Human Phys PCB4701

Synapses
Fox Chapter 7 pt 3

Synapses: Electrical or Chemical

Electrical Synapse

Continuous cytoplasm through gap junction channels. Electrical transmission by ion currents moving through gap junction channels.

Properties: **No delay** in AP moving between cells; bidirectional transmission.

Chemical Synapse

Discontinuous space between the cells.

Synapses contains presynaptic **vesicles**, postsynaptic **receptors**.

Signal is transmitted across the synapse by chemical molecules (not ions) = **neurotransmitters**.

(There are many different neurotransmitters, and many different receptor types.)

Properties: 1-5 ms **delay** between cells; unidirectional transmission.

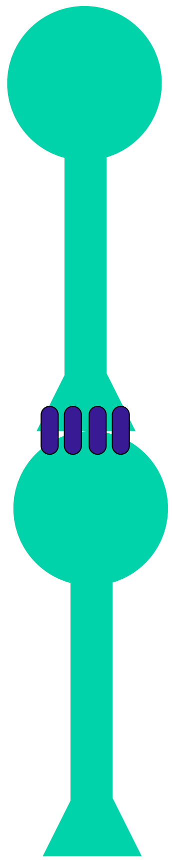
Chemical synapse can be excitatory or inhibitory

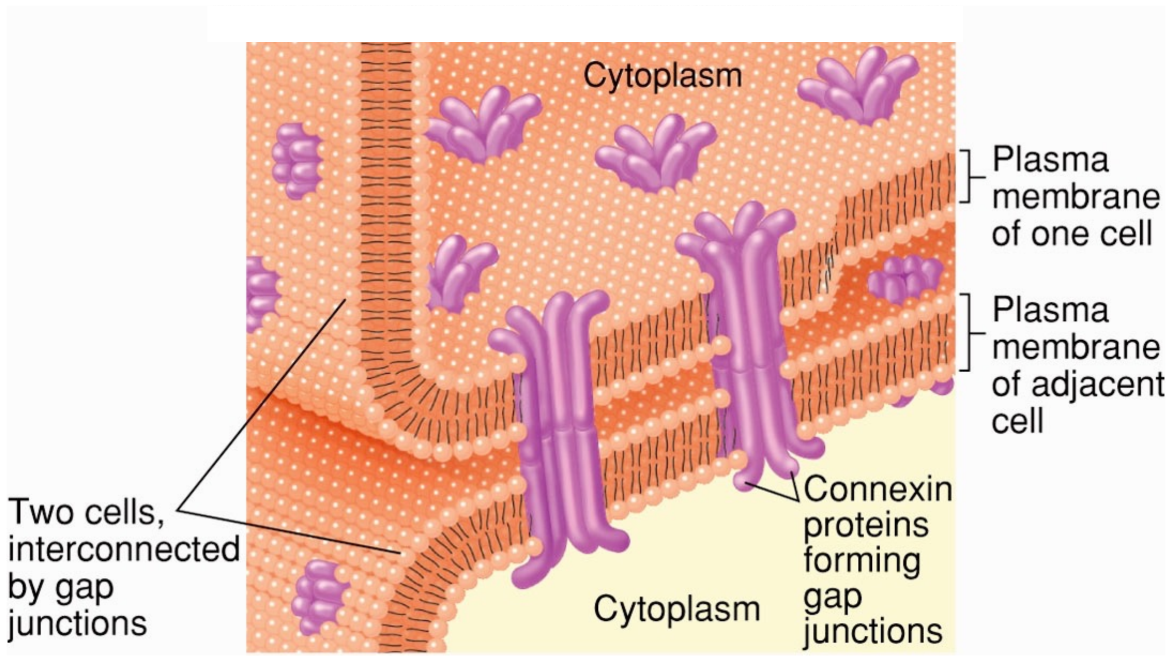
Excitatory: raise Vm closer to threshold for AP (depolarize target cell)

Inhibitory: lower Vm away from threshold (hyperpolarize target cell).

Electrical Synapse

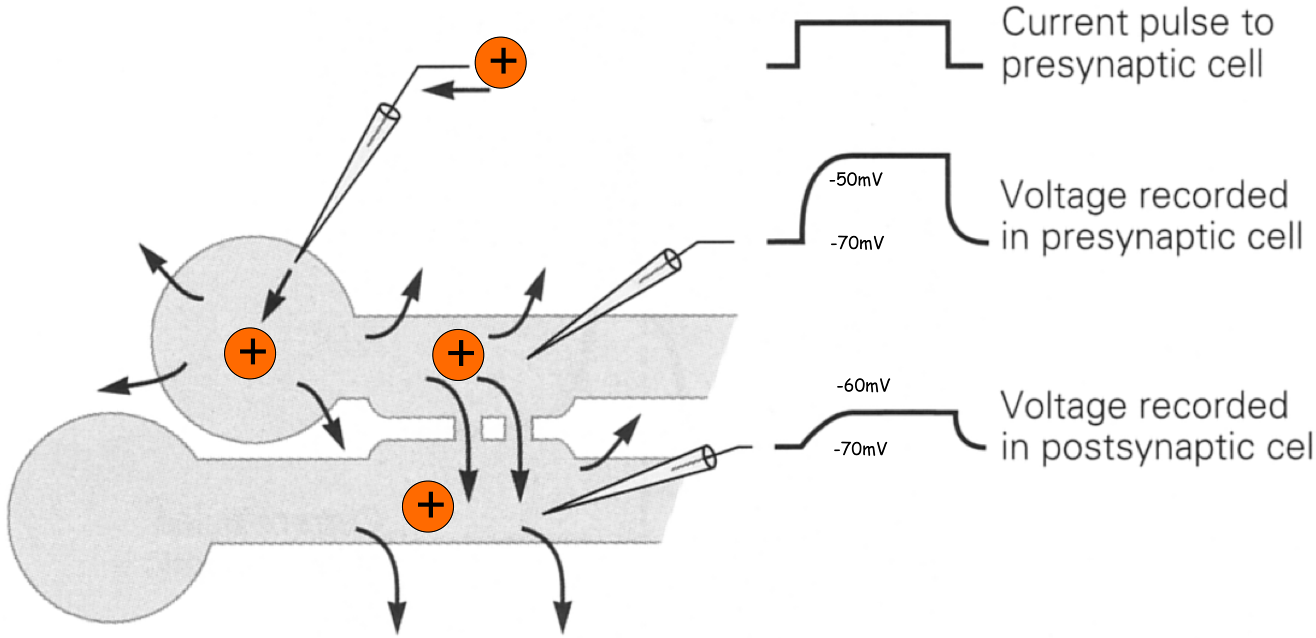
couples neurons or muscle cells



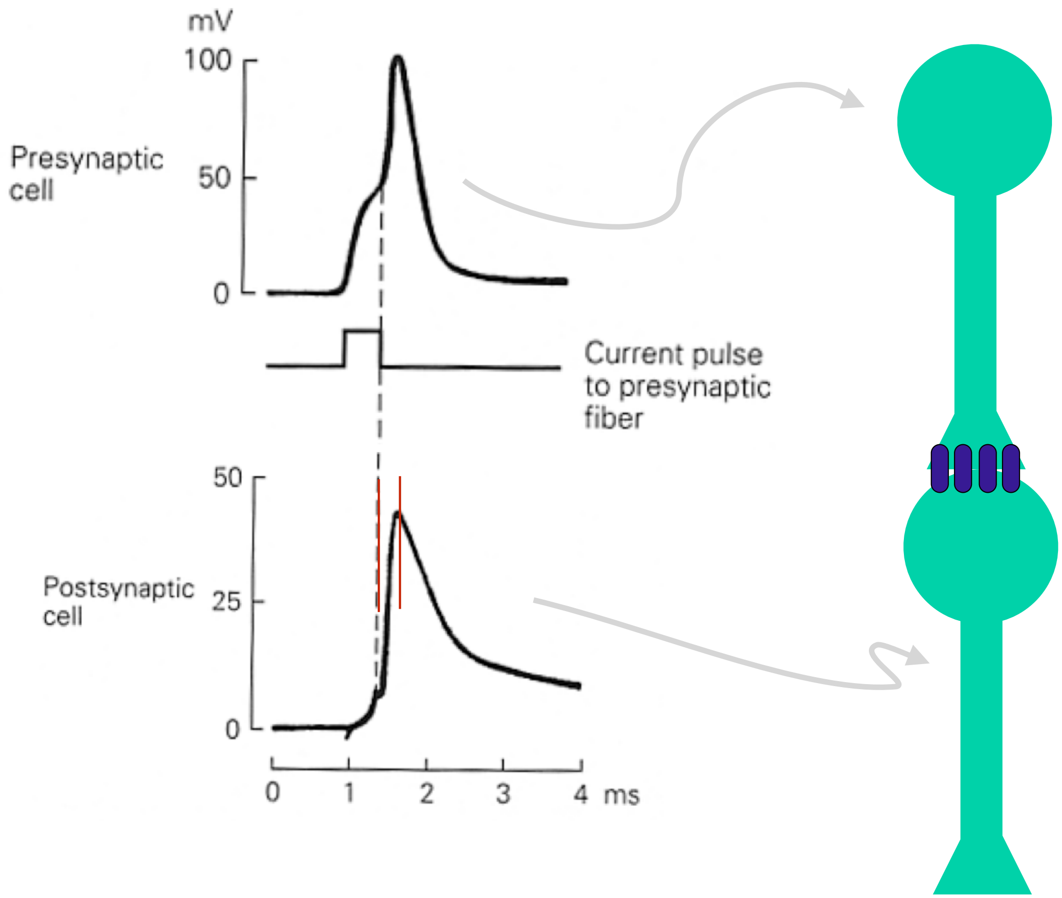


Fox Figure 7.21

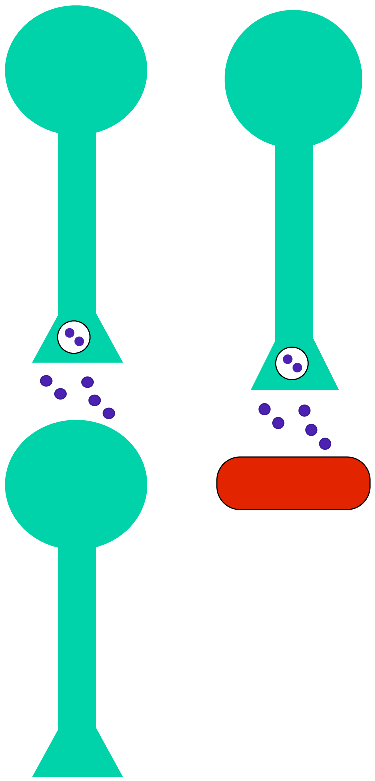
Current flows easily thru Gap Junctions

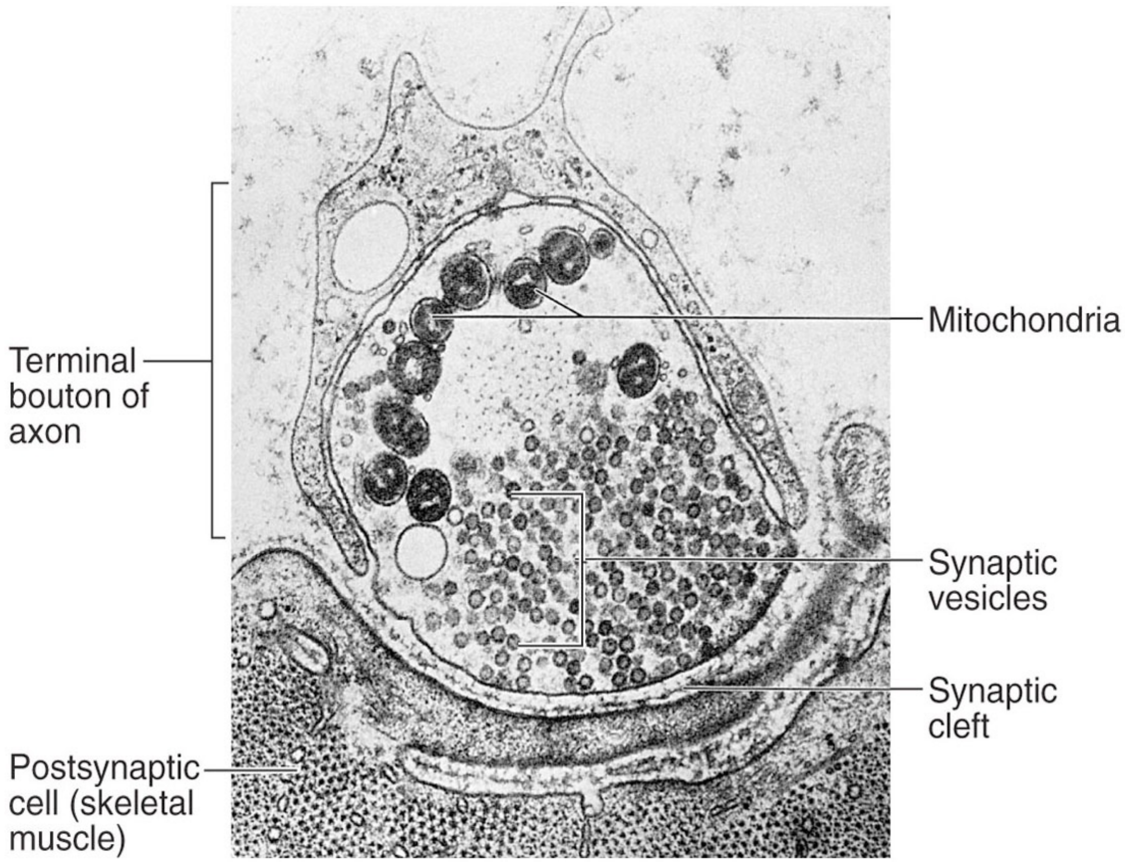


AP crosses Electrical Synapse instantly



Chemical Synapse

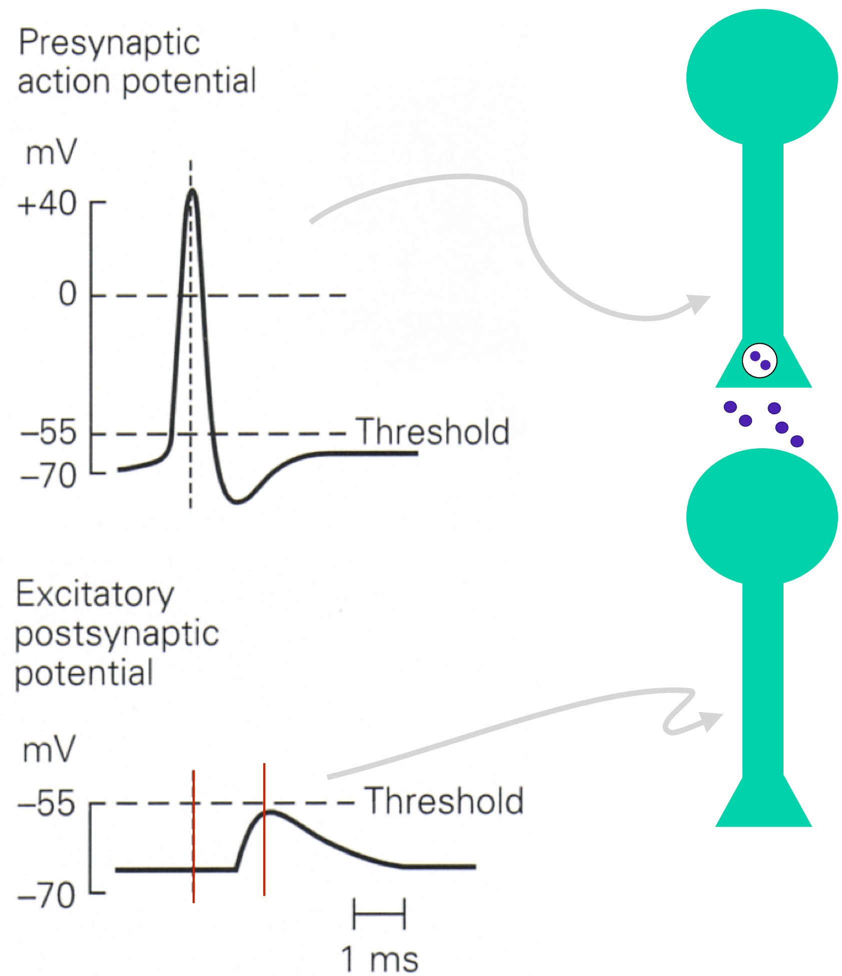




Fox Figure 7.22

AP crosses chemical synapse slowly and is diminished

epsp



Chemical Synapse

Ca2+ induced release of Neurotransmitter

1. Action potential causes voltage sensitive Ca2+ channels to open; Ca^{2+} enters the presynaptic nerve terminal.

2. Ca^{2+} causes vesicles to fuse with presynaptic membrane; neurotransmitter molecules are released into the synapse by exocytosis.

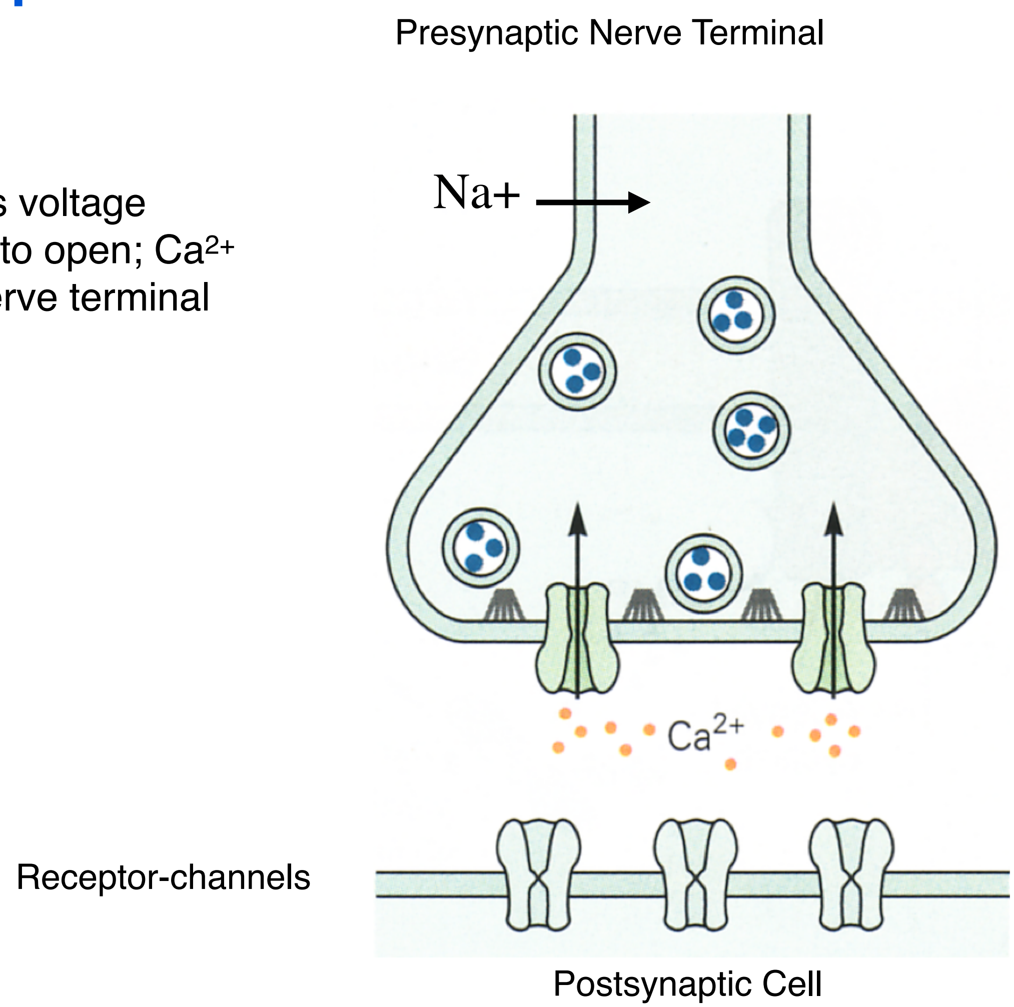
3. Neurotransmitter binds to receptors on postsynaptic cell; if receptors are ligand-gated Na^{+} channels, then Na^{+} enters postsynaptic cell.

4. Influx of Na^{+} causes depolarization of target cell.

(if Cl^{-} channels are opened, then neurotransmitter lowers V_m and thus has inhibitory effect)

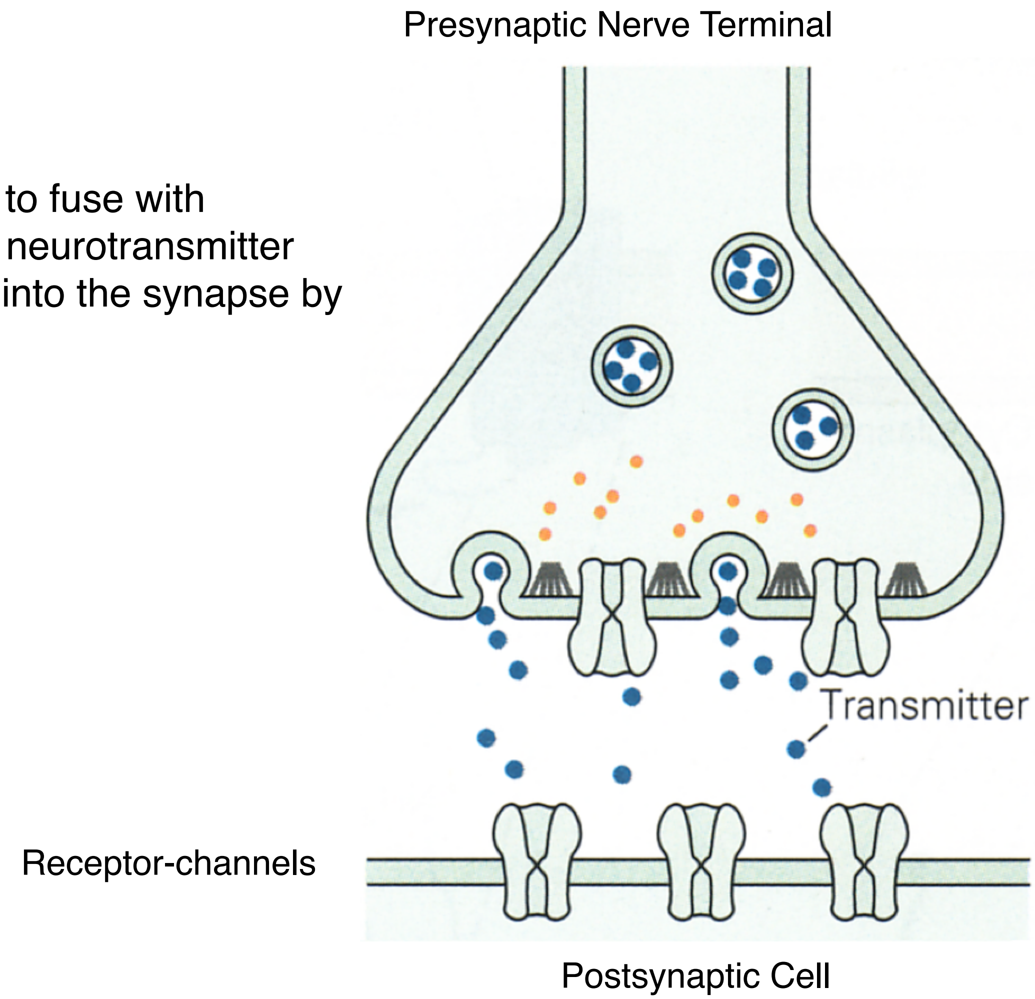
Chemical Synapse

1. Action potential causes voltage sensitive Ca2+ channels to open; Ca^{2+} enters the presynaptic nerve terminal



Chemical Synapse

2. Ca^{2+} causes vesicles to fuse with presynaptic membrane; neurotransmitter molecules are released into the synapse by exocytosis.



Chemical Synapse

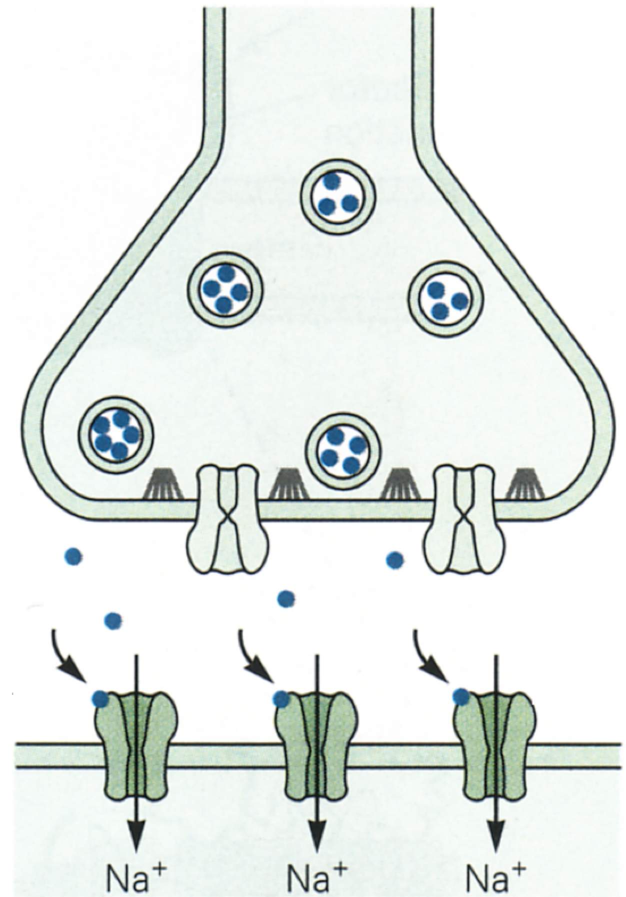
Presynaptic Nerve Terminal

3. Neurotransmitter binds to receptors on postsynaptic cell; if receptors are ligand-gated Na^+ channels, then Na^+ enters postsynaptic cell

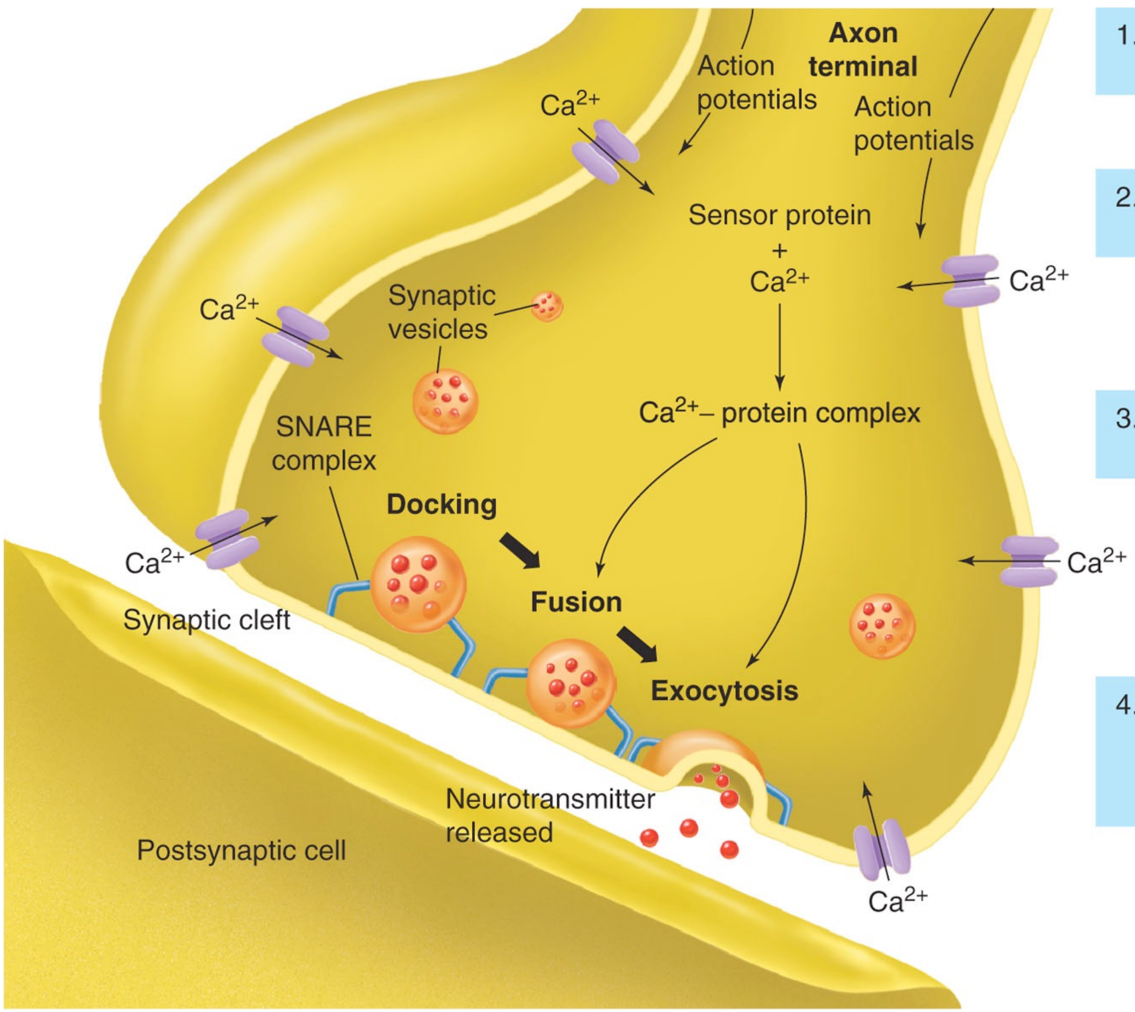
4. Influx of Na^+ causes depolarization of target cell

(if Cl^- channels are opened, then neurotransmitter lowers V_m and has inhibitory effect)

Receptor-channels



Postsynaptic Cell



1. Action potentials reach axon terminals

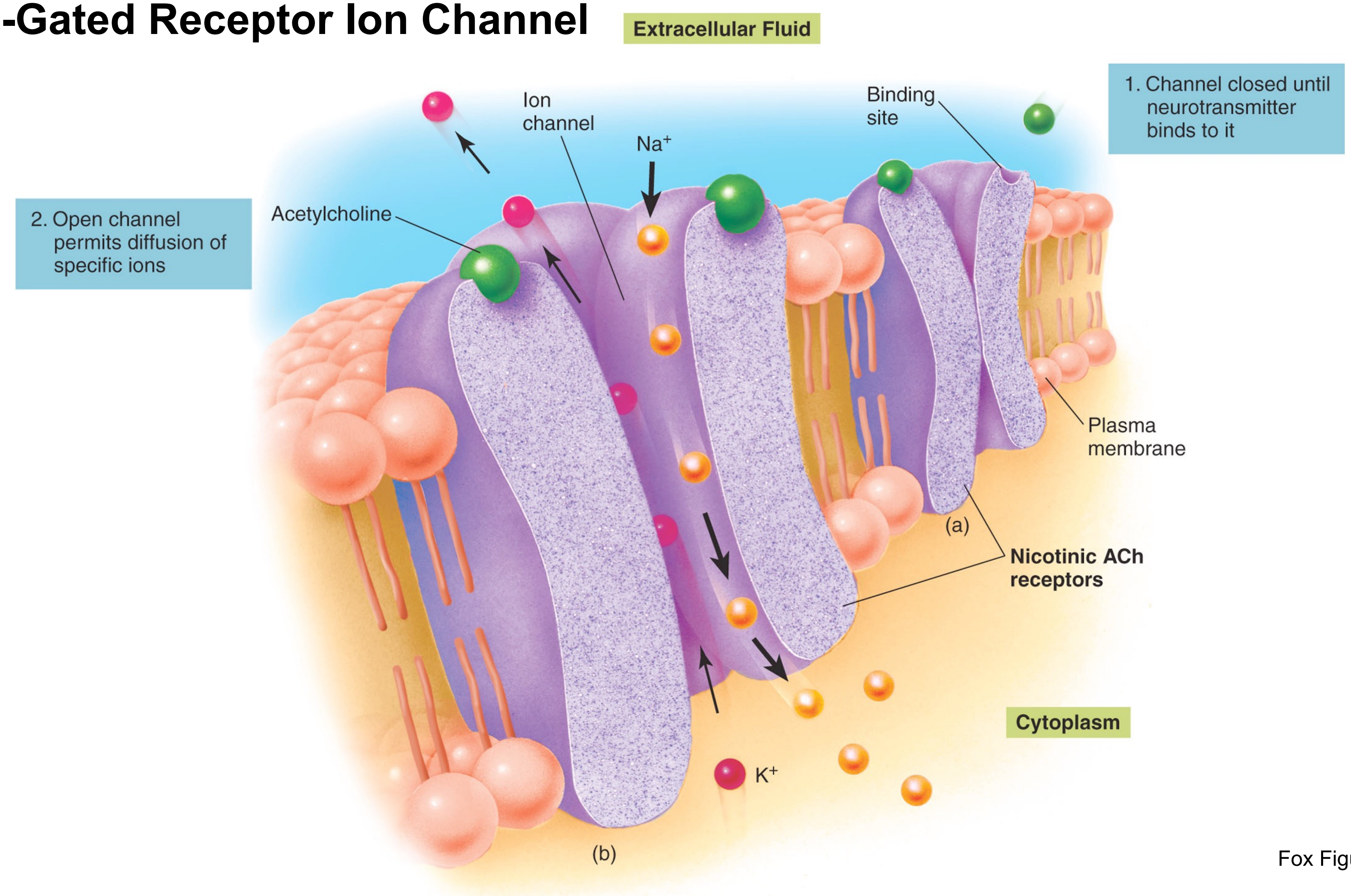
2. Voltage-gated Ca^{2+} channels open

3. Ca^{2+} binds to sensor protein in cytoplasm

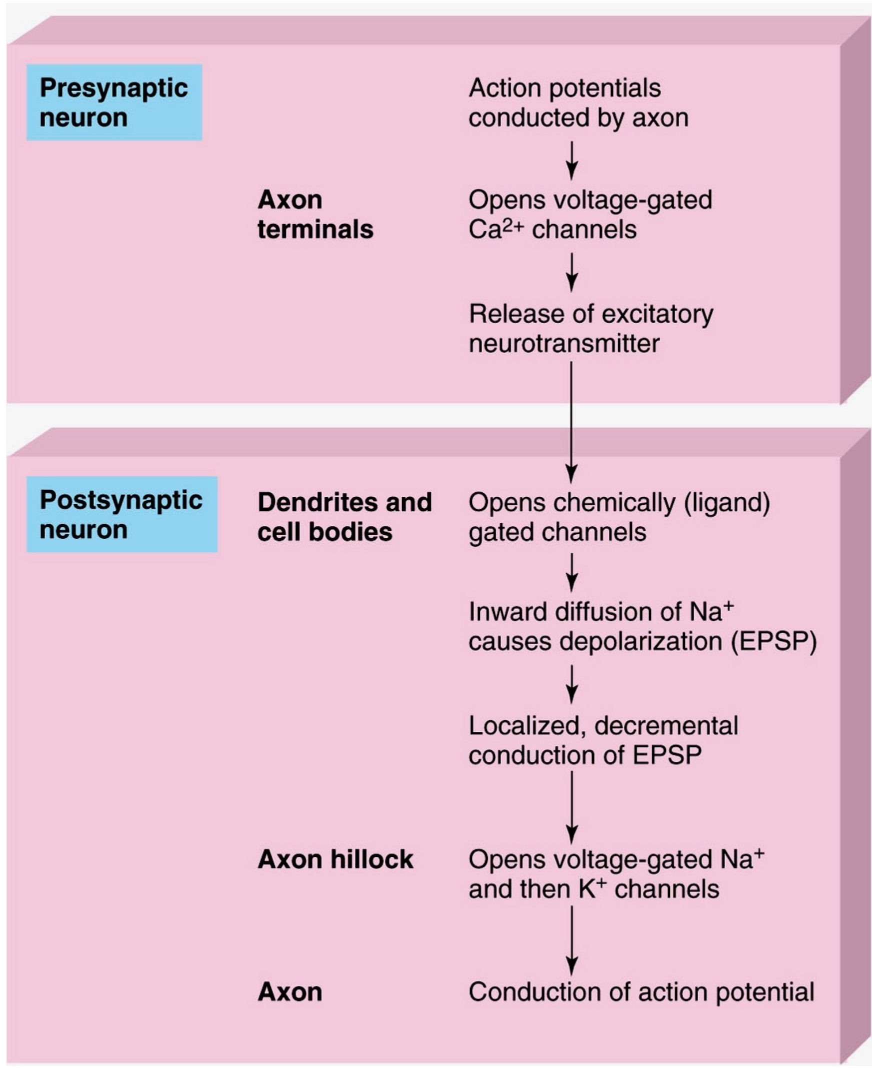
4. Ca^{2+}-protein complex stimulates fusion and exocytosis of neurotransmitter

Fox Figure 7.23

Ligand-Gated Receptor Ion Channel



Fox Figure 7.26



Fox Figure 7.25

Integration and Summation by Neurons

Neurotransmitter-gated receptor ion channels
Neurotransmitter binds to receptor channel, causing the channel to open and let ions flow into the target cell.

(There are many different neurotransmitters, and many different receptor types.)

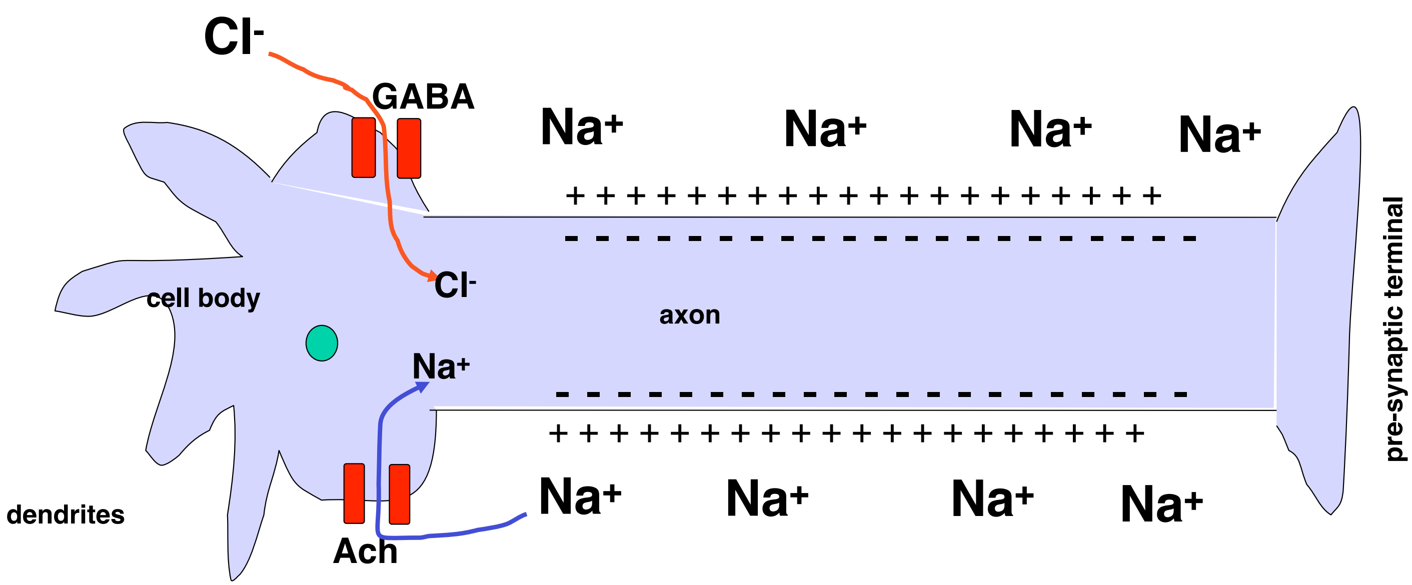
Receptor channel could be Na^+ channel or Cl^- channel
Influx of Na^+ raises V_m = excitatory postsynaptic potential (**epsp**)
Influx of Cl^- lowers V_m = inhibitory postsynaptic potential (**ipsp**)

Summation
If multiple epsp's combine to raise V_m above threshold for action potential, then neuron will fire an action potential.

If ipsp's combine with epsp's, then lower V_m due to ipsp will cancel out epsp's, and action potentials will be inhibited.

A neuron integrates excitatory and inhibitory inputs to produce a subtle pattern of firing that reflects multiple influences

Membrane Potential of Neuron

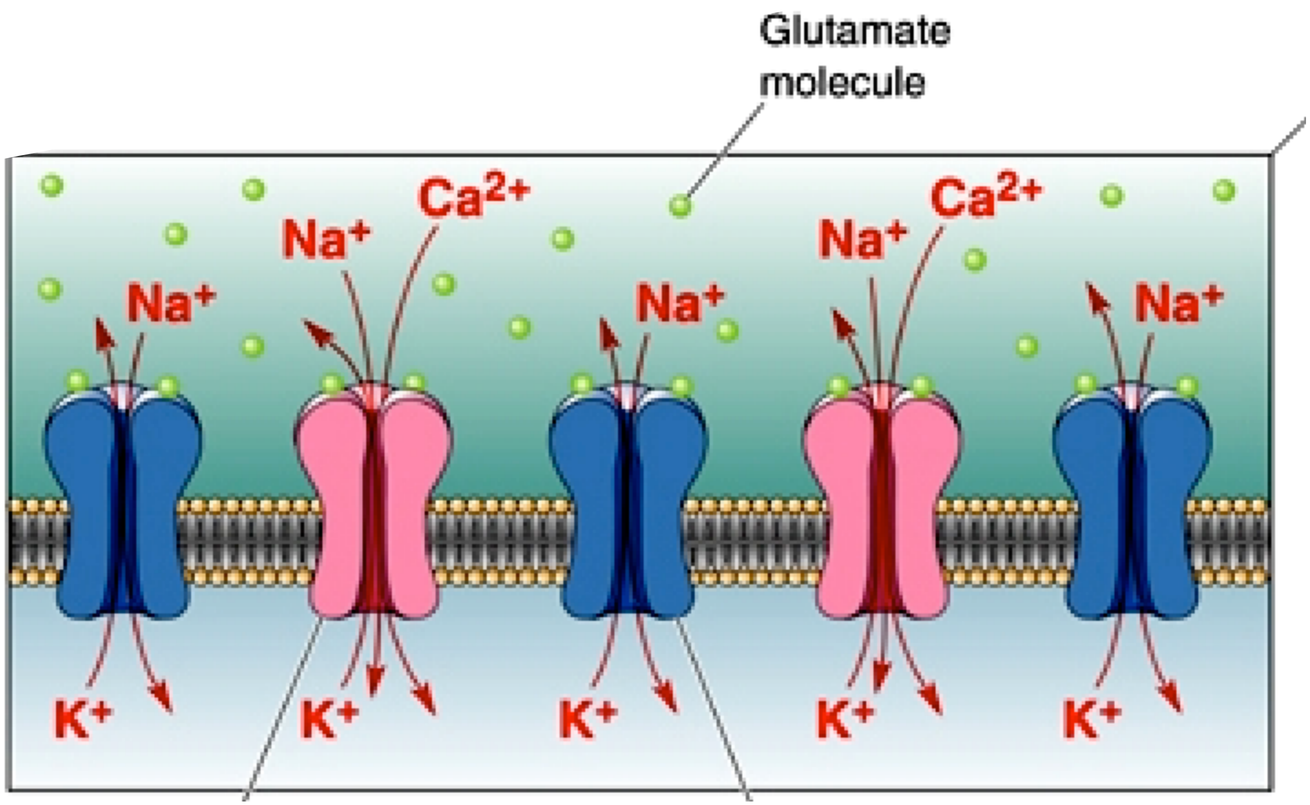


Excitatory Neurotransmitters cause Na^+ channels to open and let Na^+ into the neuron (making inside **positive**).

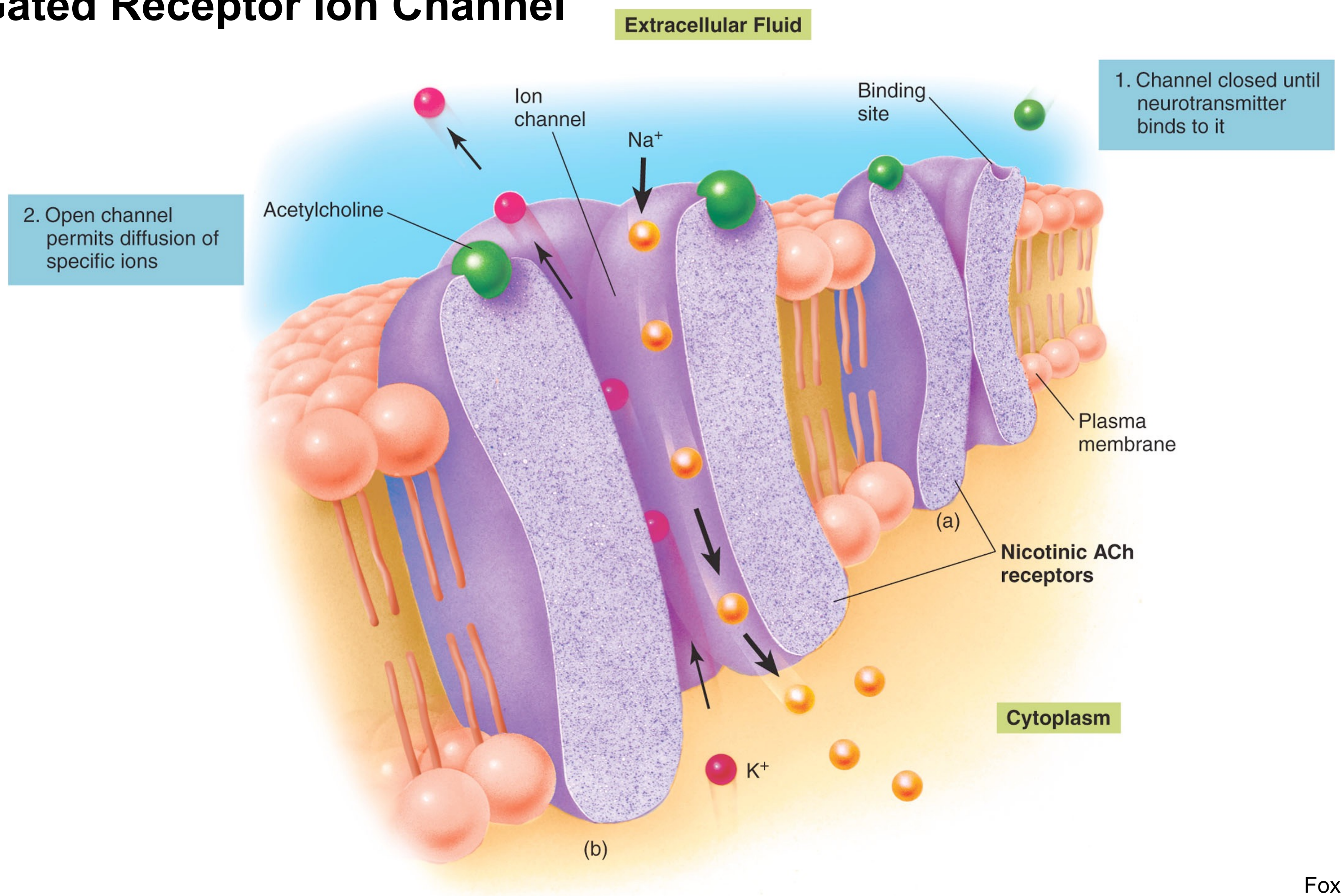
Inhibitory Neurotransmitters let Cl^- into the neuron (make inside even **more negative**).

Glutamate

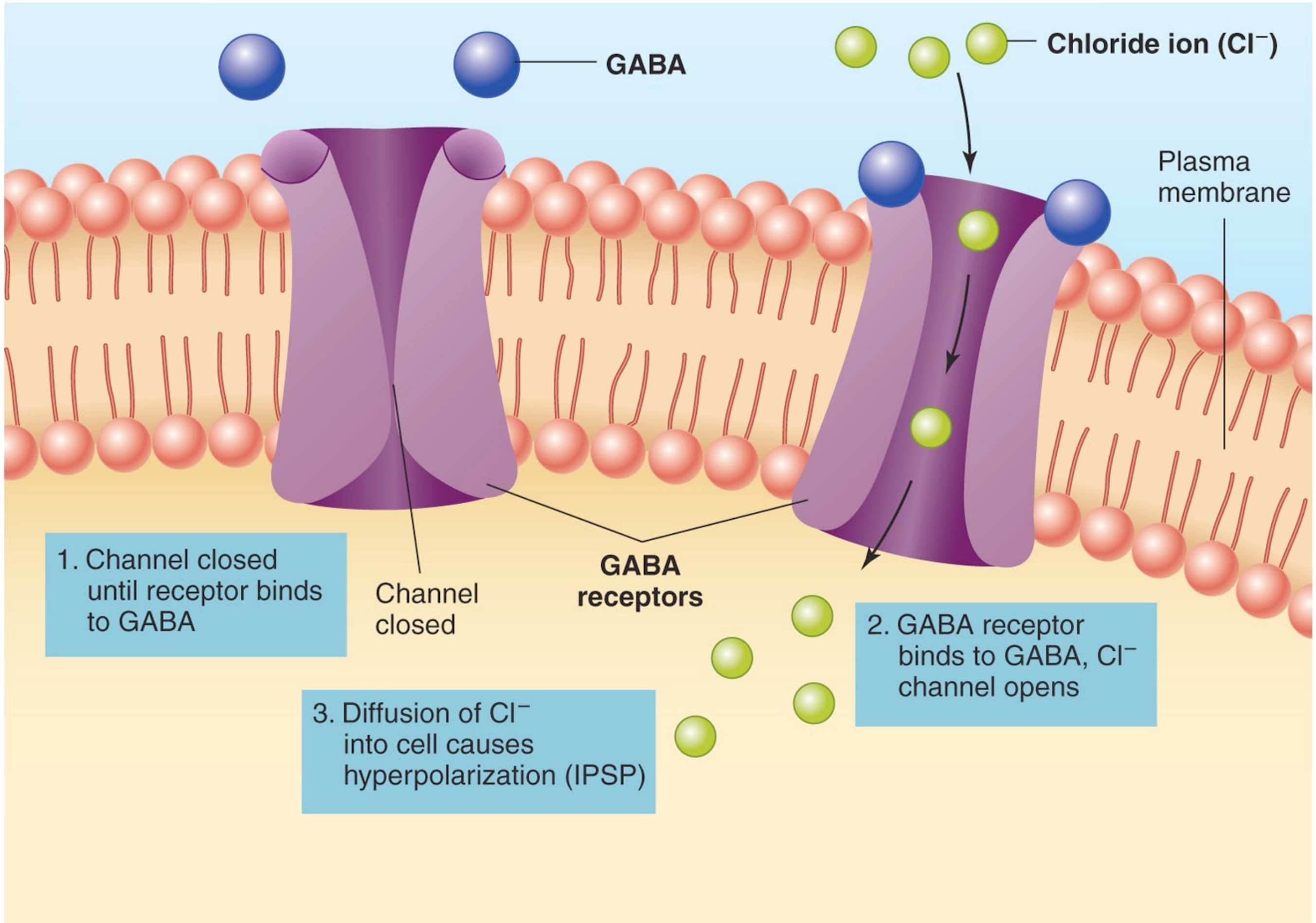
the primary excitatory neurotransmitter



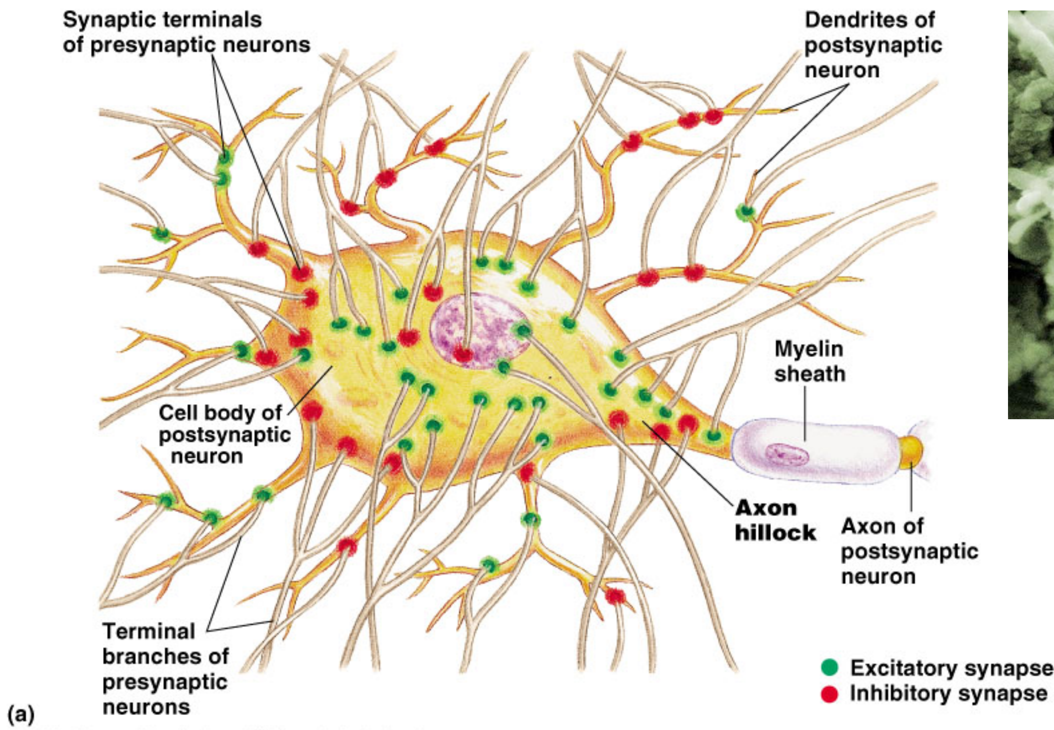
Ligand-Gated Receptor Ion Channel

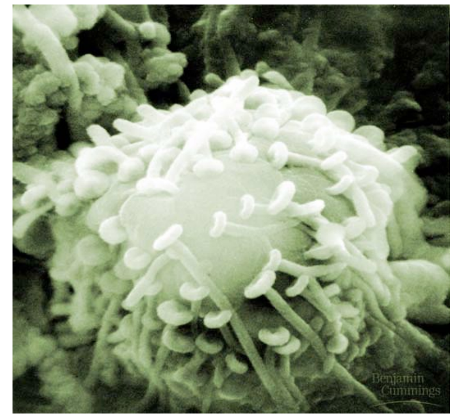


Fox Figure 7.26

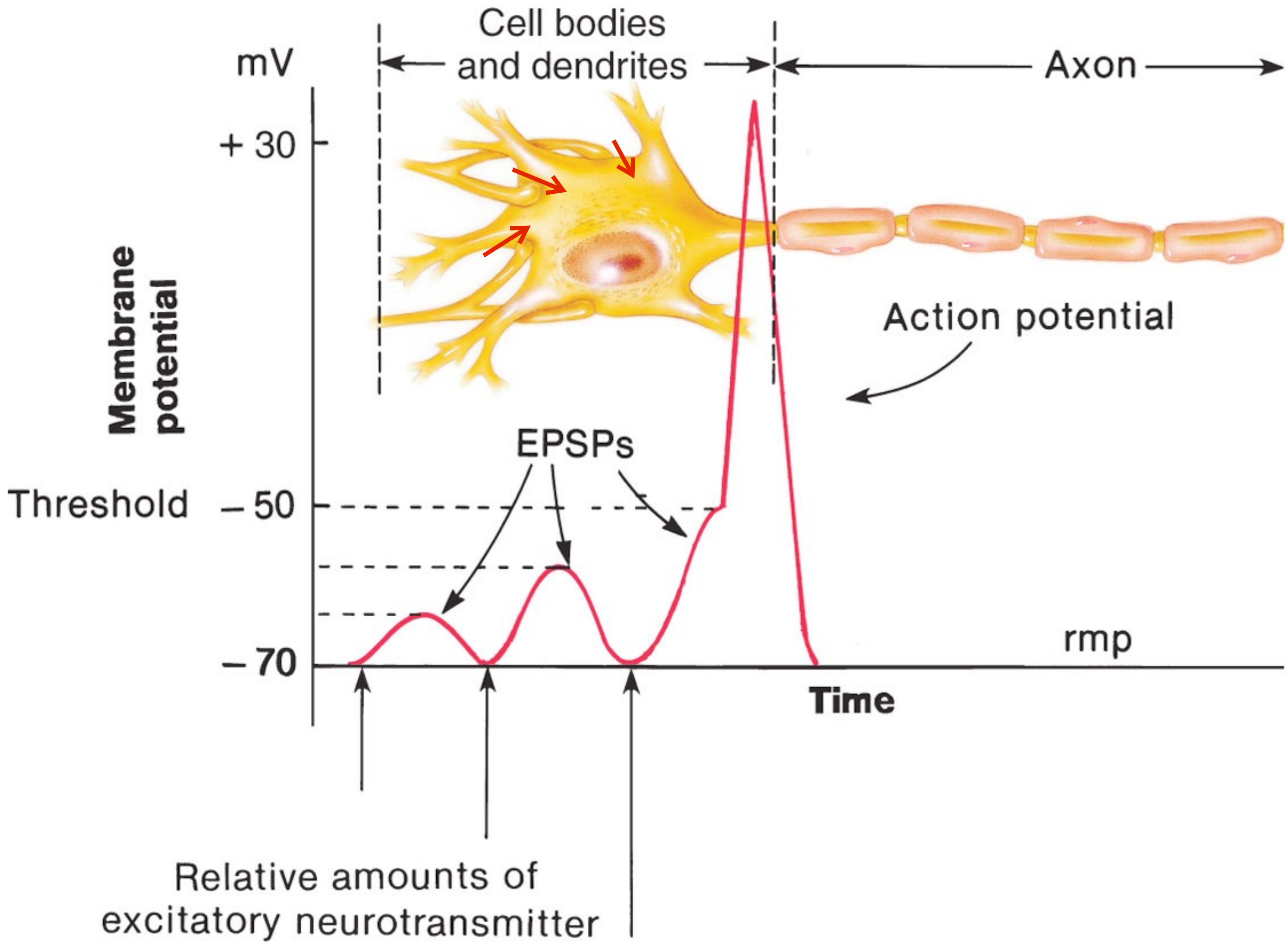


Fox Figure 7.32





Neuron sums up net change in positive and negative charges; if positive enough, then it fires.

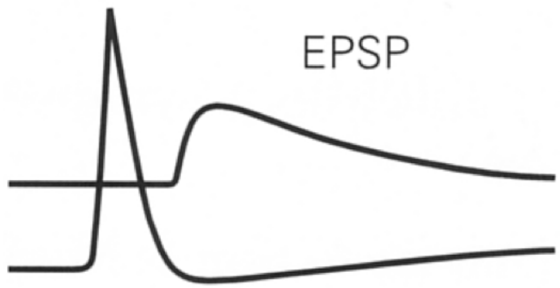


Fox Figure 7.29

epsp and ipsp:
Excitatory and Inhibitory postsynaptic potentials

target postsynaptic neuron

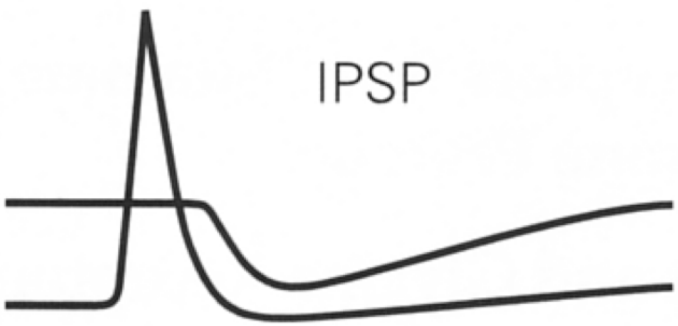
AP in presynaptic neuron



neurotransmitter
(e.g. acetylcholine)
opens Na+ channels
(positive ions flow into cell)

target postsynaptic neuron

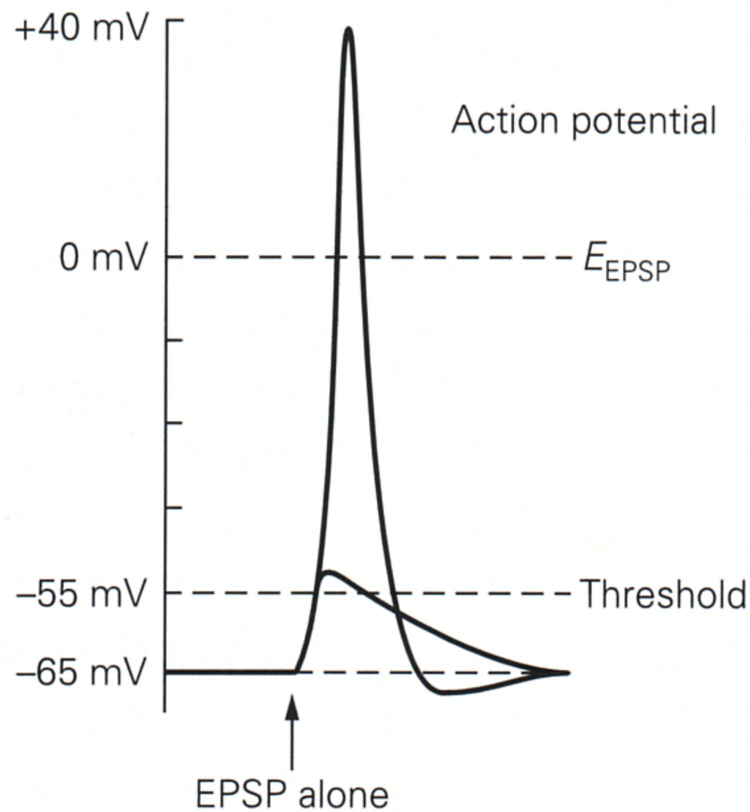
AP in presynaptic neuron



neurotransmitter
(e.g. GABA)
opens Cl- channels
(negative ions flow into cell)

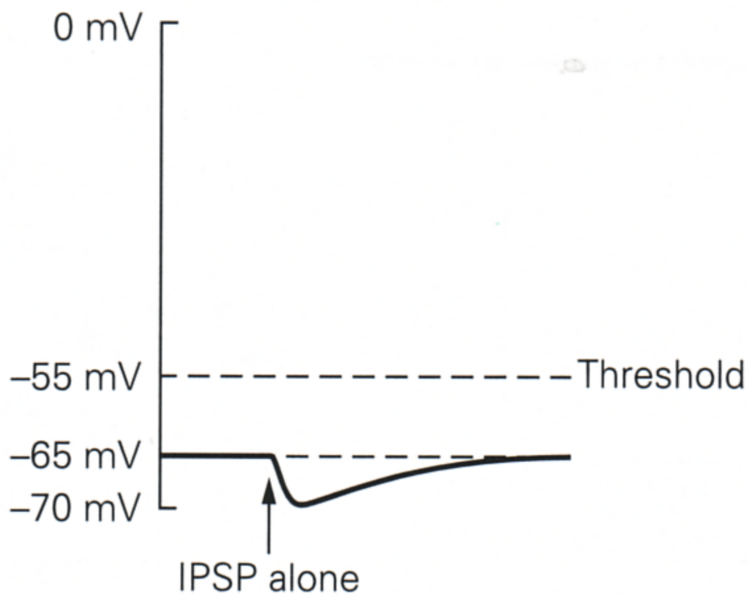
Combining epsp's and ipsp's

EPSP alone



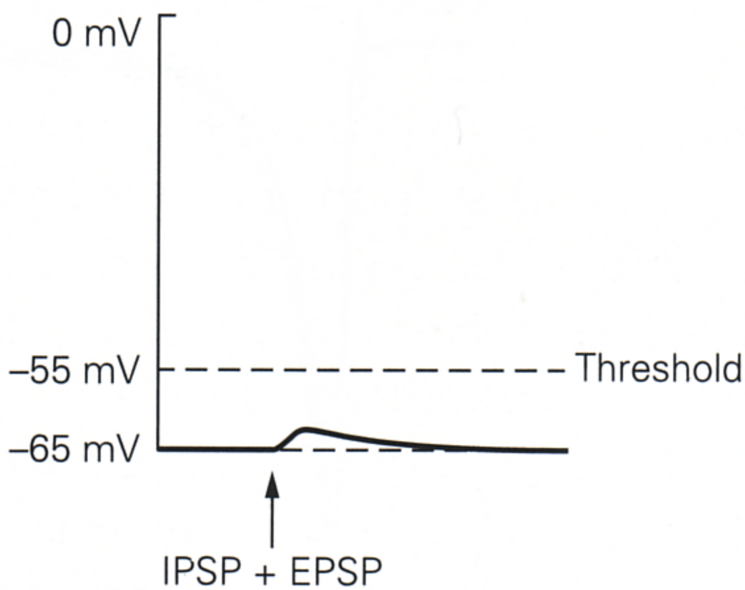
Combining epsp's and ipsp's

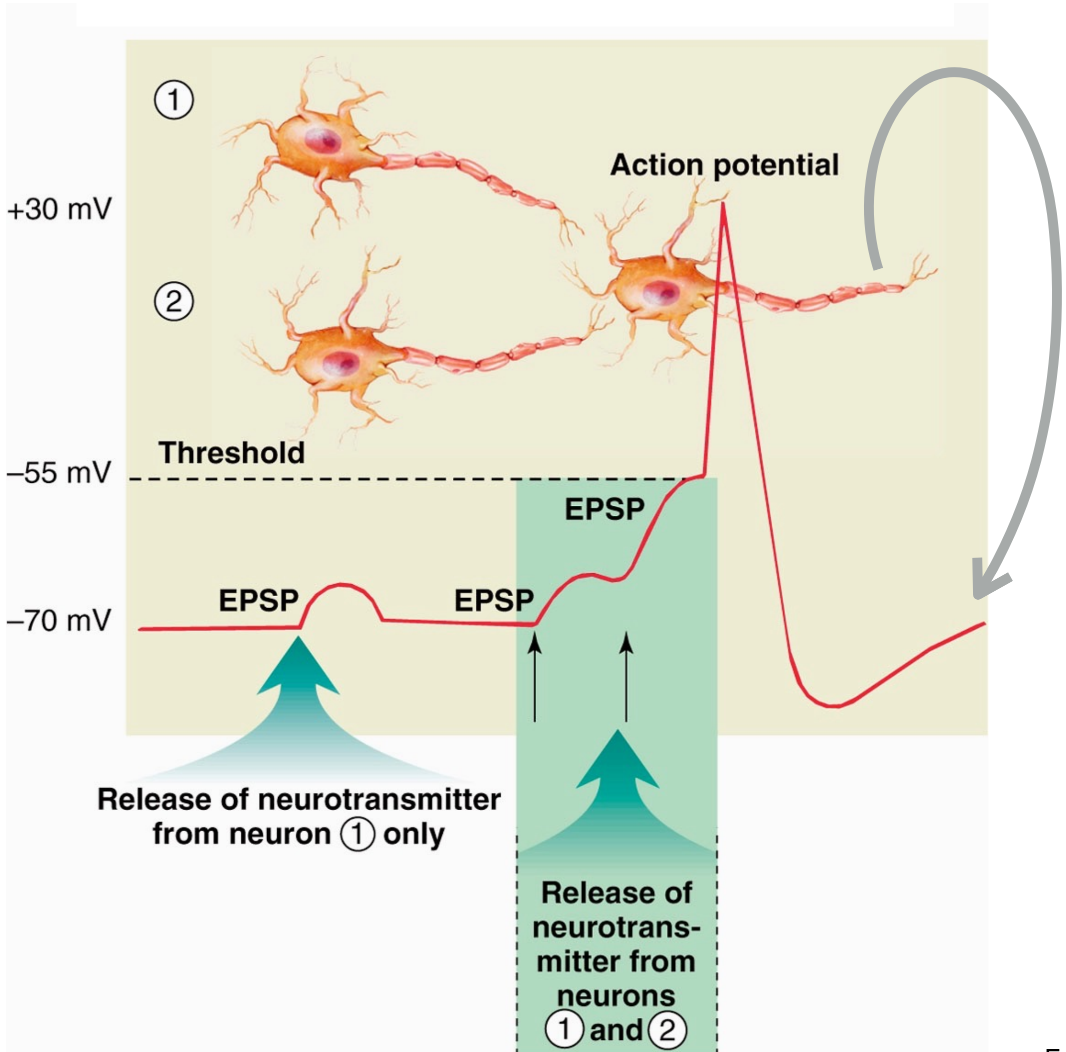
IPSP alone



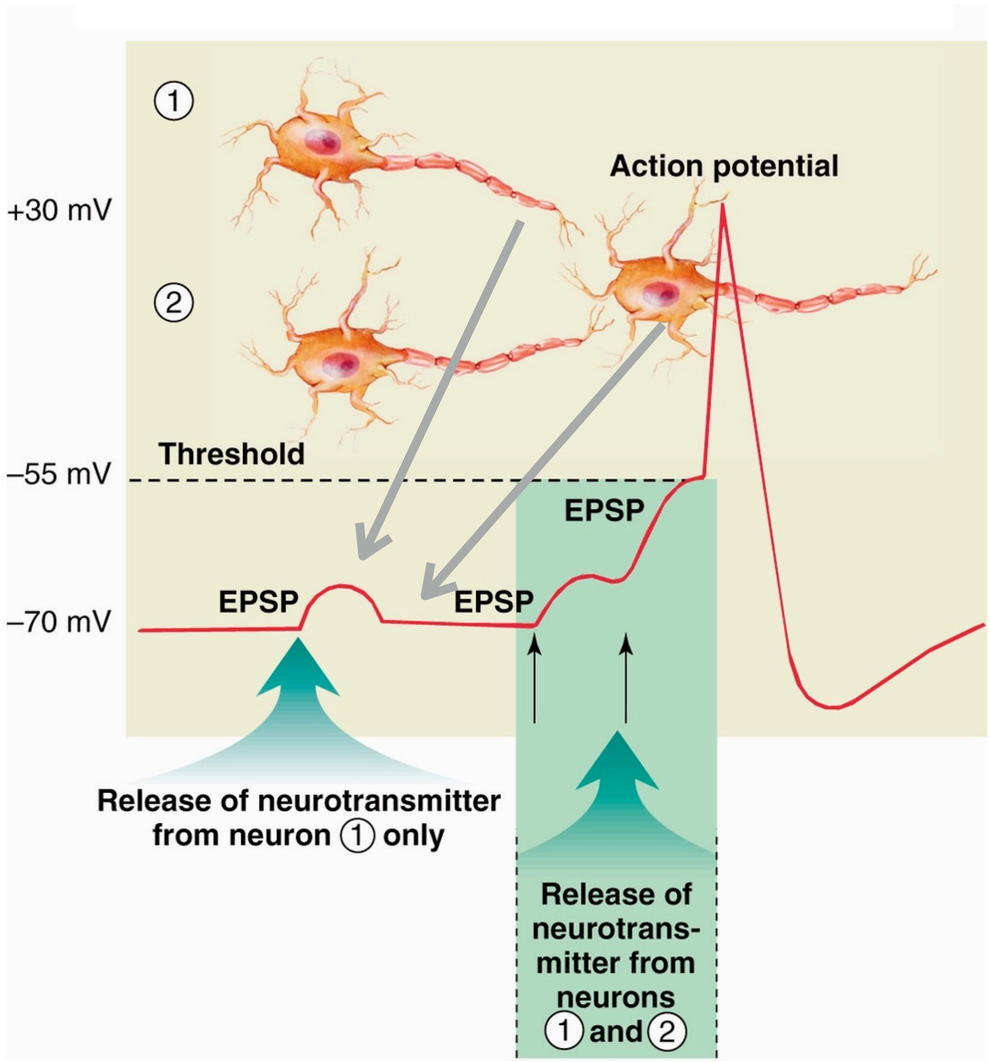
Combining epsp's and ipsp's

EPSP + IPSP

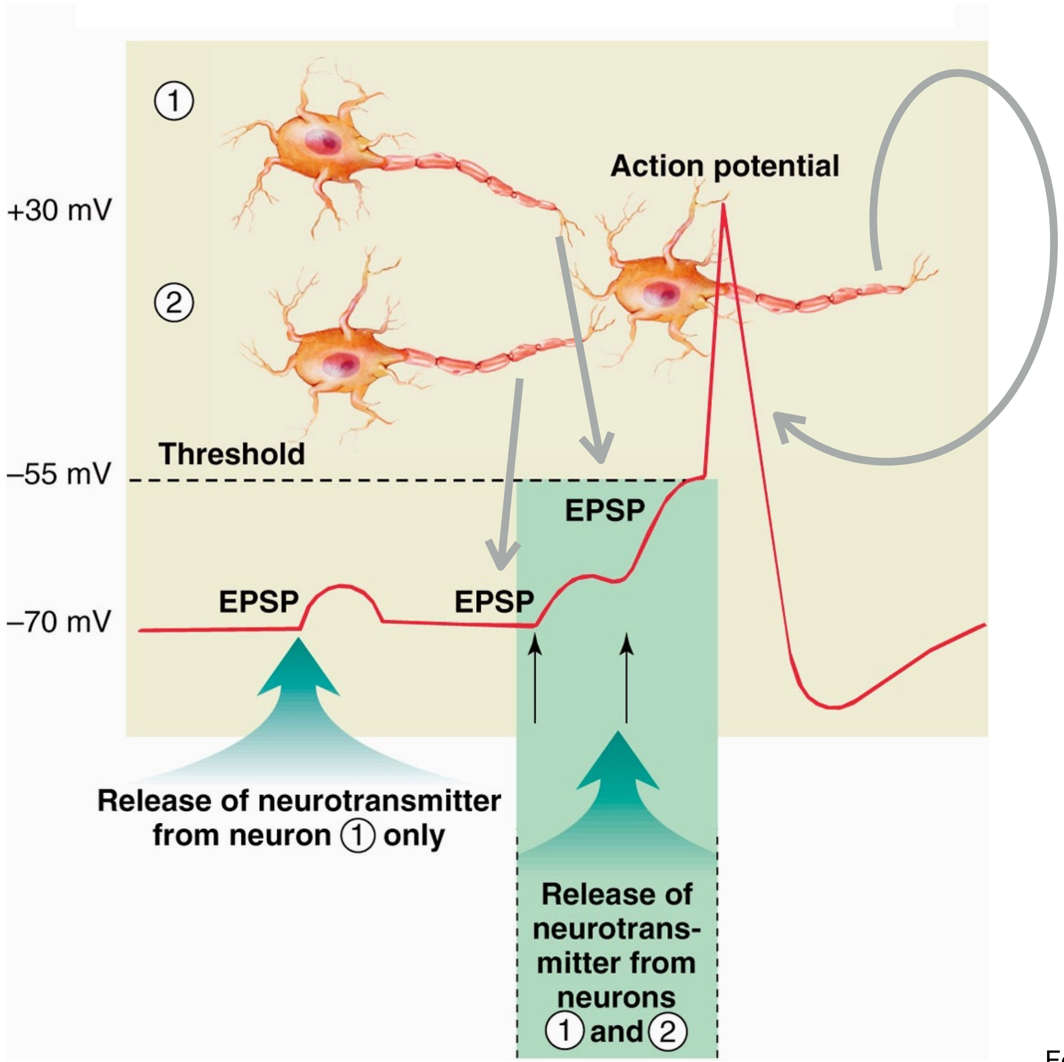




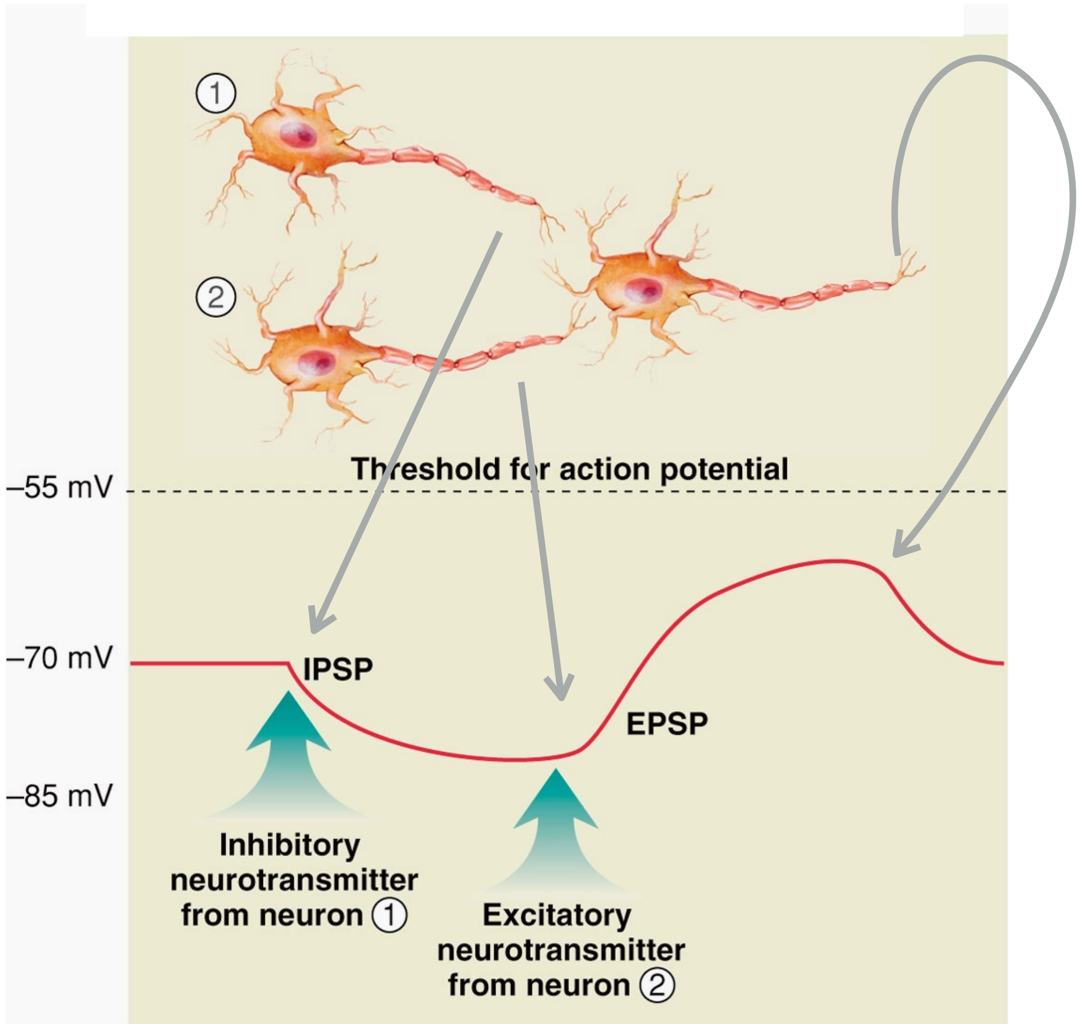
Fox Figure 7.33



Fox Figure 7.33

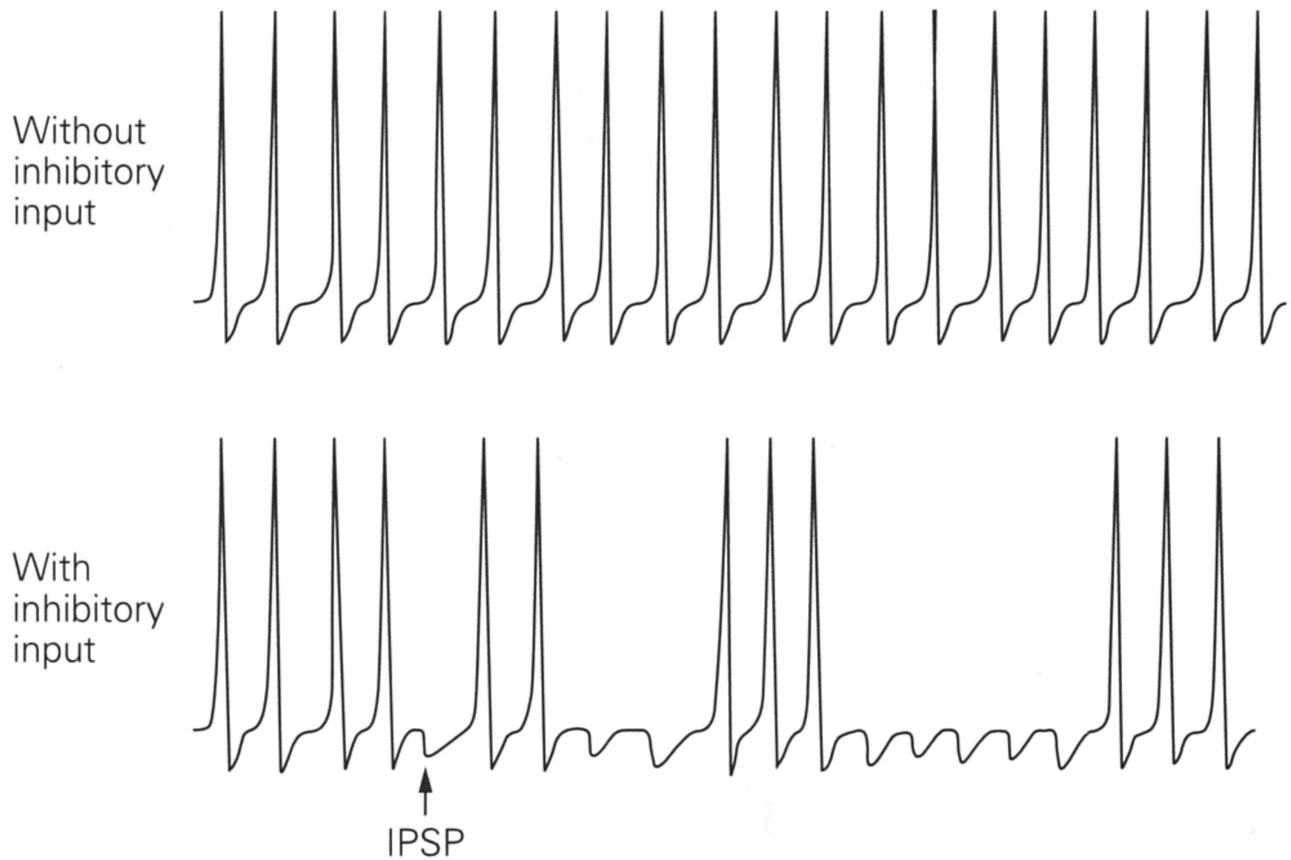


Fox Figure 7.33

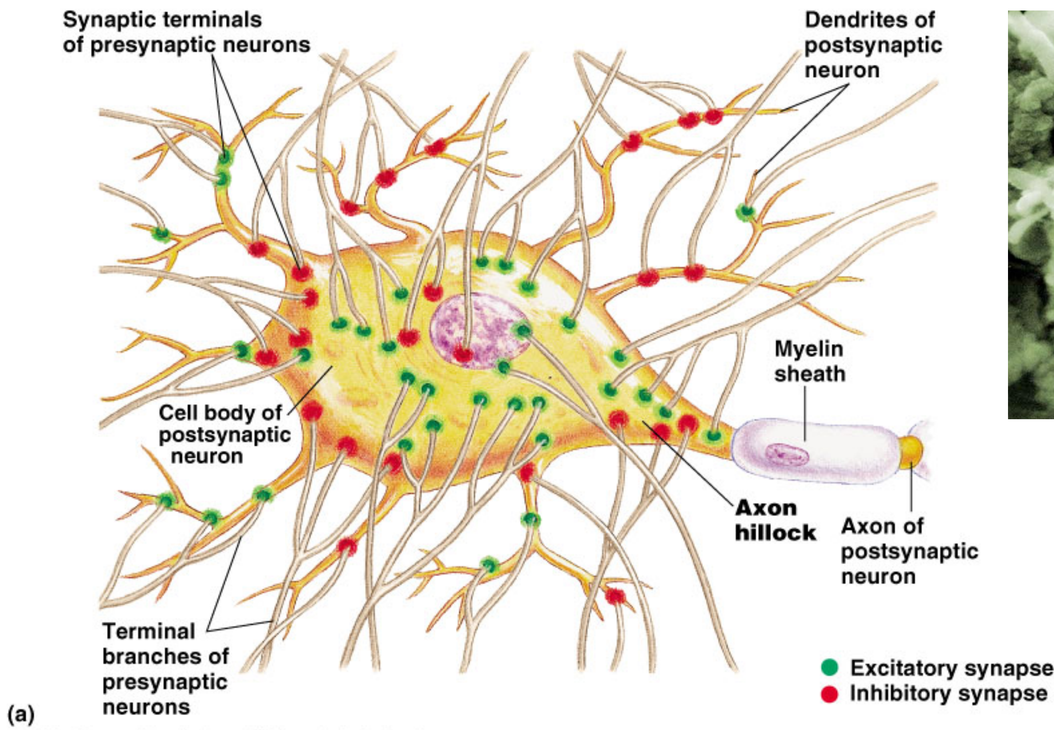


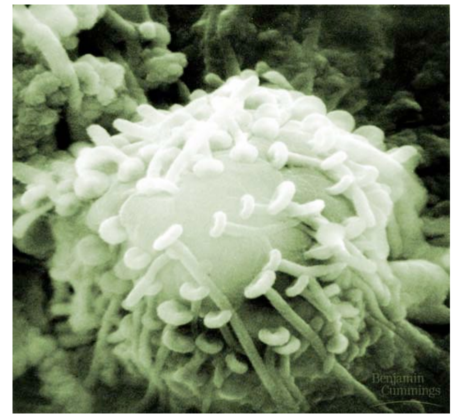
Fox Figure 7.34

Effect of ipsps on action potentials

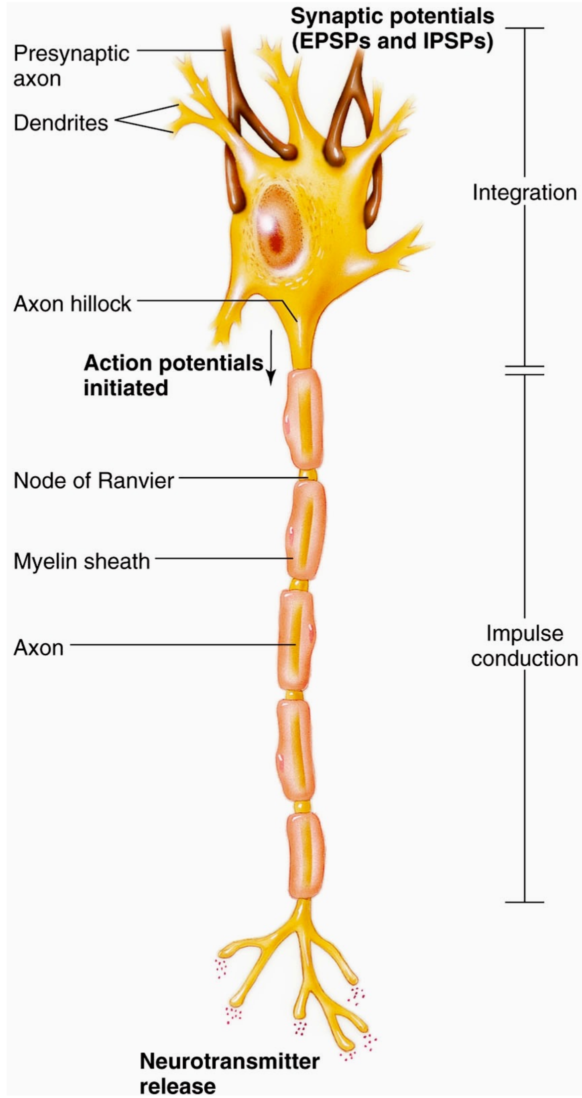


Campbell Figure 48.13 Integration of multiple synaptic inputs





Neuron sums up net change in positive and negative charges; if positive enough, then it fires.



Fox Figure 7.24

Human Phys PCB4701

Neurotransmitters
Fox Chapter 7 pt 4

Neurotransmitters & Receptors

1. Properties of Neurotransmitters
2. Classical Neurotransmitters

   Acetylcholine, Glutamate, GABA, Catecholamines

3. Neuropeptides
4. Types of Receptors

   ion channels

   G-protein coupled receptors

Properties of Neurotransmitters

1. **Synthesized** in a neuron

2. Stored in vesicles in the presynaptic terminal & released with a specific effect on target postsynaptic cell via **receptors**

3. **Exogenous** administration (e.g. injection) causes the same effect

4. A specific mechanism exists to **remove** it from the synapse

5. Each neuron makes **only one** or a few neurotransmitters

6. Neurons or target cells can have **multiple receptors**, making them sensitive to multiple NTs.

7. **Drugs** can act on receptors or affect synthesis/removal of the neurotransmitter

   agonist: drug has same or bigger effect on receptor as endogenous NT

   antagonist: drug blocks the effects of NT

Examples: Acetylcholine, Glutamate, GABA, Catecholamines, Neuropeptides

Fox Table 7.7 Examples of Chemicals that are either Proven or Suspected Neurotransmitters

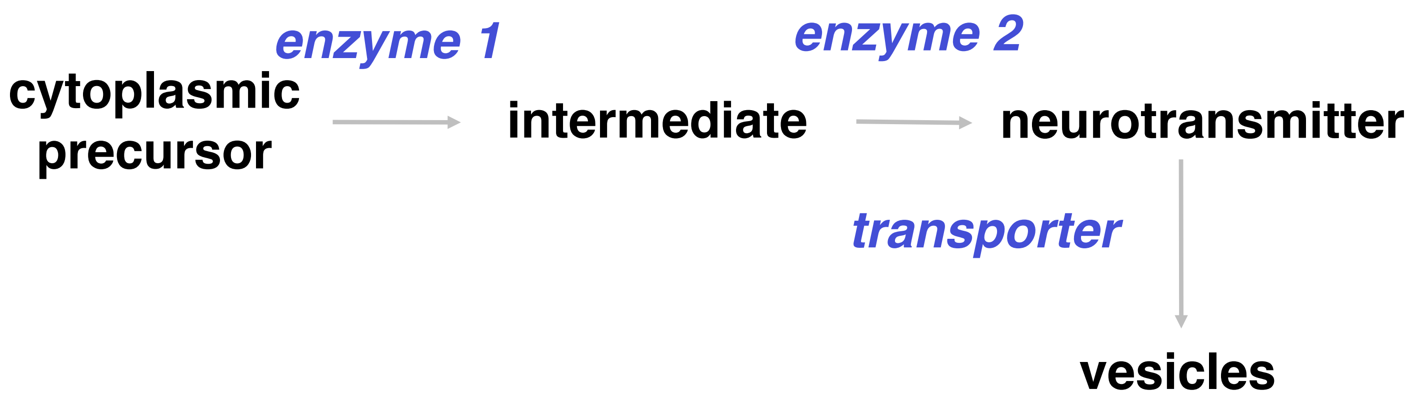
Category	Chemicals
Amines	Histamine
	Serotonin
Catecholamines	Dopamine
	(Epinephrine—a hormone)
	Norepinephrine
Choline derivative	Acetylcholine
Amino acids	Aspartic acid
	GABA (gamma-aminobutyric acid)
	Glutamic acid
	Glycine

Category	Chemicals
Polypeptides	Glucagon
	Insulin
	Somatostatin
	Substance P
	ACTH (adrenocorticotrophic hormone)
	Angiotensin II
	Endogenous opioids (enkephalins and endorphins)
	LHRH (luteinizing hormone-releasing hormone)
	TRH (thyrotrophin-releasing hormone)
	Vasopressin (antidiuretic hormone)
	CCK (cholecystokinin)
Lipids	Endocannabinoids
Gases	Nitric oxide
	Carbon monoxide
Purines	ATP

2 Types of neurotransmitters

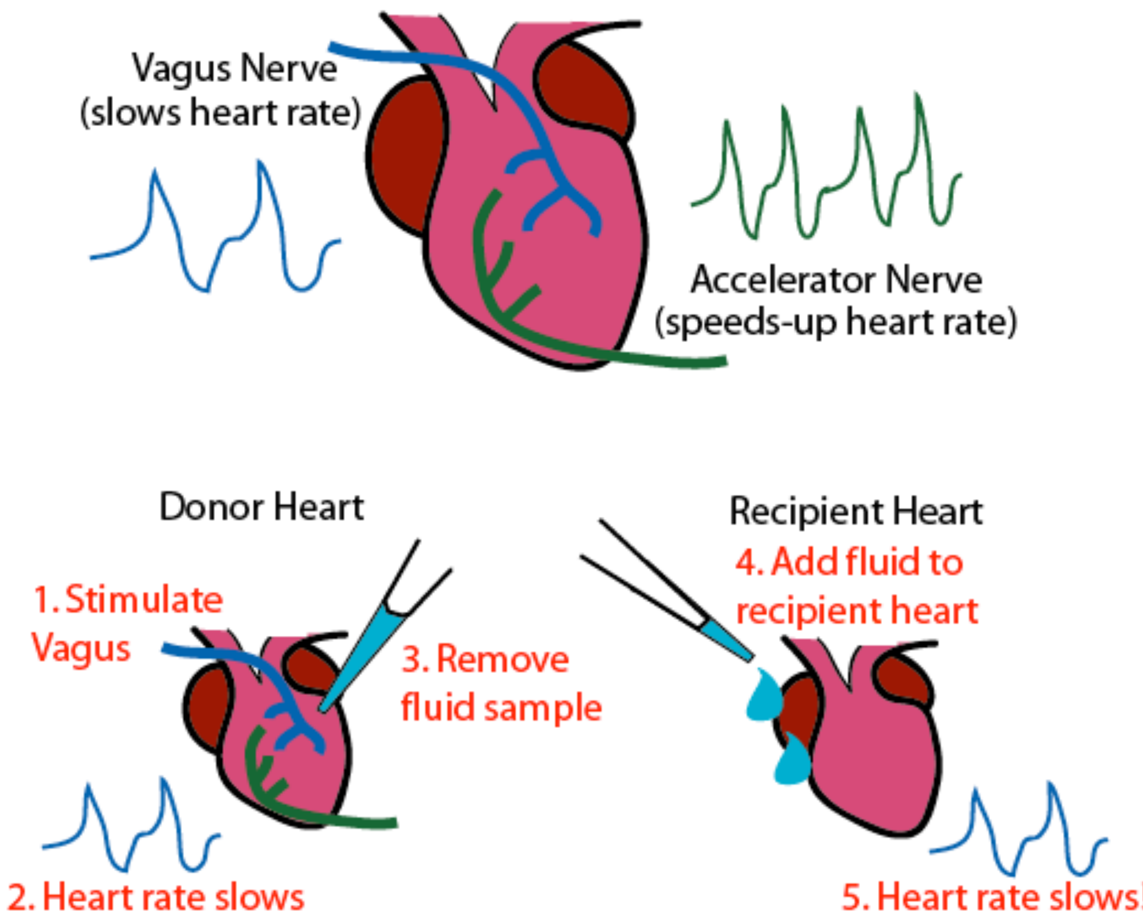
	Classical small molecules	Neuropeptides
Size	small (like amino acid or amine)	large (4-100 a.a. polypeptide)
Synthesis	uptake or enzymes	protein synthesis
Vesicles	small, filled by transporters	large secreted proteins from RER
Duration of action	fast but short	slow & long

Synthetic Pathways for Classical Neurotransmitters



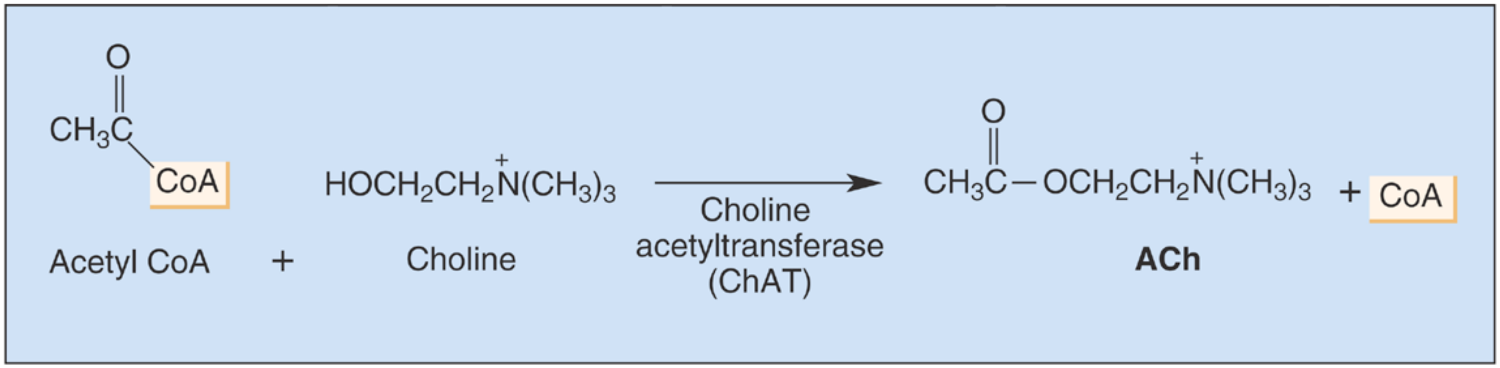
Vagusstoff

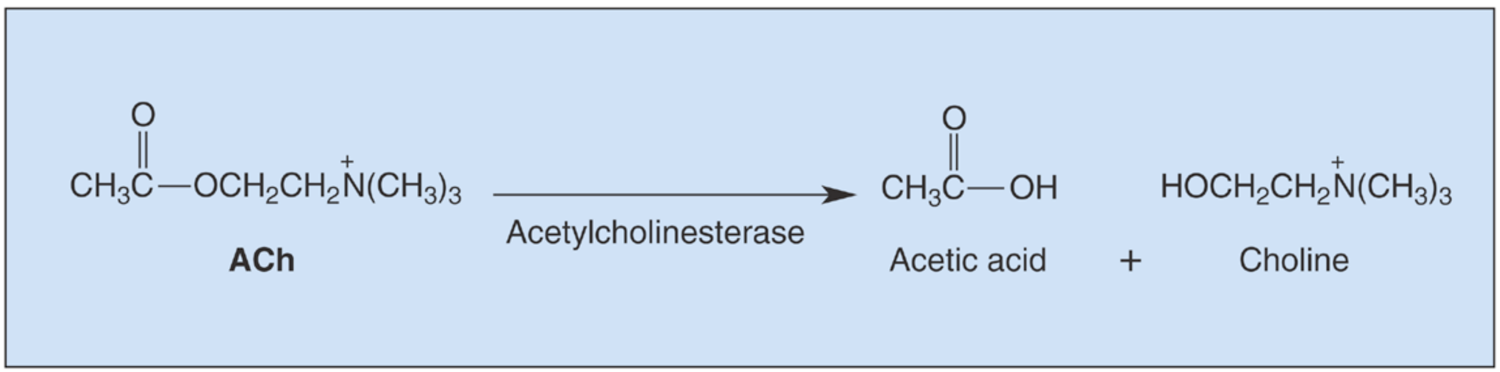
Acetylcholine, the first neurotransmiter



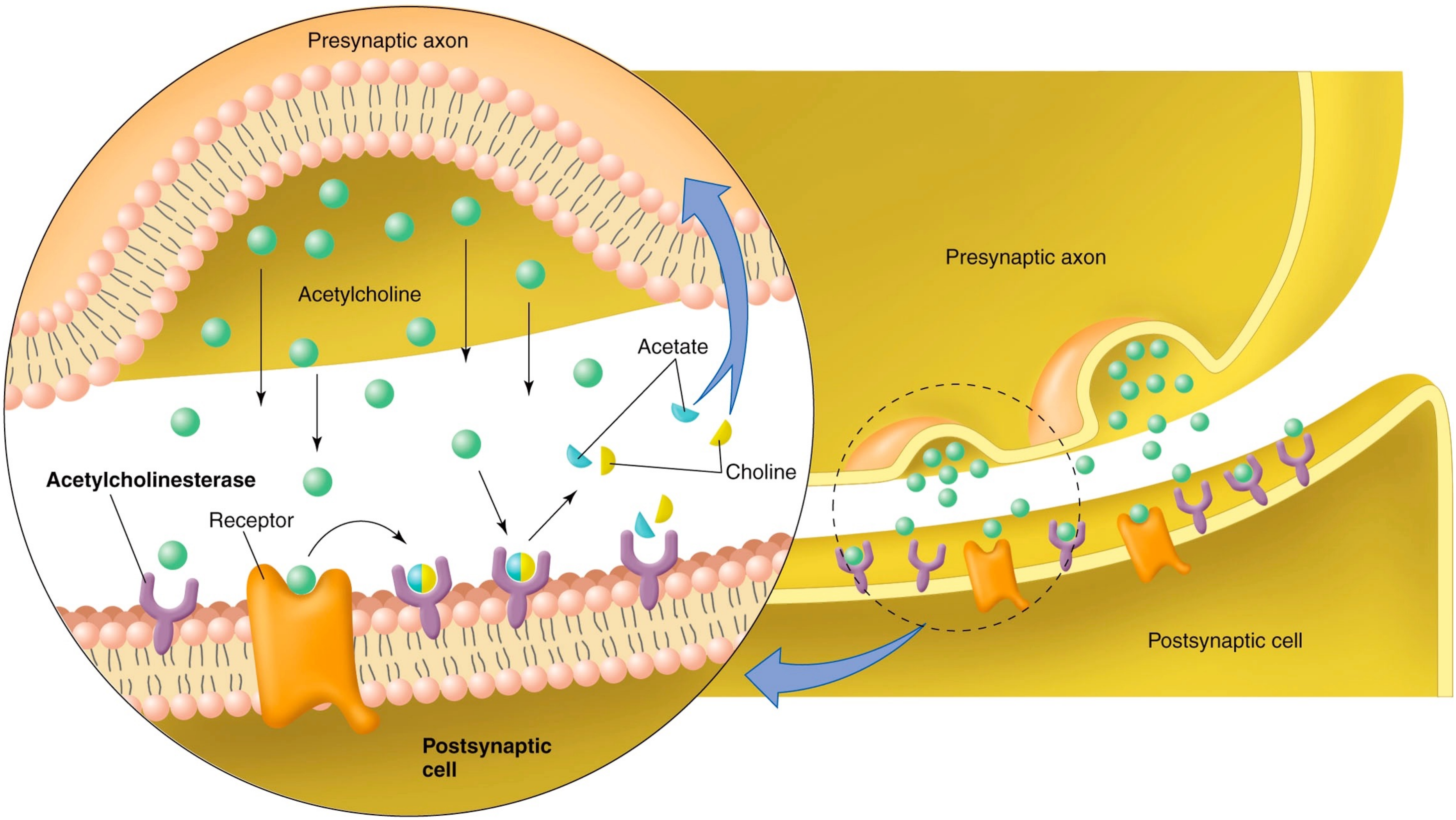
Acetylcholine - the first NT

Synthesis



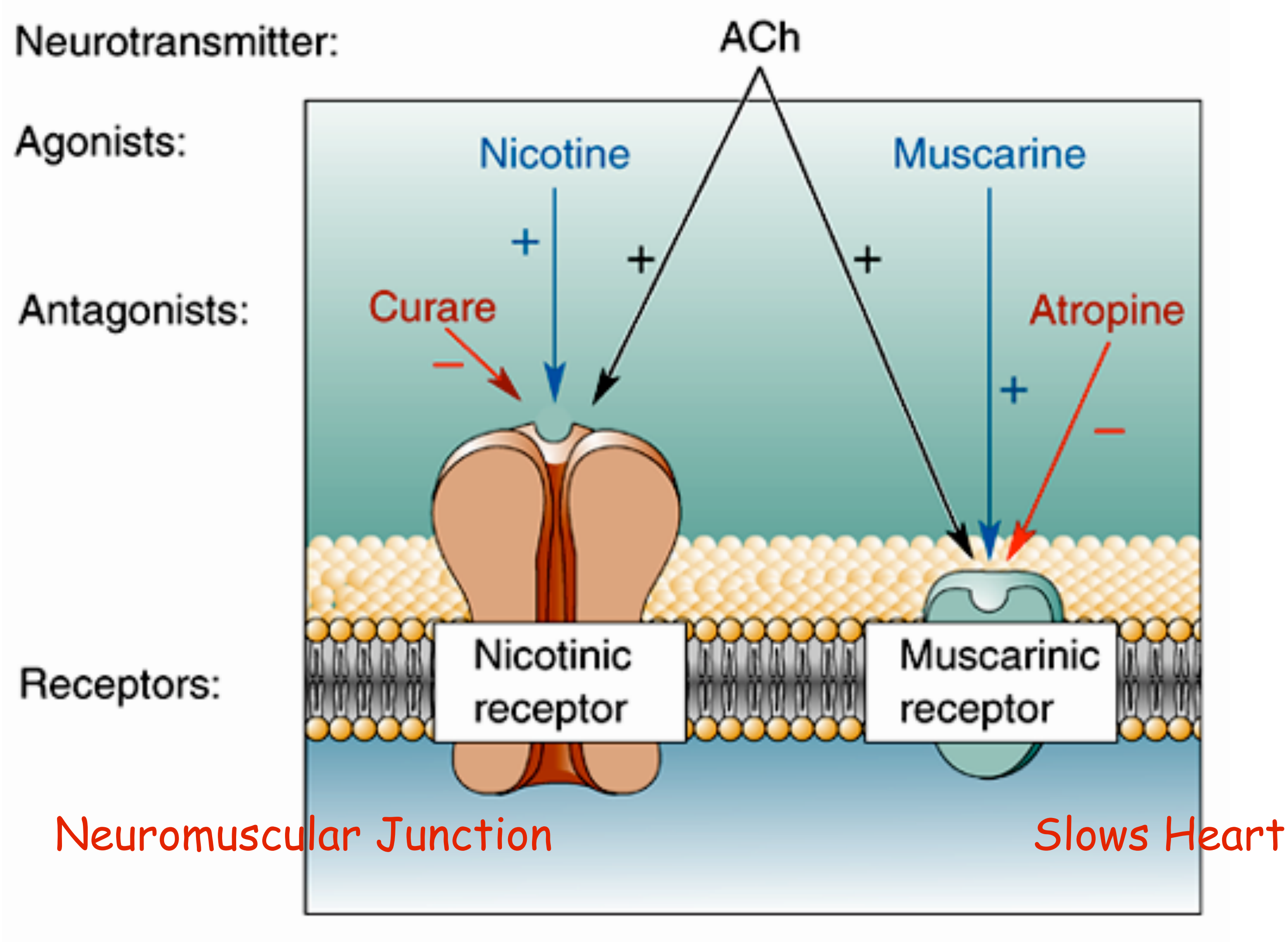


Degradation



Fox Figure 7.28

Terminology:



Classical small-molecule NTs

Amino Acids

Glycine

$HOOC-CH_2-NH_2$

Glutamate

$HOOC-CH_2-CH_2-CH(COOH)-NH_2$

$\downarrow$ **GAD**

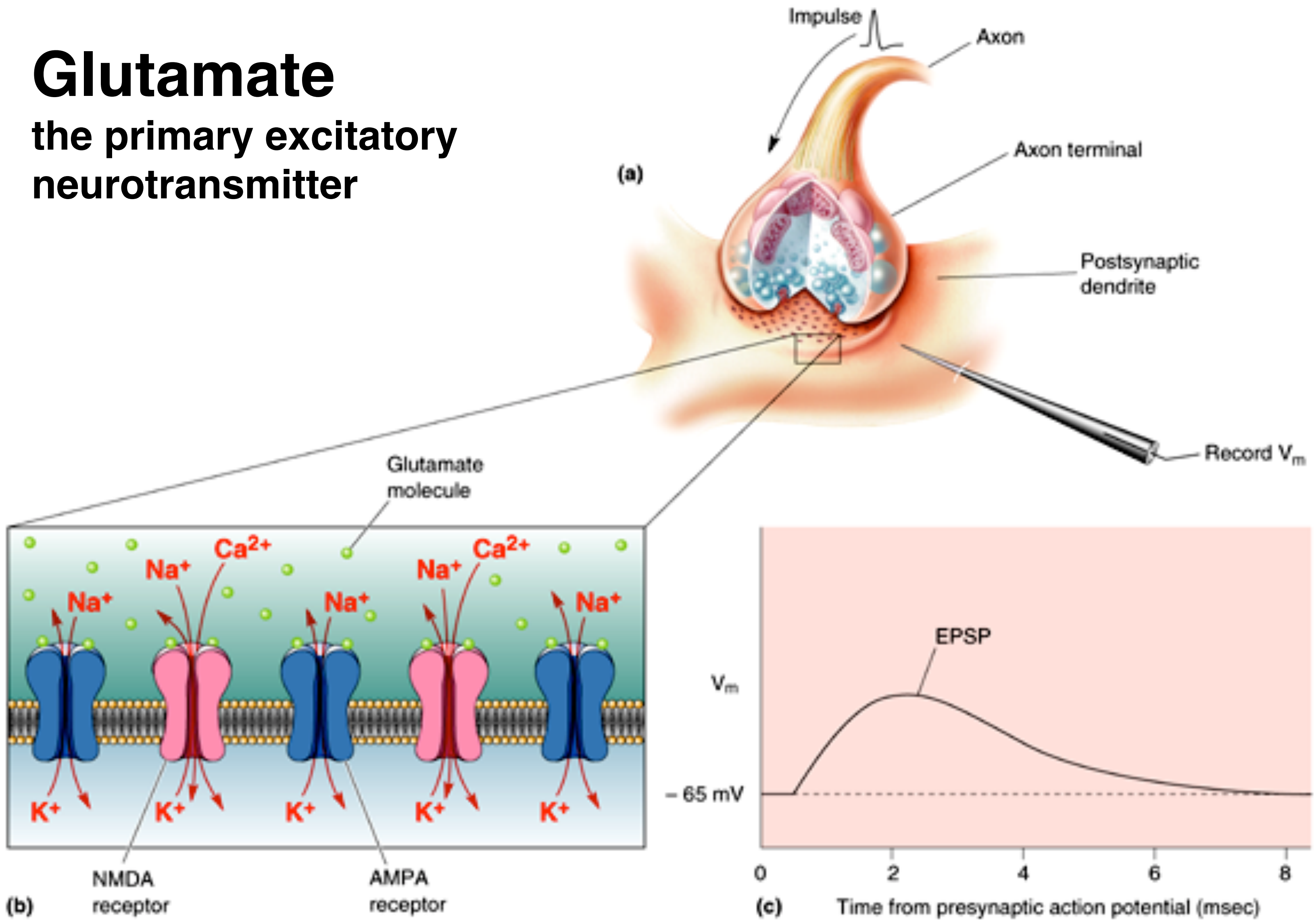
GABA
γ-amino-butyric acid

$HOOC-CH_2-CH_2-CH_2-NH_2$

common chemicals synthesized by many cells during general metabolism...

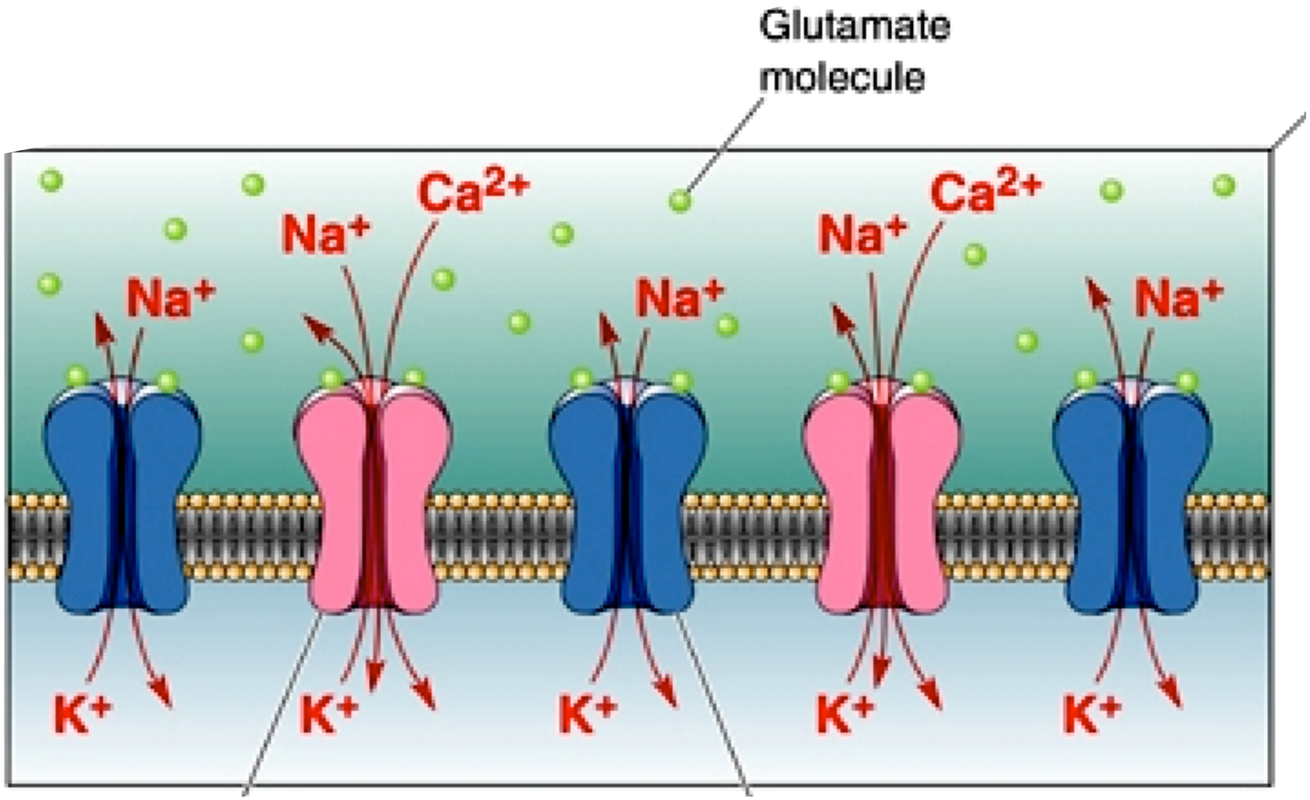
Glutamate

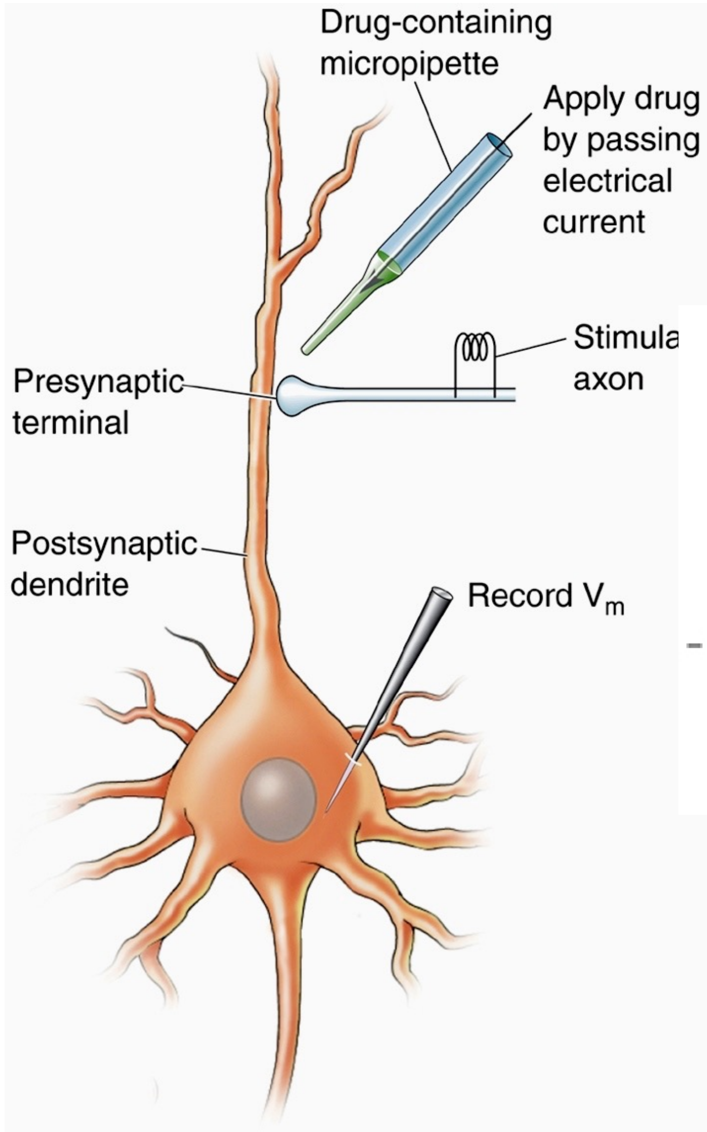
the primary excitatory neurotransmitter



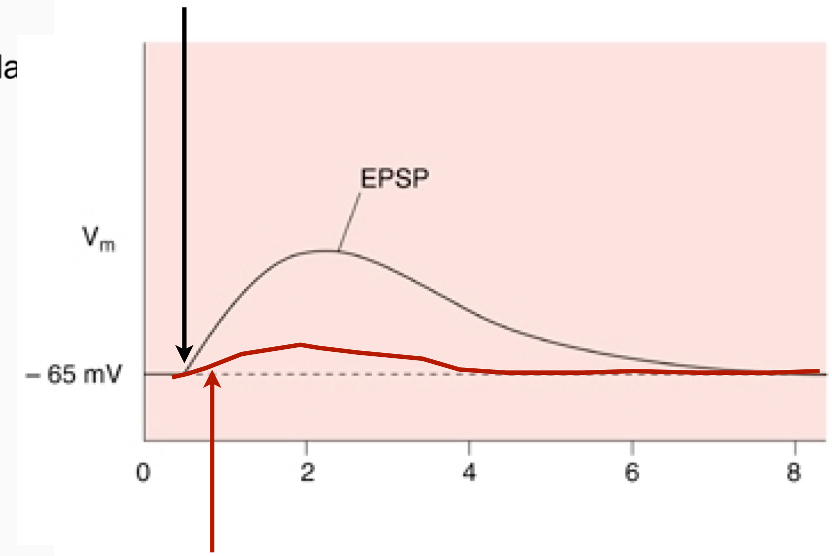
Glutamate

the primary excitatory neurotransmitter





apply NT or agonist drug
(e.g. Glutamate)

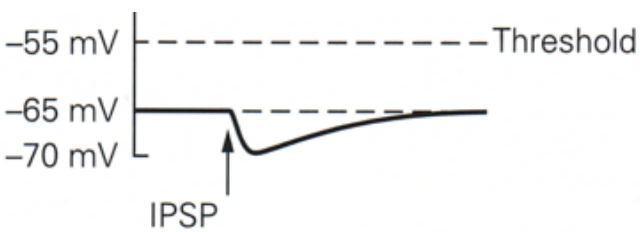


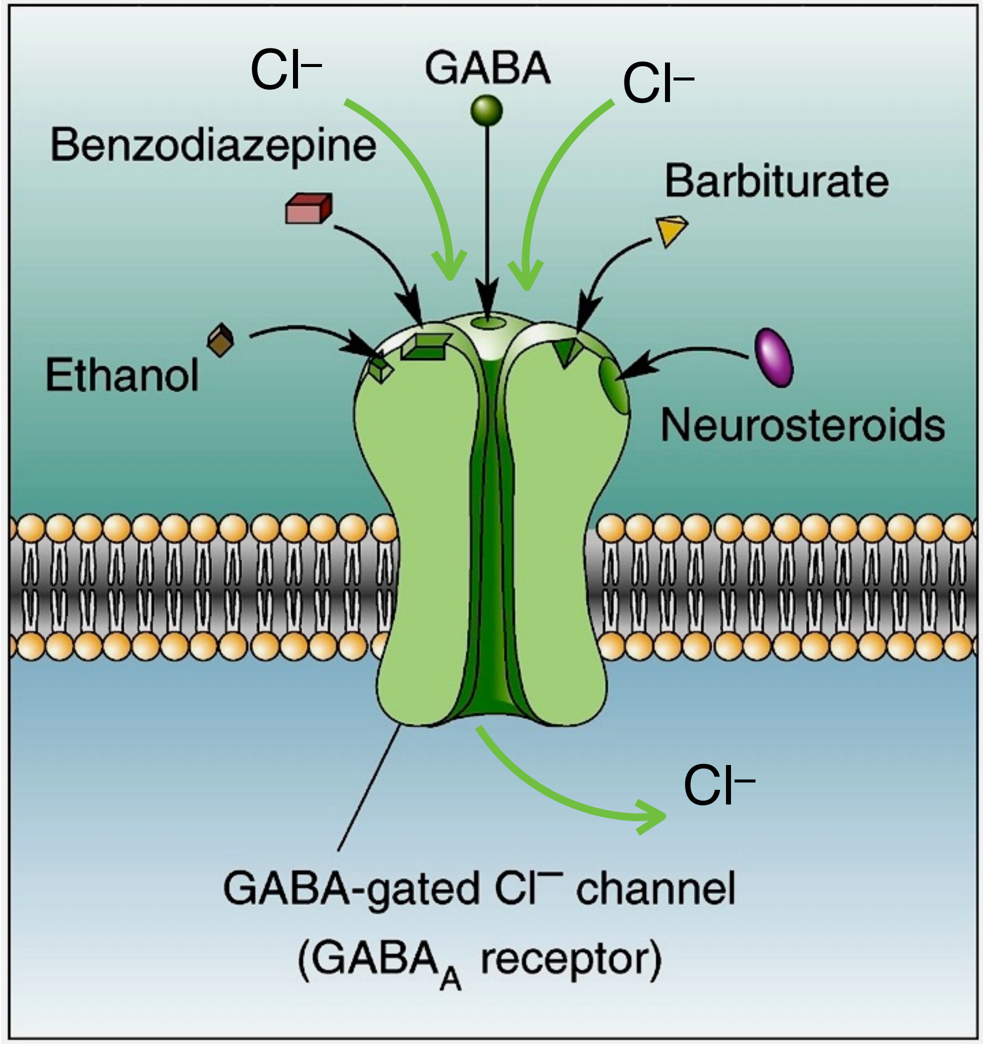
NT + antagonist drug
(e.g. Glutamate & Ketamine)

GABA:

the primary inhibitory neurotransmitter

open Cl- channels which *lowers* Vm





Catecholamine Synthetic Pathways:

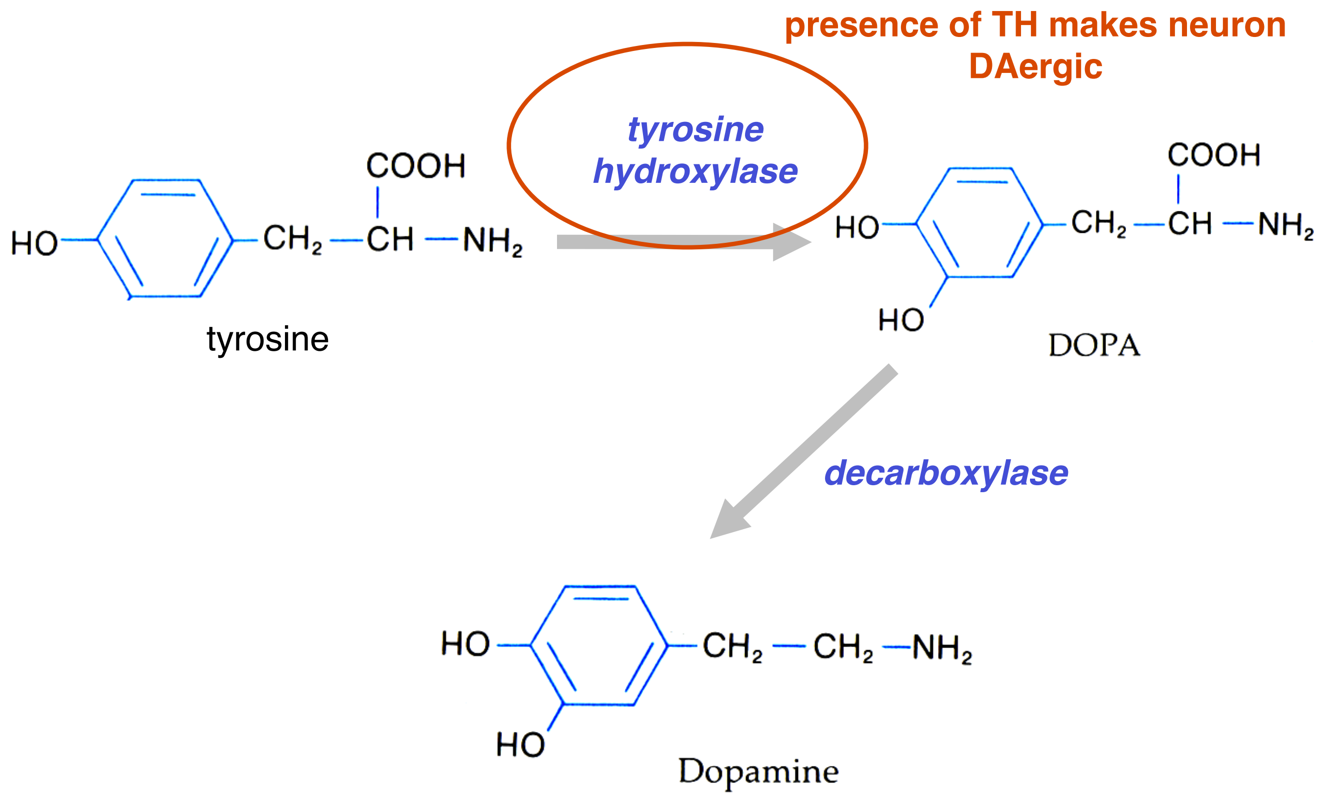
Dopamine (DA)
important for movement & in “reward” pathways
Parkinson’s Disease: DA cells die, leading to paralysis

Norepinephrine (NE) *aka noradrenalin*
Epinephrine (Epi) *aka adrenalin*
important for stress response (blood pressure, heart rate, breathing, glucose levels)

Intermediate	***Enzyme:***
tyrosine	
↓	*tyrosine hydroxylase (TH)*
L-DOPA	
↓	*amino acid decarboxylase (AADC)*
dopamine	
↓	*dopamine-B-hydroxylase (DBH)*
norepinephrine	
↓	*phenylethanolamine-N-methyl transferase (PNMT)*
epinephrine	

Epi- on top of; nephros - kidney
Ad- on top of; renal - kidney
The adrenal gland is the gland on top of the kidney that synthesizes NE and Epi.

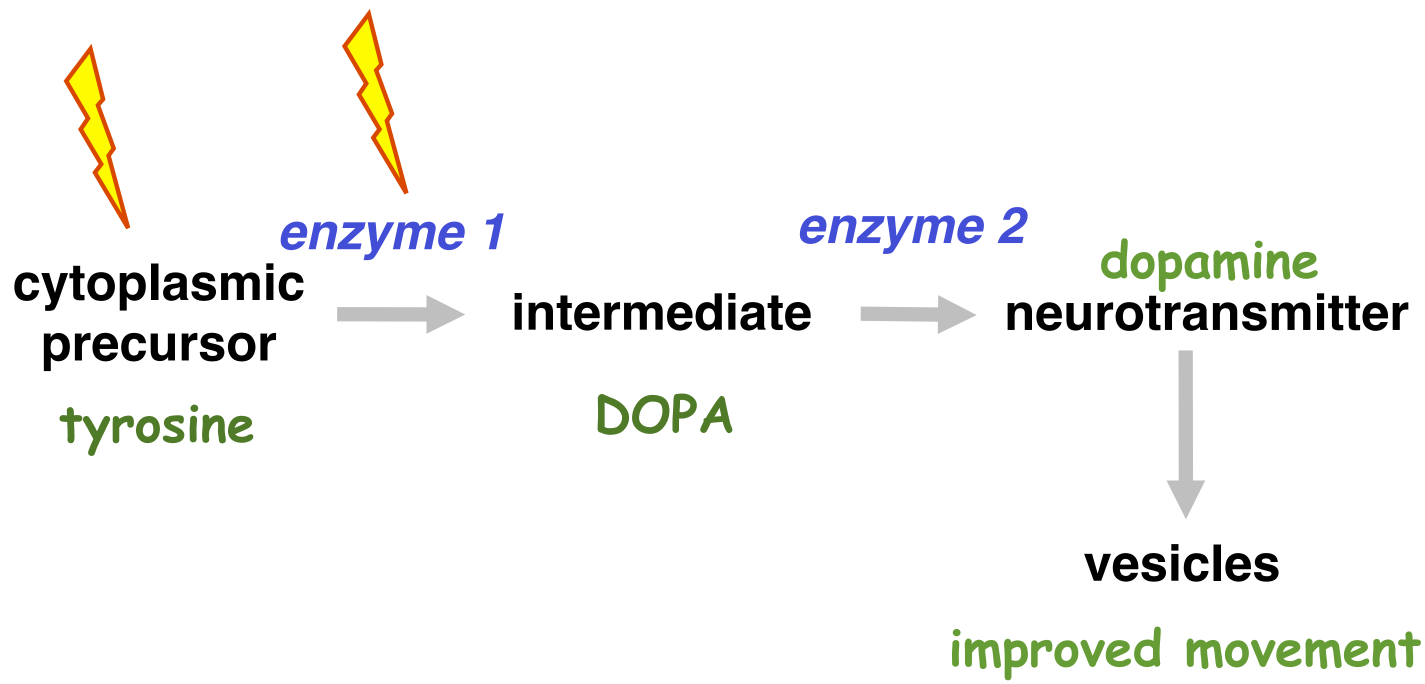
Catecholamines Synthetic Pathways:
Dopamine (DA)
Norepinephrine (NE)
Epinephrine (Epi)



Parkinson's Disease

Dopamine cells die -> paralysis

Give patients DOPA to boost DA synthesis



Parkinson's Disease; depigmentation of substantia nigra: On the right side of the slide is a transverse section through the midbrain of a normal individual. Note the pigmentation in the substantia nigra. Contrast this appearance with the midbrain on the left in which there is markedly reduced pigmentation within the substantia nigra. This is the typical appearance in an advanced case of Parkinson's disease.

www.urmc.rochester.edu/ neuroslides/slide199.html https://www.youtube.com/watch?v=5BU4CxtLkn4

Parkinsons Disease

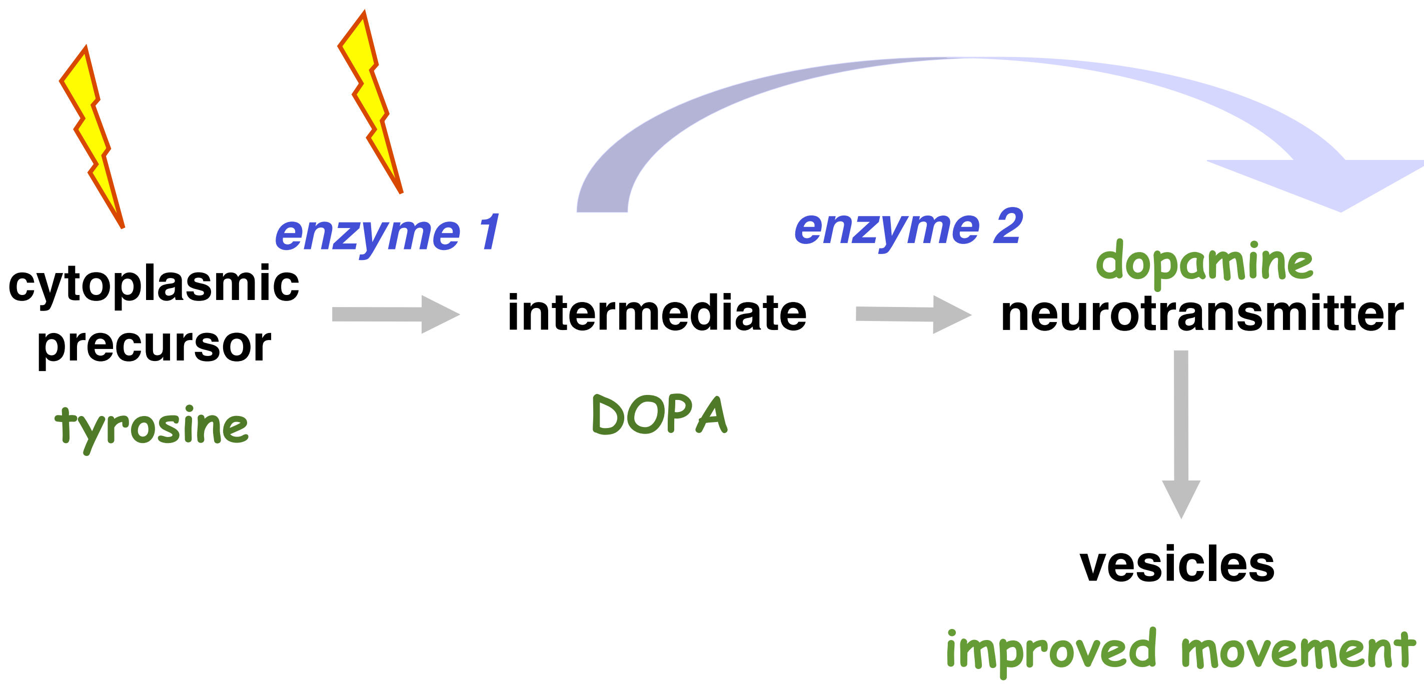
Parkinson's Disease Video - Tremor http://www.lloydtan-trust.com

Dopamine cells die -> paralysis
(cortex can’t control brainstem &
can’t suppress brainstem rhythmic output)

Parkinson's Disease

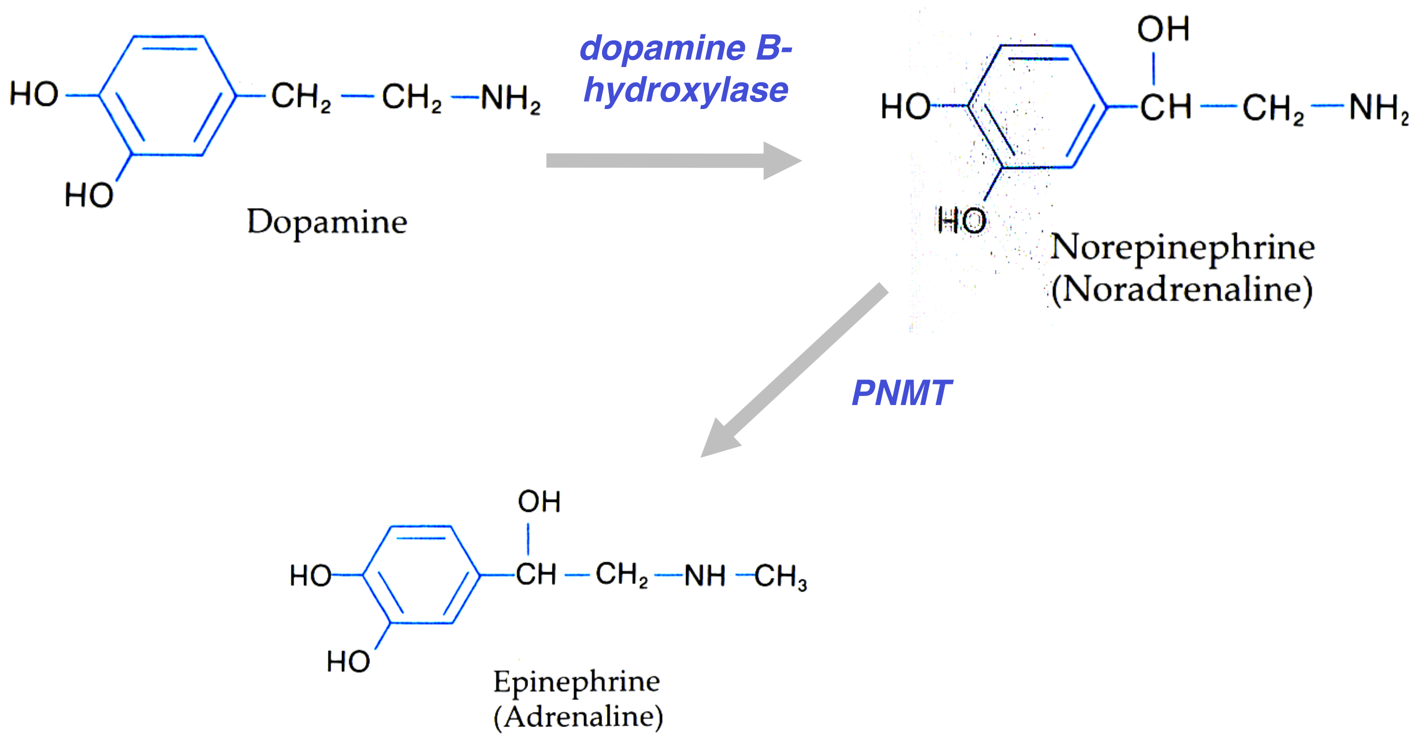
Dopamine cells die -> paralysis

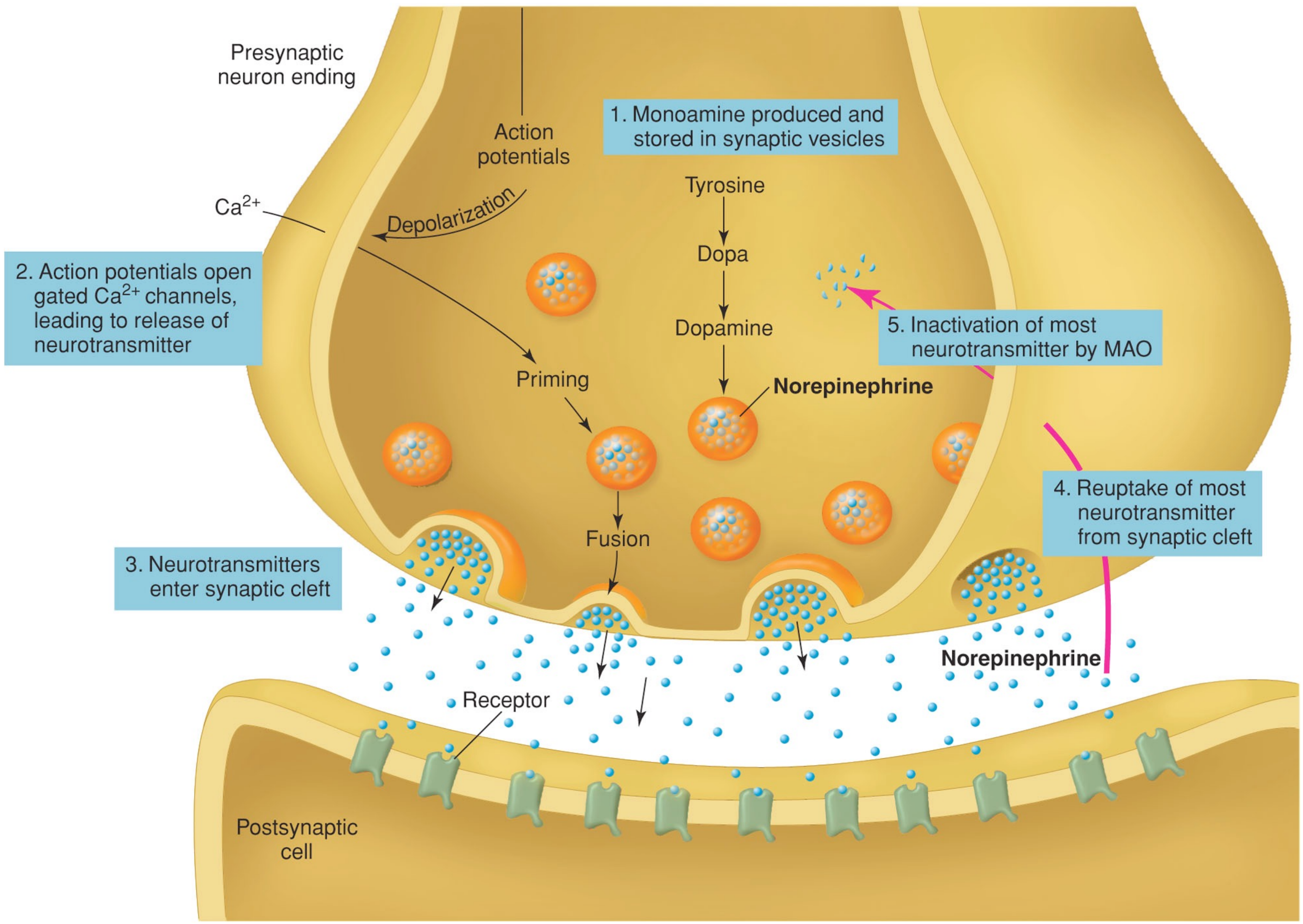
Give patients DOPA to boost DA synthesis



Classical NTs & Synthetic pathways

Amines: Catecholamines (DA, NE, Epi)





Fox Figure 7.30

Neuropeptides

Small peptides, from 4 amino acids to ~100 amino acids.

Coded for by genes, synthesized by ribosomes (like other proteins).

Signal peptide sequence directs neuropeptide into endoplasmic reticulum, Golgi apparatus, and into secretory vesicles.

In neurons, neuropeptides are co-localized and released with classical neurotransmitters.

Many neuropeptides also serve as hormones secreted by glands into the blood.

Act on G-protein coupled receptors; slow, long-lasting effect on target cells

2 Types of neurotransmitters

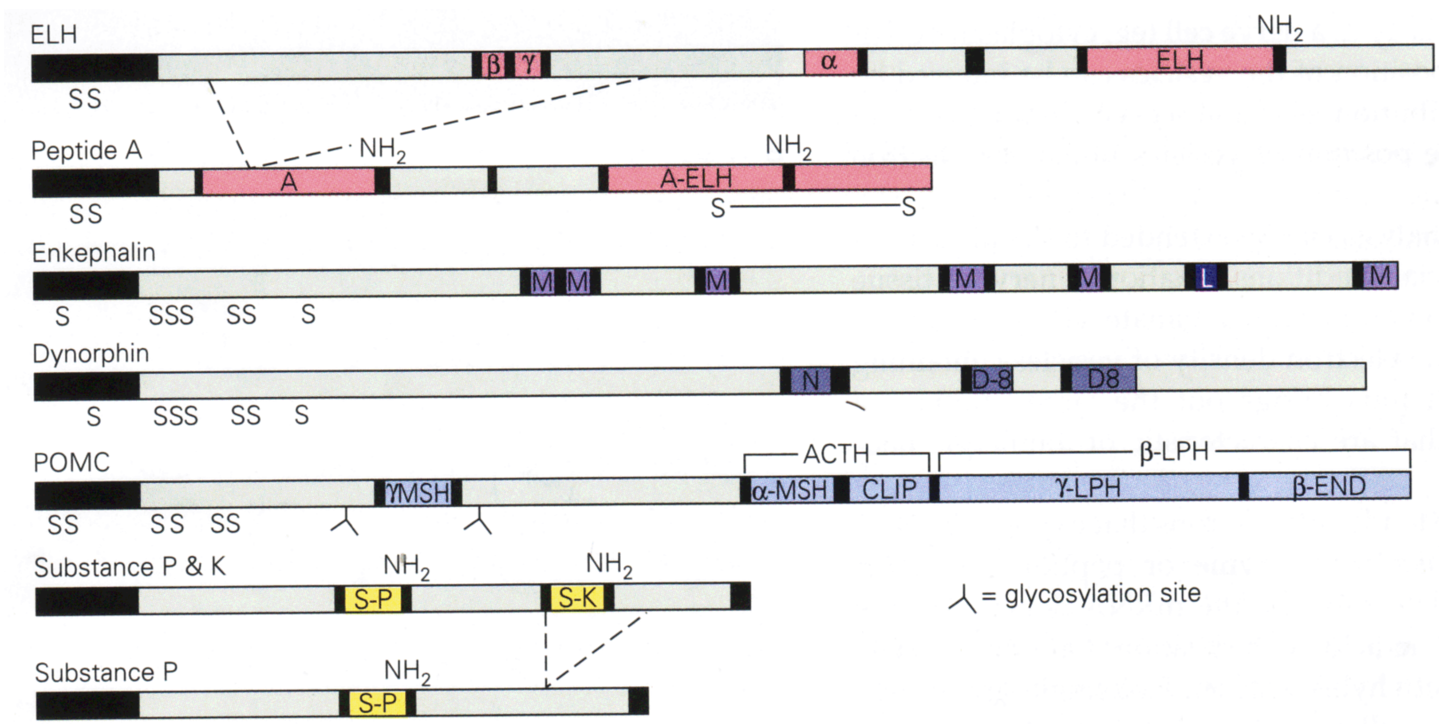
	Classical small molecules	Neuropeptides
Size	**small** (like amino acid or amine)	**large** (4-100 a.a. polypeptide)
Synthesis	uptake or enzymes	protein synthesis
Vesicles	**small,** filled by transporters	**large** secreted proteins from RER
Duration of action	fast but short	slow & long

Neuropeptides -- small chains of amino acids synthesized and released by neurons

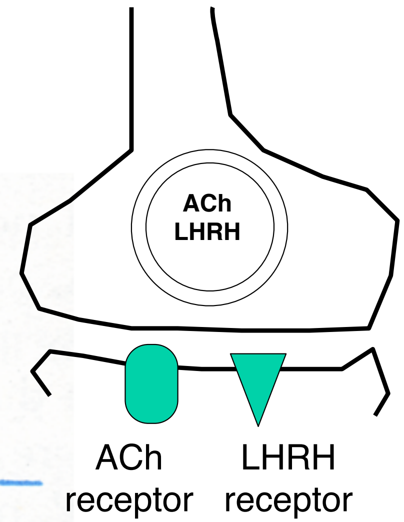
Category	Peptide
Hypothalamic releasing hormone	Thyrotropin-releasing hormone Gonadotropin-releasing hormone Somatostatin Corticotropin-releasing hormone Growth hormone-releasing hormone
Neurohypophyseal hormones	Vasopressin Oxytocin
Pituitary peptides	Adrenocorticotropic hormone β-Endorphin α-Melanocyte-stimulating hormone Prolactin Luteinizing hormone Growth hormone Thyrotropin
Invertebrate peptides	FMRFamide[1] Hydra head activator Proctolin Small cardiac peptide Myomodulins Buccalins Egg-laying hormone Bag cell peptides
Gastrointestinal peptides	Vasoactive intestinal polypeptide Cholecystokinin Gastrin Substance P Neurotensin Methionine-enkephalin Leucine-enkephalin Insulin Glucagon Bombesin Secretin Somatostatin Thyrotropin-releasing hormone Motilin
Heart	Atrial naturetic peptide
Other	Angiotensin II Bradykinin Sleep peptide(s) Calcitonin CGRP[2] Neuropeptide Y Neuropeptide Yy Galanin Substance K (neurokinin A)

more variety, because combination of 4 to 100 a.a.
(similar variety of receptors!)

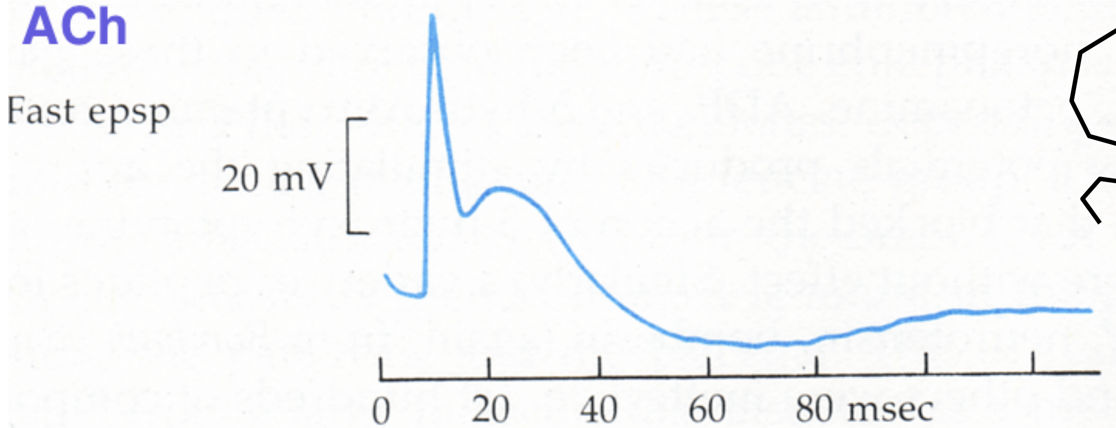
Neuropeptides are cleavage products of prepropeptides (translated from genes)



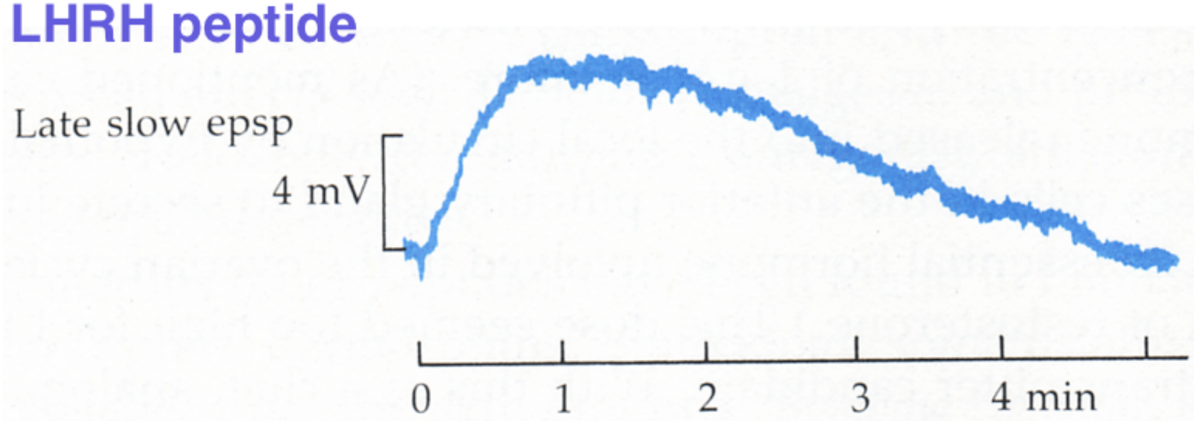
Neuropeptides & classical NTs in same synapse, but different effects via different receptors



ACh



LHRH peptide



Neurotransmitters and Receptors

1. Ligand-Gated Ion Channels
Neurotransmitter binds to channel protein, causing it to open and allow ions to move into the cell.

2. G-Protein Coupled Receptors
Neurotransmitter binds to receptor protein, which activates a complex of G-proteins (interact with GTP).

Activated G-proteins
i. can interact with ion channels in membrane to change Vm

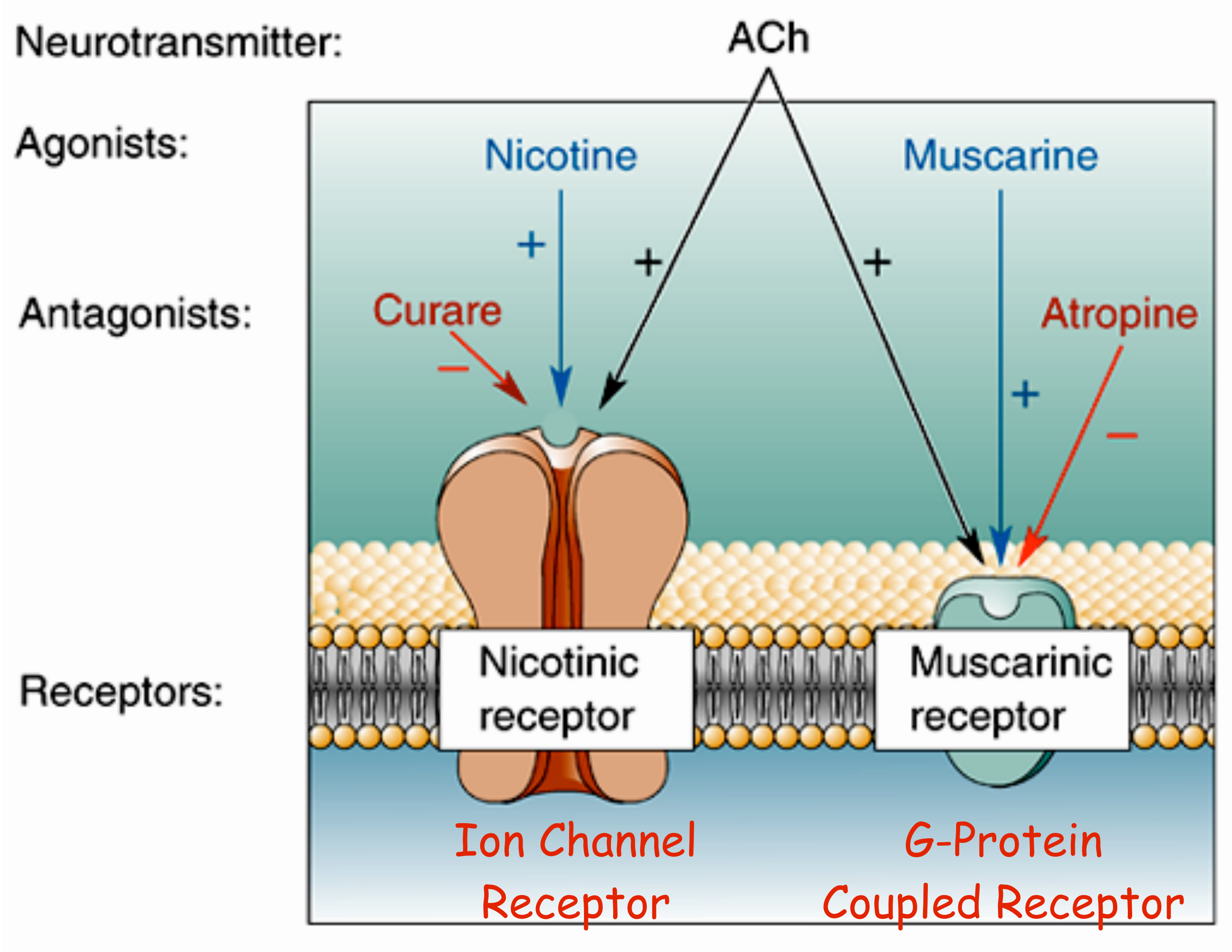
ii. can activate second messenger systems like adenylate cyclase to raise cAMP levels in the cytoplasm for slower, intracellular signaling.

iii. G-proteins can be stimulatory (G_s -> more cAMP) or inhibitory (G_i -> less cAMP)

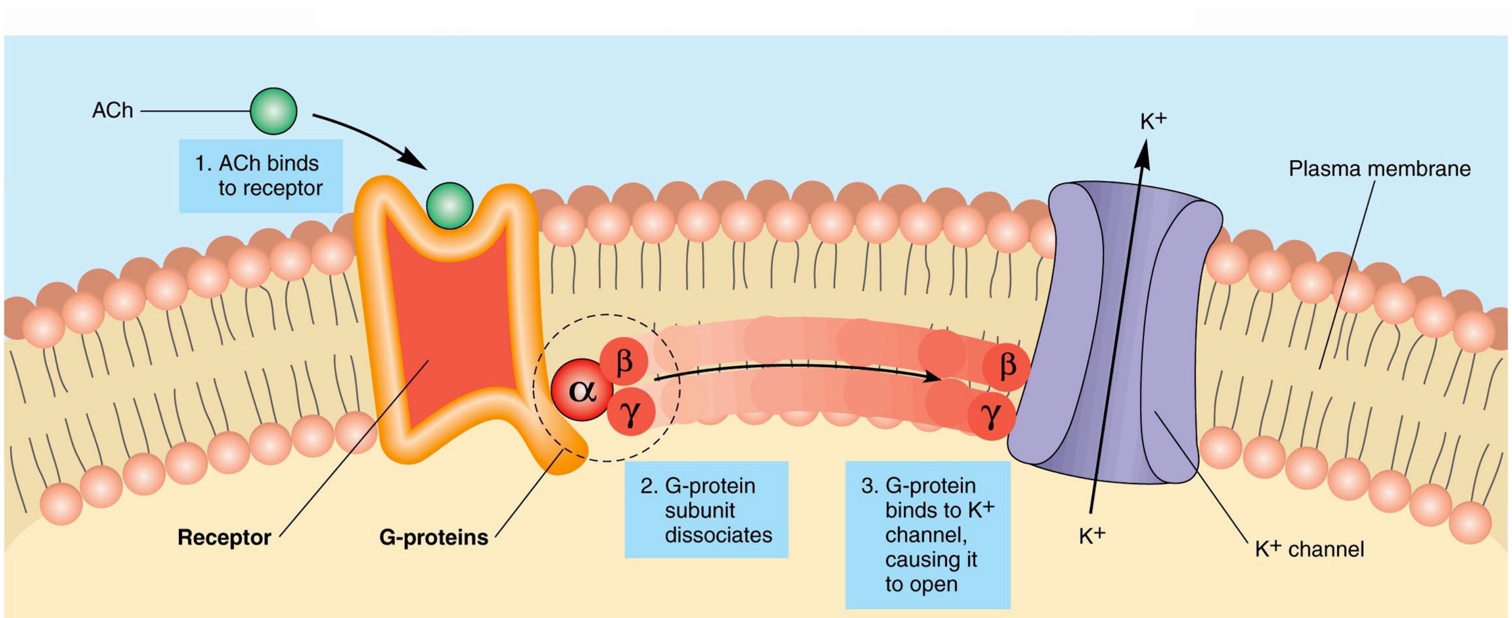
A single neurotransmitter can act on multiple types of receptors.
Type of receptor determines the response of the postsynaptic target cell.

So one neurotransmitter can have opposite effects on 2 different postsynaptic cells, if each postsynaptic cell has a different receptor type.

Terminology:



G-Proteins can directly affect ion channels



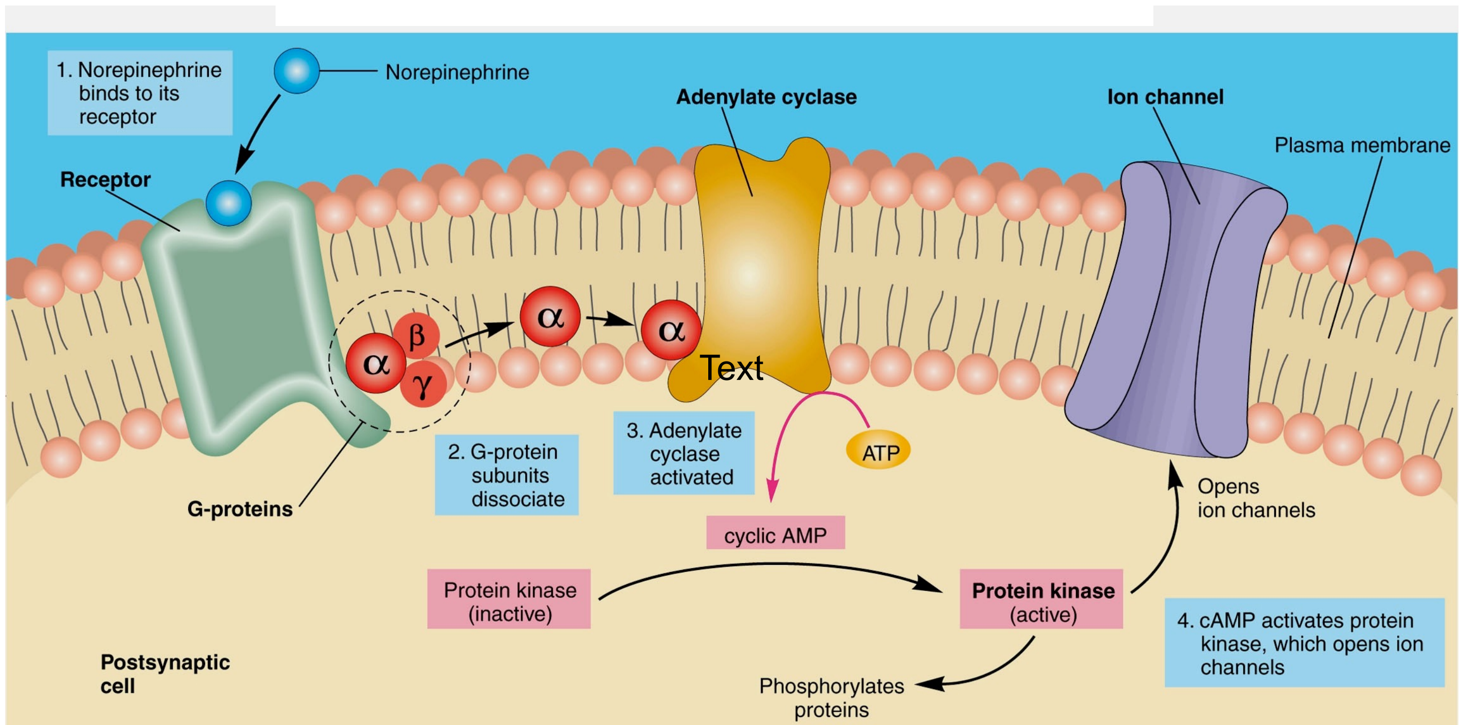
Fox Figure 7.27

Table 7.6 | Steps in the Activation and Inactivation of G-Proteins

Step 1	When the membrane receptor protein is not bound to its regulatory molecule ligand, the alpha, beta, and gamma G-protein subunits are aggregated together and attached to the receptor; the alpha subunit binds GDP.
Step 2	When the ligand (neurotransmitter or other regulatory molecule) binds to the receptor, the alpha subunit releases GDP and binds GTP; this allows the alpha subunit to dissociate from the beta-gamma subunits.
Step 3	Either the alpha subunit or the beta-gamma complex moves through the membrane and binds to a membrane effector protein (either an ion channel or an enzyme).
Step 4	Deactivation of the effector protein is caused by the alpha subunit hydrolyzing GTP to GDP.
Step 5	This allows the subunits to again reaggregate and bind to the unstimulated receptor protein (which is no longer bound to its regulatory molecule ligand).

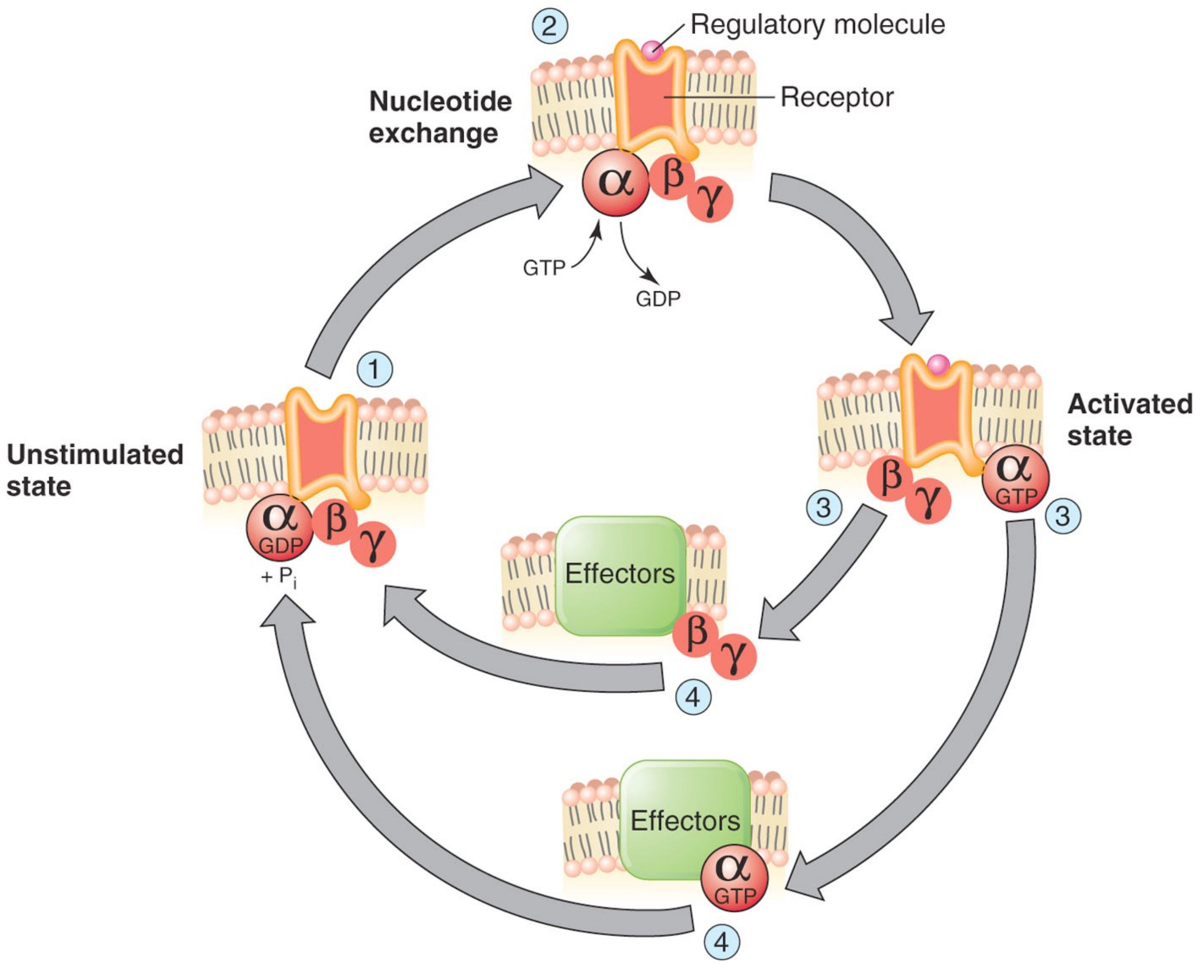
- Fox Table 7.6

G-Proteins can affect second messenger signaling (e.g. cAMP levels in the cytoplasm)



Fox Figure 7.31

Figure 6.31


2
Regulatory molecule
Nucleotide exchange
Receptor
α
β
γ
GTP
GDP
1
Unstimulated state
α
GDP
β
γ
+ P_i
Activated state
β
γ
α
GTP
3
3
Effectors
β
γ
4
Effectors
α
GTP
4

Life Cycle of a Neurotransmitter

- source of neurotransmitter
  - *simple amino acid (glutamate)*
  - *synthesis by enzymes:*
    - *acetylcholine*
    - *GABA*
    - *catecholamines*
  - *protein synthesis of neuropeptides*
  - *(one neuron makes 1 neurotransmitter ± neuropeptide)*

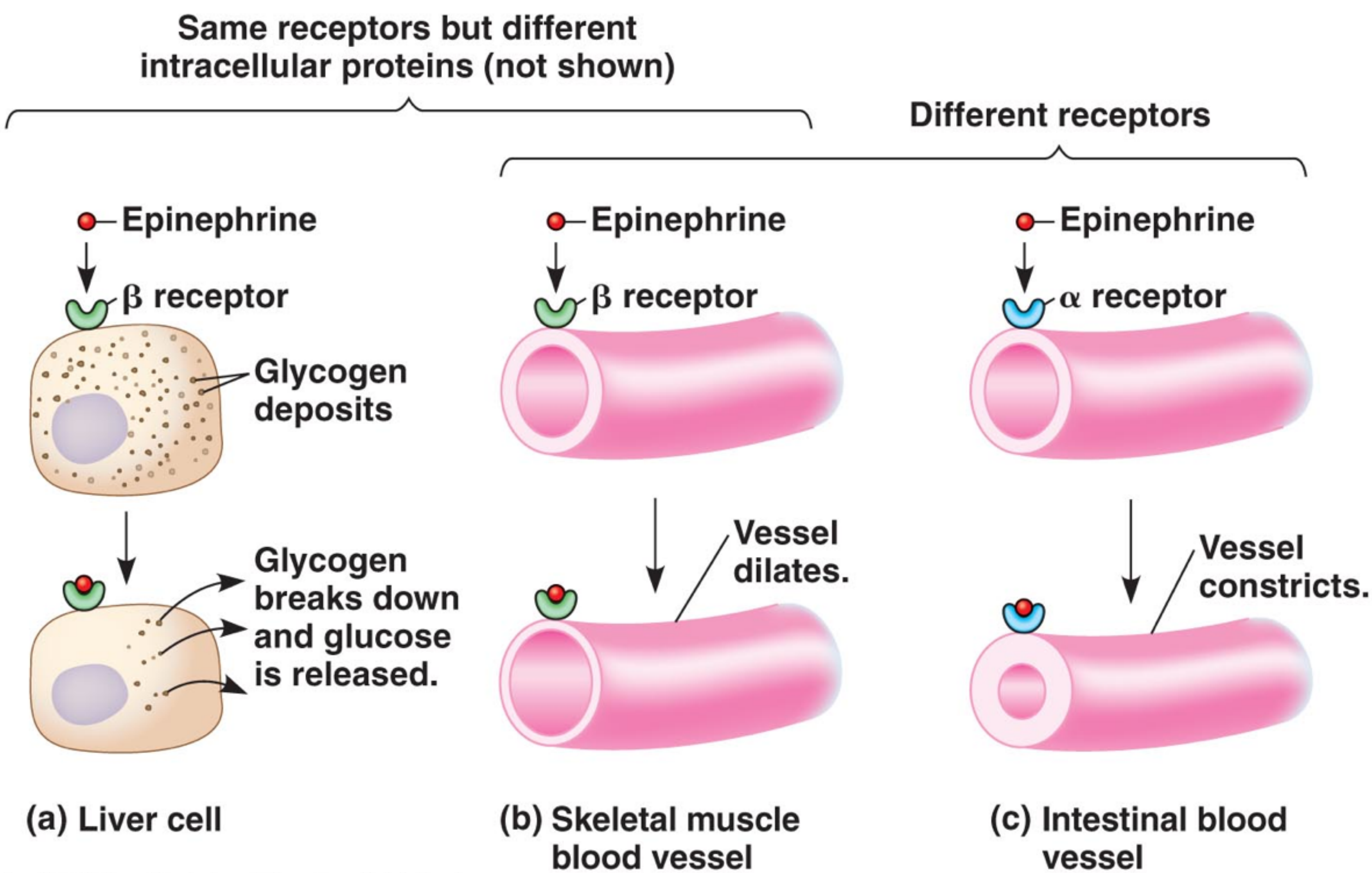
- packaging in vesicle

- release into synapse

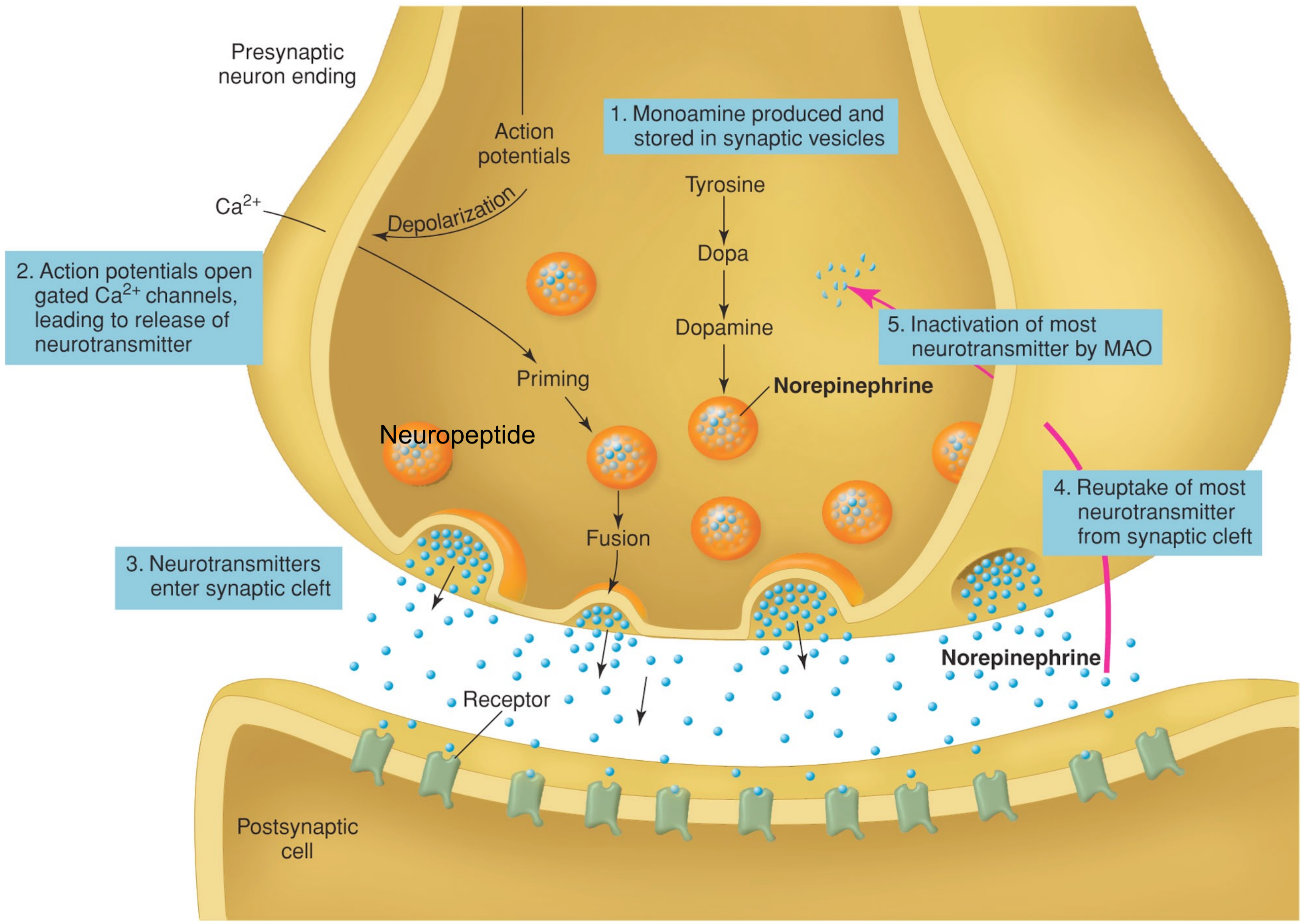
- act on receptors on target cell
  - *ligand-gated ion channels*
  - *G-protein coupled receptors*
  - *(same transmitter -> different receptors on different targets)*

- removal from synapse
  - *degradation by enzymes (acetylcholine)*
  - *re-uptake by transporters (catecholamines)*

Epinephrine (Adrenalin) secreted from Adrenal Gland & Autonomic Neurons during stress (one NT -> multiple effects)

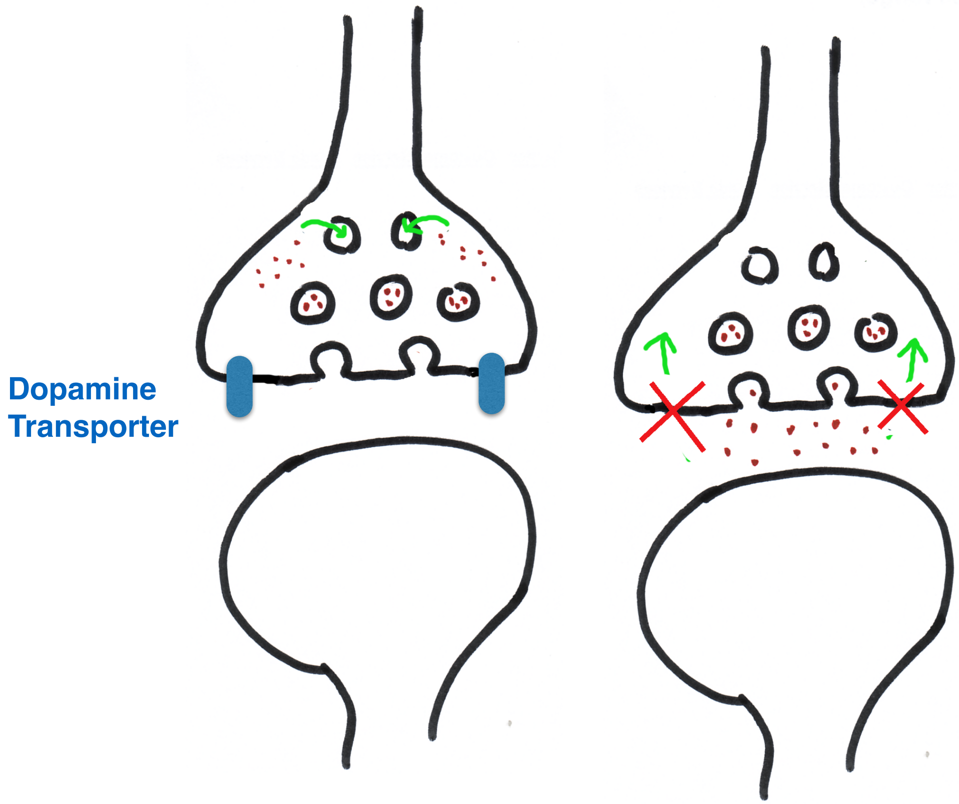


Life Cycle of a Neurotransmitter



Fox Figure 7.30

Transporters clear synapse and recycle NT; re-uptake inhibitors prolong synaptic action



cocaine blocks dopamine transporter

(ecstasy, prozac block serotonin transporter)