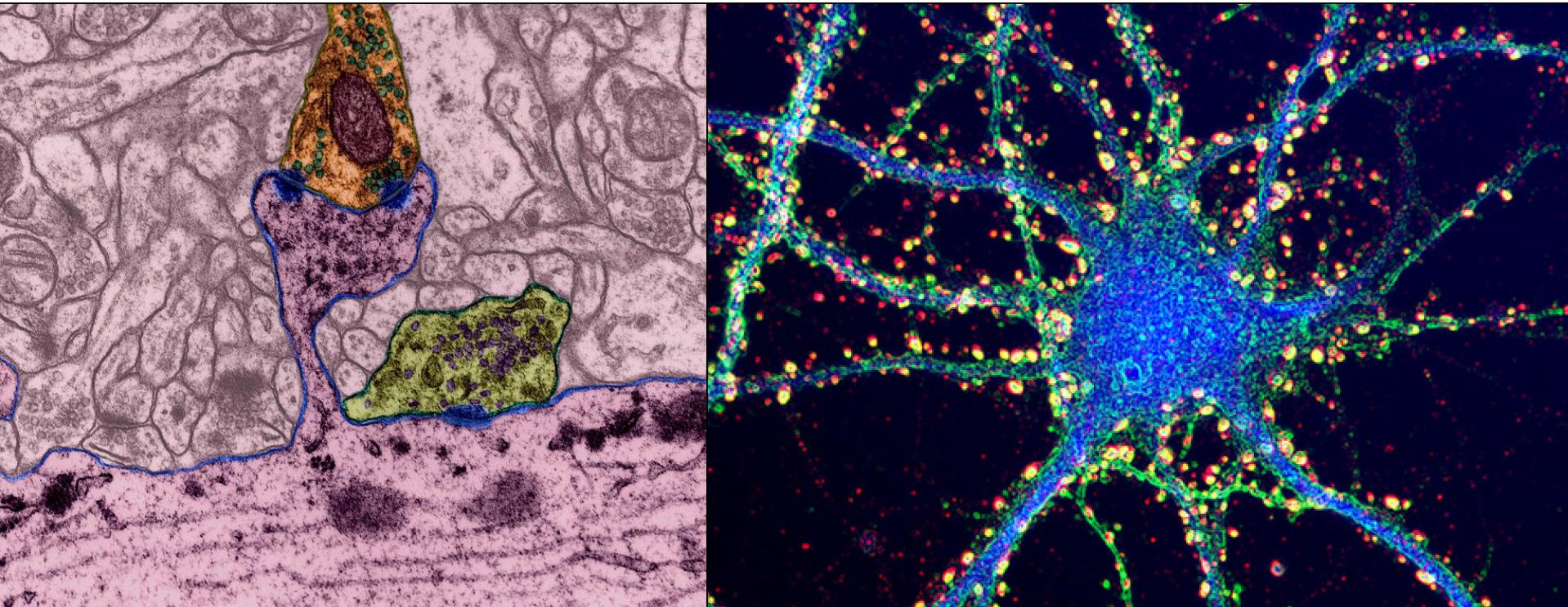
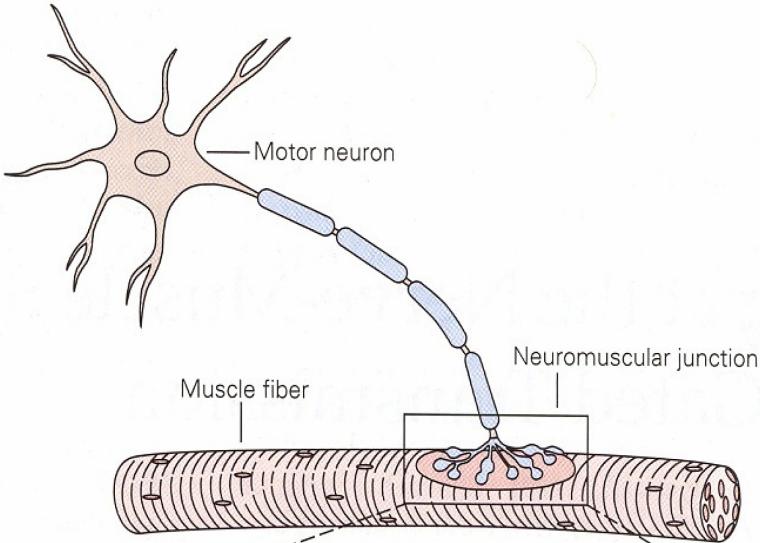


Chapter 13:

Synaptic Integration in the

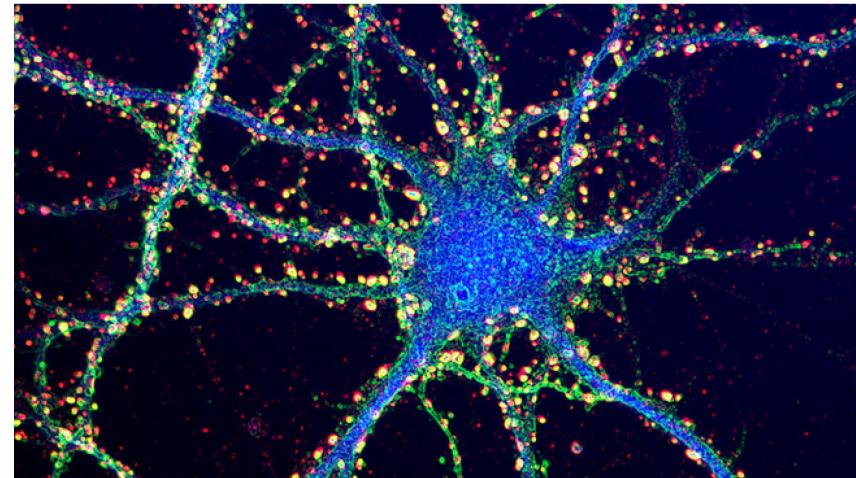
Central Nervous System





Neuromuscular Junction

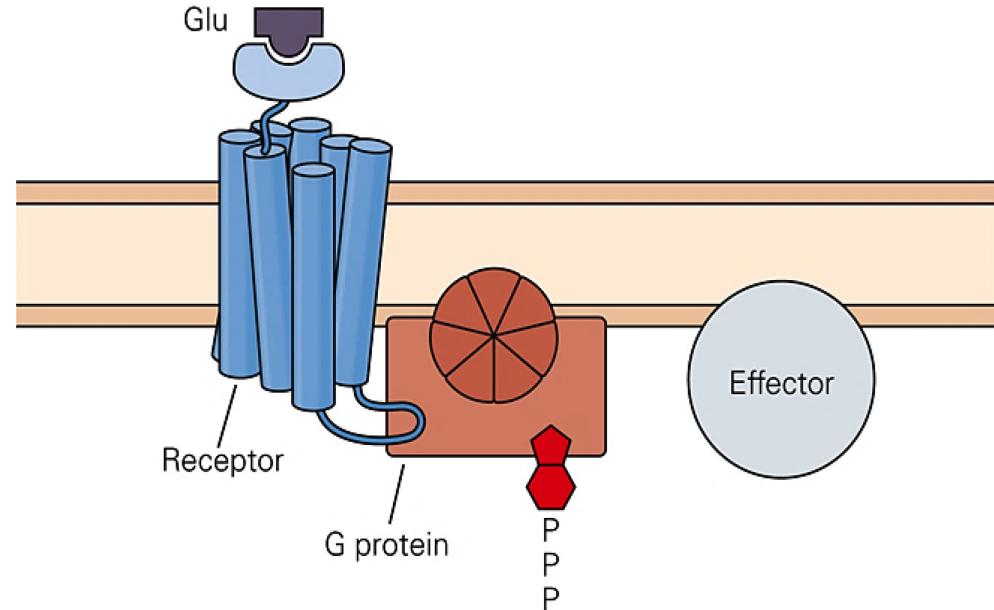
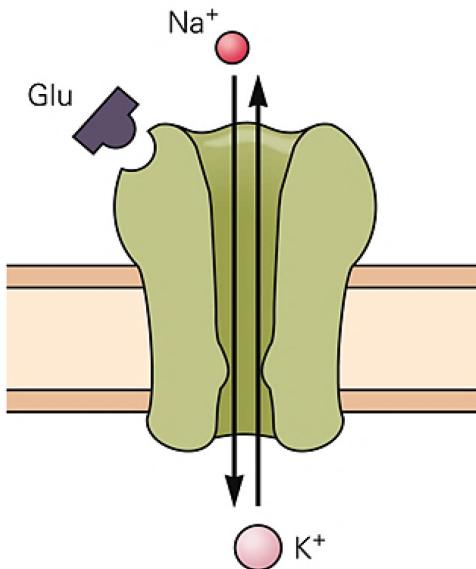
- Input from one motor neuron
- **Excitatory input only**
- One neurotransmitter (ACh)
- One receptor type (ionotropic nicotinic AChR)
- ~200 vesicles released
- Huge end-plate potential always causes an action potential in the muscle cell



CNS Synapses

- Input from hundreds or thousands of neurons
- **Excitatory (EPSP) or inhibitory (IPSP) input**
- Many different neurotransmitters
- Many different ionotropic and metabotropic receptors
- 1-2 vesicles released
- Small EPSPs or IPSPs (typically 0.2-0.4 mV) must summate to reach threshold

Receptor Types



Ionotropic receptors

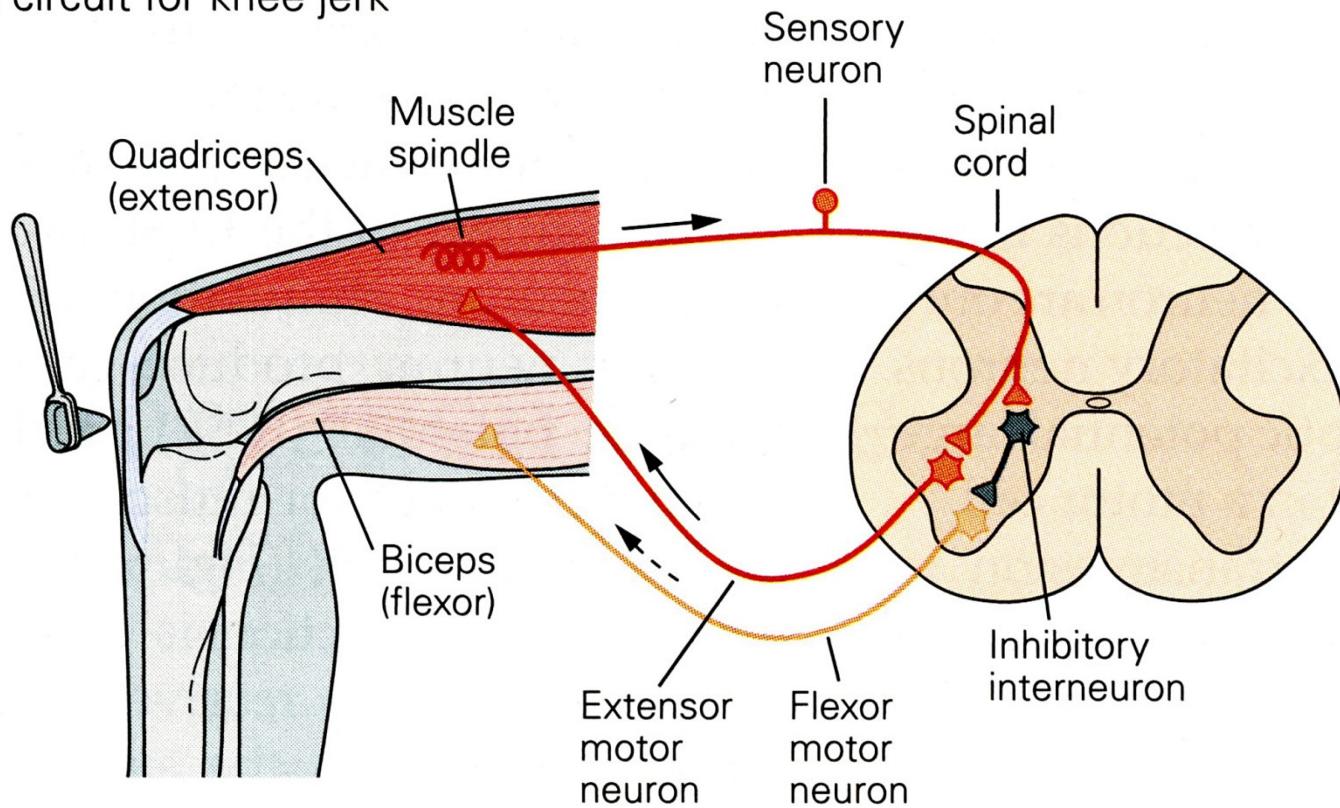
- Directly conduct ion flow
- Mediate rapid changes in membrane potential

Metabotropic receptors

- Activate second messenger systems
- Mediate slower but longer lasting changes in membrane potential and other cellular processes

Excitatory and Inhibitory Synapses

Stretch reflex circuit for knee jerk



EPSPs, EPSCs, IPSPs and IPSCs

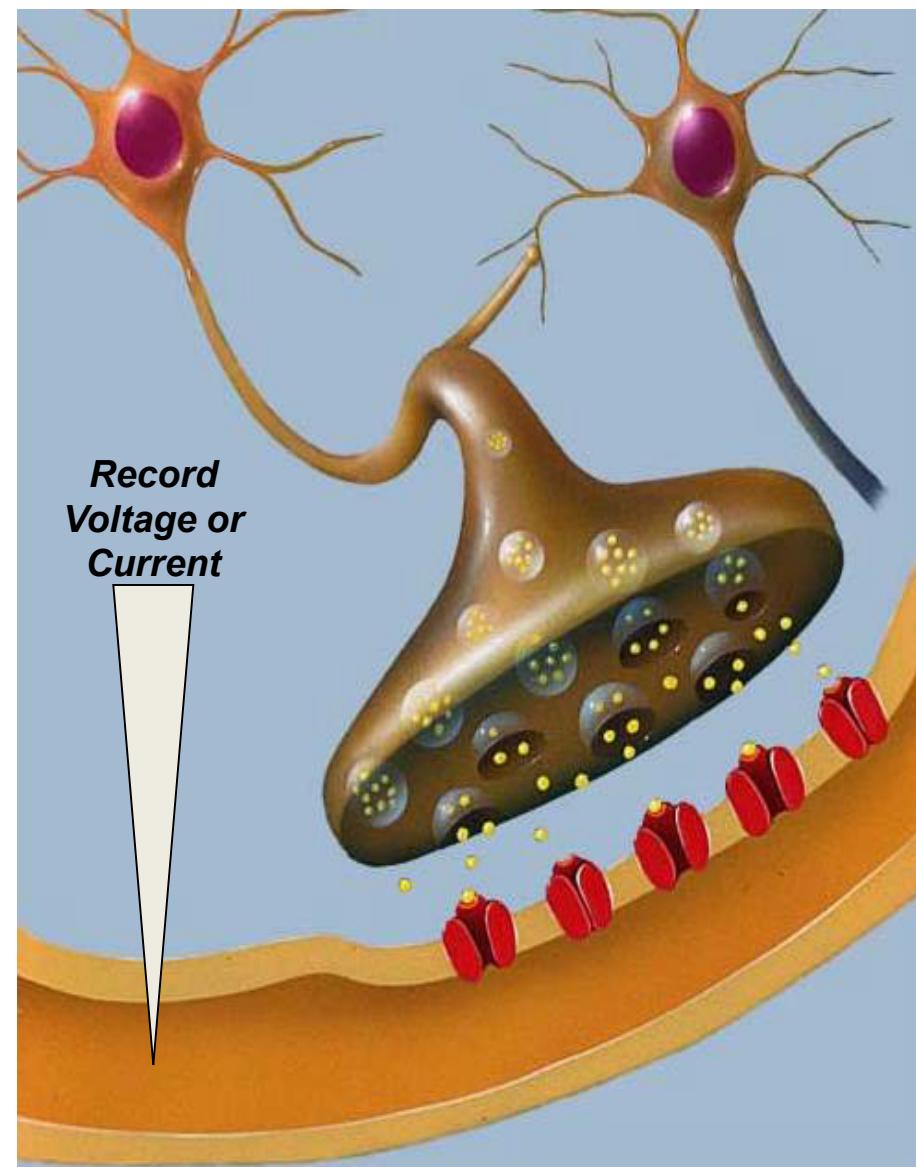
Change in voltage can be measured

In voltage clamp mode, currents are measured

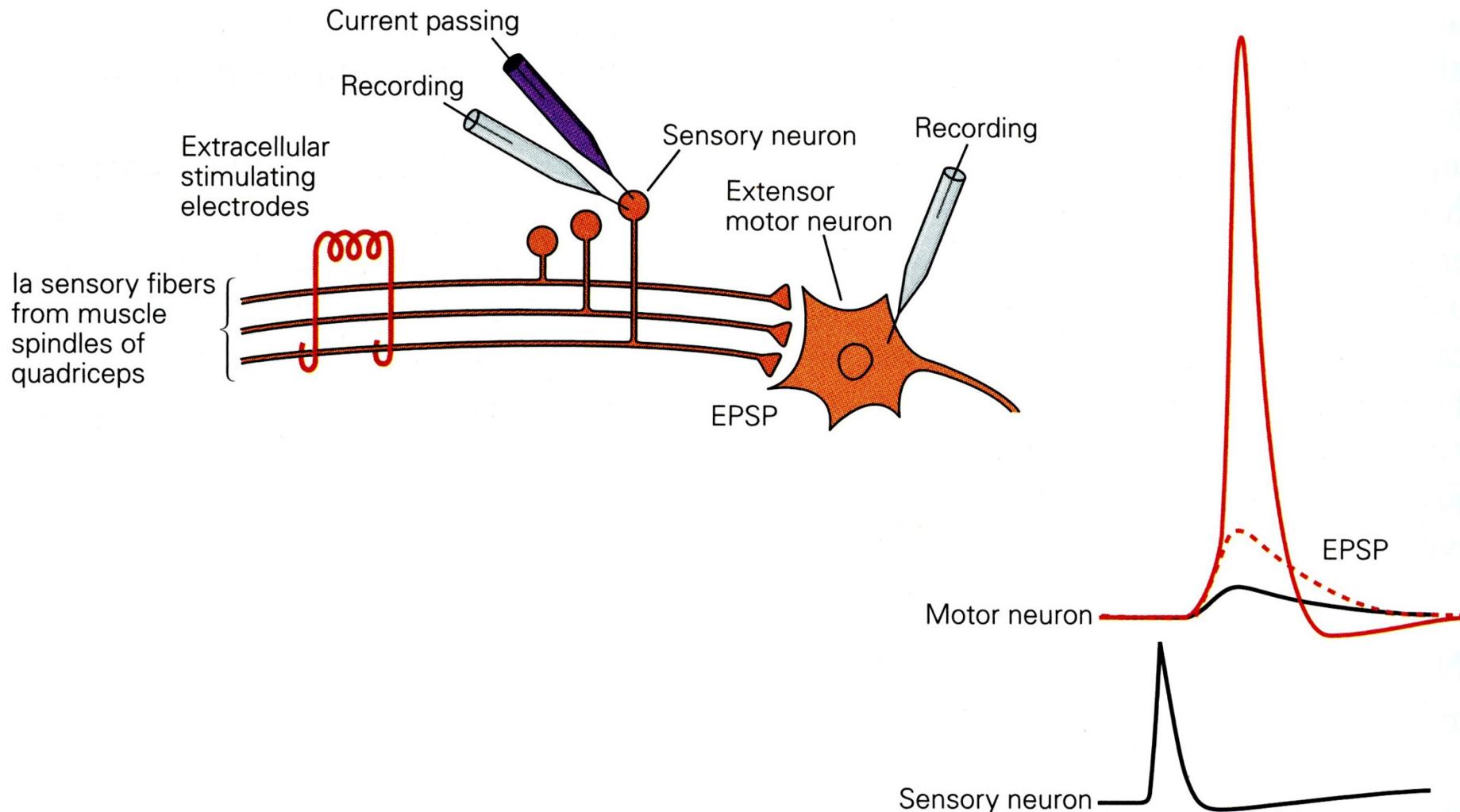
Excitatory Synapse



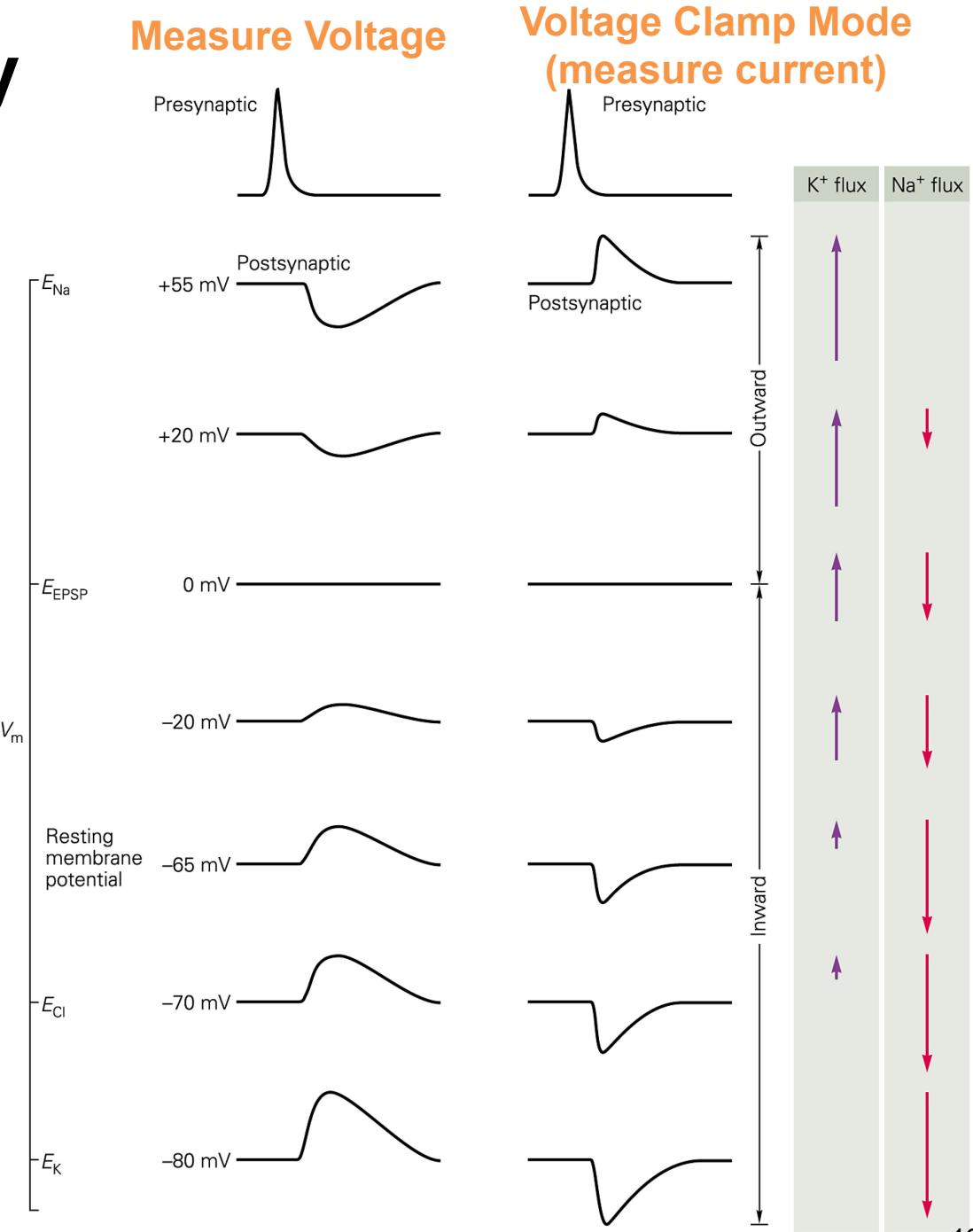
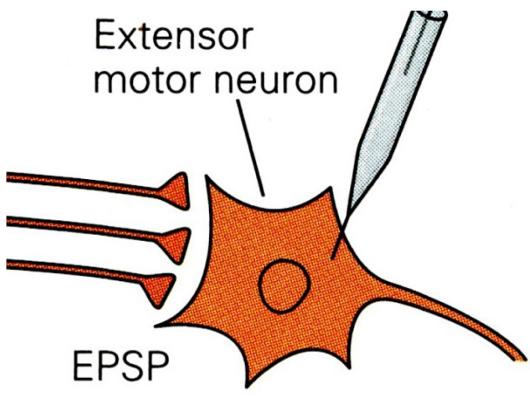
Inhibitory Synapse



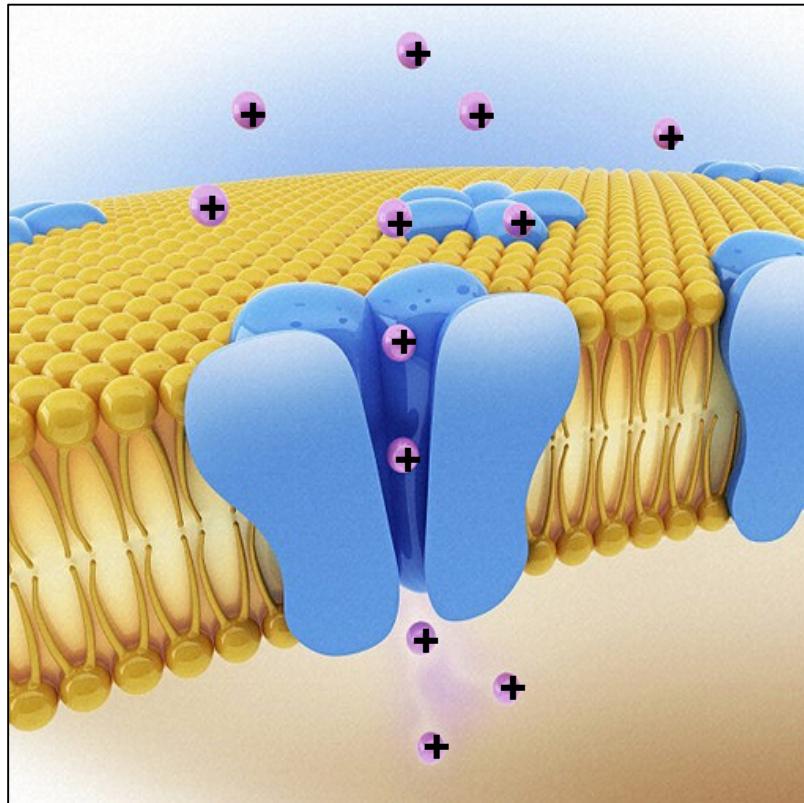
Excitatory Synapses



Electrophysiology at a Typical Excitatory Synapse



Excitatory Ionotropic Receptors are Non-Specific Cation Channels



Na⁺ and K⁺ permeable

- Nicotinic receptors (*most*)
- AMPA receptors (*most*)
- Kainate receptors
- 5-HT₃ receptors

Na⁺, K⁺ and Ca⁺² permeable

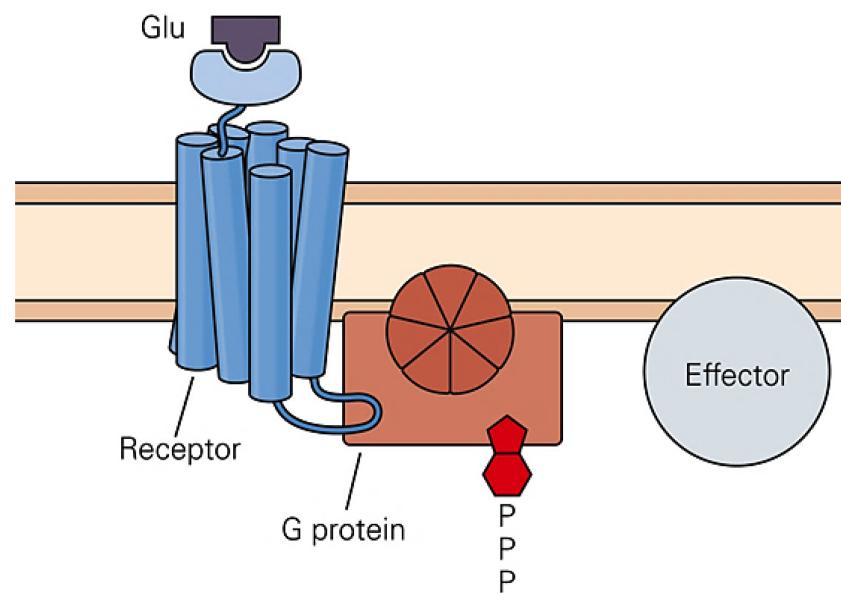
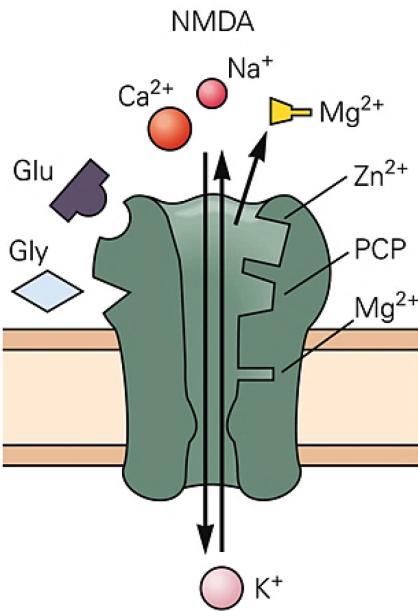
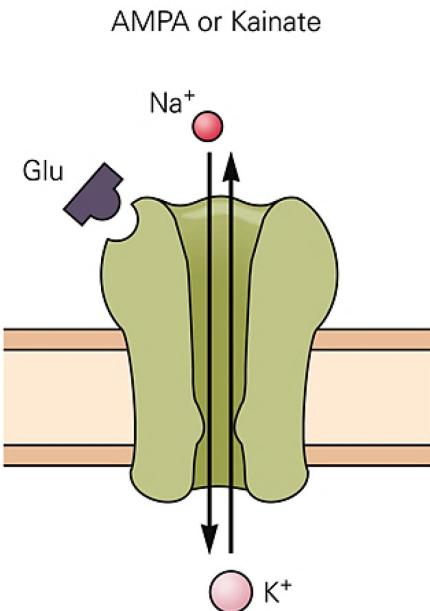
- NMDA receptors
- Some AMPAR and nAChR

The reversal potential of non-specific cation channels is 0 mV.

Why do these channels cause EPSPs?

Glutamate Receptors

Glutamate is the major excitatory transmitter in the CNS



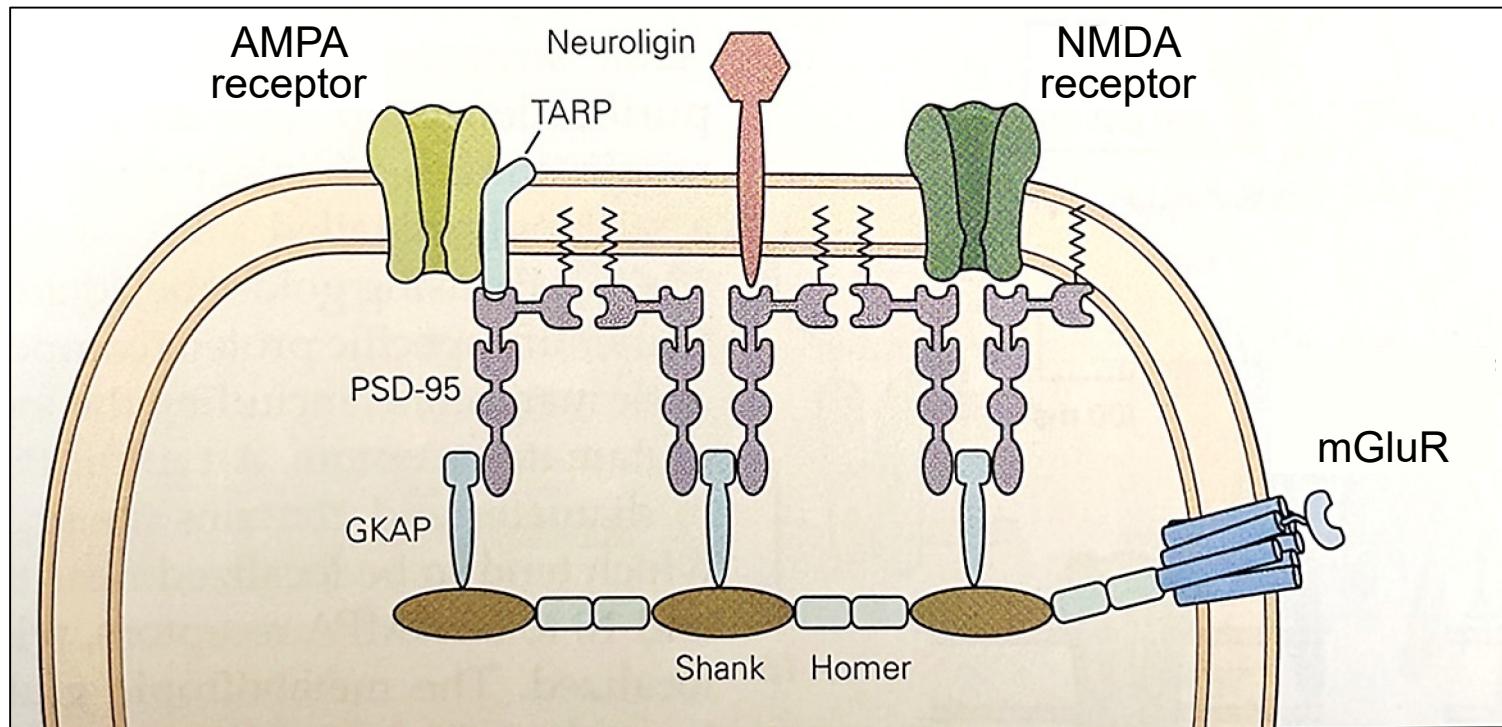
Ionotropic Glutamate Receptors

- NMDA receptors
 - AMPA receptors
 - Kainate receptors
- } Non-NMDA receptors

Metabotropic Glutamate Receptors (mGluR's)

- Excitatory or inhibitory, depending on the second messenger pathway and ion channels that are impacted

Glutamate Receptor Location

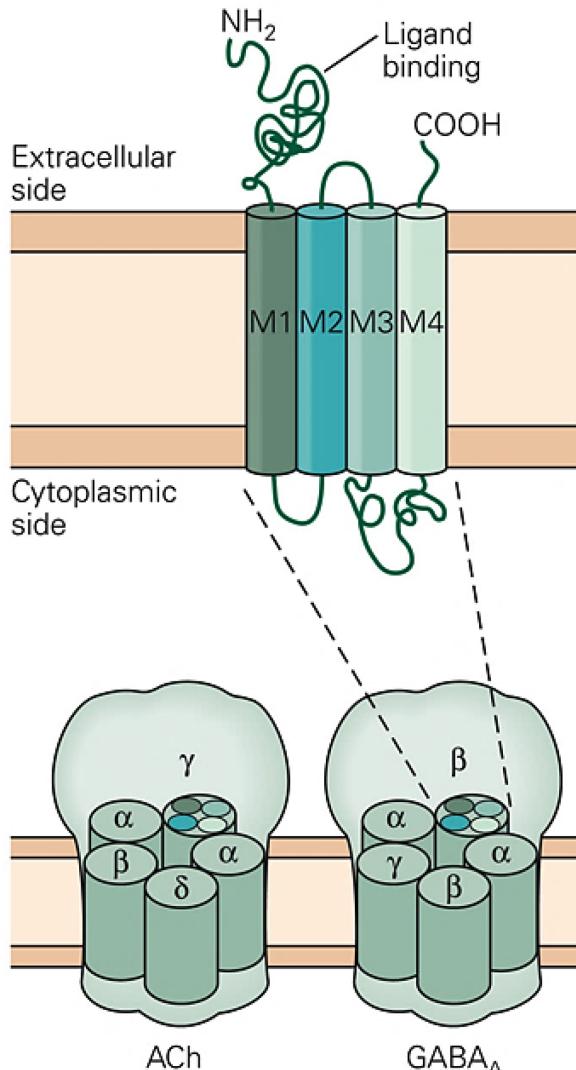


Glutamatergic synapses are often on spines

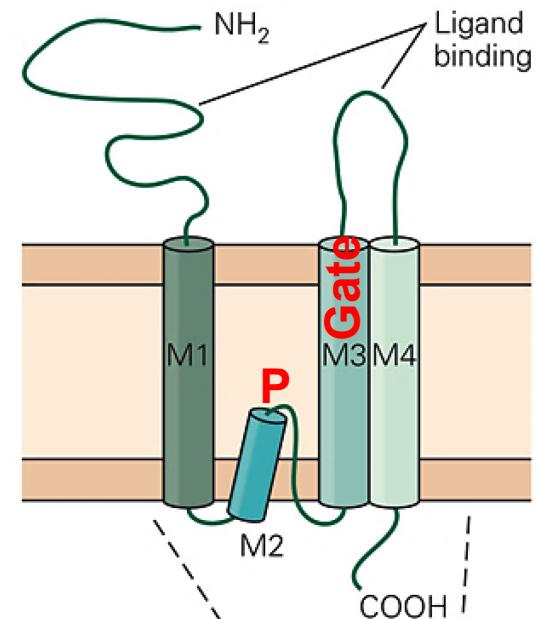
- Ionotropic receptors are typically in the *postsynaptic* membrane, held in place by *PSD-95*
- Metabotropic receptors are often in the *perisynaptic* membrane, held in place by *Homer*

Ionotropic GluR Structure

A ACh, GABA, and glycine receptor-channels



B Glutamate receptor-channels



GluR Subunits

- GluA1-4 (AMPA)
- GluK1-5 (Kainate)
- GluN1-3 (NMDA)

Ionotropic GluR Subunit Structure

Amino-terminal domain

- Assembly of the four GluR subunits
- Modulation of receptor function
- Synapse development and organization

Ligand-binding domain

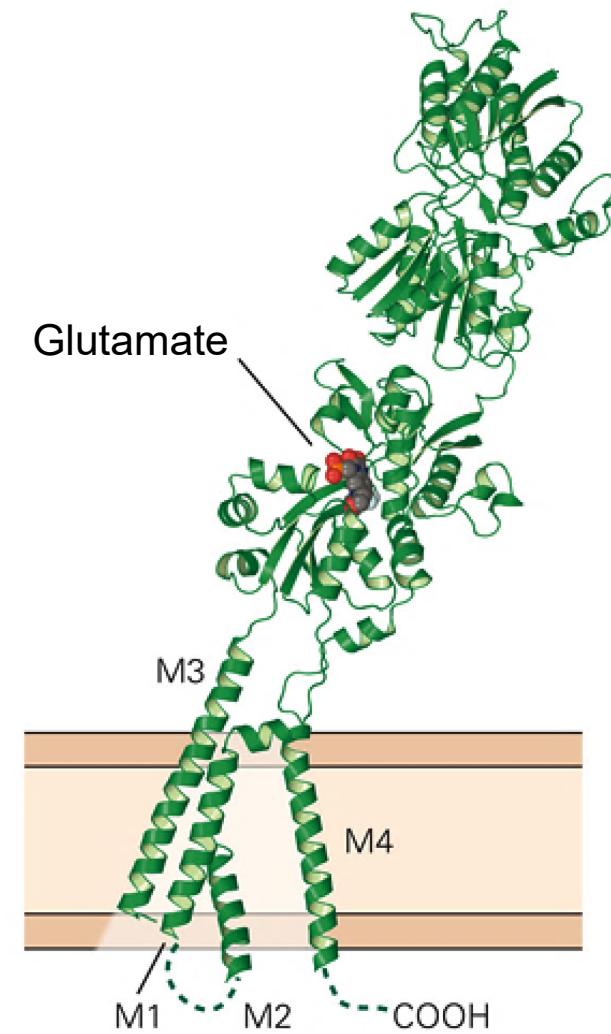
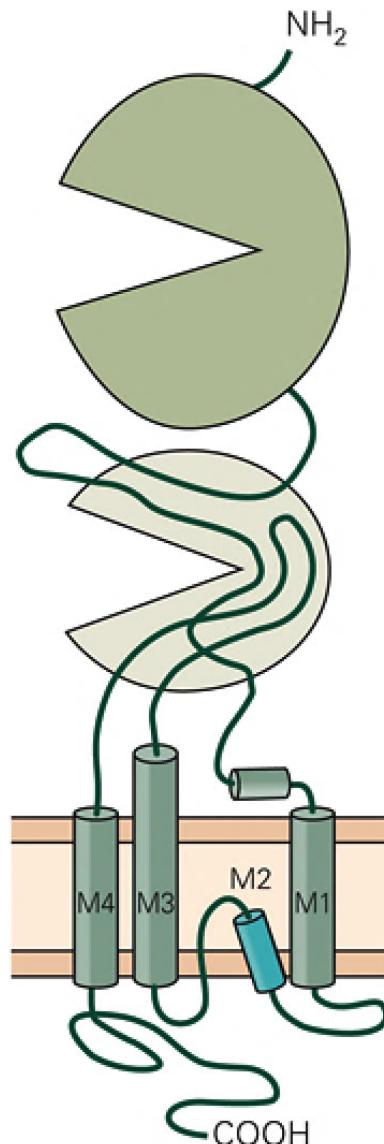
- Bind neurotransmitter

Transmembrane domain

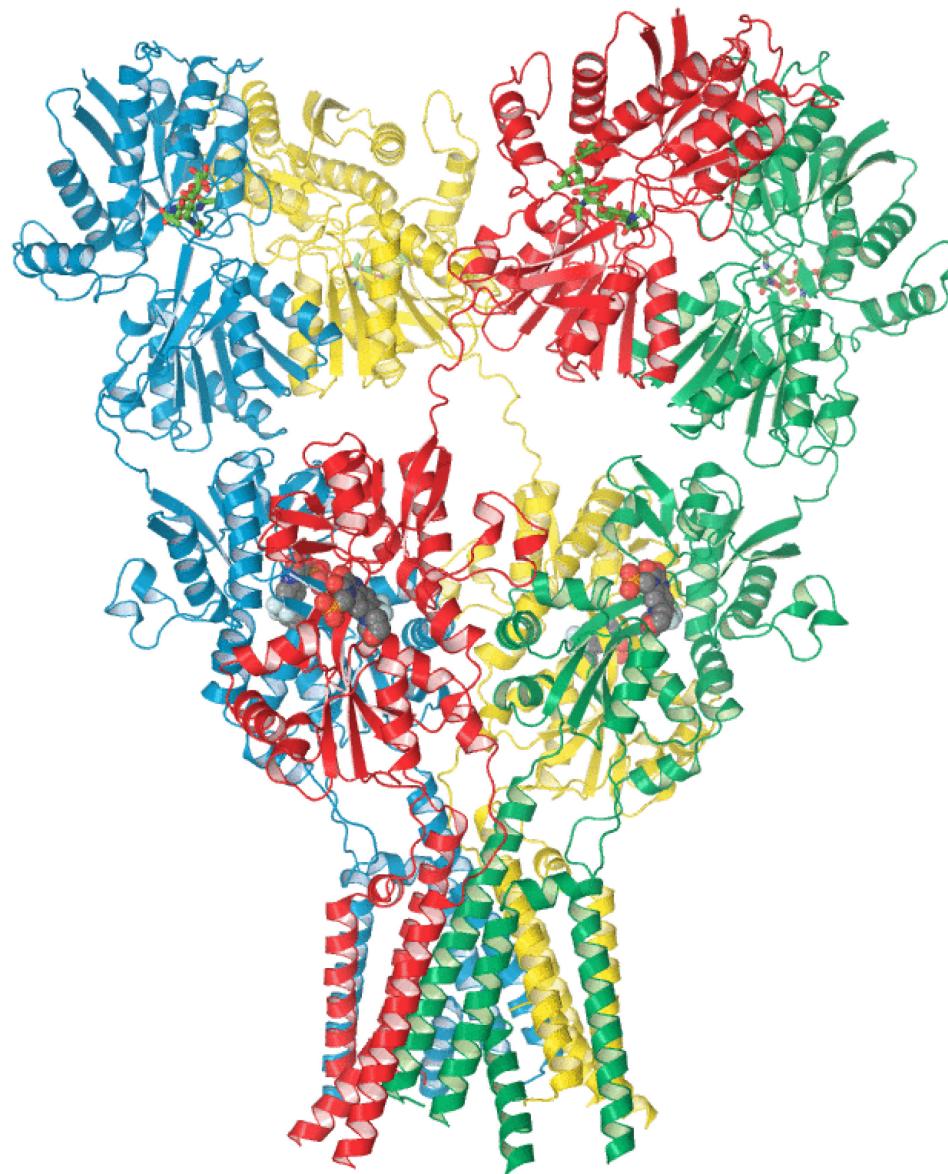
- M2 is the selectivity filter
- M3 is the gate

Intracellular domain

- Receptor regulation, trafficking and localization

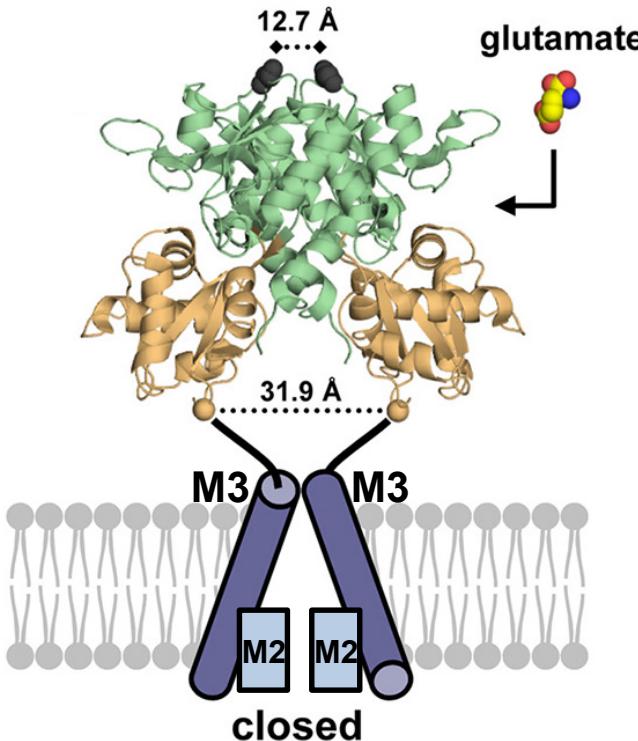


Ionotropic GluR Structure

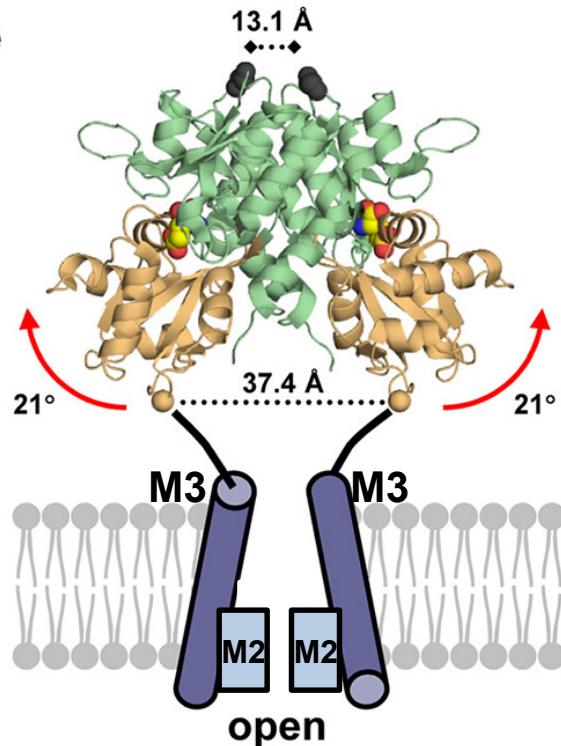


Ionotropic GluR Activation & Desensitization

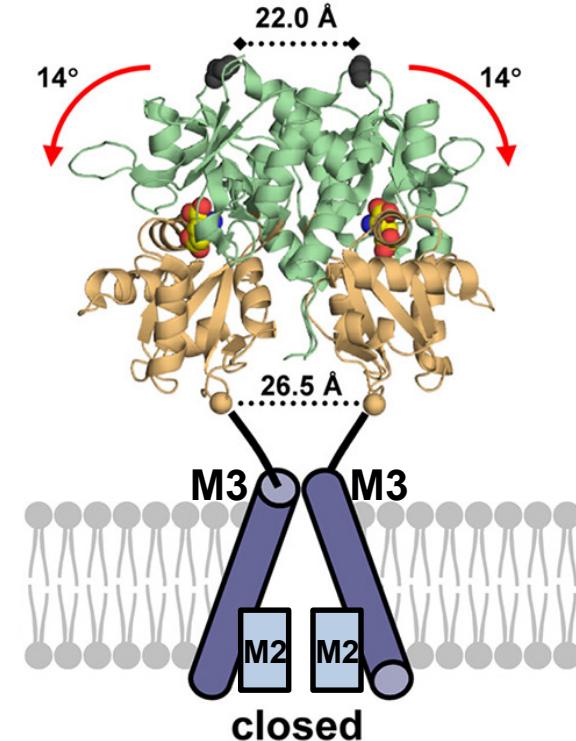
Closed & Resting



Open



Desensitized



Ligand-binding clamshells are open and M3 gates are closed

Ligand-binding clamshells close, pulling the M3 gates open

Closed ligand-binding clamshells sag downward, pushing the M3 gates closed

NMDA Receptors

Agonists

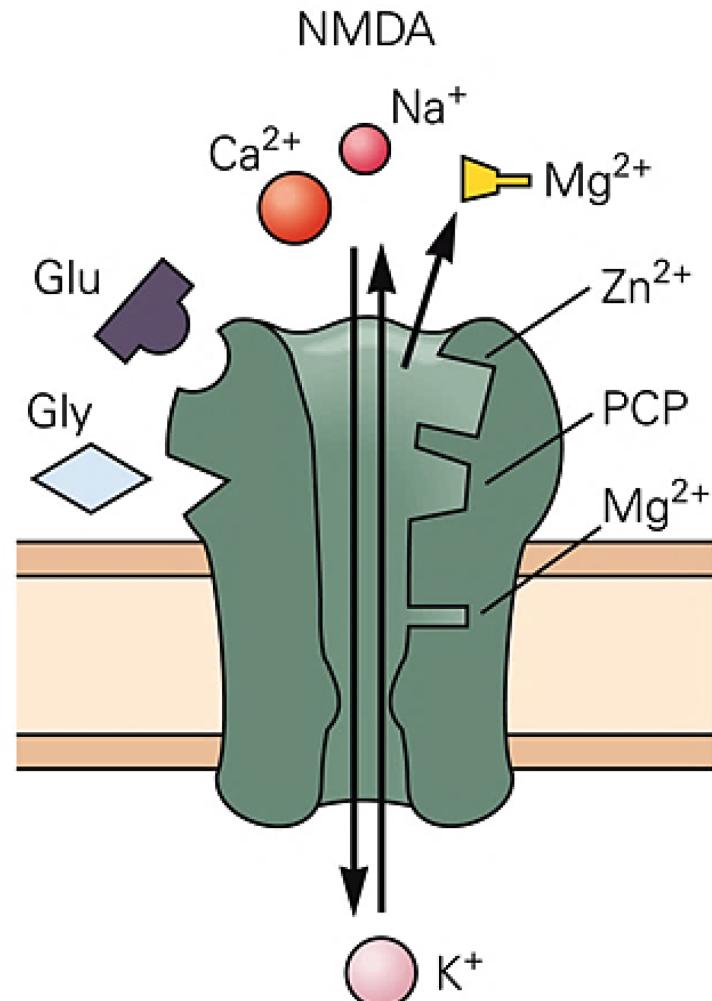
- Endogenous: Glutamate
- Exogenous: NMDA
- Glycine or D-serine is a required co-agonist

Antagonists

- MK801, APV, PCP and Zinc

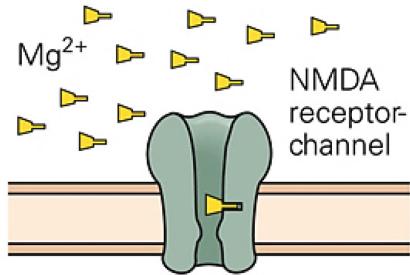
Mg²⁺ blocks the pore at RMP

- Depolarization of the cell to -40 to -45 mV is required to remove this block

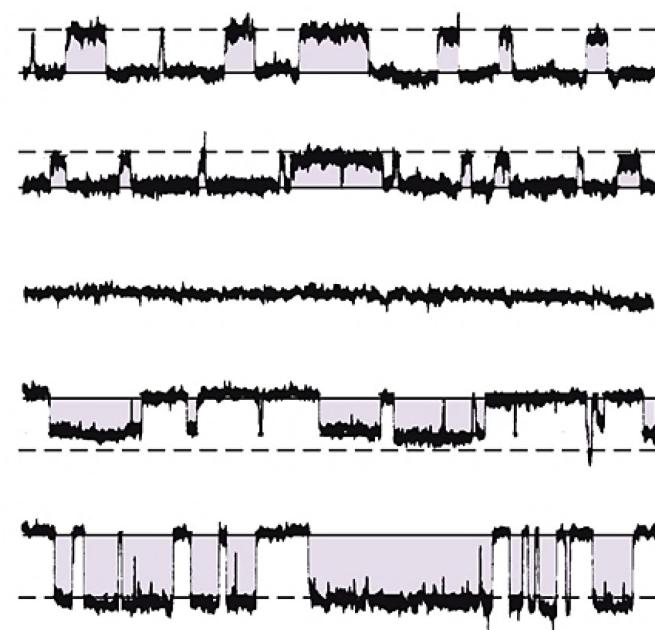
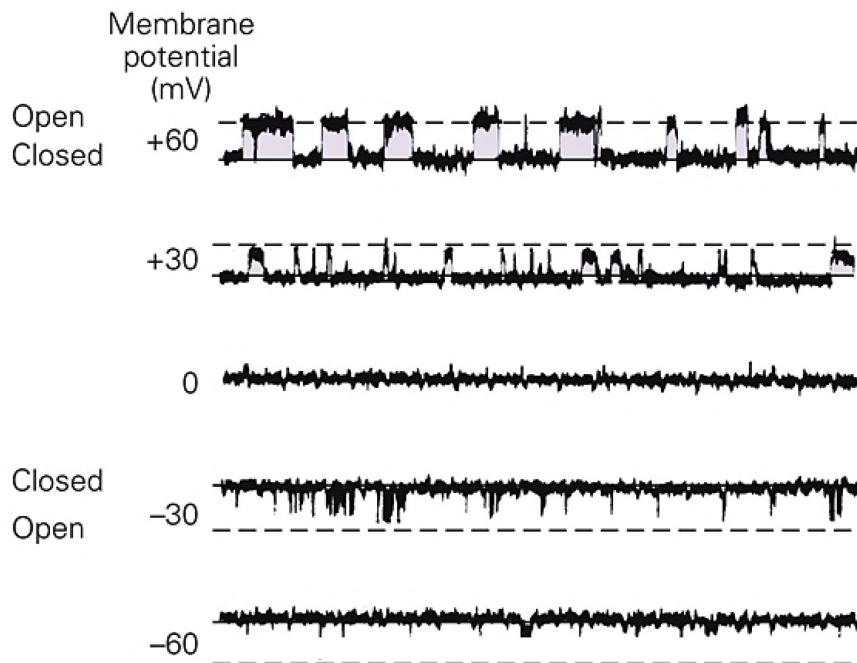
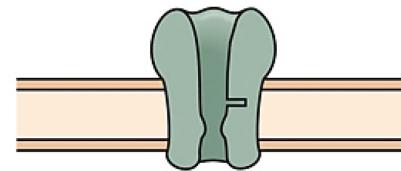


NMDA Receptors

A Normal extracellular Mg^{2+}



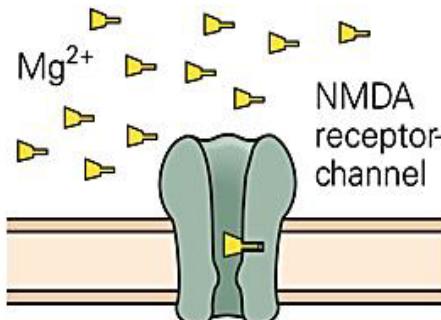
B No extracellular Mg^{2+}



2 pA
25 ms

NMDA Receptor IV Plot

Blocked by Mg^{+2}



Not blocked by Mg^{+2}

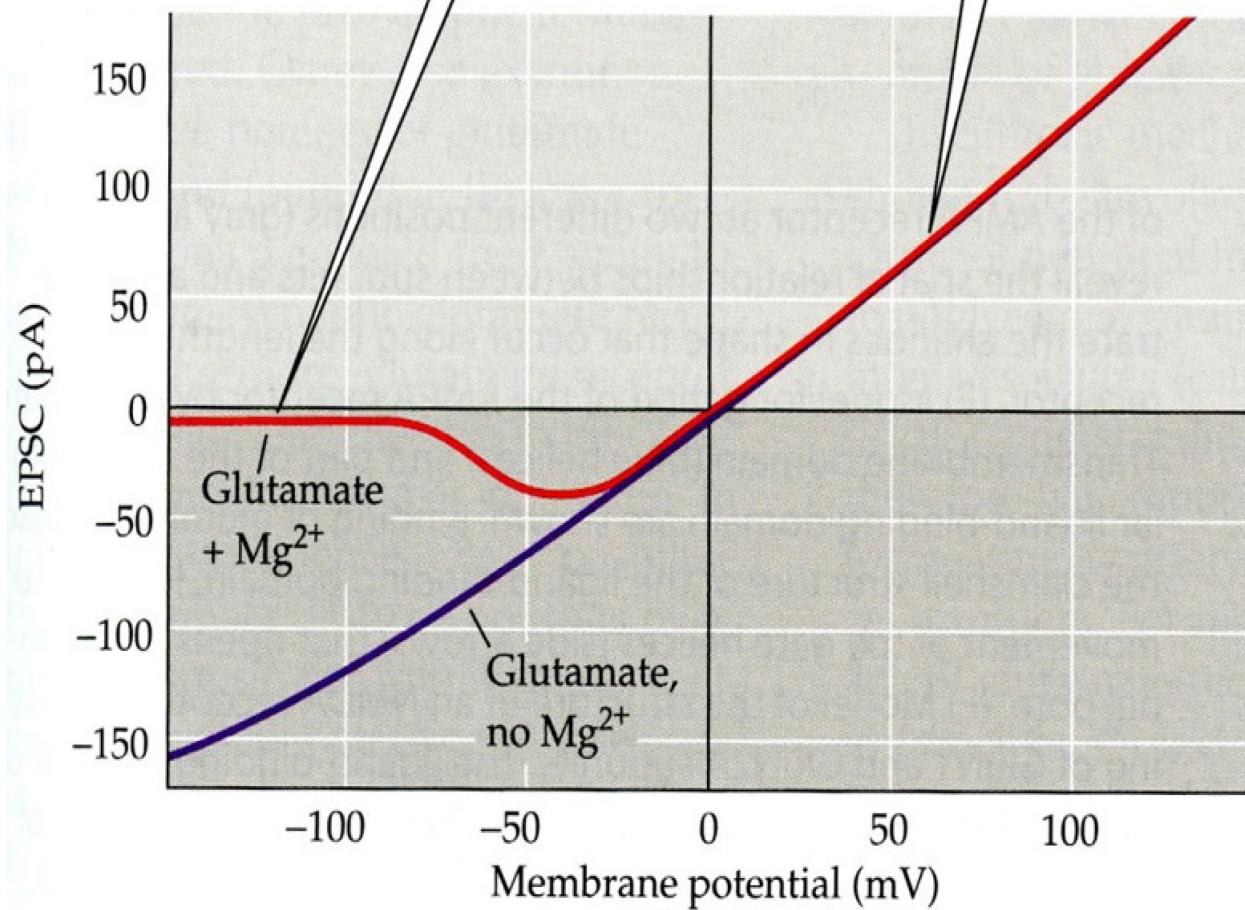
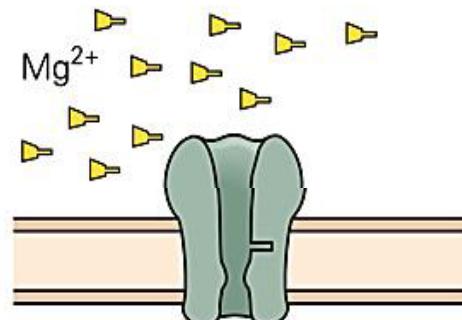


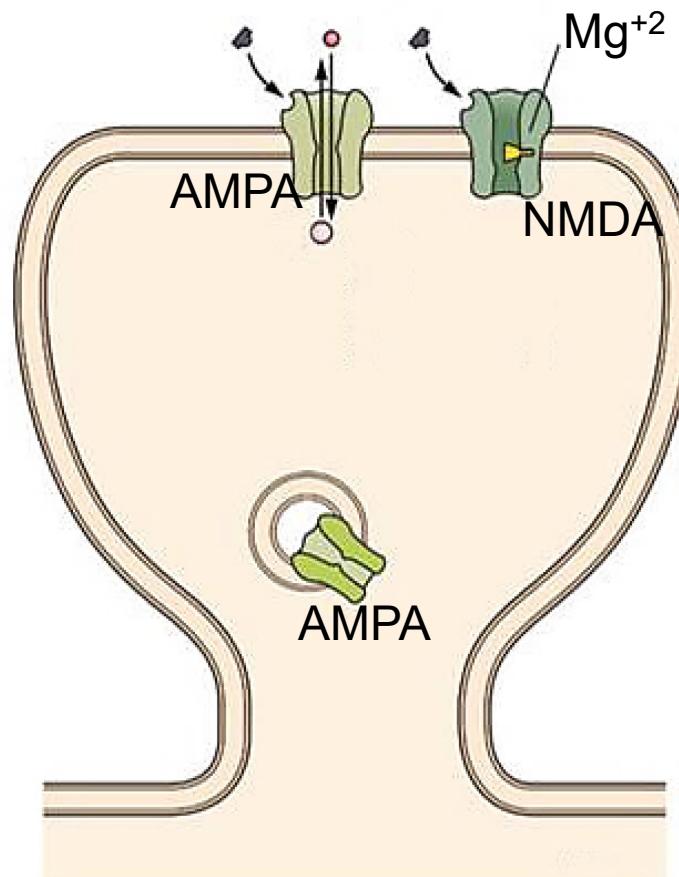
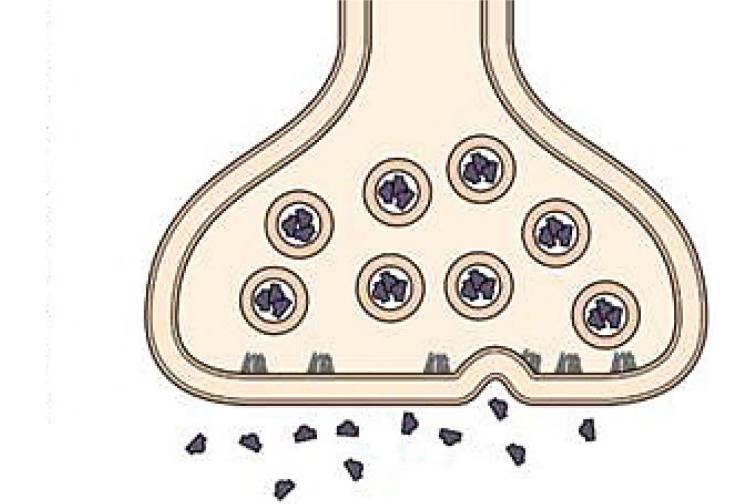
Figure 6.6, Purves

Glutamatergic Synapses

How do NMDA receptors become activated?

In other words, what depolarizes the membrane to remove the Mg^{2+} in the presence of glutamate?

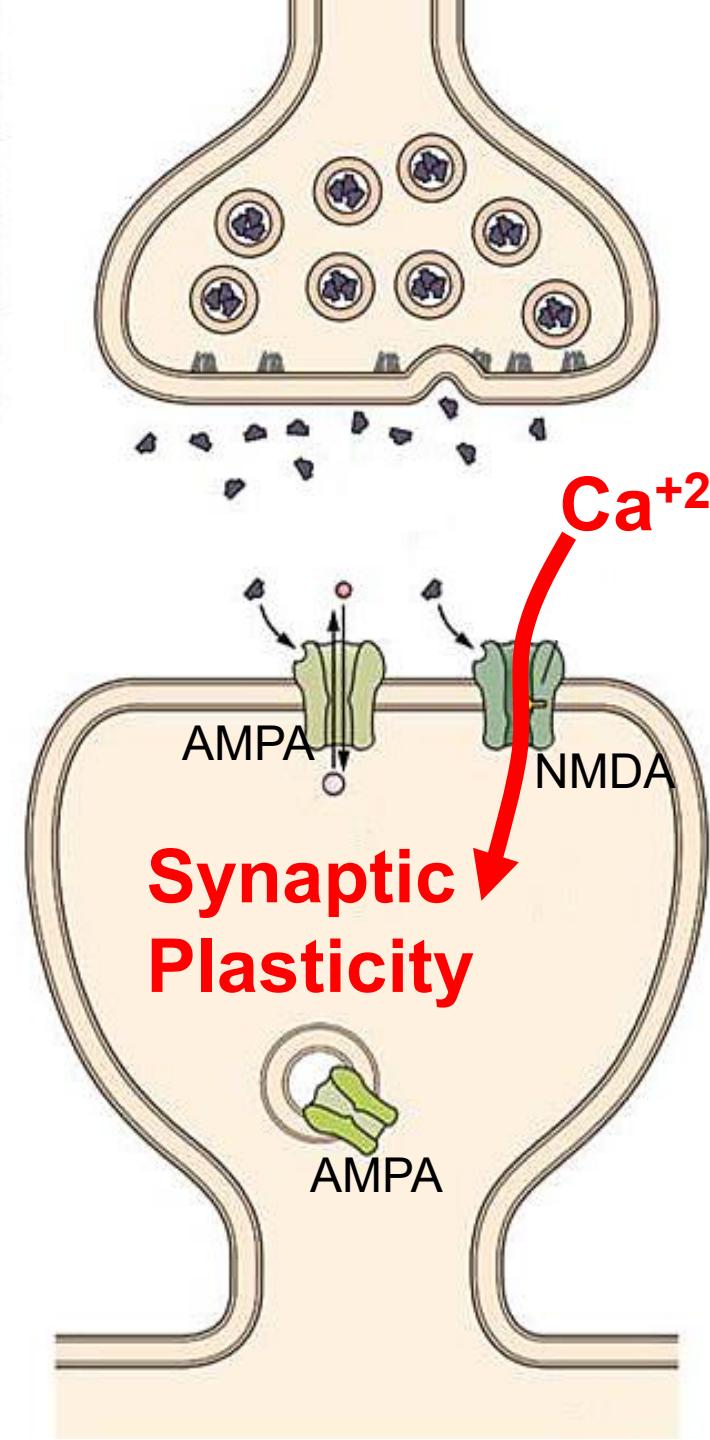
NMDA receptors are called *co-incidence receptors*.
Why?



Glutamatergic Synapses

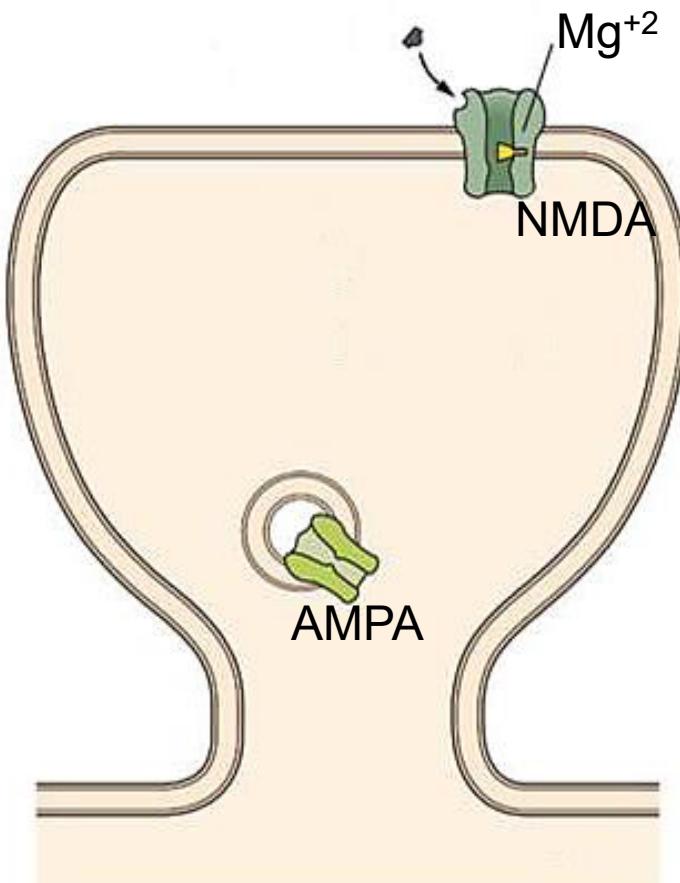
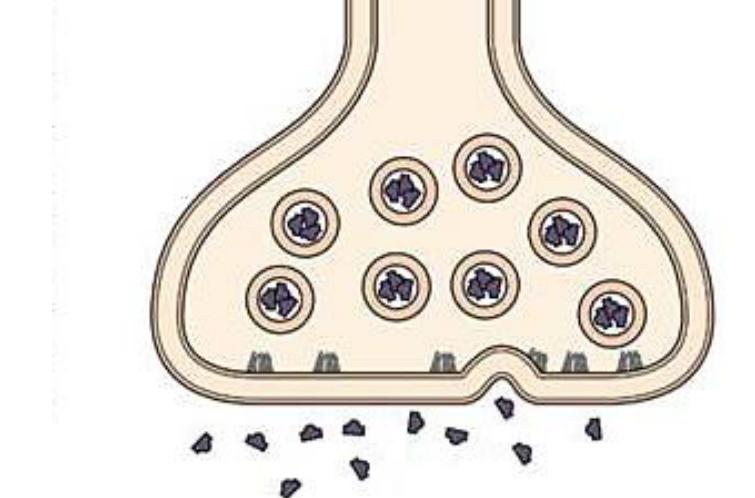
Open NMDA receptors allow Na^+ , K^+ and Ca^{2+} to flow, depolarizing the cell

Ca^{2+} also acts as a second messenger, resulting in biochemical and anatomical changes to the synapse



Silent Synapses

(Glutamatergic synapses
with only NMDA receptors)



Health Implications of NMDA Receptors

Glutamate hypothesis of Schizophrenia

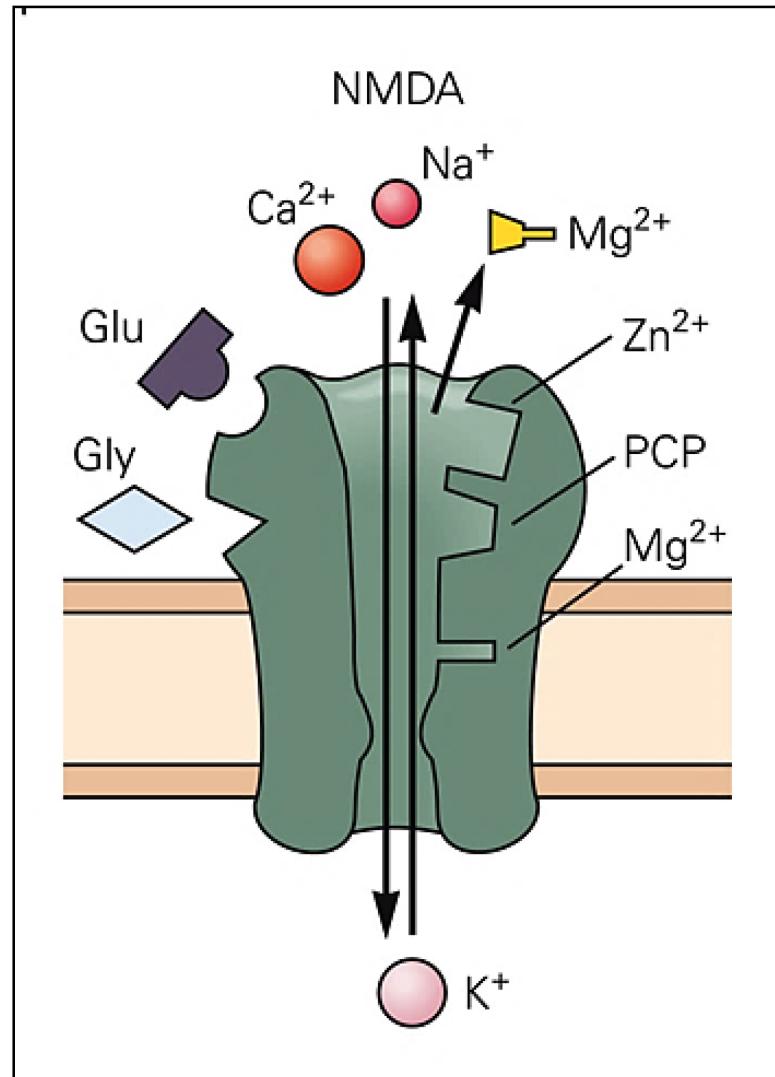
- NMDA receptor antagonists produce hallucinations that resemble those in schizophrenia
- Many antipsychotic drugs increase NMDA current

Glutamate excitotoxicity

- Overstimulation of NMDA receptors leads to cell death
- Results in brain injury during stroke or repeated seizures

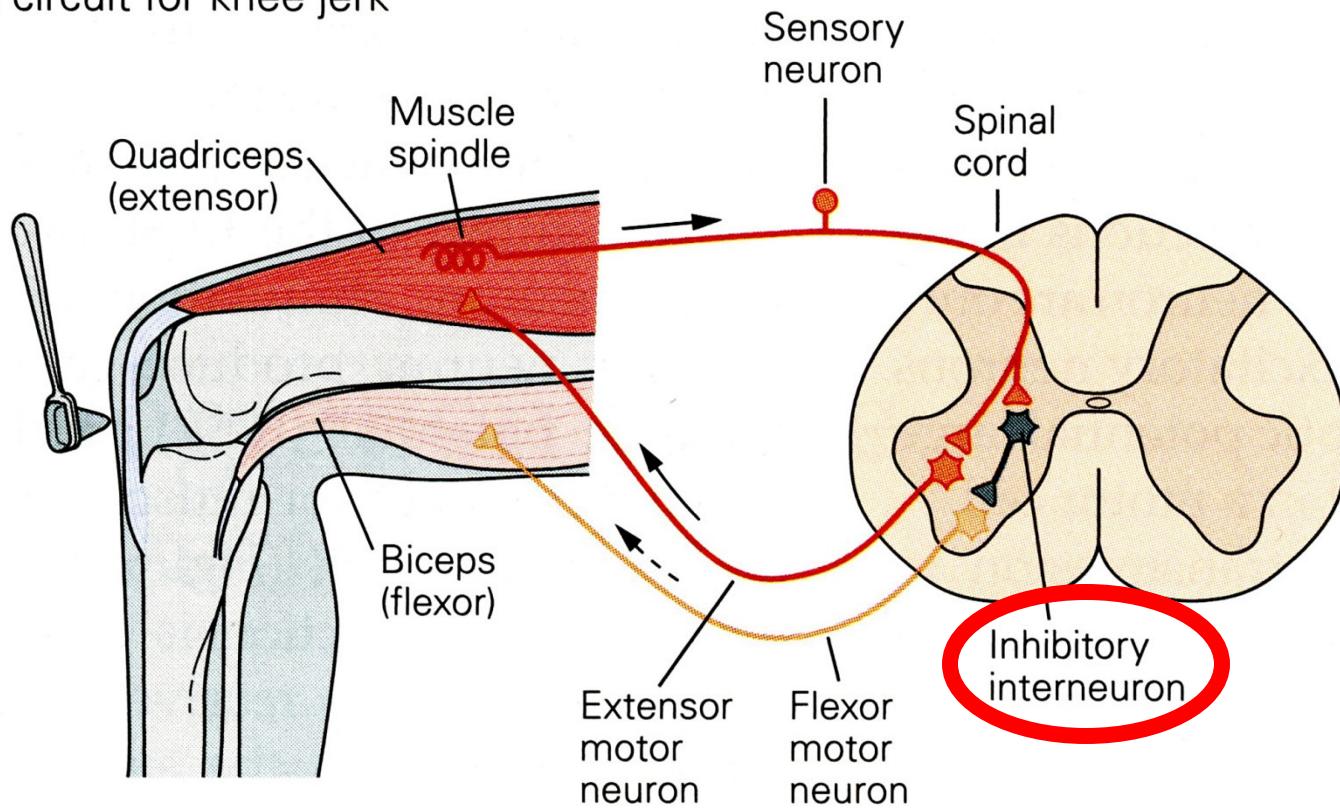
Alzheimer's disease

- Memantine, an NMDA antagonist, is used to treat moderate-to-severe Alzheimer's disease.

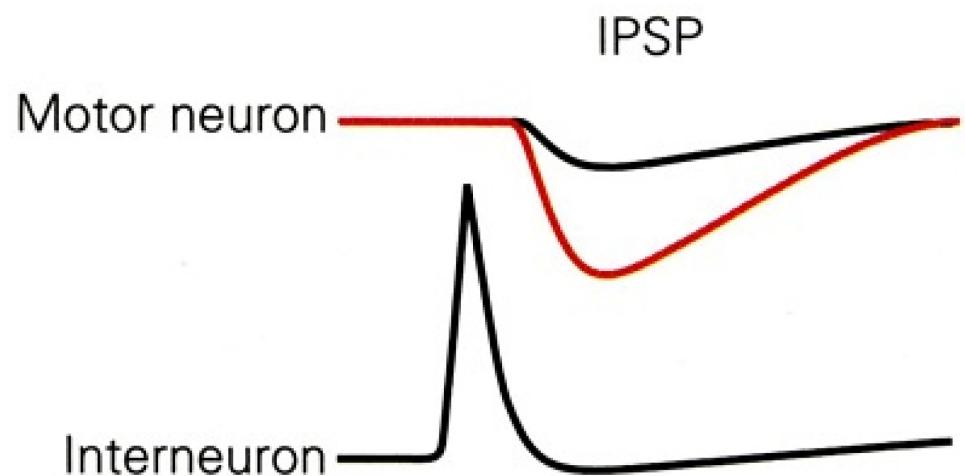
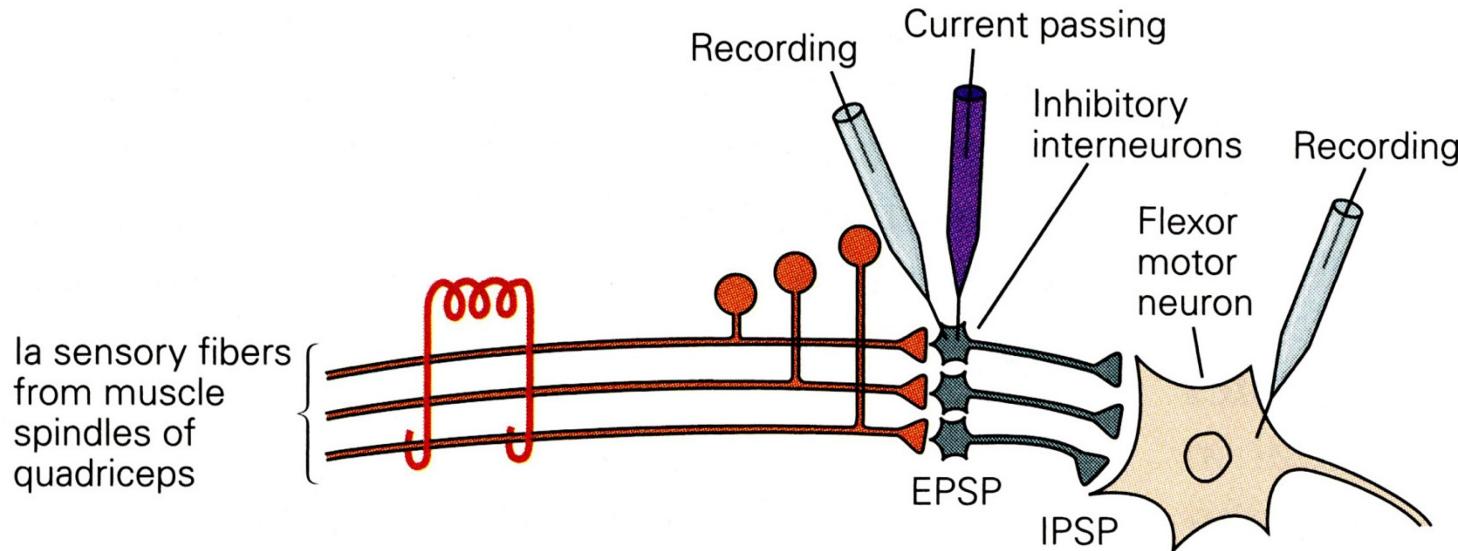


Excitatory and Inhibitory Synapses

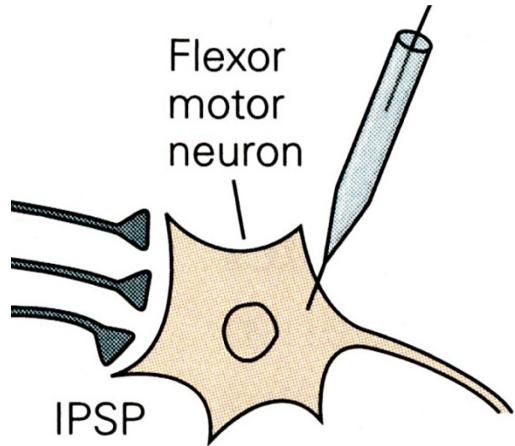
Stretch reflex circuit for knee jerk



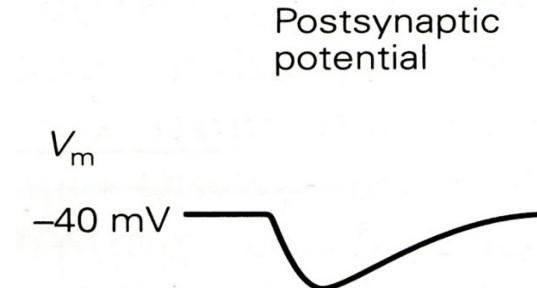
Inhibitory Synapses



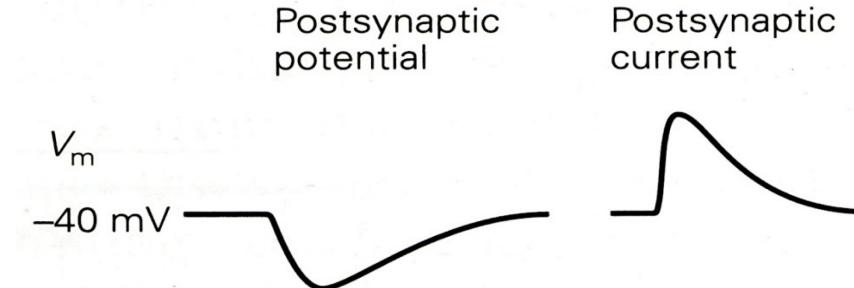
Electrophysiology at a Typical Inhibitory Synapse



Measure Voltage



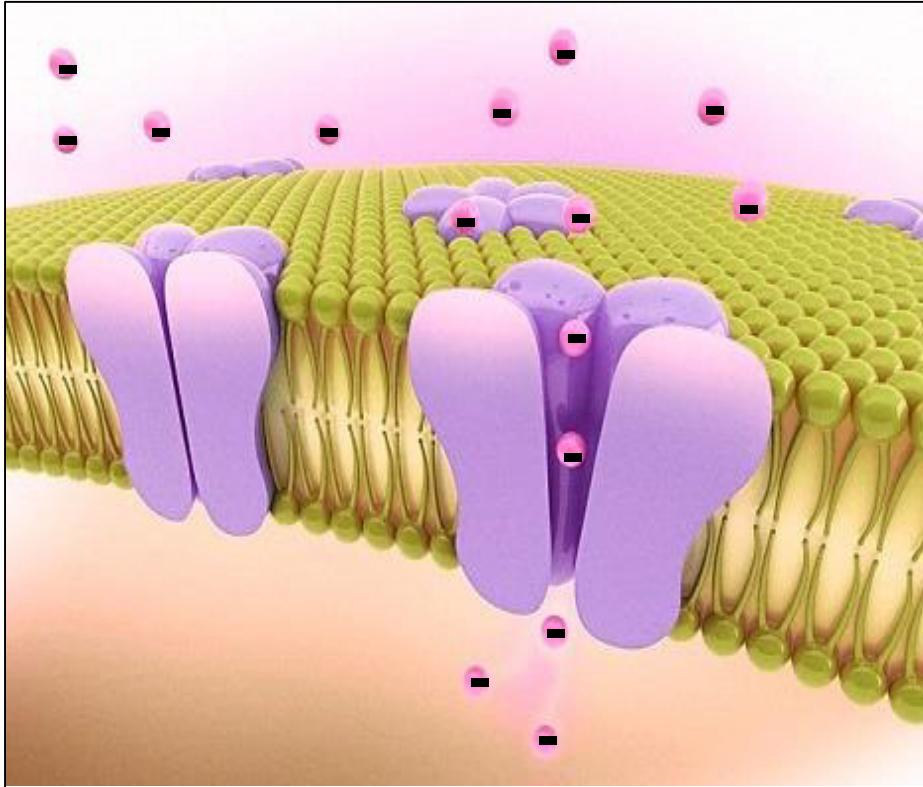
Voltage Clamp Mode
(measure current)



Cl^-
flux



Inhibitory Ionotropic Receptors are Chloride Channels

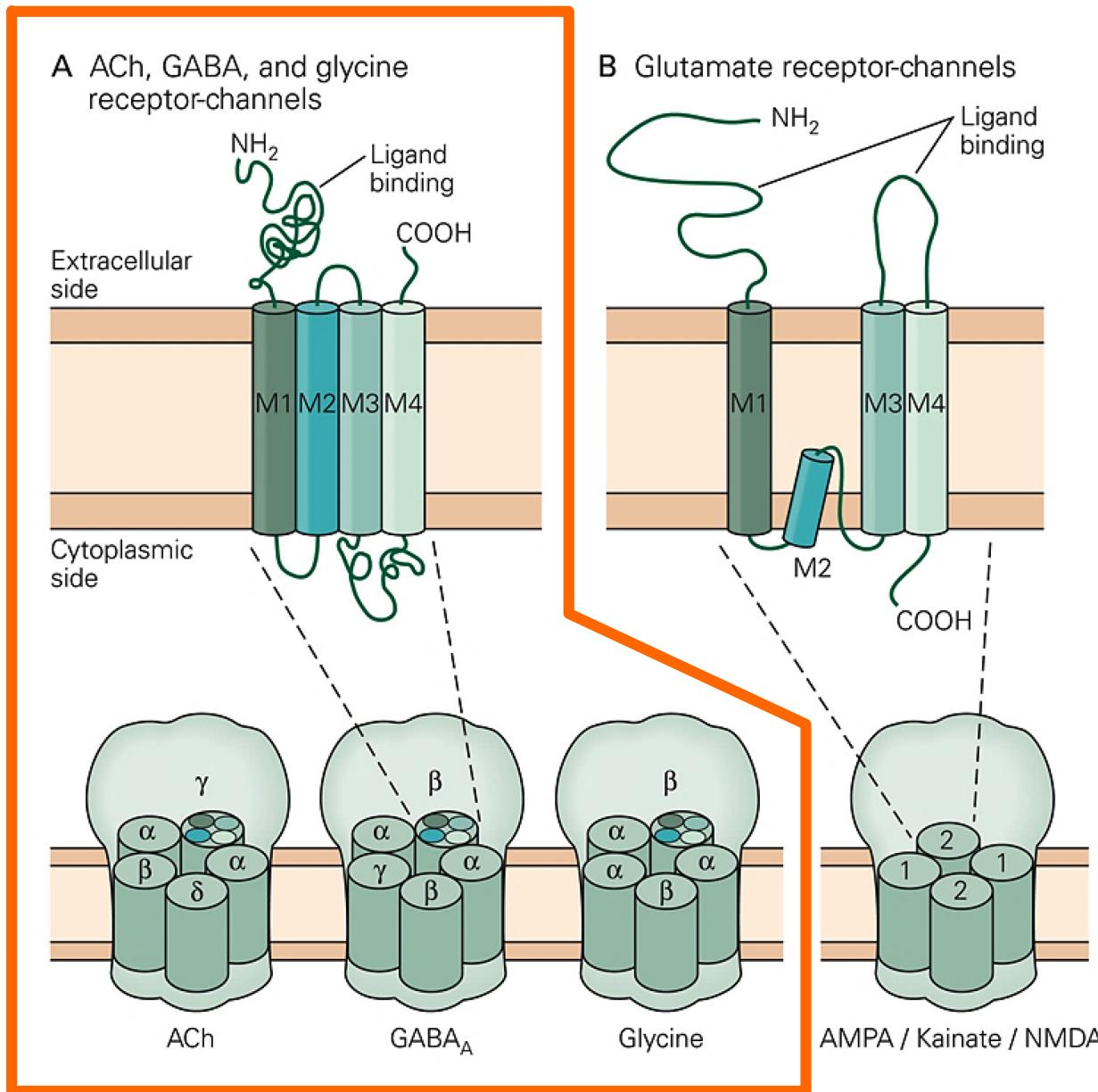


Cl⁻ permeable

- GABA_A receptors
- Glycine receptors

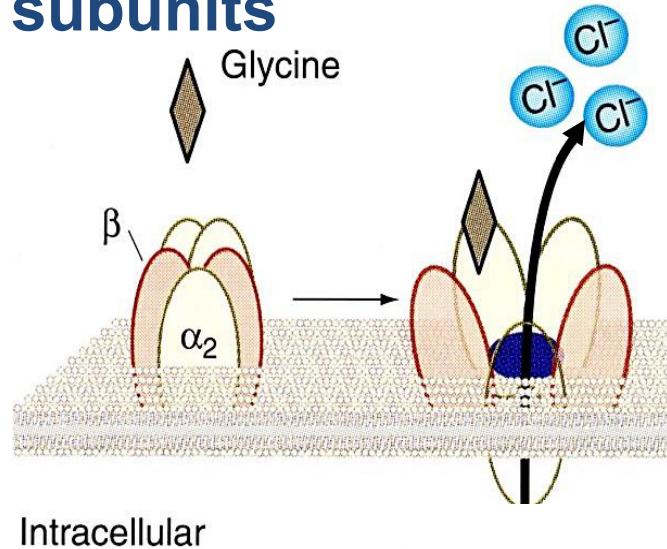
The reversal potential of these channels is between -60 mV to -70 mV.
Why do these channels cause IPSPs?

GABA_A and Glycine Receptor Structure

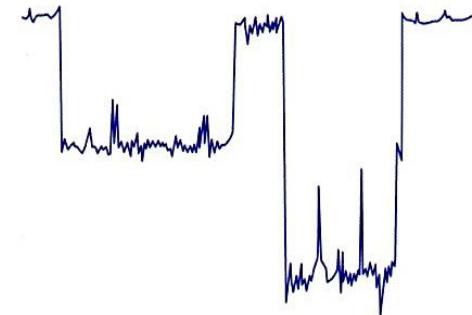


Subunits Confer Different Properties

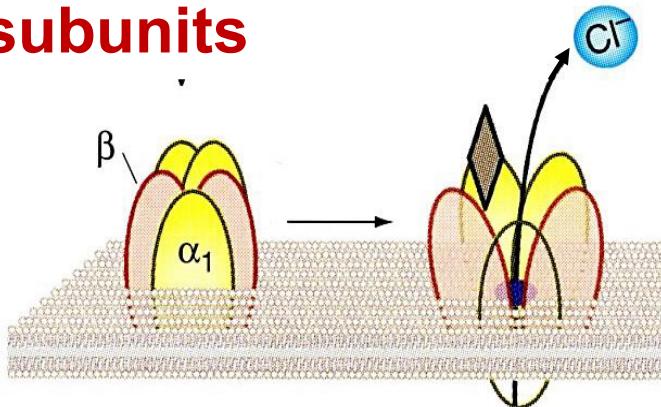
β and α_2 subunits



Long open times, large currents



β and α_1 subunits

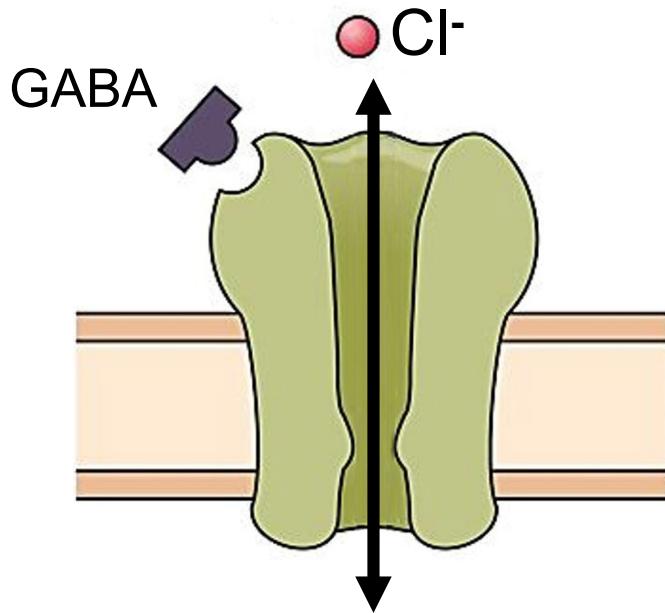


Short open times, small currents



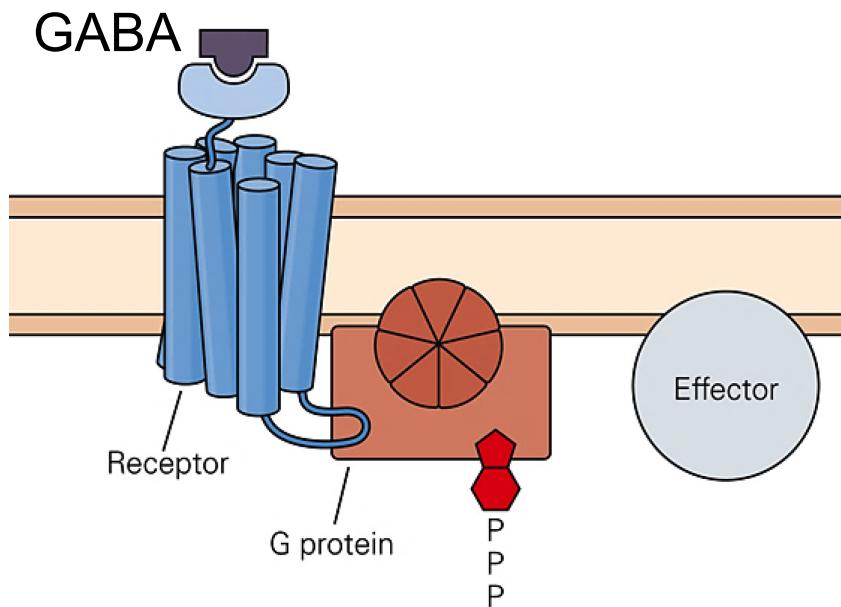
GABA Receptors

GABA is the major inhibitory transmitter in the CNS



GABA_A Receptor

- Ionotropic chloride channel
- $E_{\text{Cl}} = -60 \text{ mV}$ to -70 mV

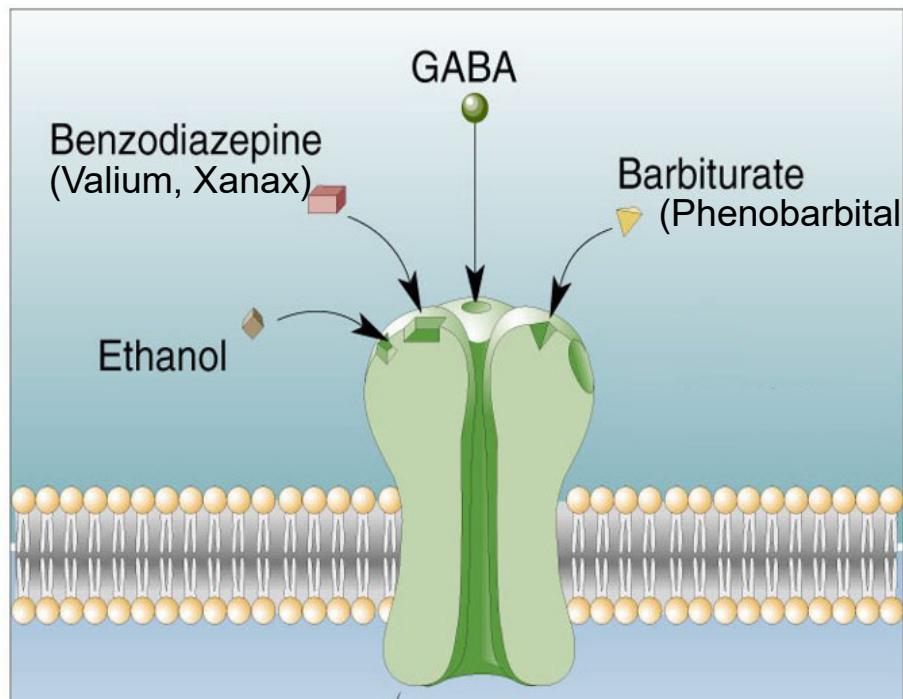


GABA_B Receptor

- Metabotropic receptor
- Causes the opening of K^+ channels ($E_{\text{K}} = -80 \text{ mV}$)

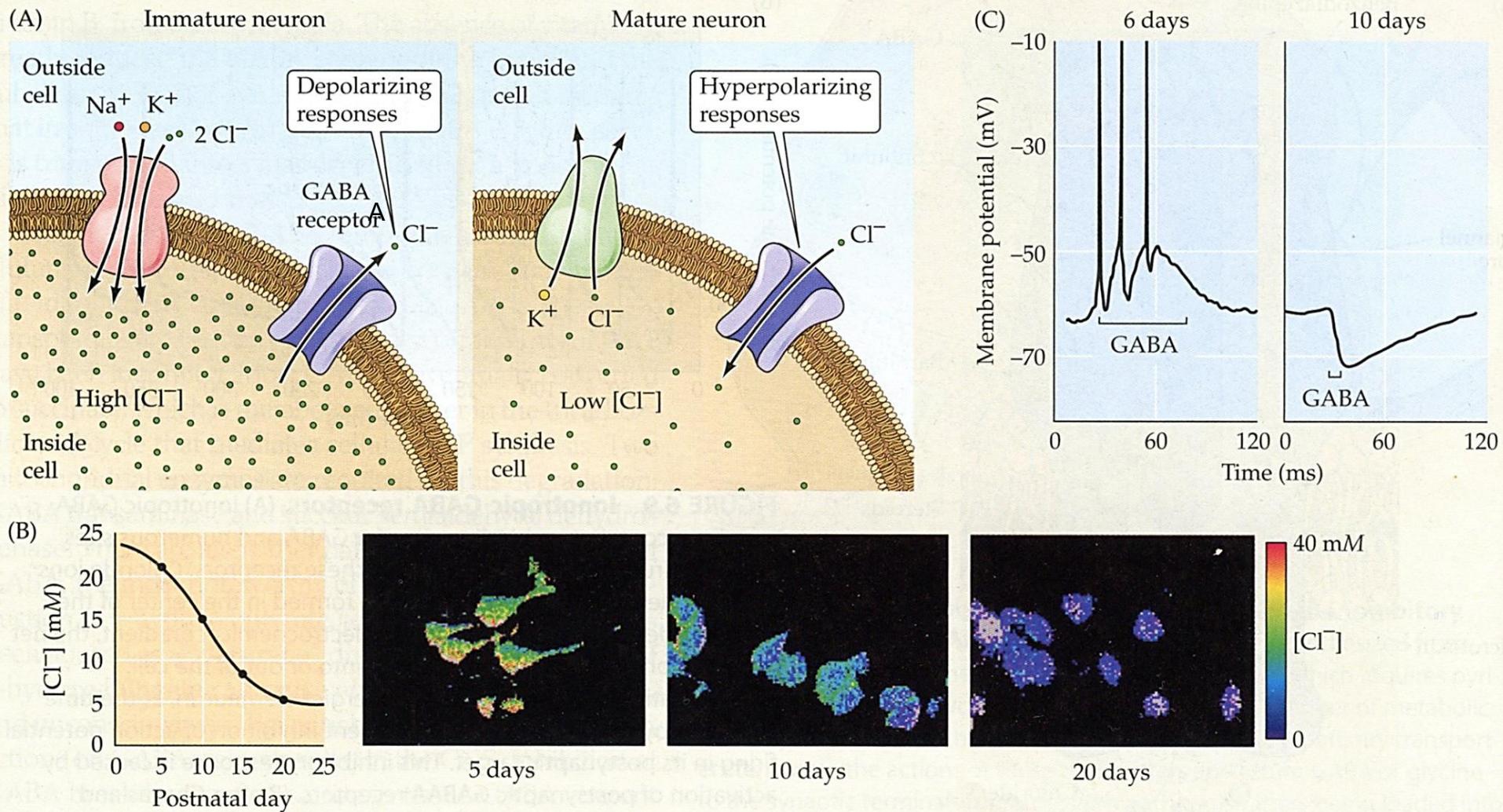
Health Implications of GABA_A Receptors

- The GABA_A receptor has many medically-important modulators:

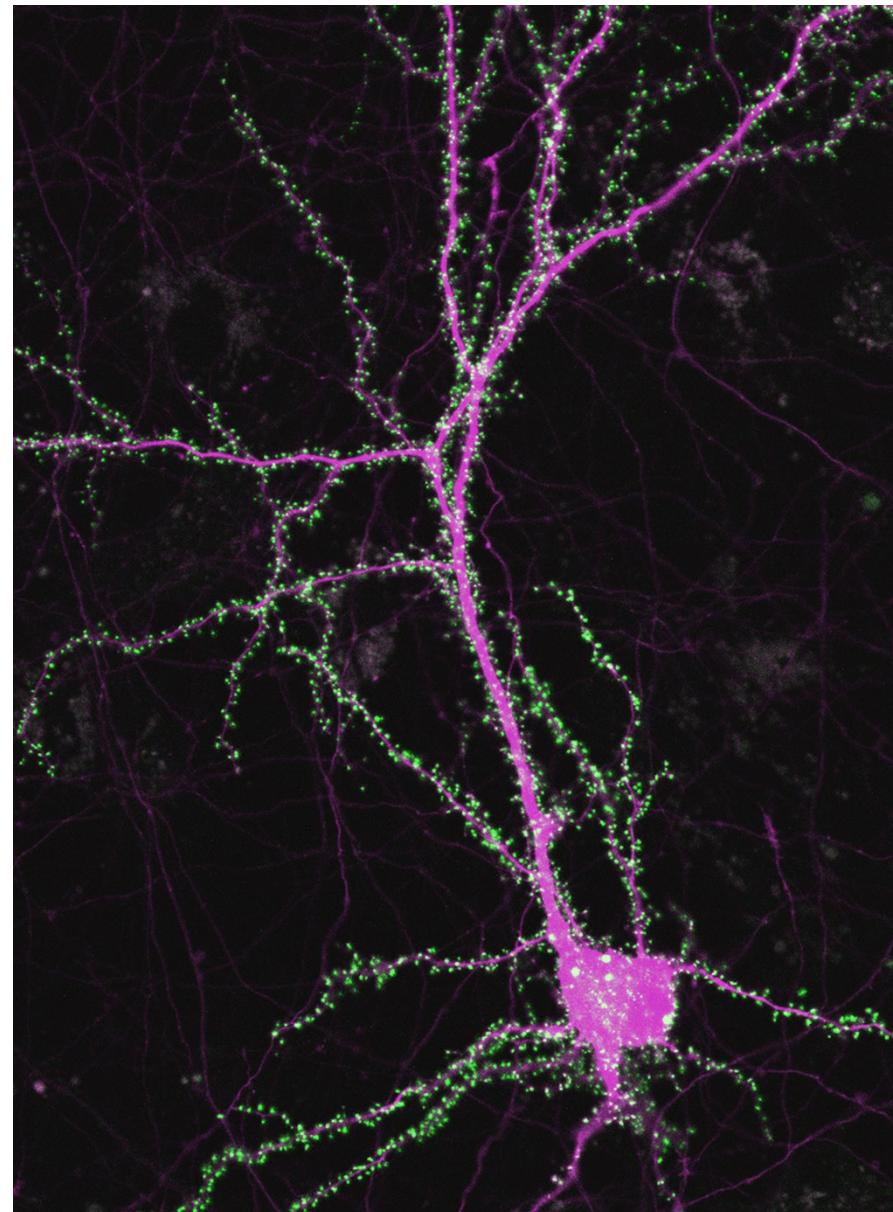
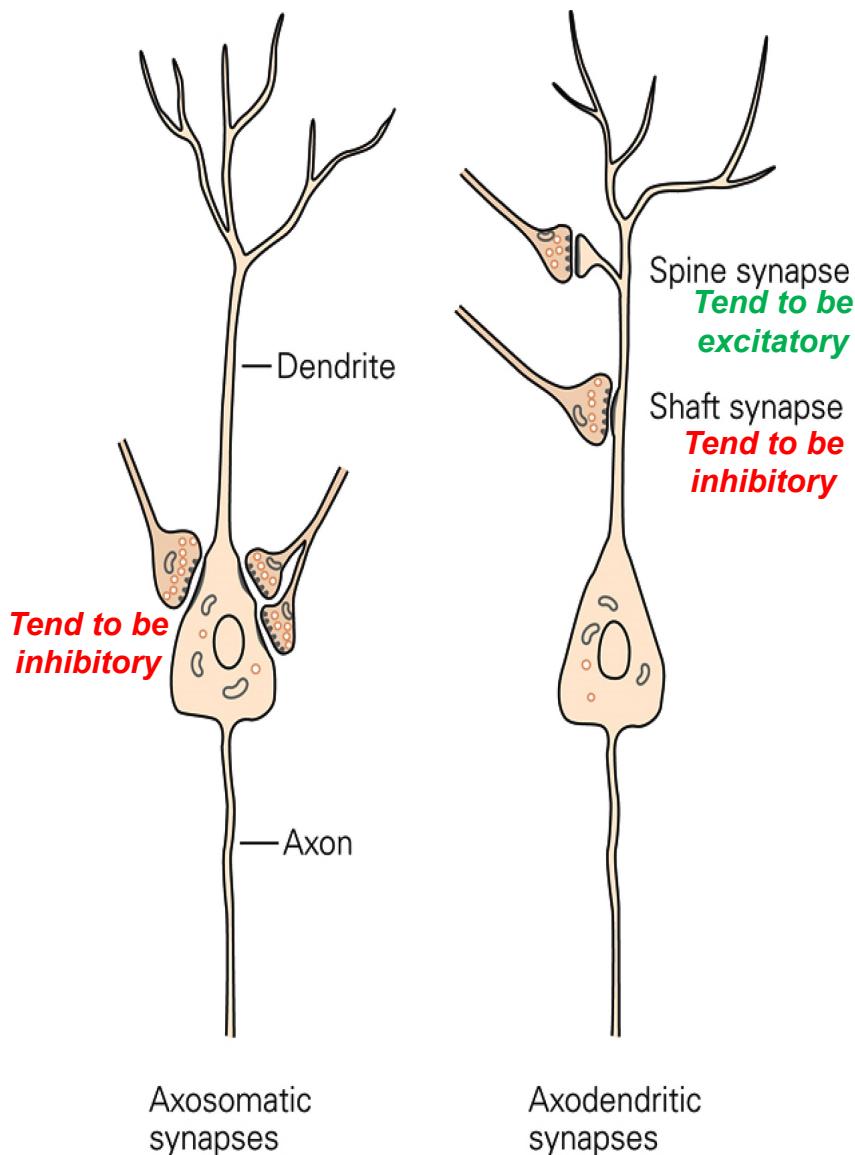


- GABA_A agonists are used to treat epilepsy, anxiety, and sleeping disorders. They are also used as muscle relaxants.

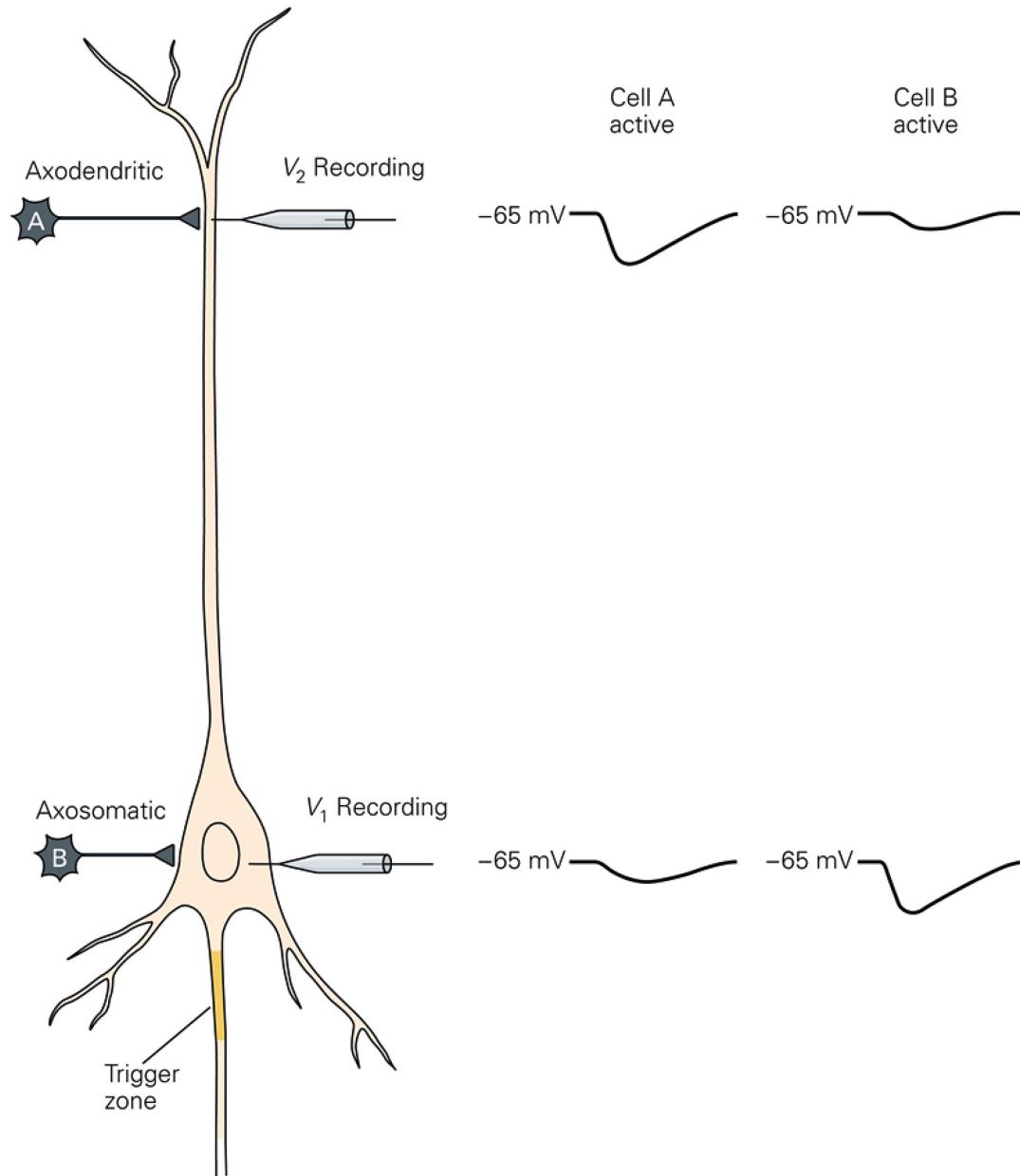
GABA_A Responses Change During Development



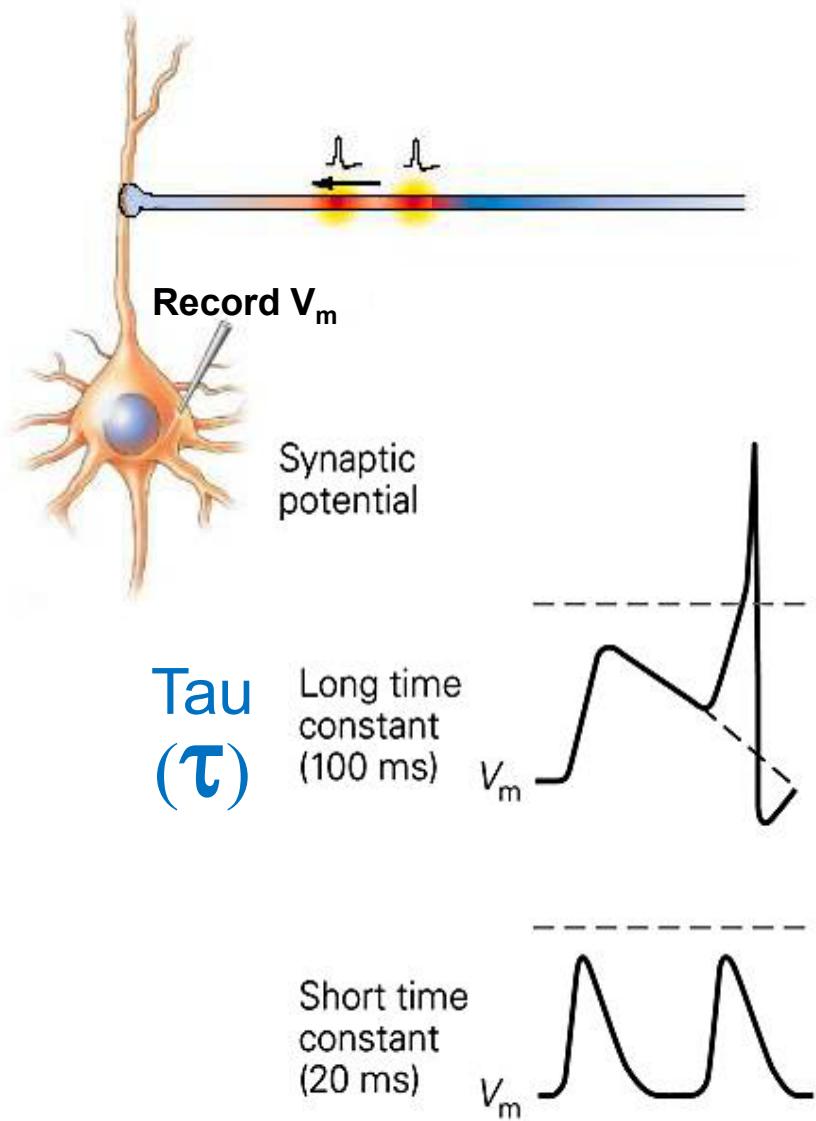
Location of Synaptic Inputs



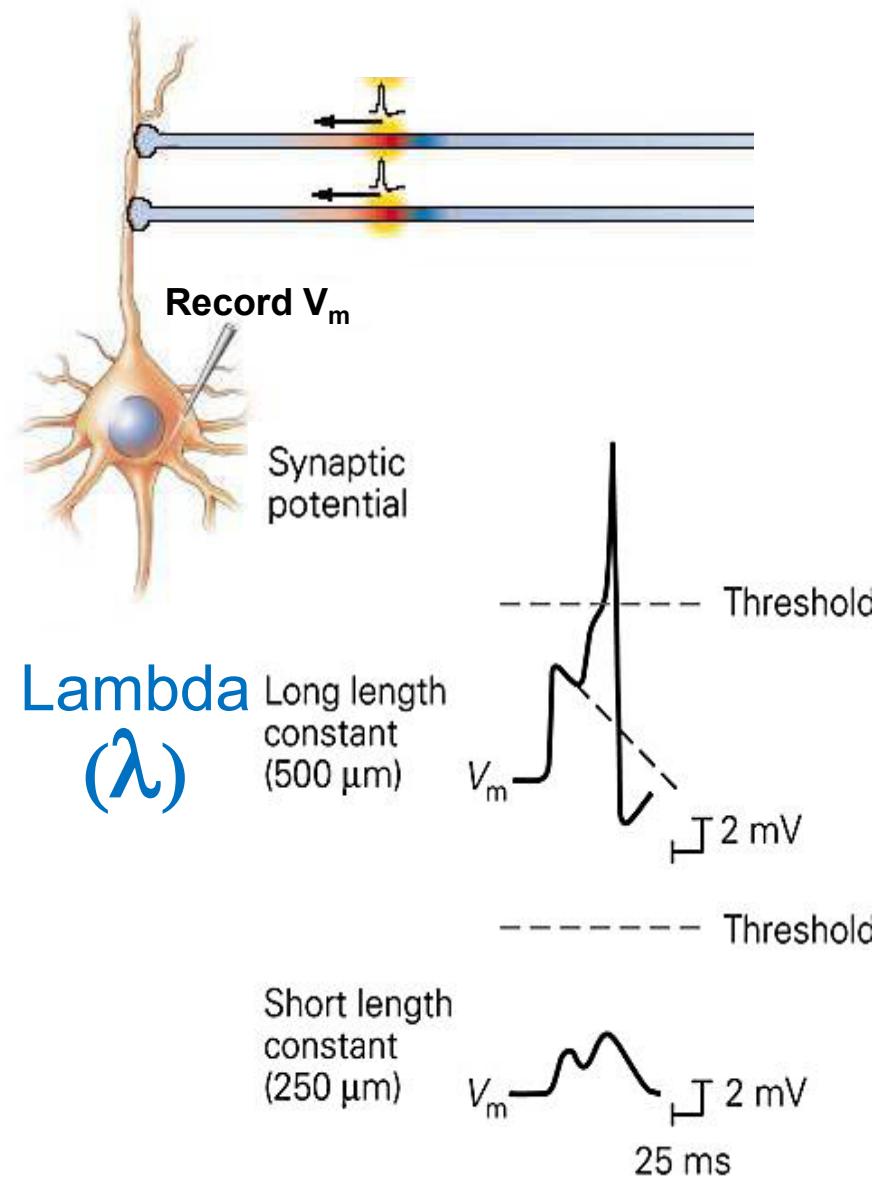
Effect of Synapse Location



Temporal Summation



Spatial Summation



Action Potentials are Initiated at the Axon Hillock

