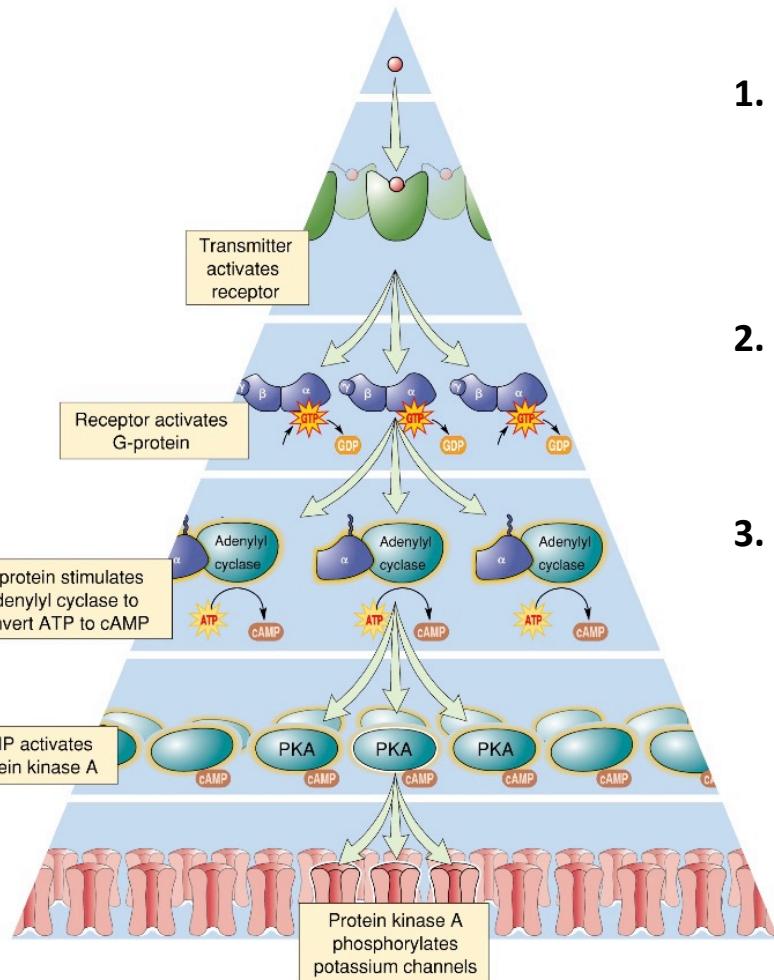
In one neuron, serotonin increases excitability by activating the G_s pathway. The same neuron receives dopamine synapses, which activate the G_i - pathway. What effect will dopamine have on the serotonin-induced excitability increase?



- A. Enhance the effect of serotonin
- B. Reduce the effect of serotonin**
- C. Make the serotonin effect last longer
- D. No effect

Opposite actions on the cAMP signaling cascade

Second messenger systems can lead to signal amplification



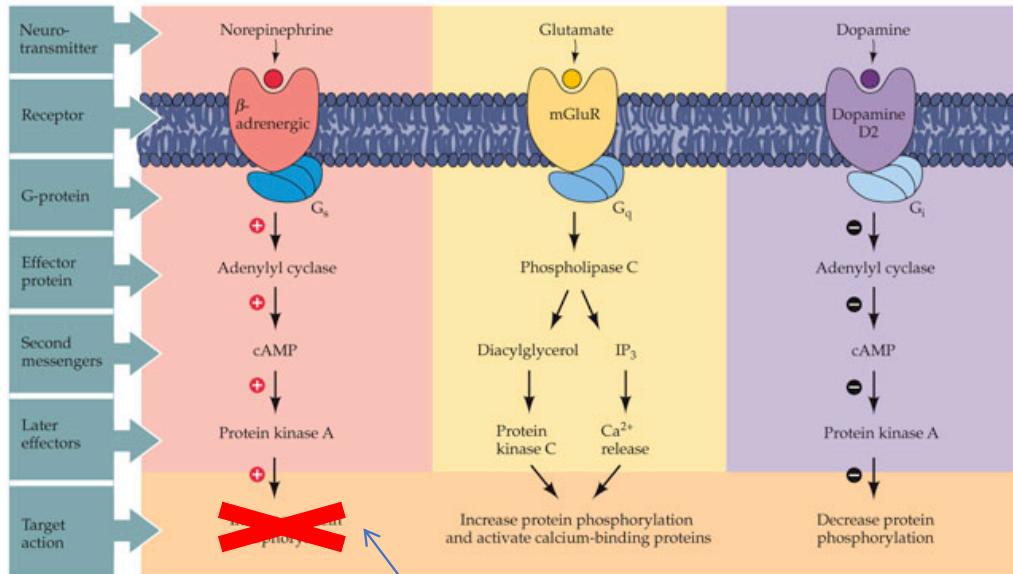
- 1. Amplification:** from one molecule of modulator to thousands of activated proteins
- 2. Temporal spread:** biochemical changes can last from minutes to hours
- 3. Spatial spread:** second messengers can spread elsewhere in the neuron, including the nucleus

These same pathways play roles in:
Sensory transduction
Development
Learning and memory

Clicker question

In many neurons, dopamine activates DARPP-32, which then becomes a potent inhibitor of phosphoprotein phosphatase. What effect will this have on G_S-mediated modulatory responses?

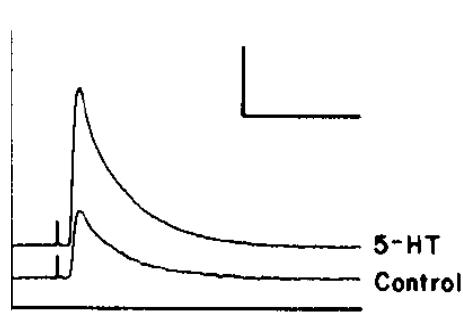
- A. Block them
- B. Make them smaller
- C. Make them last longer
- D. Make them larger and last longer
- E. Make them smaller and last for a shorter time



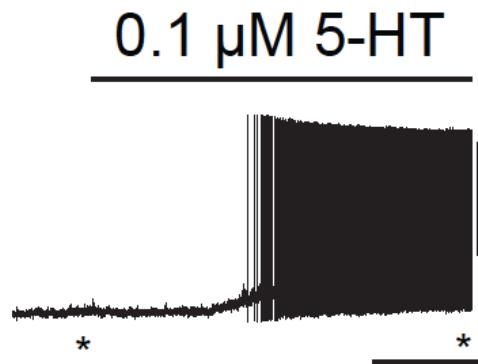
Phosphoprotein phosphatases: remove phosphates from proteins

Using these tools, neuromodulators can

1. Change the strength of synapses mediated onto neurons

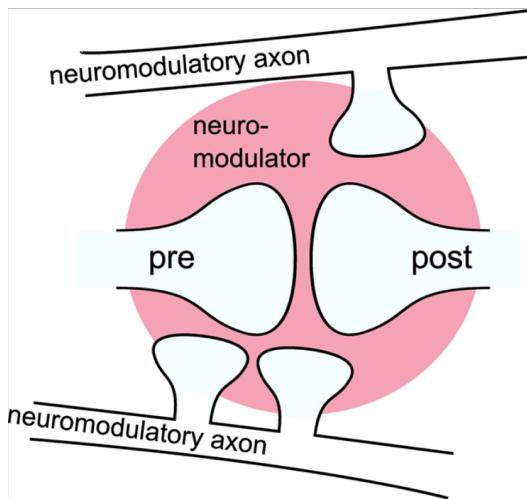


2. Alter the intrinsic firing properties of neurons



Neuromodulation can be local ...

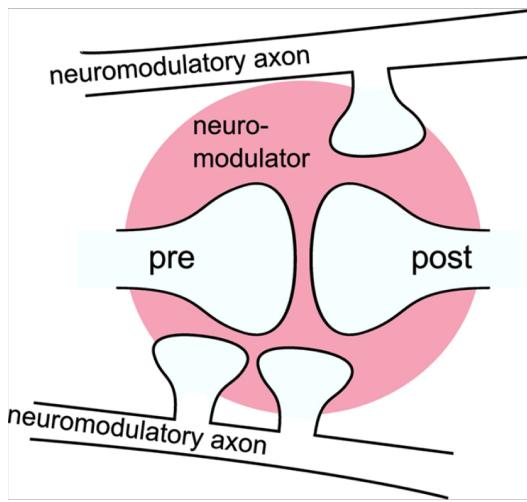
Single synapse: increase or decrease synaptic strength



Potjans et al. 2010

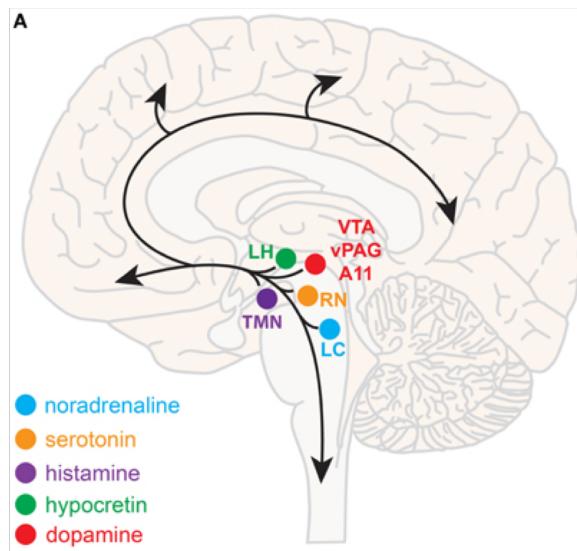
Neuromodulation can be local ...or change the entire brain state

Single synapse: increase or decrease synaptic strength



Potjans et al. 2010

Whole brain: sleep → wake

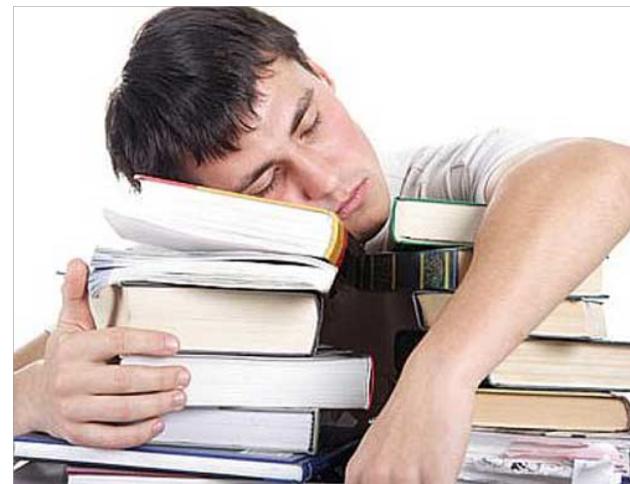


Chiu and Prober 2013

By changing the properties of the cells and synapses, neuromodulation can make networks flexible to change in response to different conditions

Neuromodulators involved in:

- Sleep
- Attention
- Empathy
- Drug addiction
- Reward
- Mate pair-bonding
- Mental disorders
- Learning and memory



By changing the properties of the cells and synapses, neuromodulation can make networks flexible to change in response to different conditions

Neuromodulators involved in:

- Sleep
- Attention
- Empathy
- Drug addiction
- Reward
- Mate pair-bonding
- Mental disorders
- Learning and memory



Summary

1. Any transmitter (except glycine, so far) can act as a modulator. The response depends on the receptor, not the transmitter structure.
2. **Slow** synaptic action: seconds → minutes → hours
3. **Subtle** action: effect may only be measurable when the neuron is in a particular voltage range, or when another synapse is active
4. Can **change the intrinsic firing properties of neurons, and the strength of other synapses onto the target neuron**, via complex electrophysiological mechanisms
5. Act via complex biochemical mechanisms within the cell: **Signal Transduction**

Next lecture: Plasticity

What are changes in synaptic strength for?