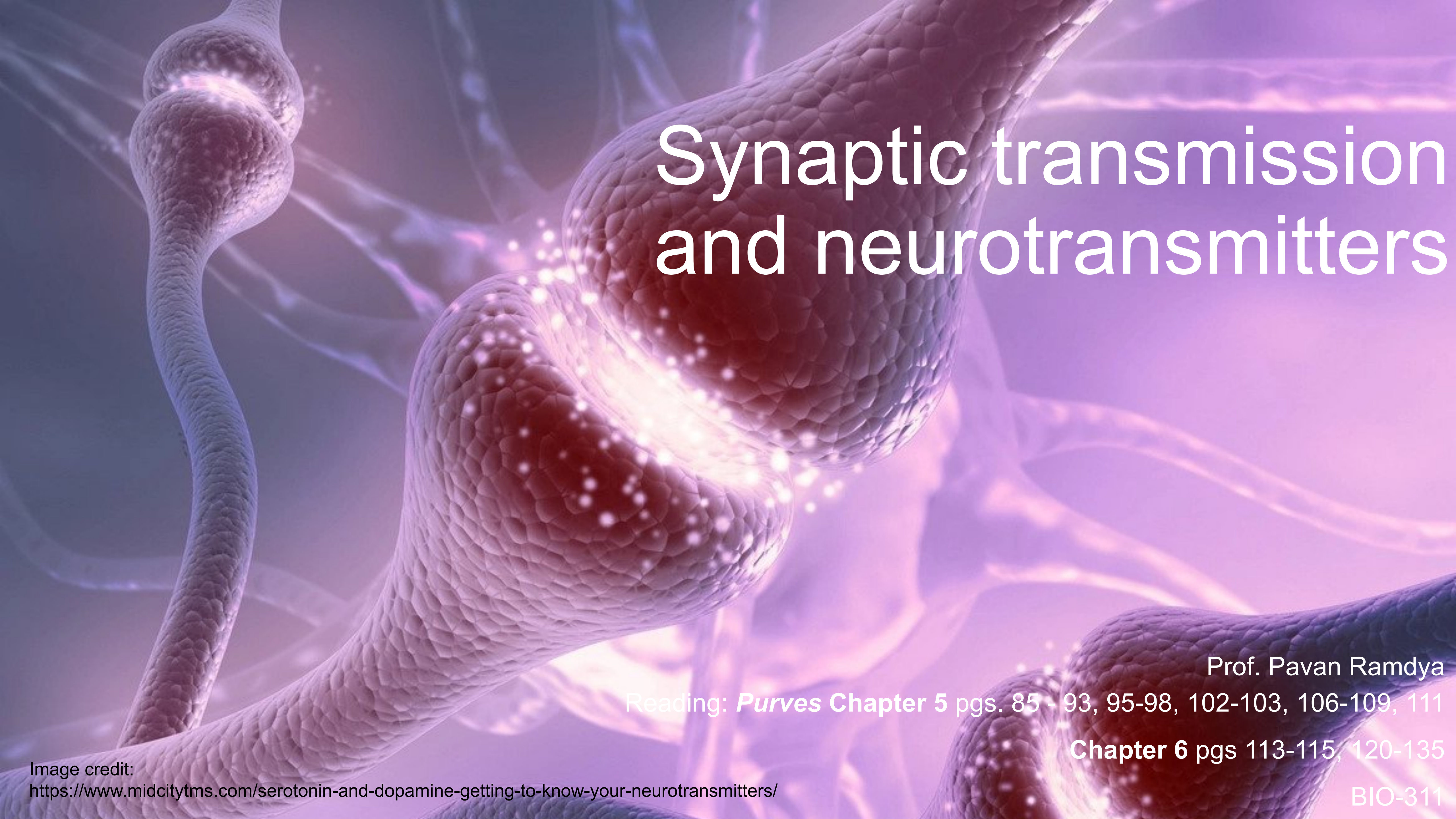


# Synaptic transmission and neurotransmitters

Prof. Pavan Ramdya

Reading: ***Purves* Chapter 5** pgs. 85 - 93, 95-98, 102-103, 106-109, 111

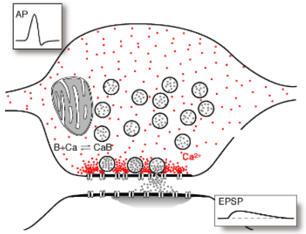
**Chapter 6** pgs 113-115, 120-135

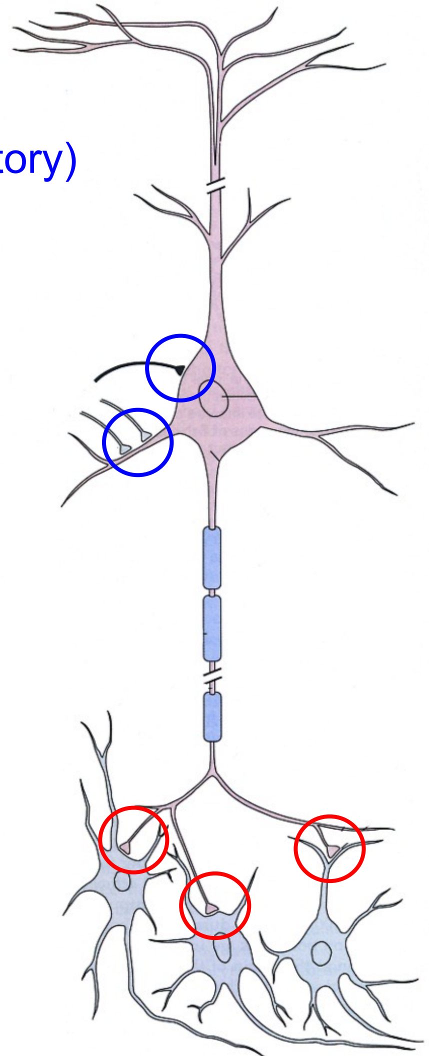
BIO-311

Image credit:
https://www.midcitytms.com/serotonin-and-dopamine-getting-to-know-your-neurotransmitters/

# Synaptic transmission enables neuron-neuron (and neuromuscular) communication

~10,000 inputs to dendrites
And somata (excitatory and inhibitory)



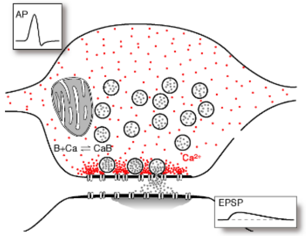



**Dendrite**

**Soma** (cell body)

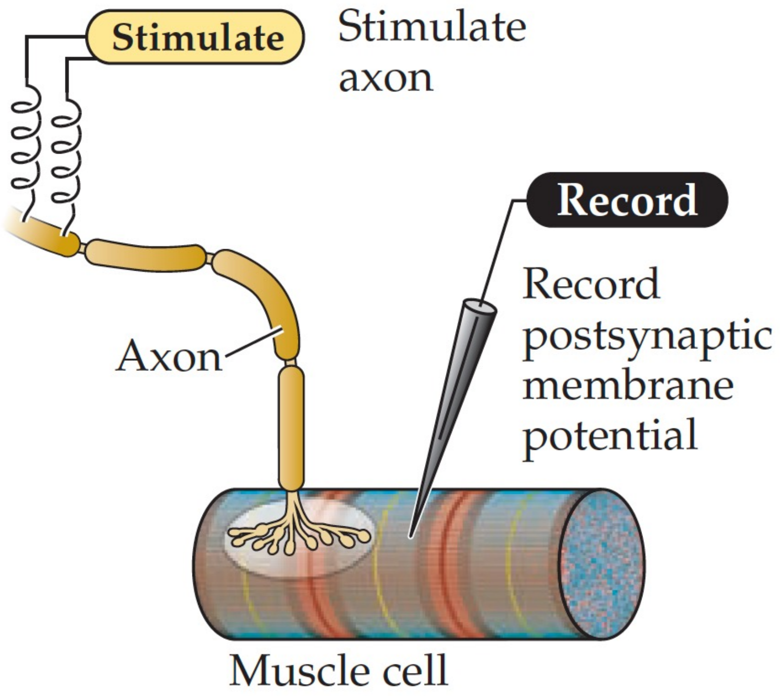
**Axon**

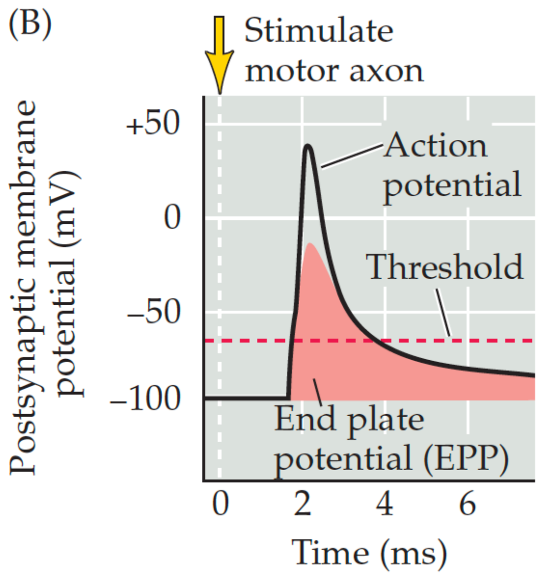
~1,000 output synapses




**nerve terminal**
~ 1 µm at *most* synapses

# Early insights were drawn from the Neuromuscular Junction (NMJ)



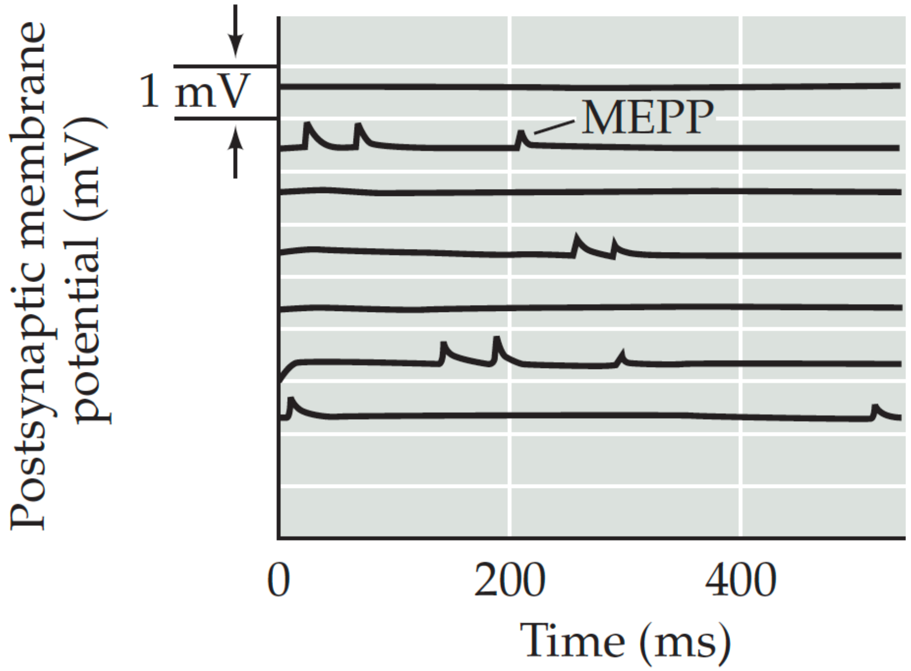




- Acetylcholine (ACh) is the transmitter released at the NMJ

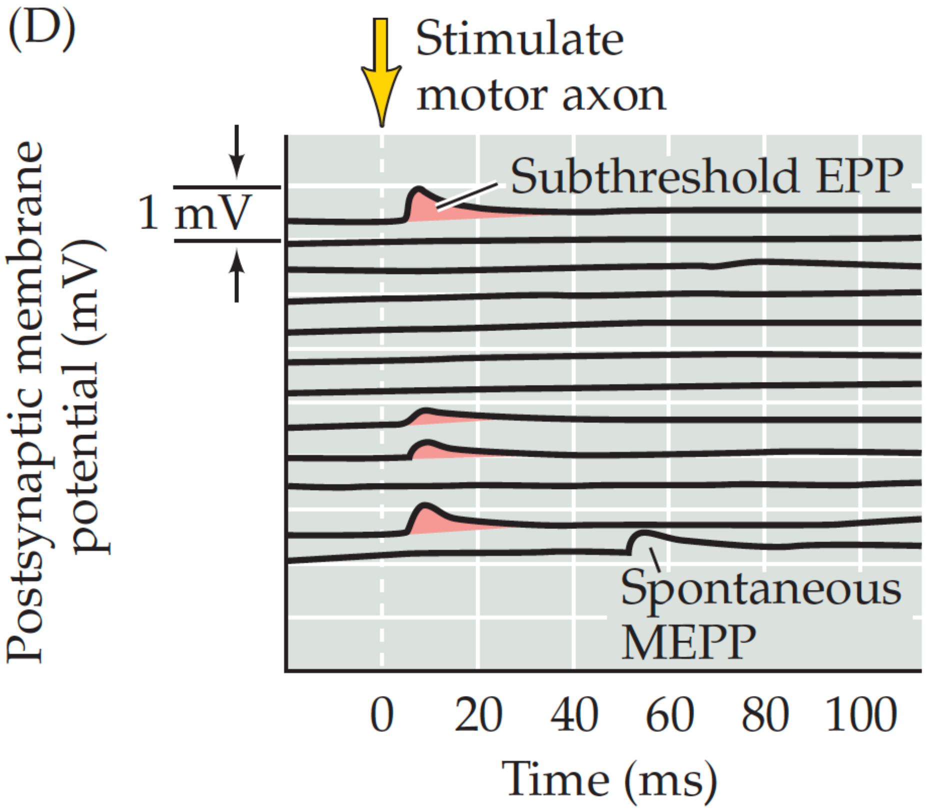
Purves, Figure 5.5

# Early insights were drawn from the Neuromuscular Junction (NMJ)

Spontaneous EPSP events

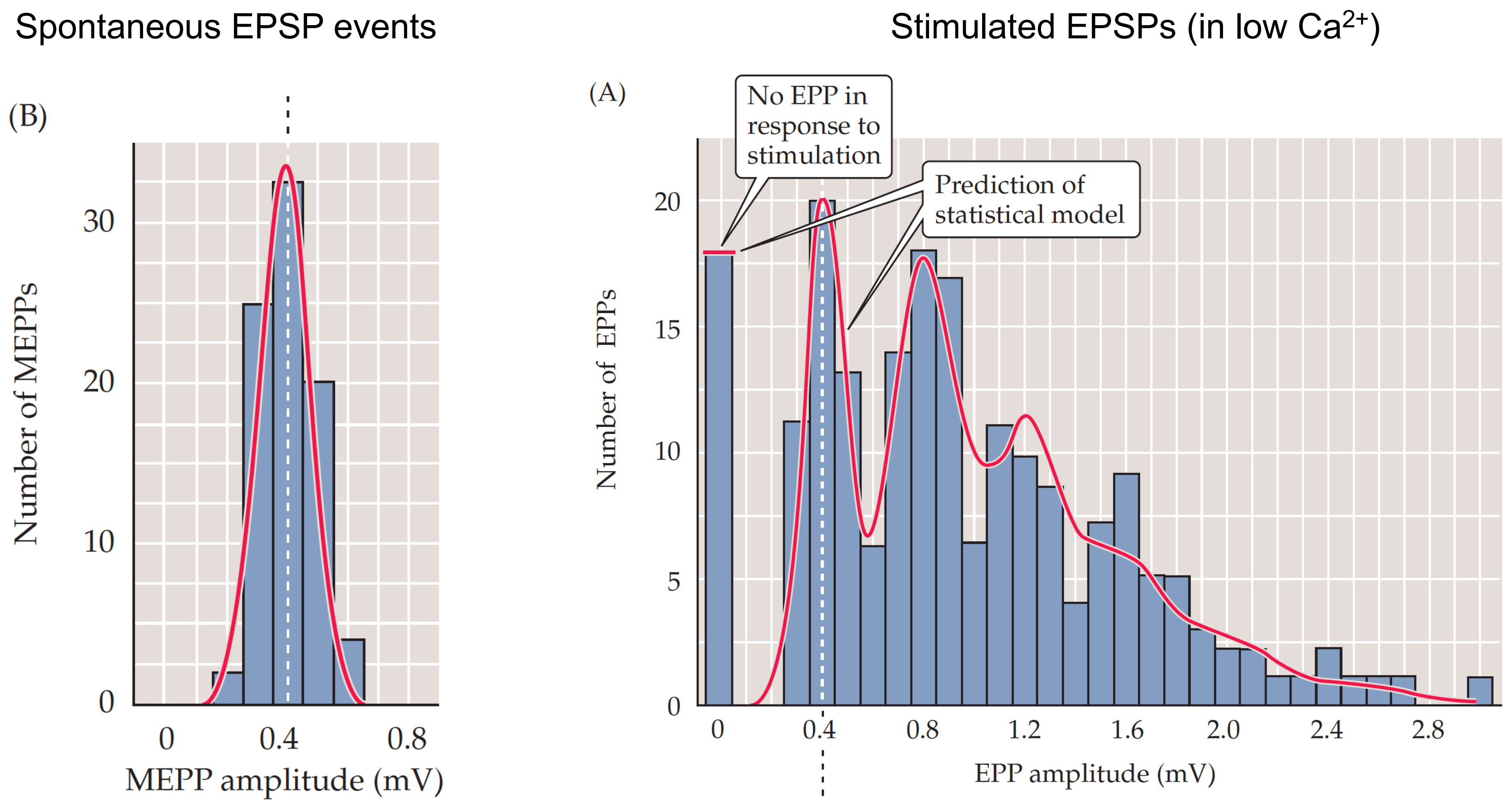



Stimulated EPSP (in low $Ca^{2+}$)



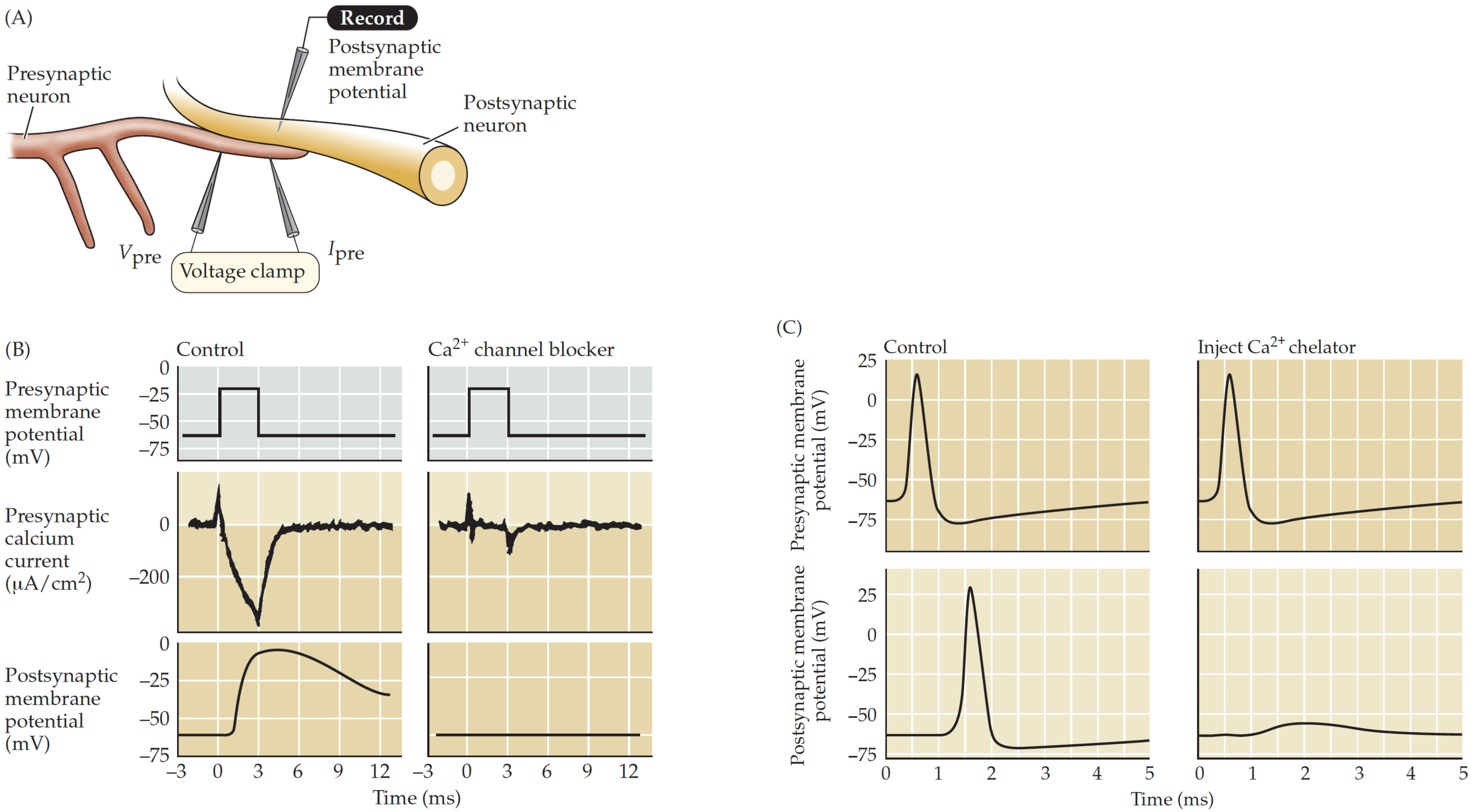

Purves, Figure 5.5

# Neurotransmitter is released in fixed increments or quanta




Purves, Figure 5.6

# Presynaptic $Ca^{2+}$ is required for transmitter release

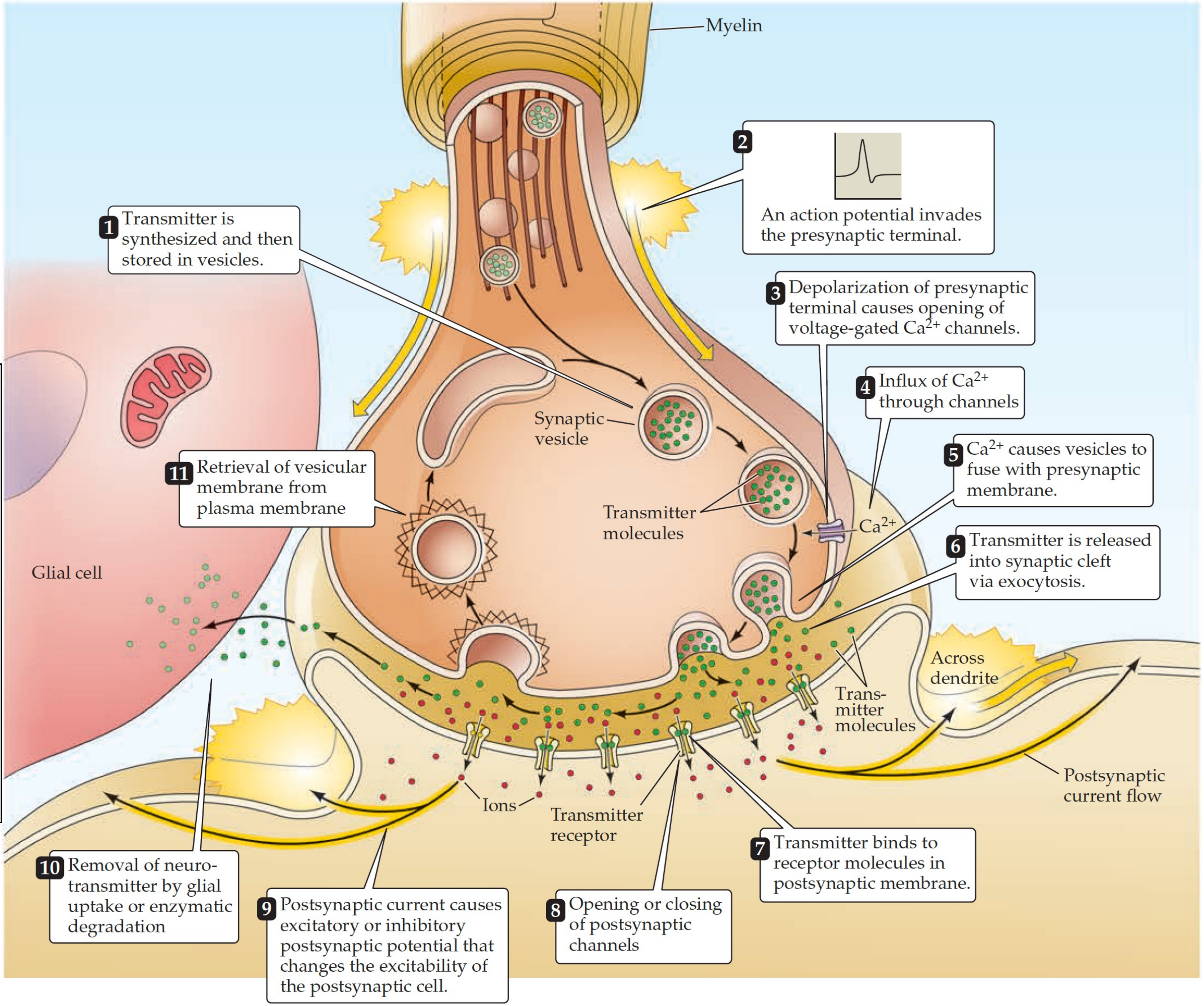



Purves, Figure 5.9

Purves, Figure 5.10

# General sequence of events occurring at a typical chemical synapse during transmission

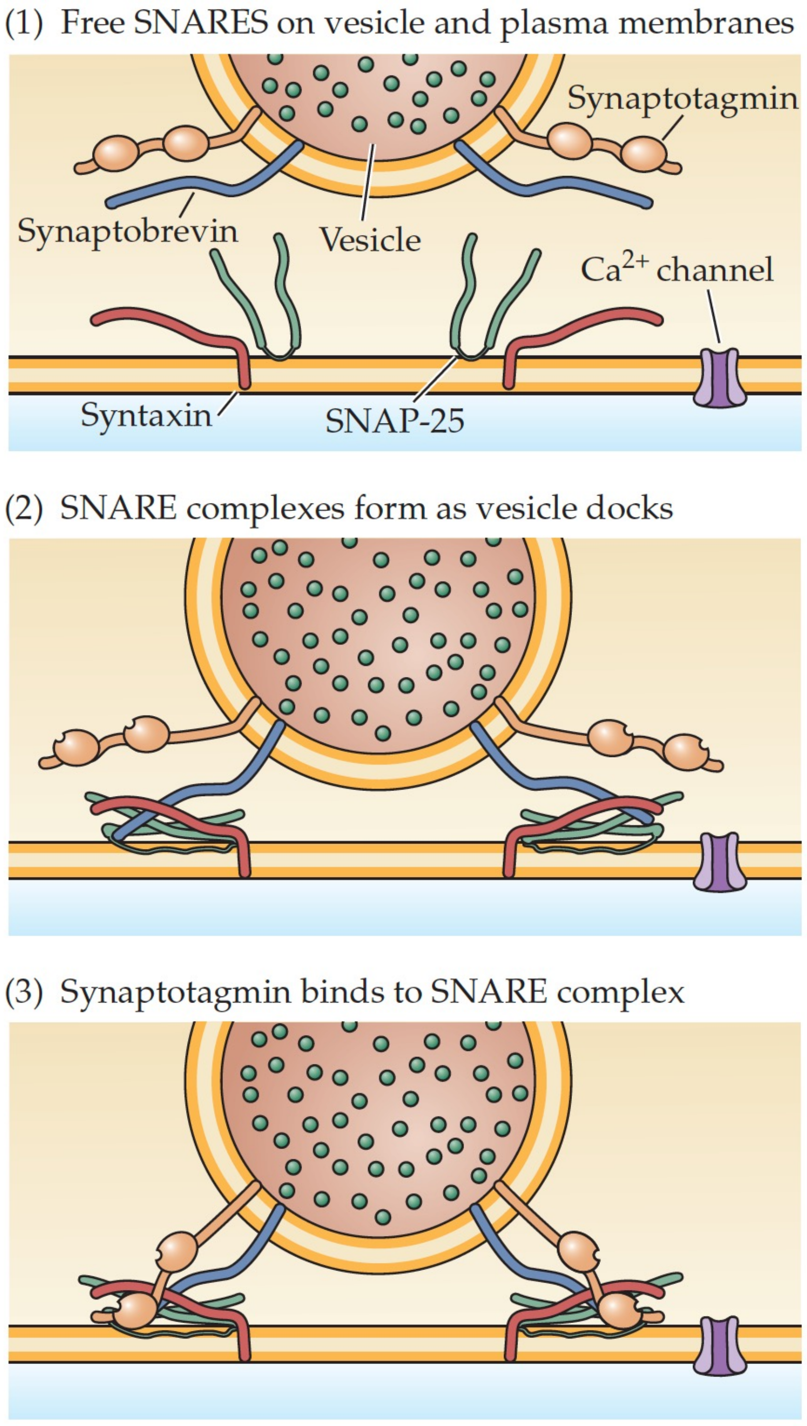
- Action potential arrives at nerve terminal
- Voltage-gated $Ca^{2+}$ channels open
- $Ca^{2+}$ flows into terminal along gradient
- $Ca^{2+}$ binds to $Ca^{2+}$ sensor on vesicle
- Vesicle fuses with terminal membrane
- Neurotransmitter is released and binds to its post-synaptic receptors

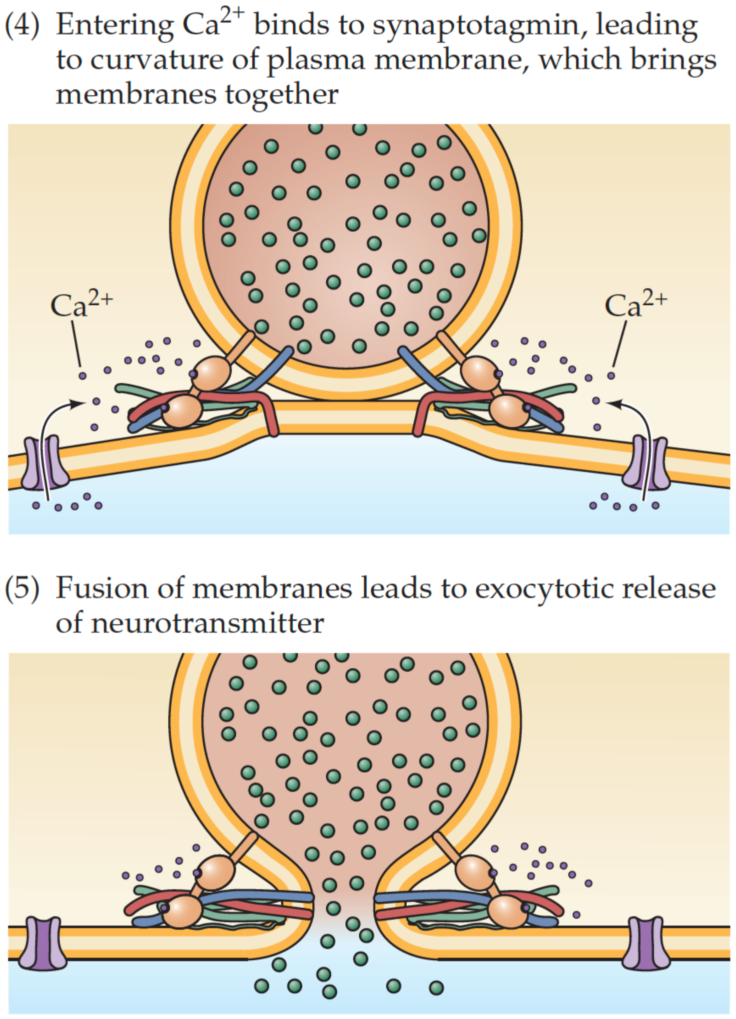



Purves, Figure 5.4

# Vesicle docking and fusion depend on SNARE-proteins and synaptotagmin

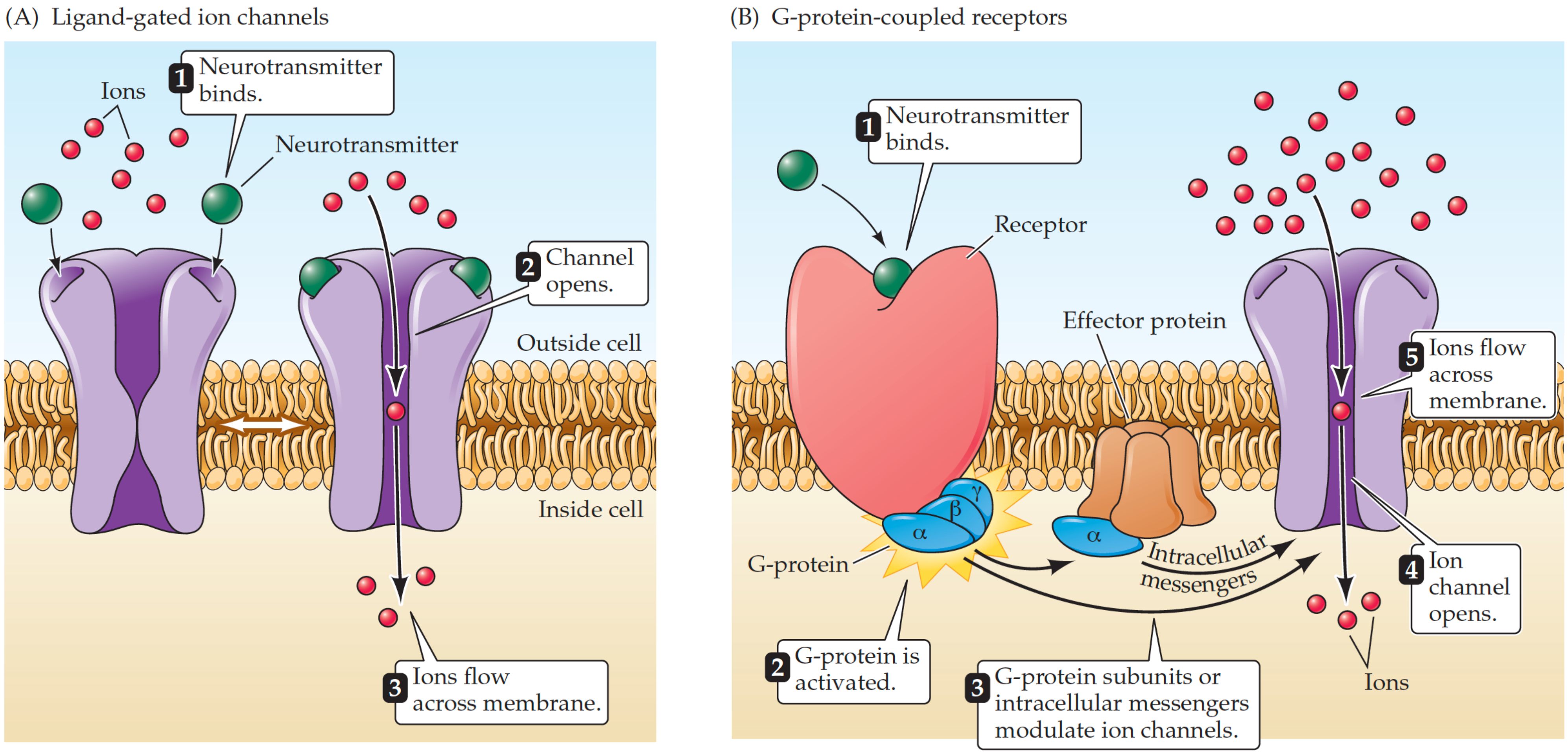
- Note: small synaptic vesicles are ~40 nm



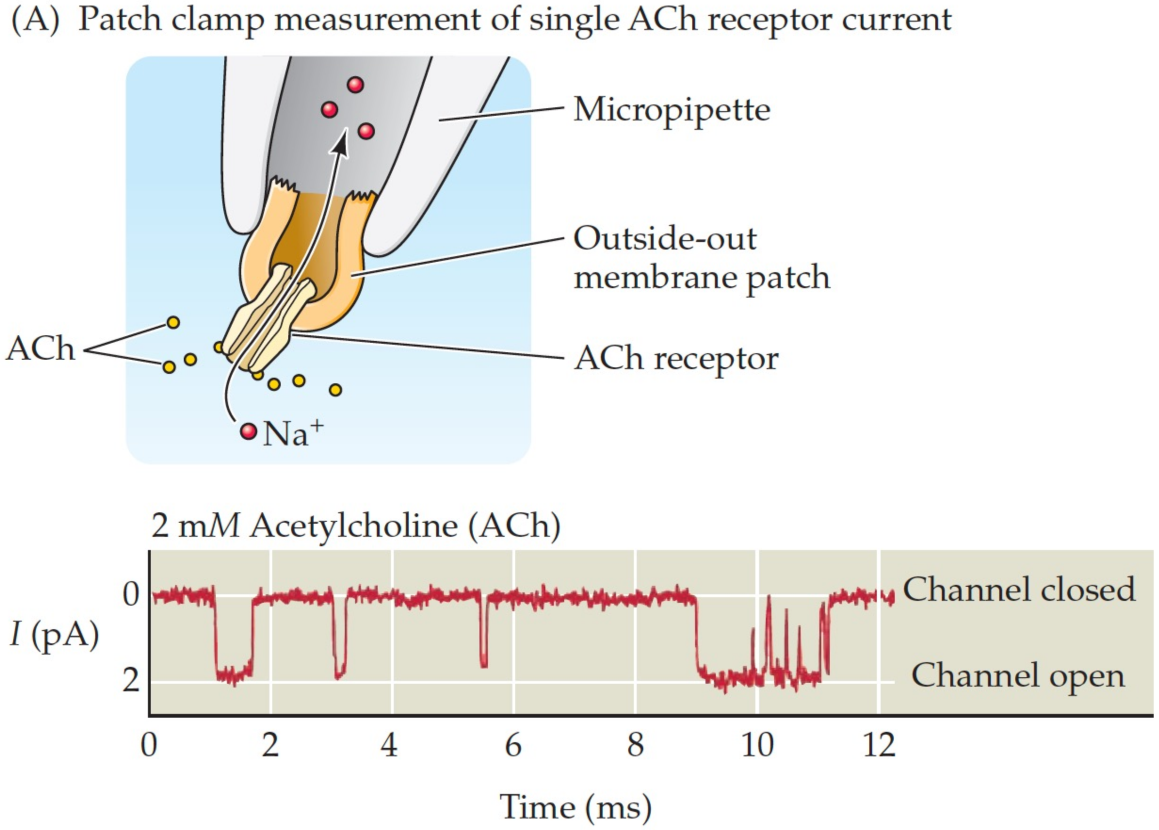

Purves, Figure 5.12

# Two classes of neurotransmitter receptors




Purves, Figure 5.14

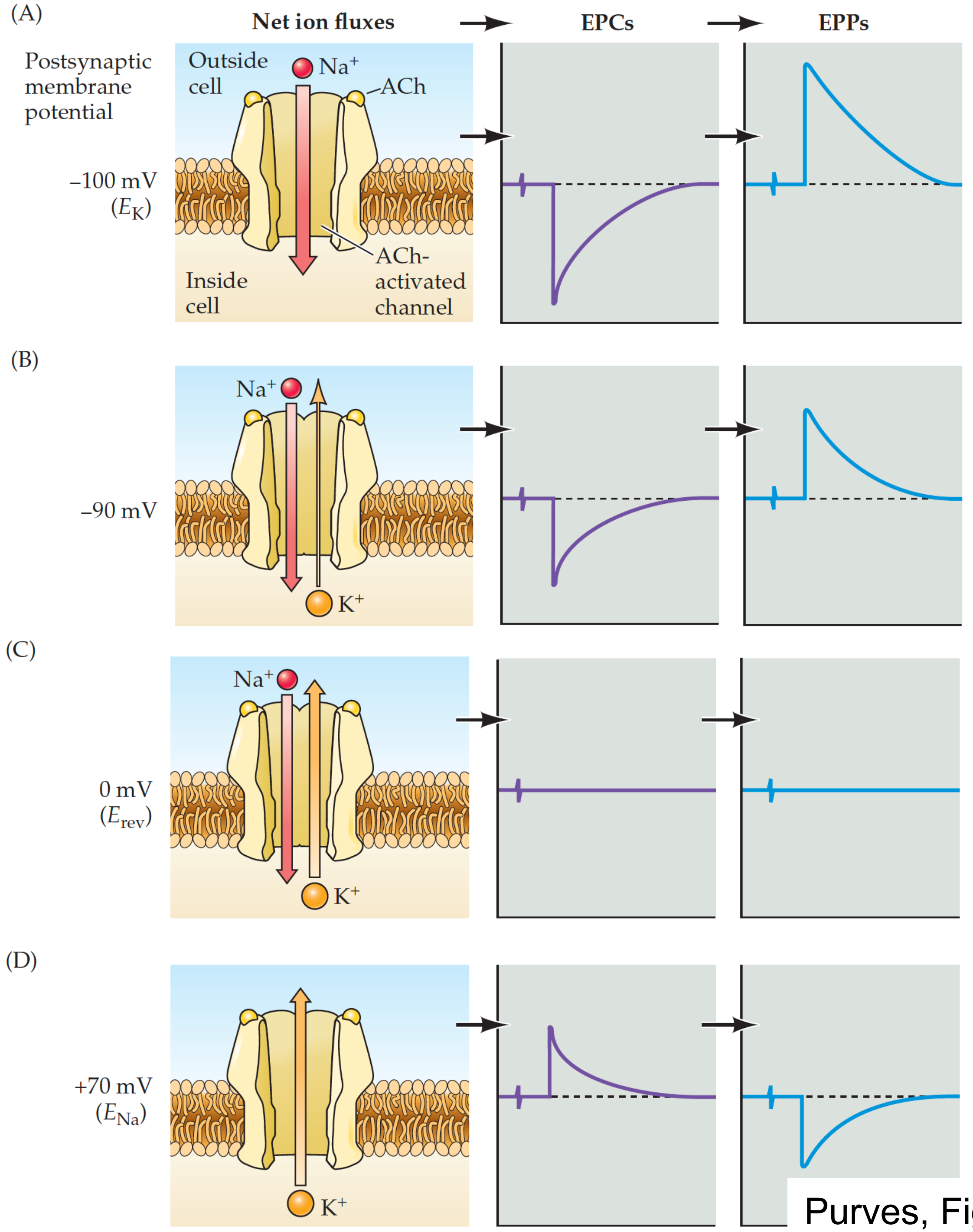
# Current-voltage relationships




- *Inward cationic* current is *depolarizing*
- *Outward cationic* current is *hyperpolarizing*

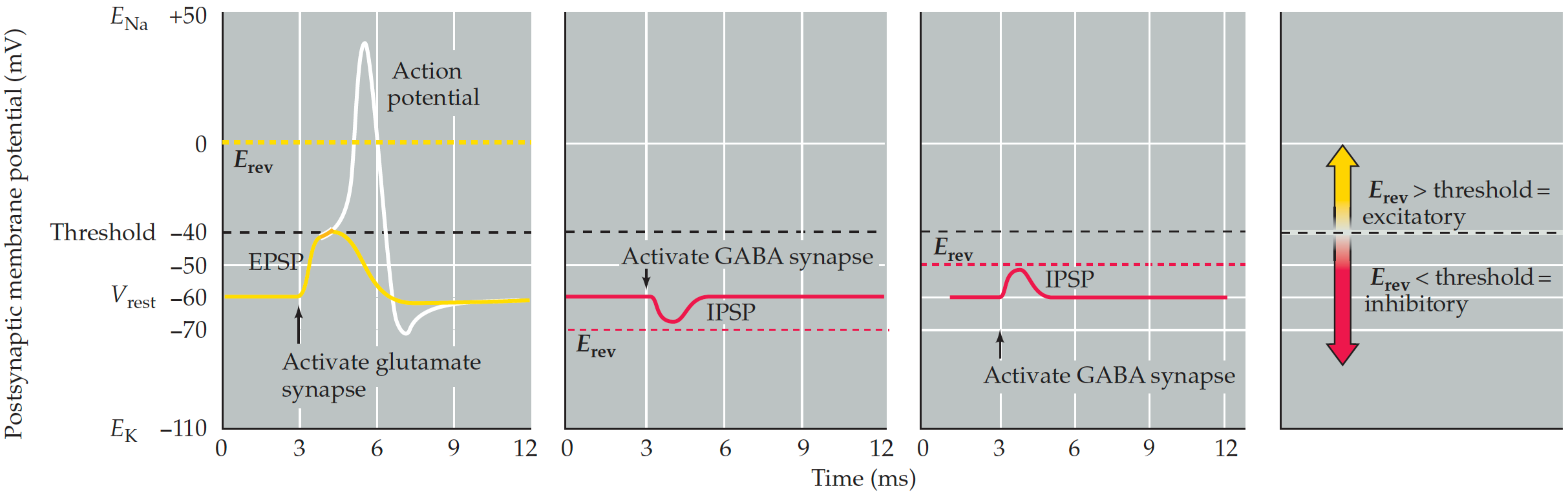
What about for an *anionic* current?

Purves, Figure 5.15



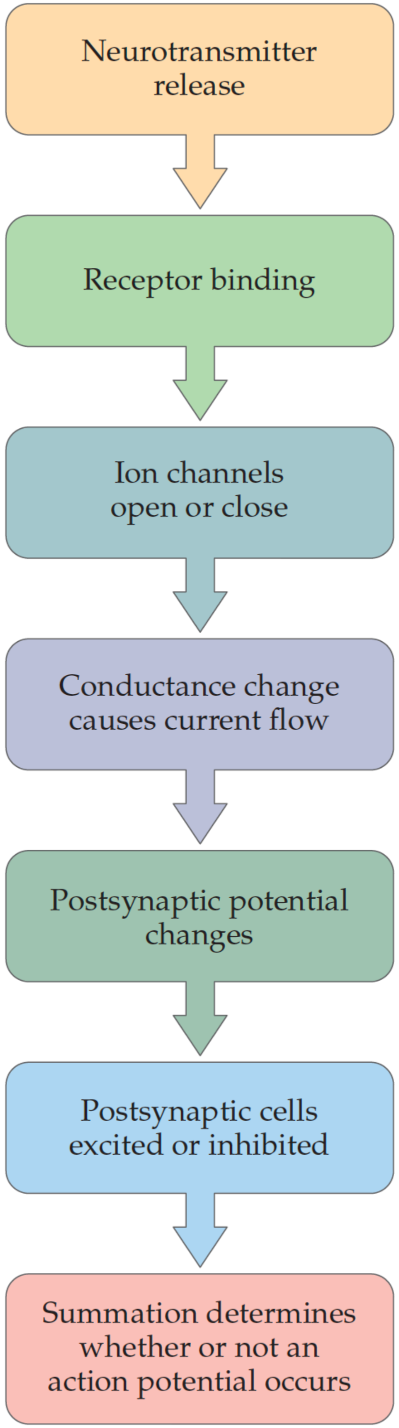

Purves, Figure 5.18

# Reversal potentials and threshold potentials determine postsynaptic excitation and inhibition.



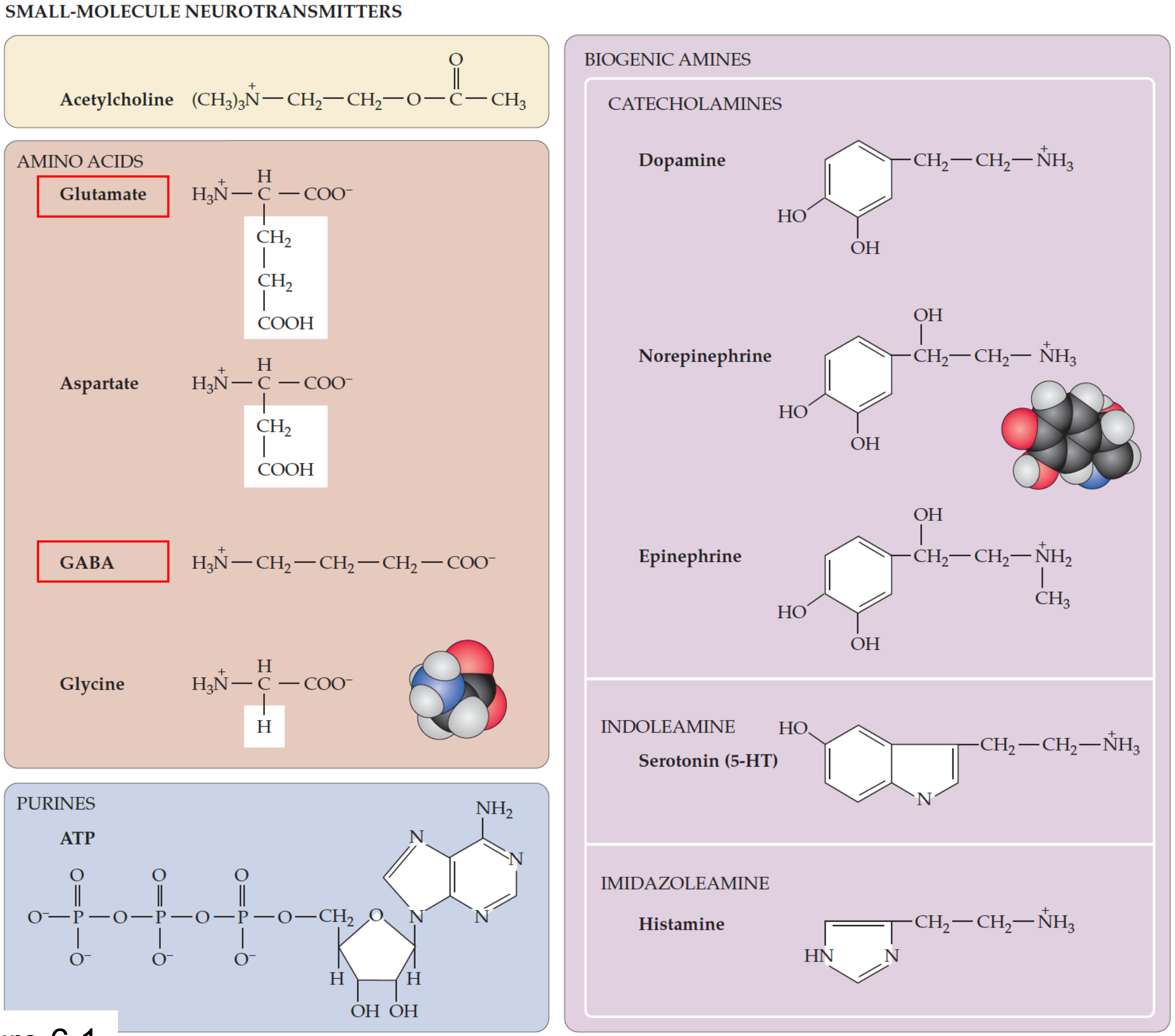

Purves, Figure 5.19

# Review of events leading to postsynaptic signaling




Purves, Figure 5.21

# Overview of small molecule neurotransmitters



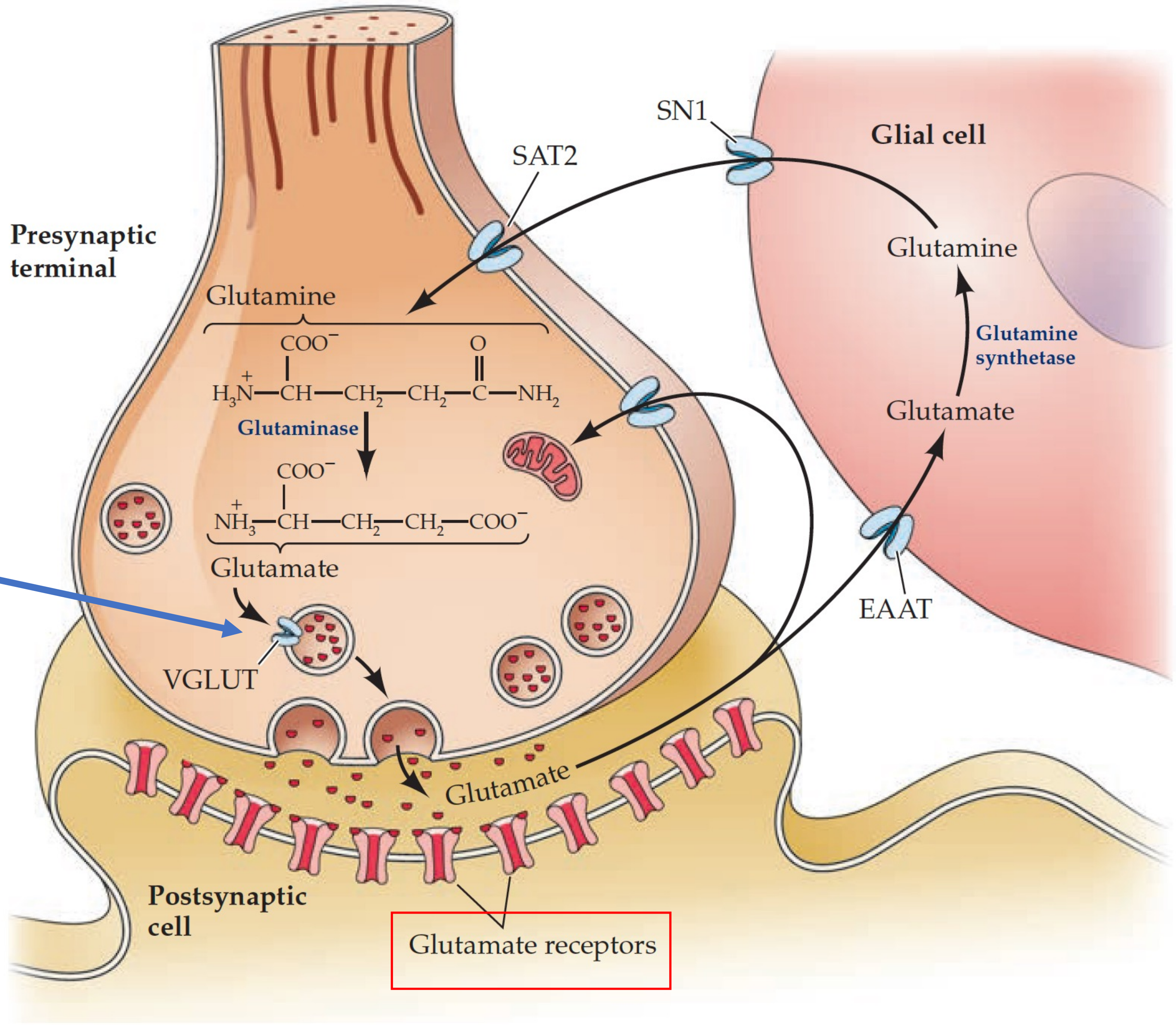

Purves, Figure 6.1

| Neurotransmitter | Postsynaptic effect[a] |
|---|---|
| ACh | Excitatory |
| Glutamate | Excitatory |
| GABA | Inhibitory |
| Glycine | Inhibitory |
| Catecholamines (epinephrine, norepinephrine, dopamine) | Excitatory |
| Serotonin (5-HT) | Excitatory |
| Histamine | Excitatory |
| ATP | Excitatory |
| Neuropeptides | Excitatory and inhibitory |
| Endocannabinoids | Inhibits inhibition |
| Nitric oxide | Excitatory and inhibitory |

Purves, Table 6.1

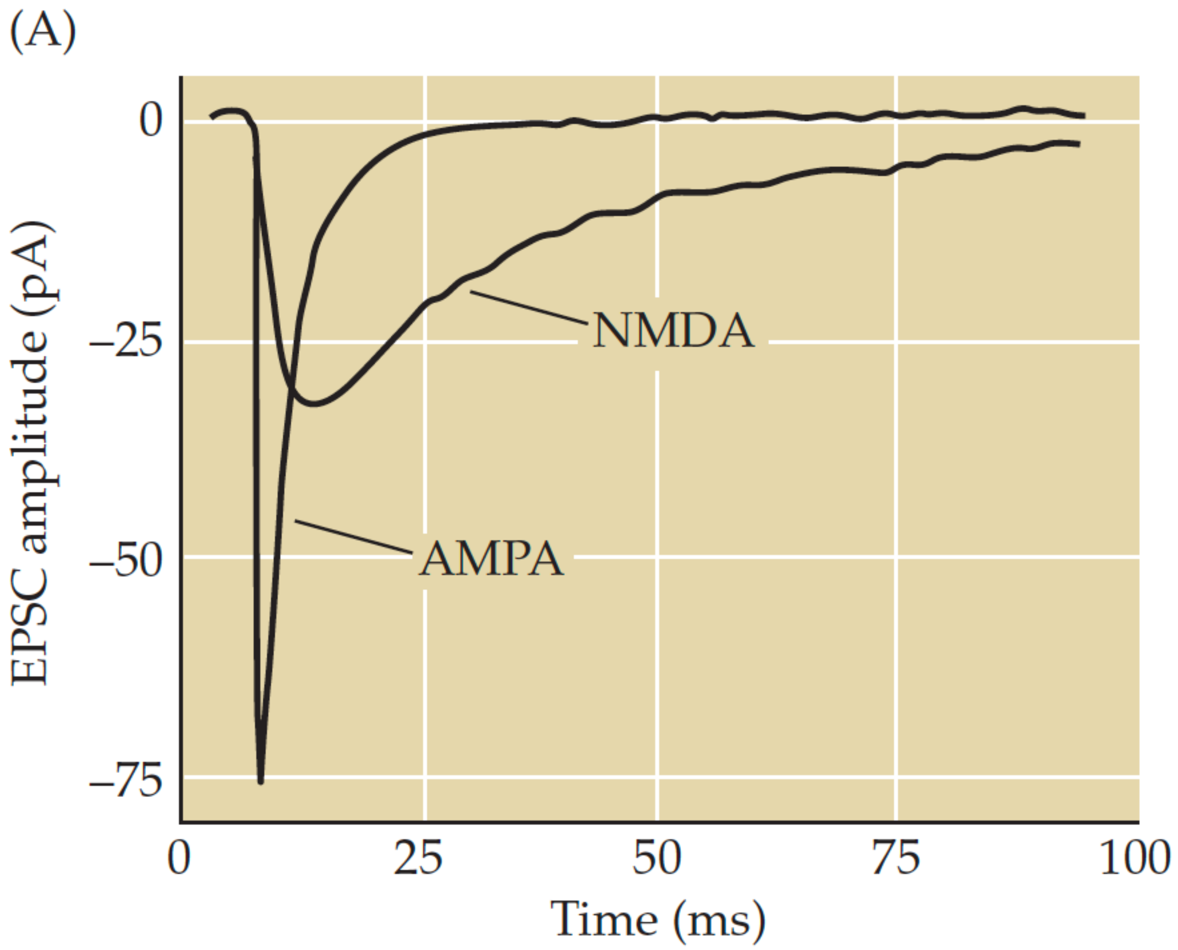
# Glutamate – the dominant excitatory neurotransmitter in the CNS

- VGLUT: vesicular glutamate transporter
- Vesicle is acidic (~5.5 pH inside)
- pH gradient is used by VGLUT to pump glutamate into the vesicle



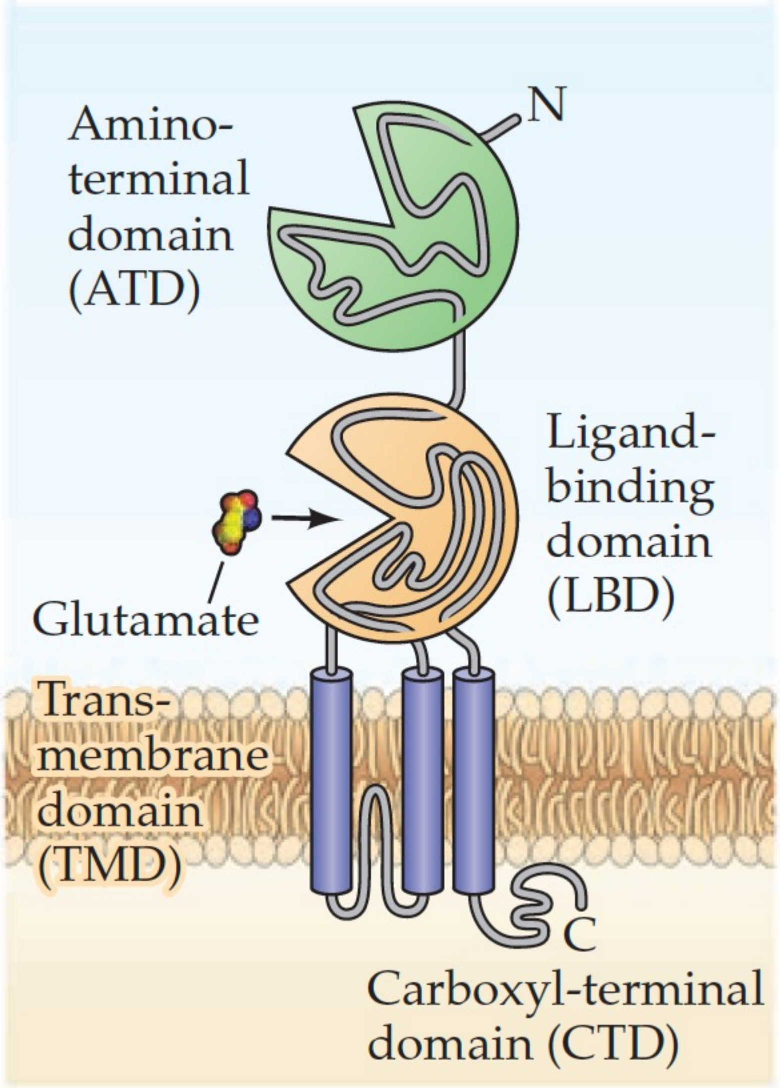

Purves, Figure 6.5

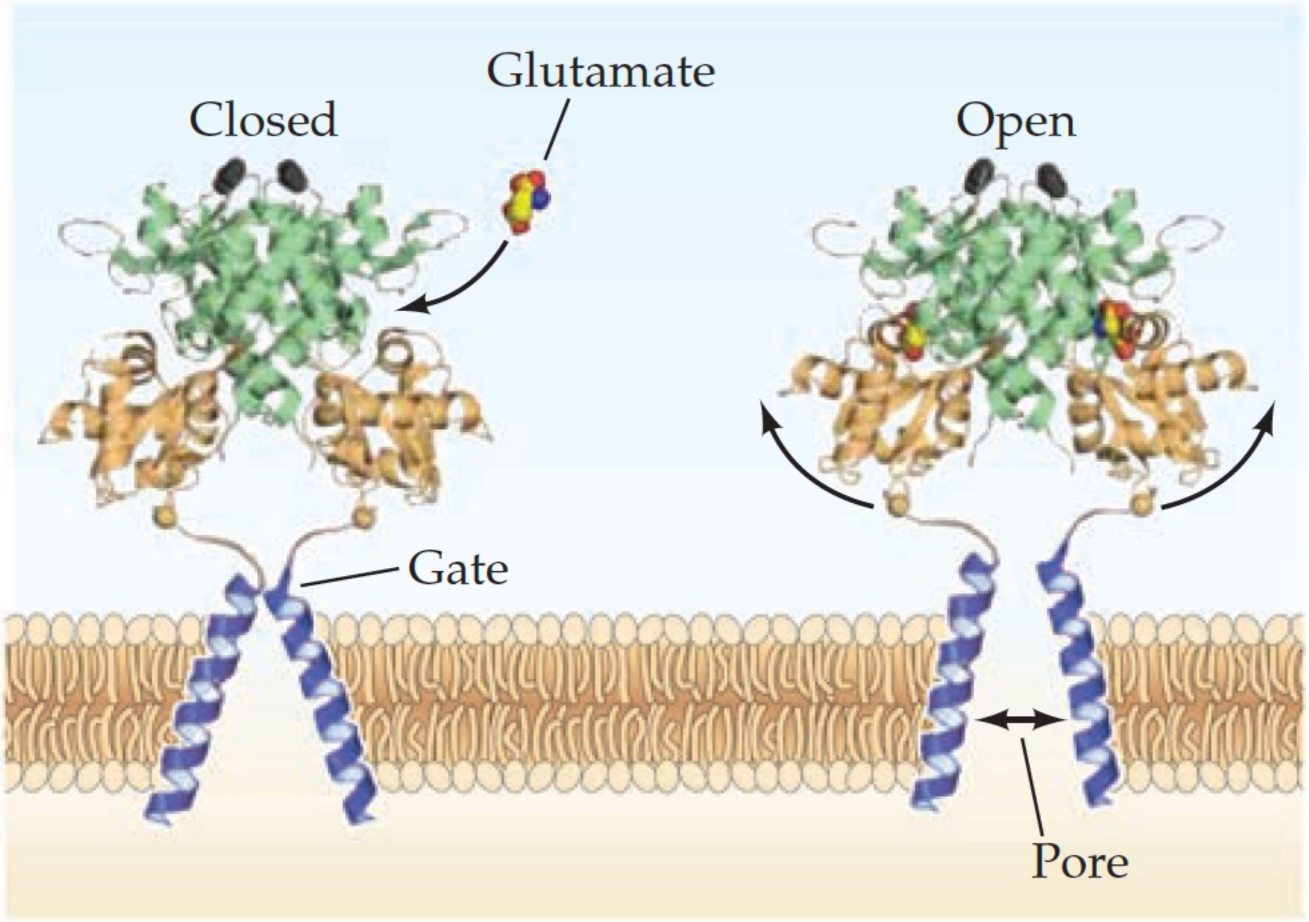
# Two classes of ionotropic glutamate receptors




Purves, Figure 6.6

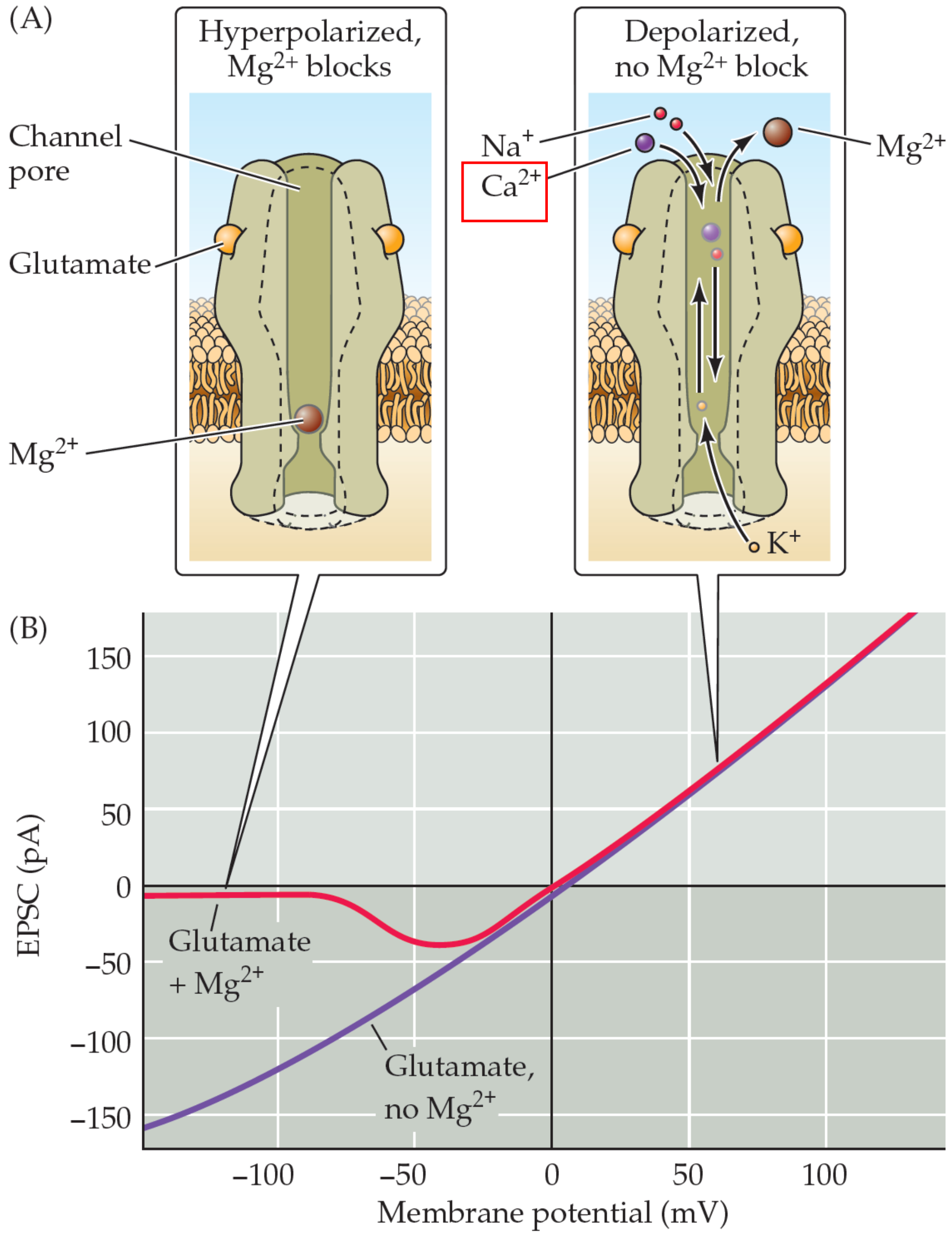
# AMPA receptor structure and function




Purves, Figure 6.7

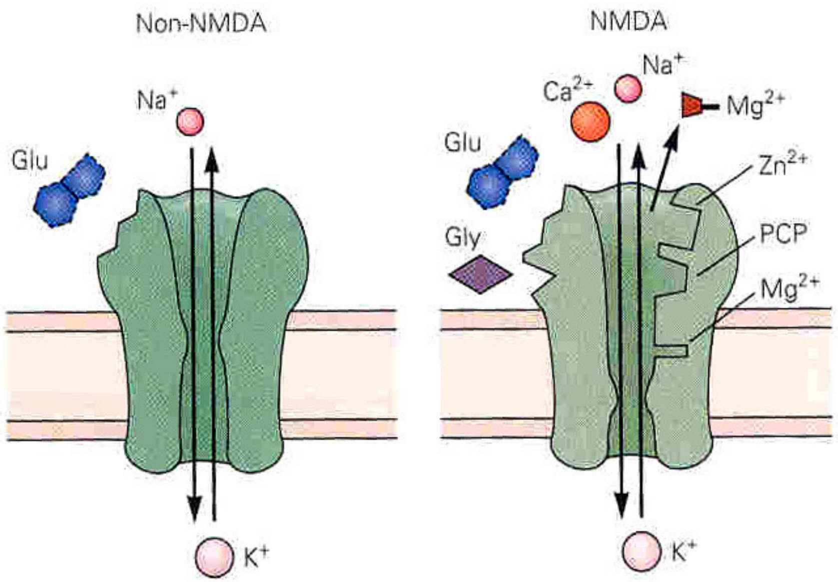
# NMDA receptor structure and function




Purves, Figure 6.8

# Summary of AMPA versus NMDA receptors

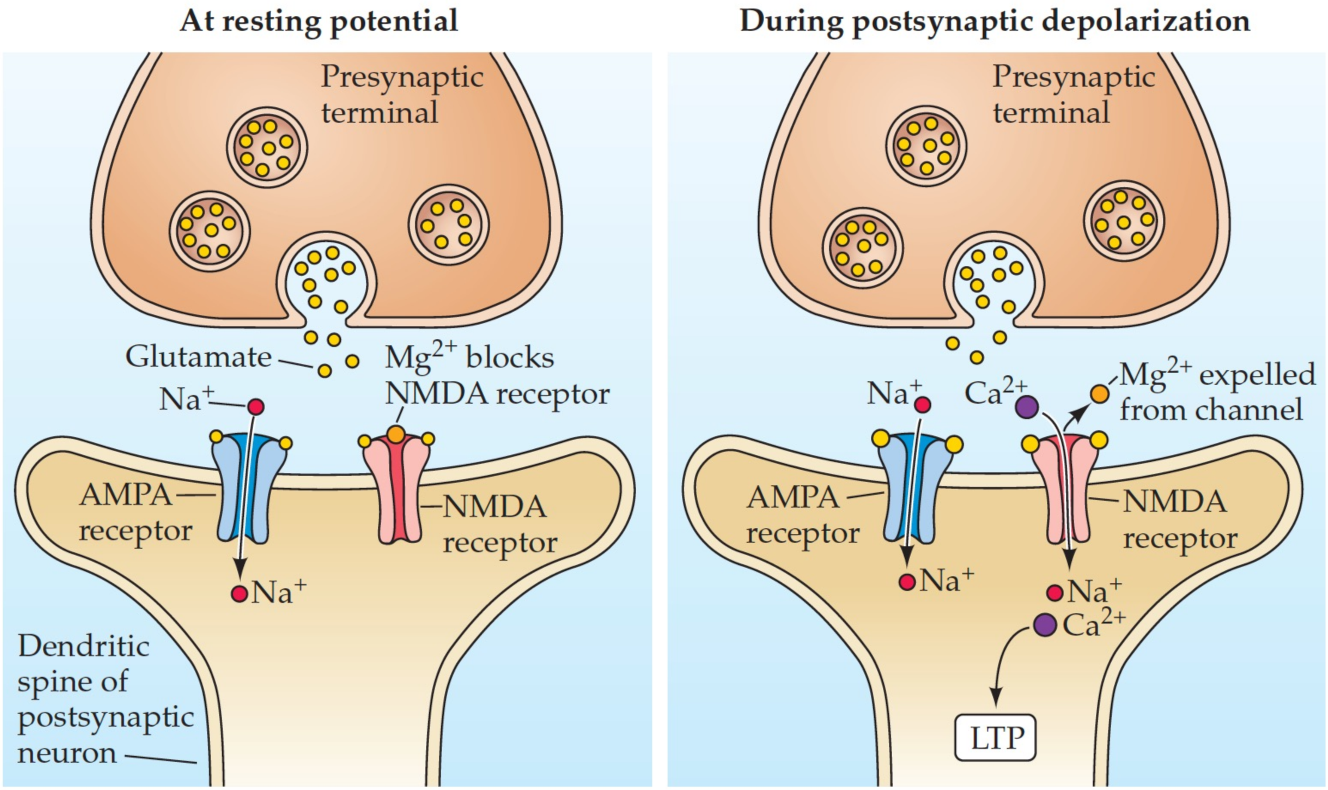
AMPA mediates Fast EPSC NMDA mediating slow EPSC




| | | |
|---|---|---|
| Selective agonist: | () | (N-methyl-D-aspartate) |
| Natural agonist | L-glutamate | L-glutamate |
| *Co-agonist* | -- | glycine, D-serine |
| Antagonist | CNQX | APV |
| Ionic permeability: | $Na^+$, $K^+$ | $Na^+$, $K^+$, $Ca^{2+}$ |
| Ionic block by: | | $Mg^{2+}$ (only at hyperpolarized $V_m$) |

Kandel

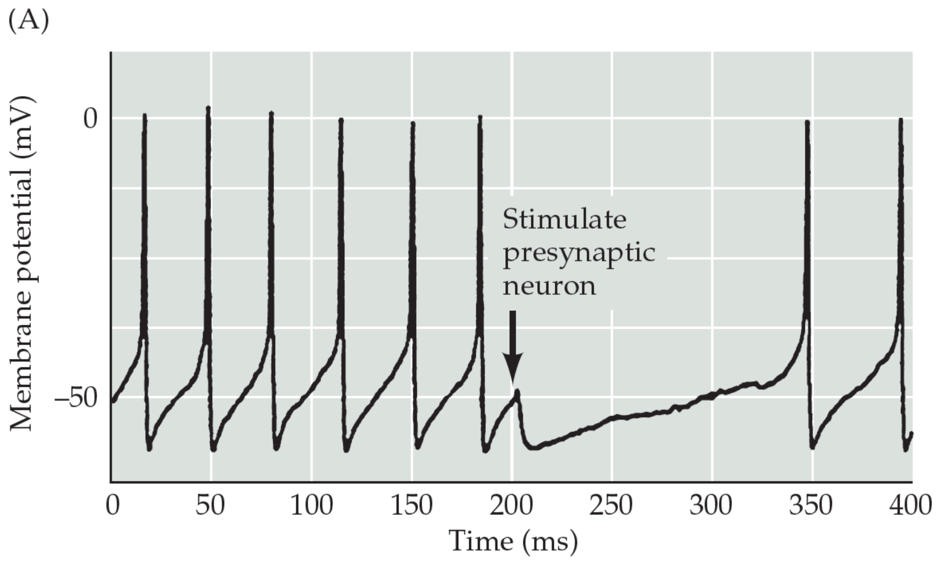
# Roles for AMPA- and NMDA-receptor channels during baseline transmission and coincident pre- and postsynaptic activity

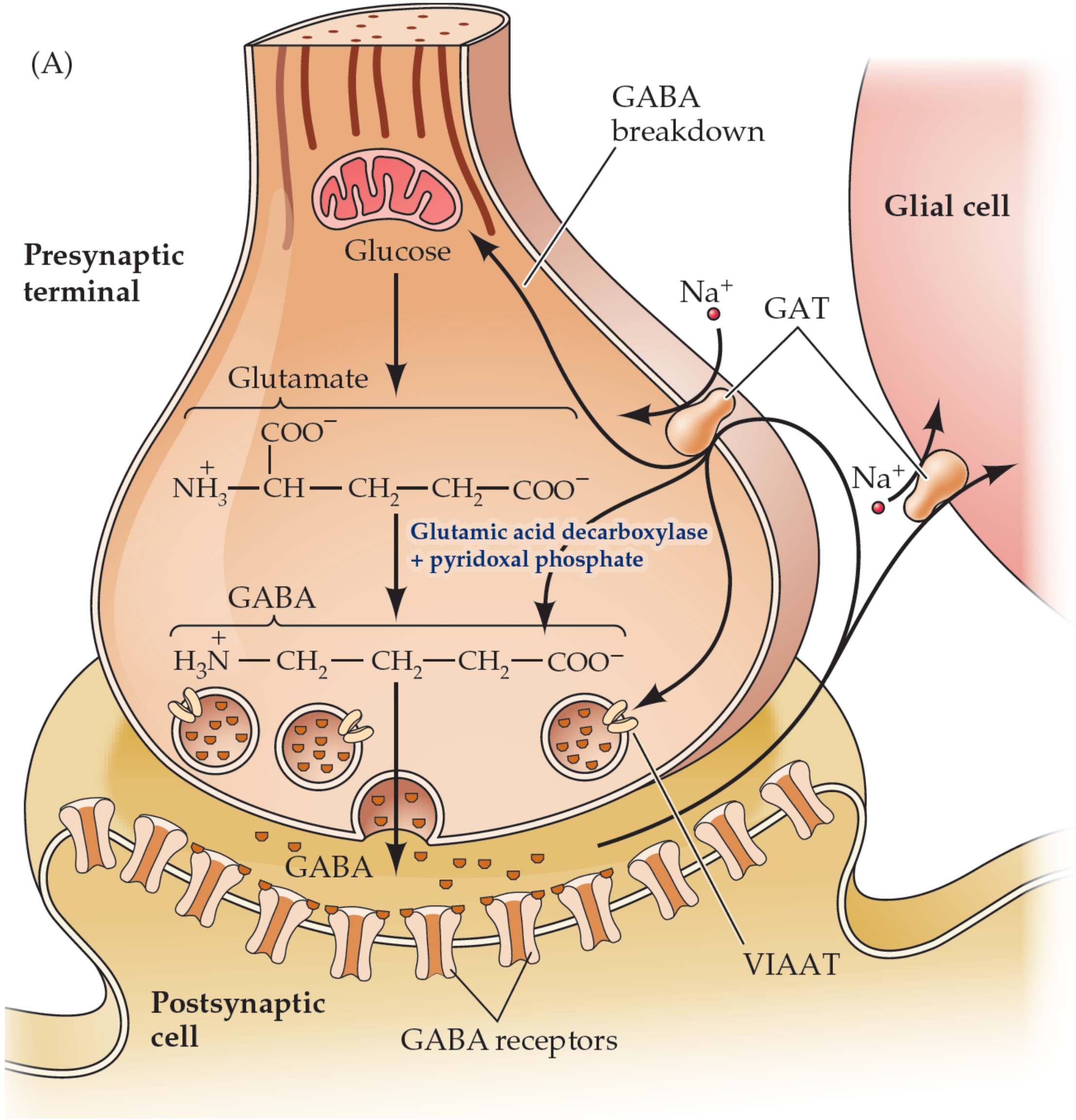



- Voltage-dependent $Mg^{2+}$ ion block of NMDA channel means the channel can only function if
  - (i) glutamate is bound (**pre**synaptic activity) **AND**
  - (ii) the $Mg^{2+}$ block is relieved (**post**synaptic depolarization)
- This serves as a means of **"coincidence detection"** for pre- and postsynaptic activity
- The resulting $Ca^{2+}$ influx induces synaptic plasticity via long-term potentiation (LTP)

Purves, Figure 8.10

# GABA – the predominant inhibitory neurotransmitter in the CNS

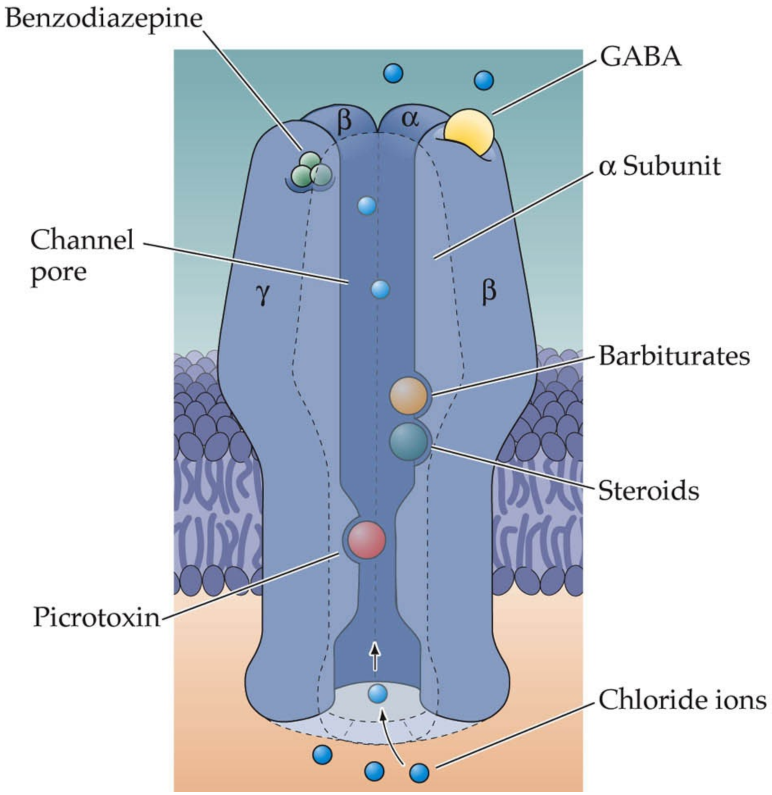



Purves, Figure 6.11

Purves, Figure 6.10

# The GABA receptor, some facts

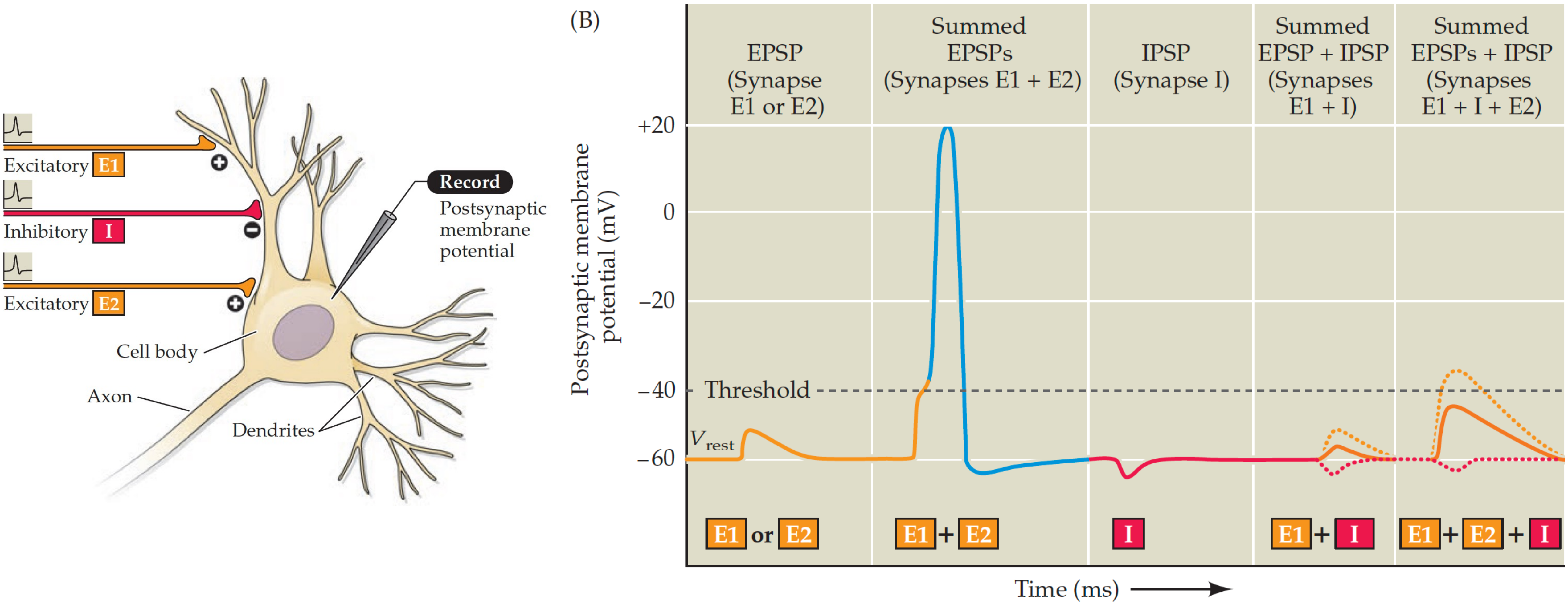



- Ionic permeability: $Cl^-$
- Natural agonist: GABA (γ-amino-butyric acid)
- Competitive antagonist: Bicuculline (a plant alkaloid)
- Allosteric binding site for Benzodiazepines
  agonist: Diazepam ("Valium") which is tranquilizing
- Further modulatory site for Barbiturates (hypnotics; anesthesia)

Note: Cl- normally enters the cell (hyperpolarizing) due to a higher extracellular concentration

Purves, older edition

# The dendritic summation of postsynaptic potentials




Purves, Figure 5.20

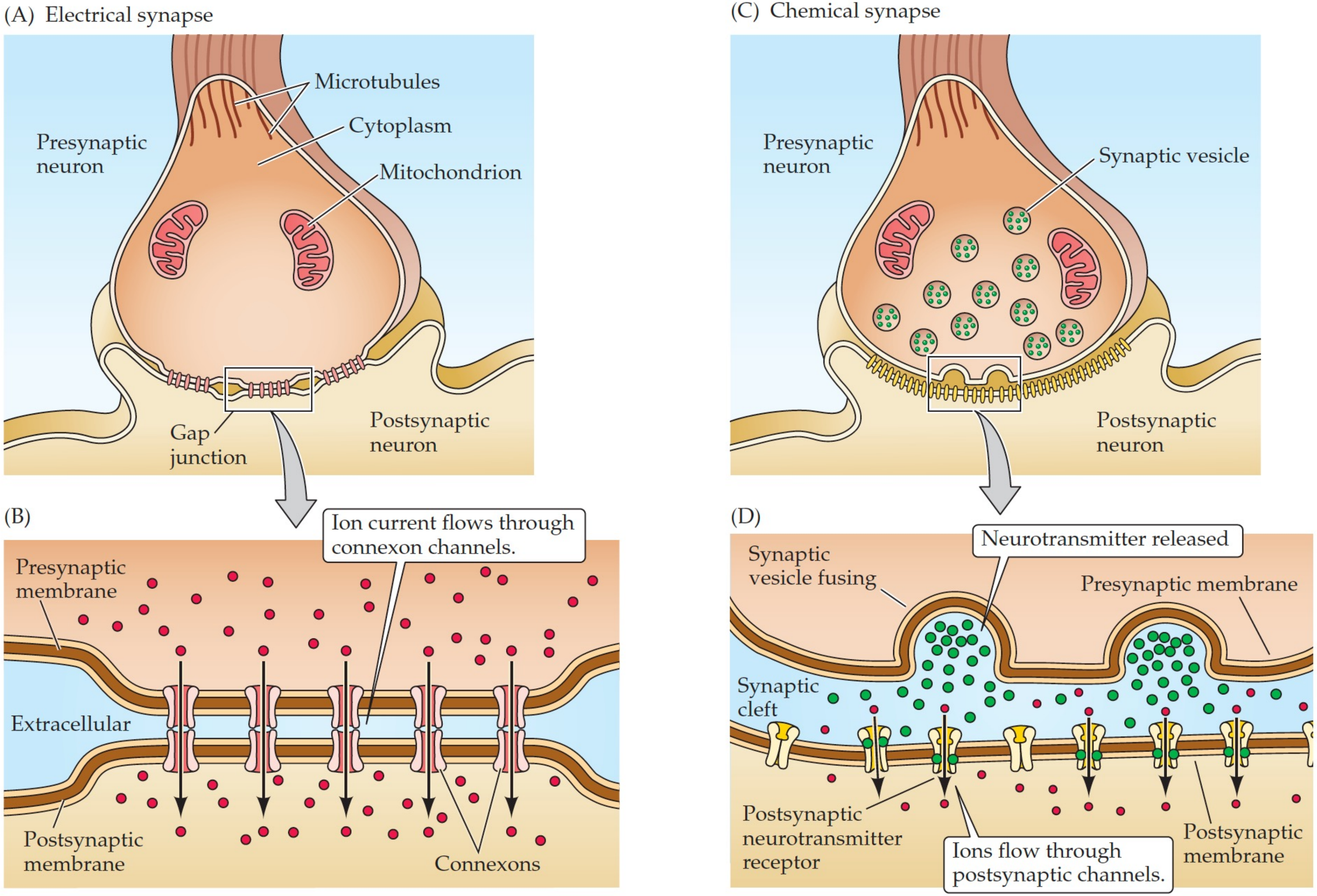
# Dale‘s principle: A given neuron usually uses only 1 small neurotransmitter

| Neuron is called | Transmitter | important (defining) enzyme/transporter |
|---|---|---|
| **"glutamatergic"** | **glutamate** | **vesicular glutamate transporter, VGluT** |
| **"GABA-ergic"** | **GABA** | **Glutamic acid decarboxylase, GAD<br>(vesicular GABA transporter, VGAT)** |
| **"glycinergic"** | **glycine** | **(vesicular GABA transporter, VGAT)** |
| "cholinergic" | ACh | choline acetyltransferase (ChAT)<br>vesicular aceytcholine transporter (VAChT) |
| "dopaminergic" | dopamine | Tyrosine-Hydroxylase, TH |
| "noradrenergic" | noradrenaline<br>(=norepinephrine) | Tyrosine-Hydroxylase, TH<br>AND Dopamine-$\beta$-Hydroxylase |

in vertebrates these transmitters only act on Metabotropic receptors

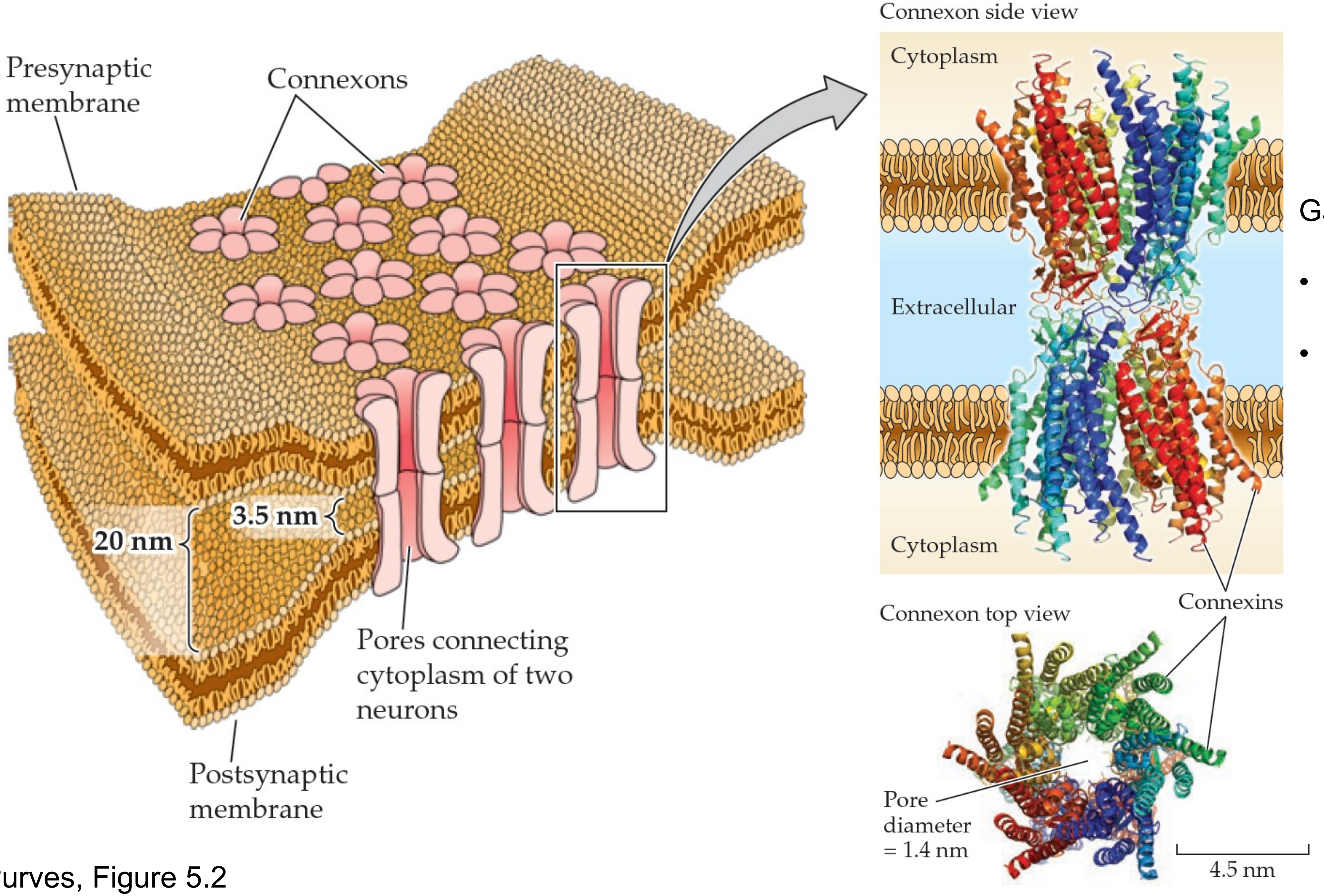
Dale‘s principle is only a first approximation. There are many exceptions.

# Electrical versus chemical synapses




Purves, Figure 5.1

# Gap junctions (electrical synapses) consist of connexons



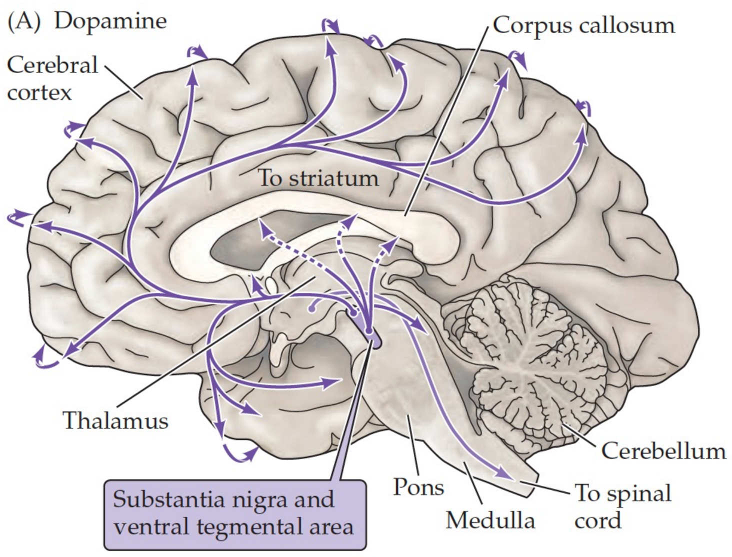

Gap junctions:

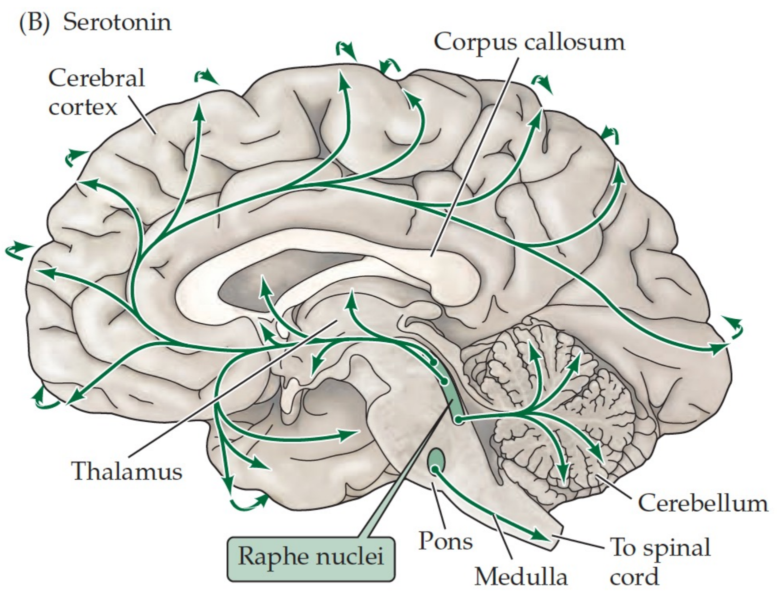
- Mediate fast neurotransmission
- Facilitate synchronization between neurons

Purves, Figure 5.2

# Neuromodulators with widespread projections through the brain

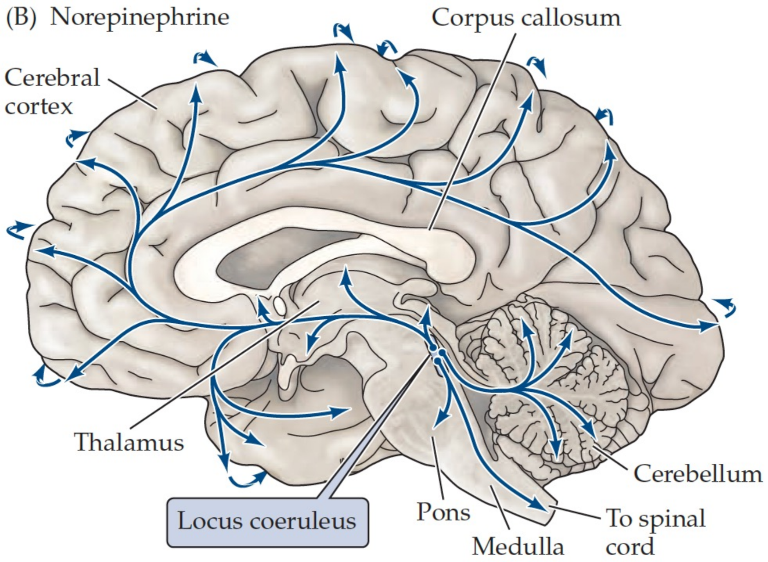
Dopamine

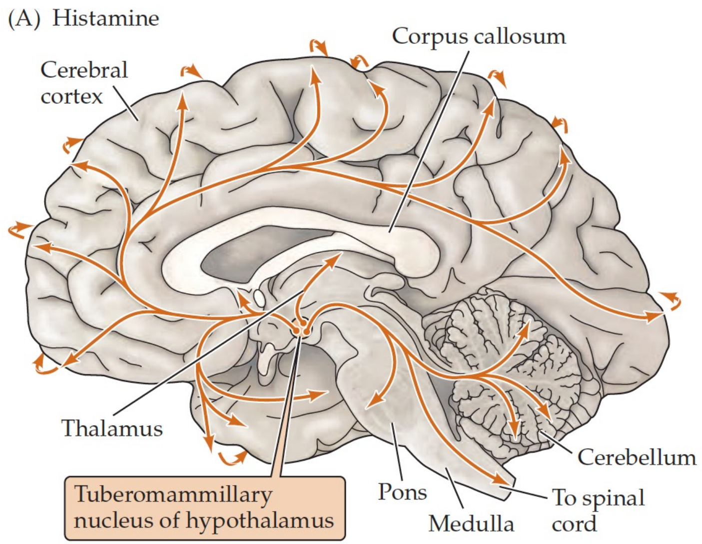



Serotonin

Norepinephrine



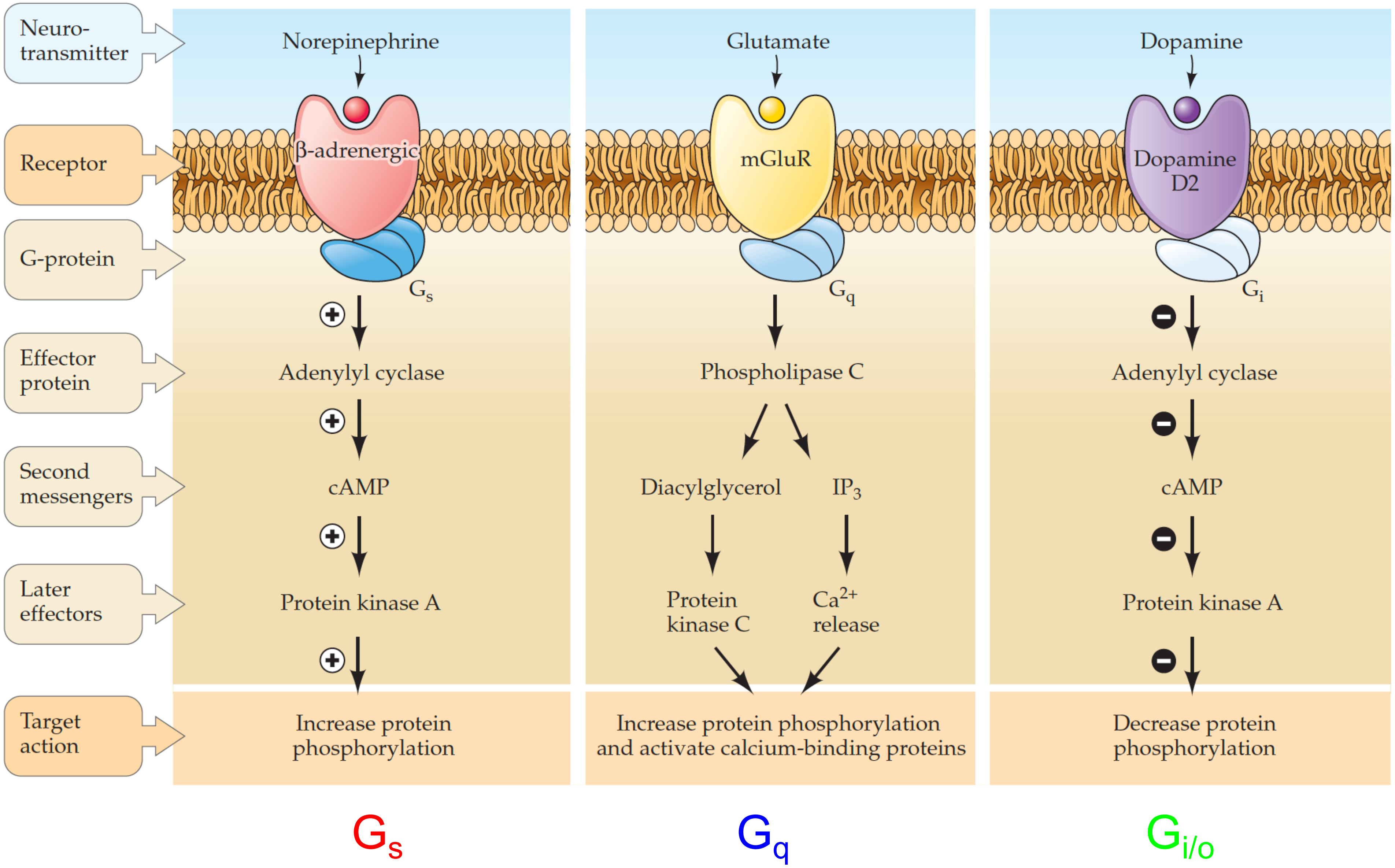




Histamine

Purves, Figure 6.15

Purves, Figure 6.17

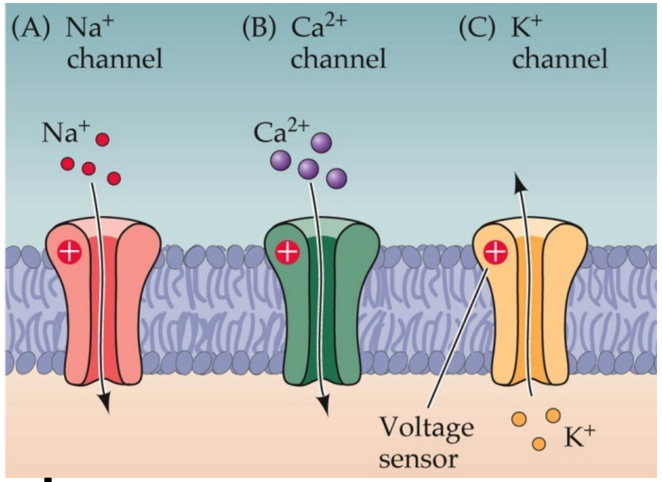
# Effector pathways associated with G-protein coupled receptors



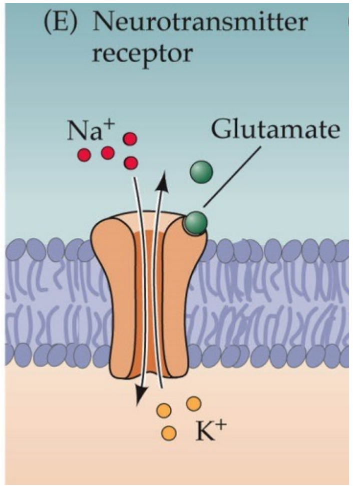

Purves, Figure 7.6

# Summary: ion channels, and membrane receptors

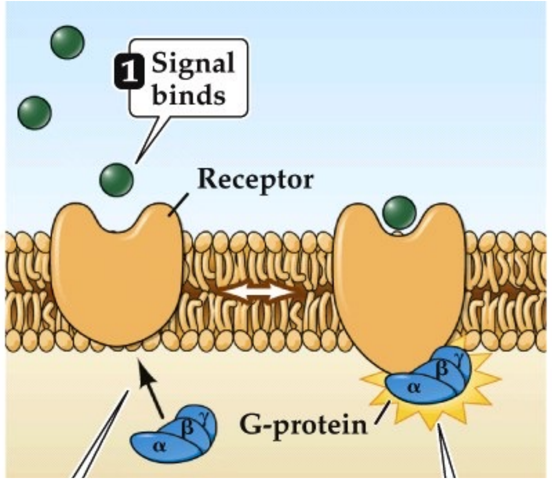
Voltage-gated channel




Ligand-gated channels
or "ionotropic receptor"




G-Protein coupled receptor (GPCR)
or "metabotropic receptor"




Ion channels

Membrane receptors

Purves, Figure 4.4

Purves, Figure 7.4C

# <u>Summary</u>: Important concepts and keywords

- Nerve terminal components (voltage-gated $Ca^{2+}$ channels, vesicles with neurotransmitters)
- Quantized presynaptic transmission
- $Ca^{2+}$ regulation of vesicle fusion; SNARE proteins, Synaptotagmin
- Excitatory Postsynaptic Potential (EPSP) versus Excitatory Postsynaptic Current (EPSC)
- Glutamatergic receptors: roles and mechanisms for AMPA versus NMDA
- GABA as an inhibitory transmitter; $GABA_A$ receptor ($Cl^-$ permeability; Bicuculline, Benzodiazepines)
- Inhibitory postsynaptic potential, IPSP
- Integration of excitatory and inhibitory synaptic inputs in the dendrite of neurons
- Gap junctions
- Neuromodulation