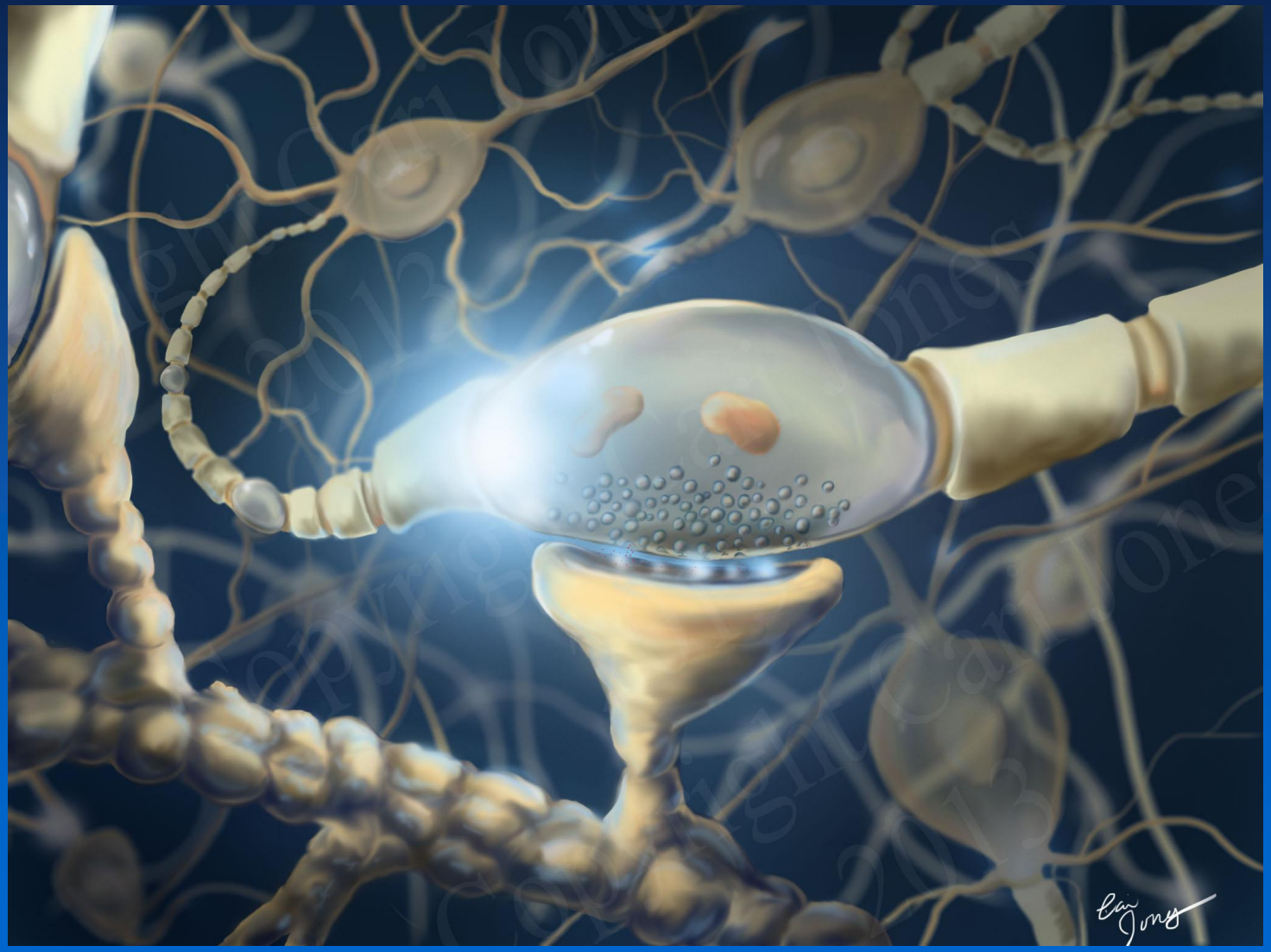
SYNAPTIC TRANSMISSION



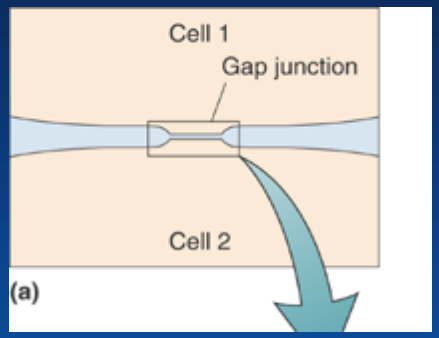
A **synapse** is a site where information is transmitted from one cell to another

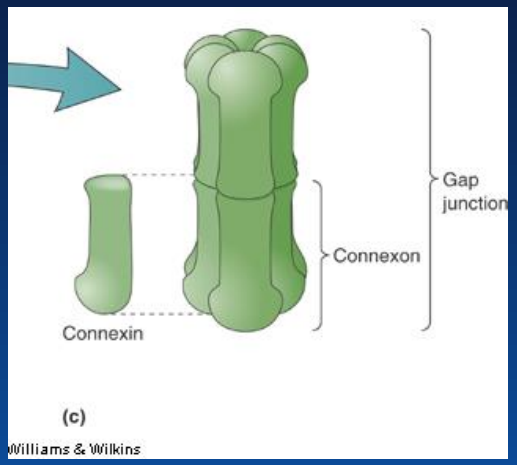
Two main classes of synapses are distinguished;

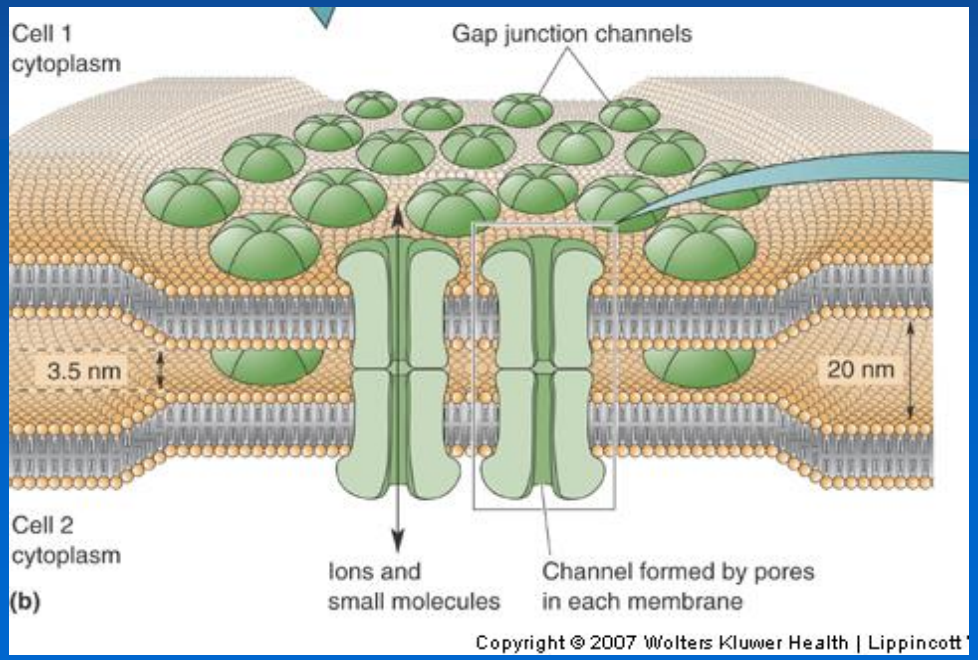
- **Electrical synapses**
  - Electrical synapses allow current to flow from one excitable cell to the next via low resistance pathways between the cells called **gap junctions** *(i.e.; cardiac muscle, some kinds of smooth muscle like uterus or bladder)* .
- **Chemical synapses**
  - In chemical synapses, there is a gap between the presynaptic cell membrane and the postsynaptic cell membrane, known as the **synaptic cleft**. Information is transmitted across the synaptic cleft via a neurotransmitter, a substance that is released from the presynaptic terminal and binds to receptors on the postsynaptic terminal.

Electrical Synapses

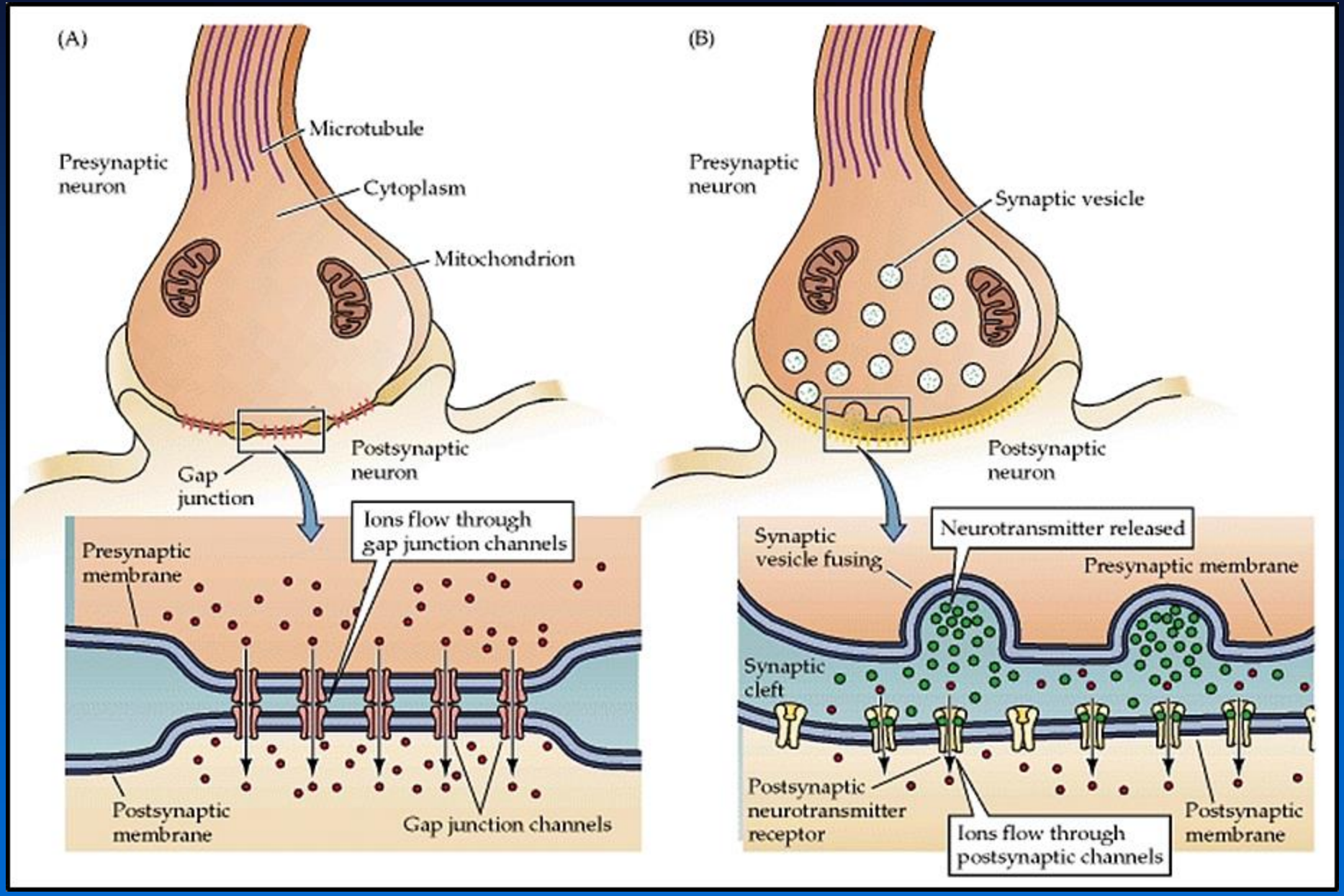
- **Direct transfer of ionic current from one cell to the next**
- **Gap junction**
  - The membranes of two cells are held together by clusters of *connexins*
  - Connexon
    - ✓ A channel formed by six connexins
  - Two connexons combine to from a gap junction channel
    - ✓ Allows ions to pass from one cell to the other
    - ✓ 1-2 nm wide : large enough for all the major cellular ions and many small organic molecules to pass





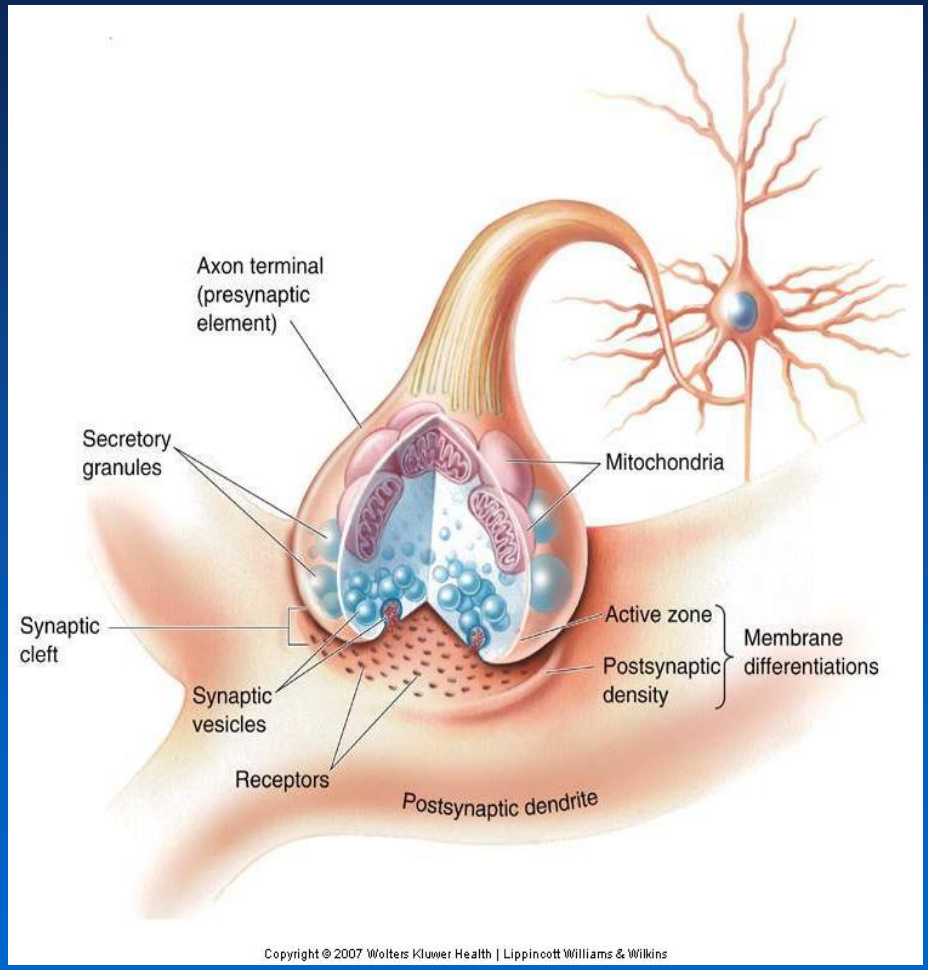


- Cells connected by gap junctions are said to be 'electrically coupled' and they act as 'low-pass filters'.
  - Flow of ions from cytoplasm to cytoplasm bidirectionally
  - Very fast, fail-safe transmission
  - Almost simultaneous action potential generations
- Paired recording reveals synchronous voltage responses upon depolarizing or hyperpolarizing current injections
- Often found where normal function requires that the neighboring neurons be highly synchronized
- Common in mammalian CNS as well as in invertebrates

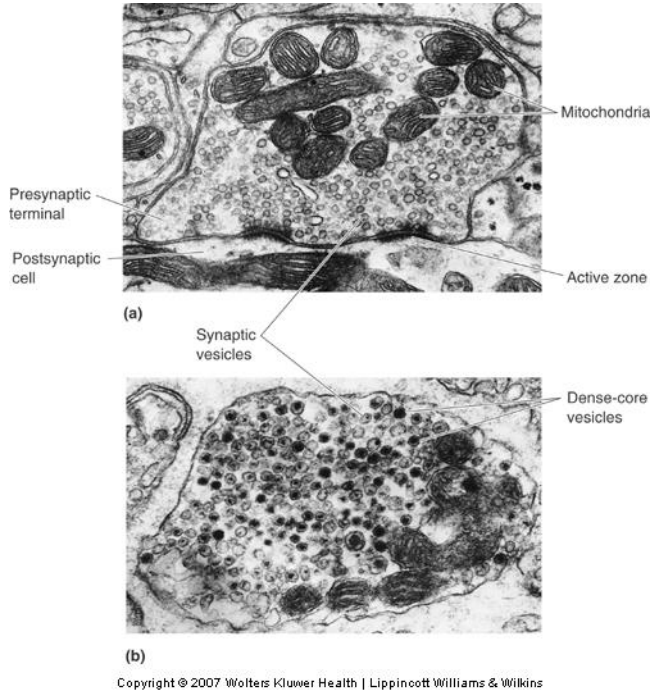

(A)
Microtubule
Presynaptic neuron
Cytoplasm
Mitochondrion
Postsynaptic neuron
Gap junction
Ions flow through gap junction channels
Presynaptic membrane
Postsynaptic membrane
Gap junction channels
(B)
Presynaptic neuron
Synaptic vesicle
Postsynaptic neuron
Neurotransmitter released
Synaptic vesicle fusing
Presynaptic membrane
Synaptic cleft
Postsynaptic neurotransmitter receptor
Ions flow through postsynaptic channels
Postsynaptic membrane

Chemical Synapses

- Synaptic cleft : 20-40 nm wide (gap junctions : 4 nm)
- Adhere to each other by the help of a matrix of fibrous extracellular proteins in the synaptic cleft
- Presynaptic element (= axon terminal) contains synaptic vesicles
- Membrane differentiations
  - Active zone
  - Postsynaptic density



Chemical Synapses



Electrical synapses

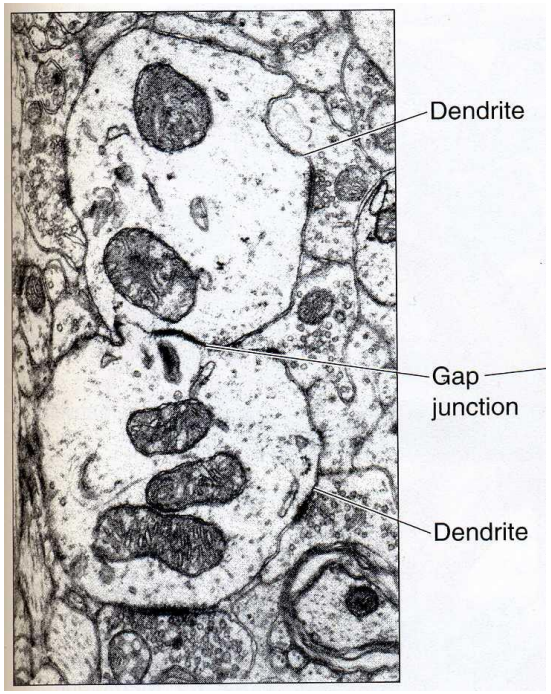
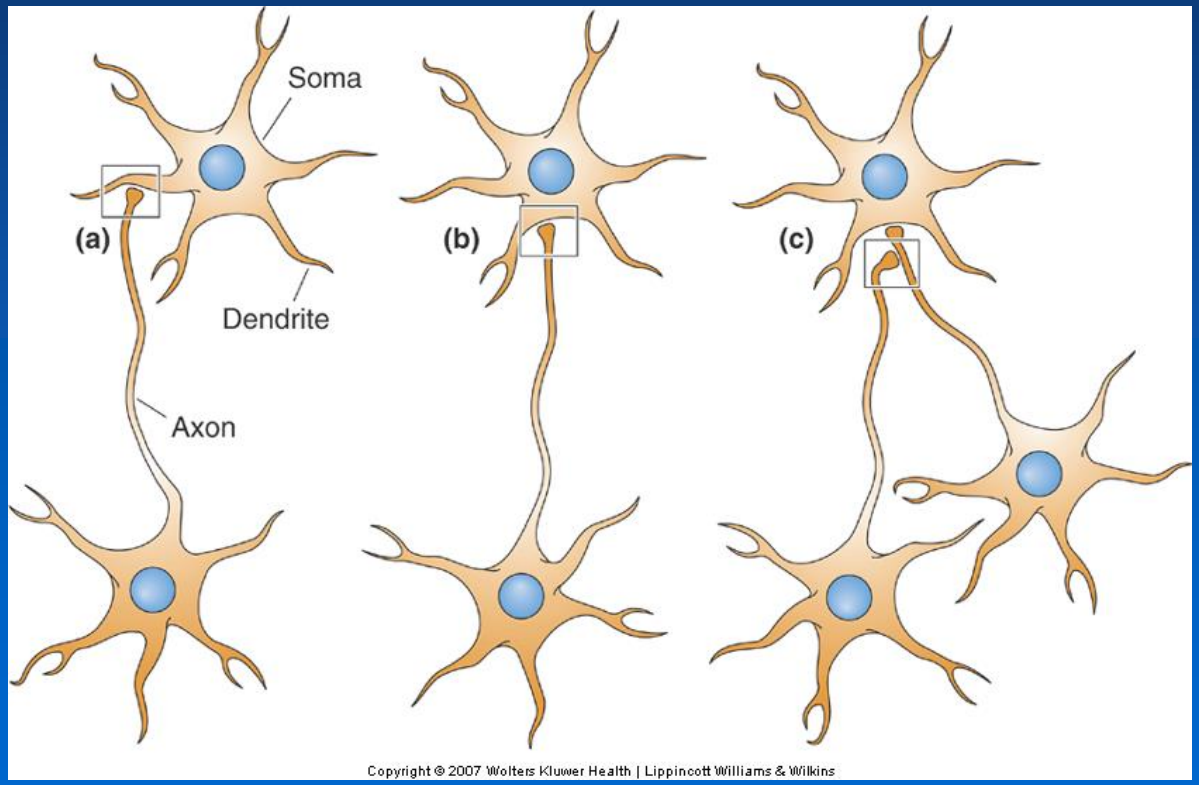


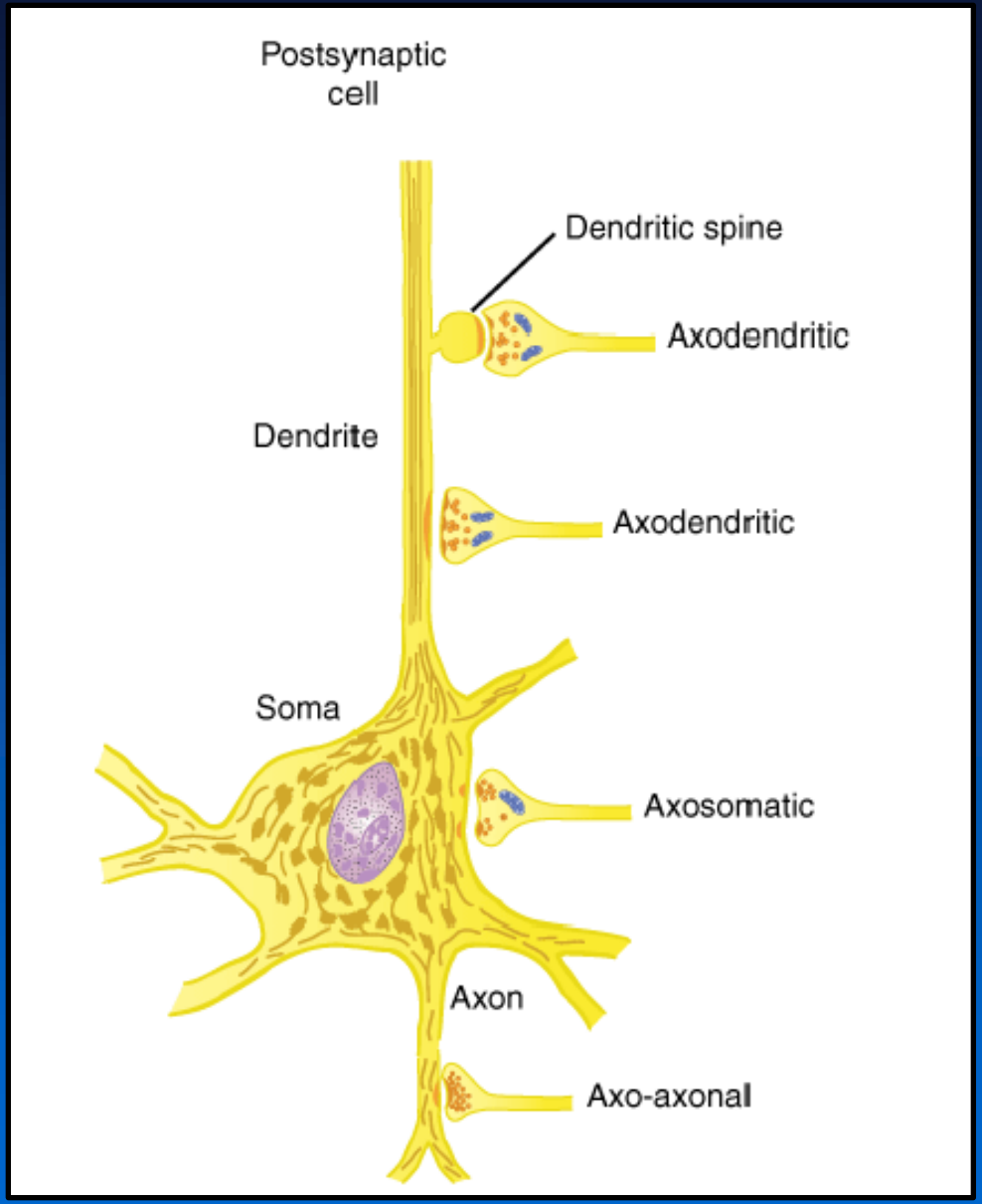
Table 10-1 Distinguishing Properties of Electrical and Chemical Synapses

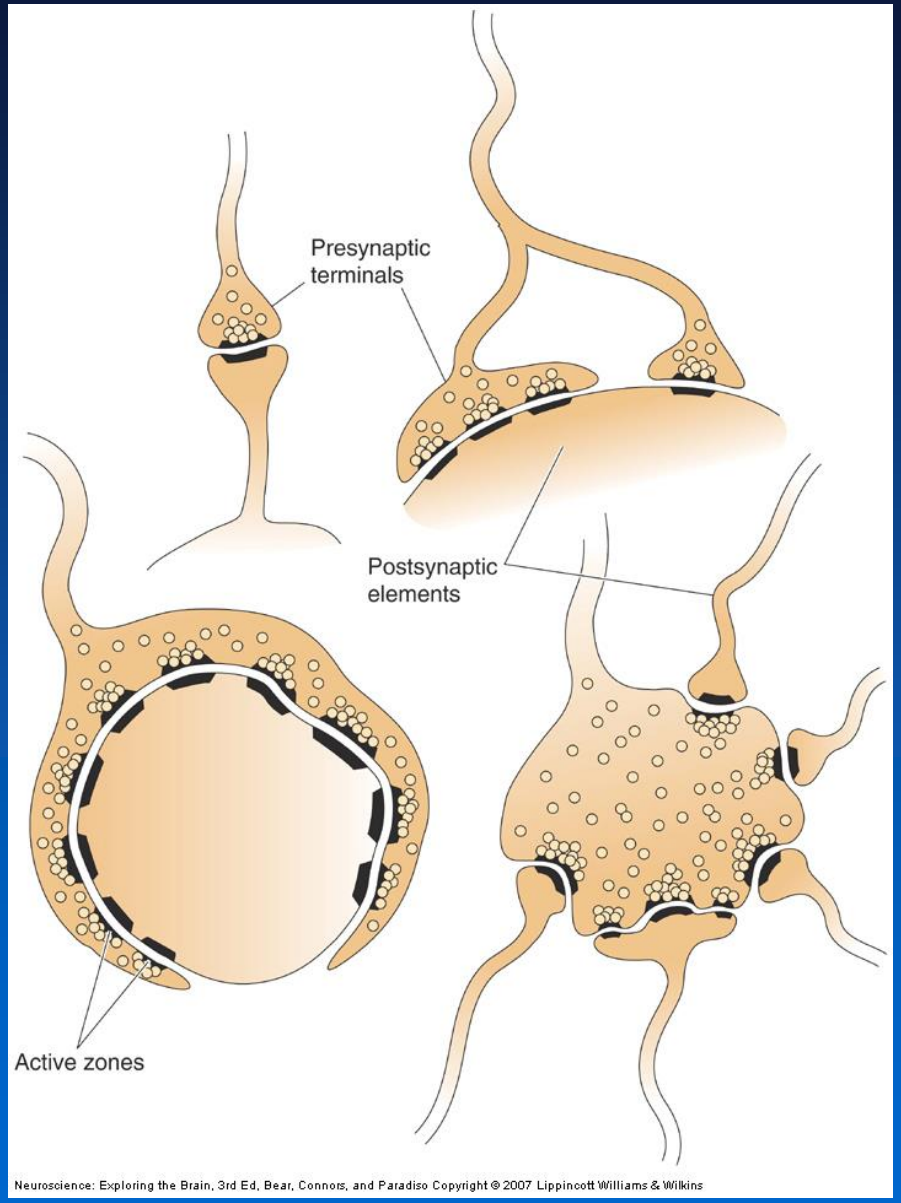
Type of synapse	Distance between pre- and postsynaptic cell membranes	Cytoplasmic continuity between pre- and postsynaptic cells	Ultrastructural components	Agent of transmission	Synaptic delay	Direction of transmission
Electrical	3.5 nm	Yes	Gap-junction channels	Ion current	Virtually absent	Usually bidirectional
Chemical	20–40 nm	No	Presynaptic vesicles and active zones; postsynaptic receptors	Chemical transmitter	Significant: at least 0.3 ms, usually 1–5 ms or longer	Unidirectional

Types of Chemical Synapses

- Chemical synapses occur between different parts of neurons
  - Axodendritic: Axon to dendrite
  - Axosomatic: Axon to cell body
  - Axoaxonic: Axon to axon
  - Dendrodendritic: Dendrite to dendrite

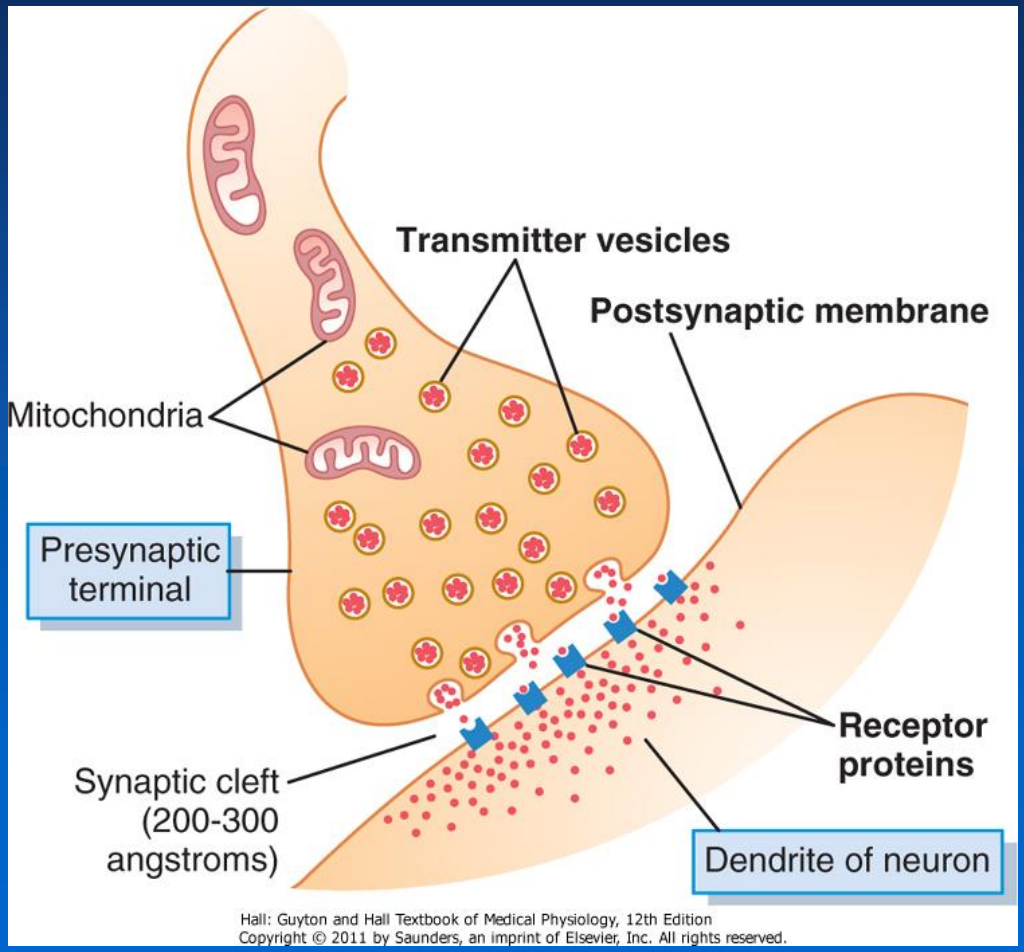


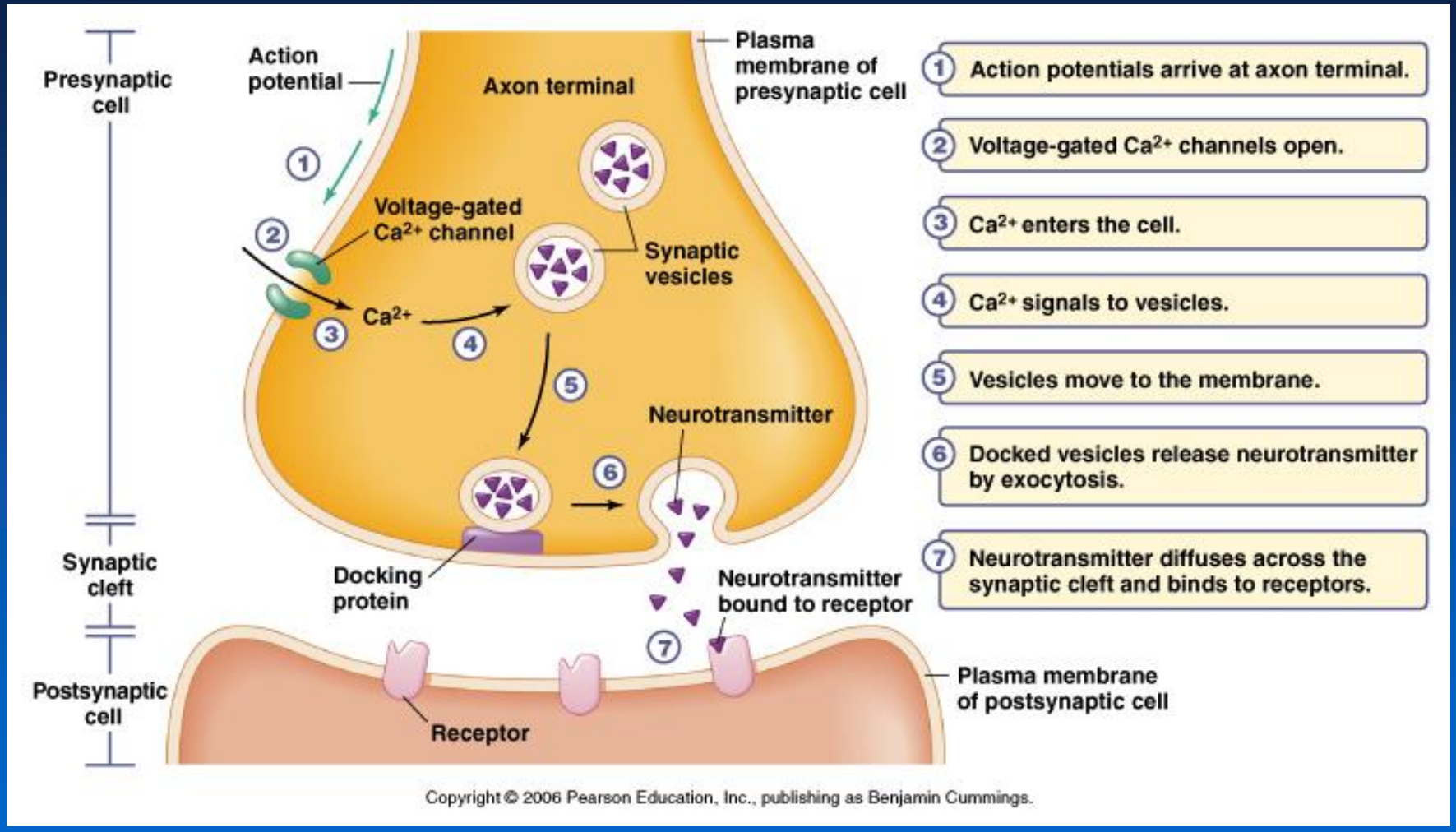

Postsynaptic cell
Dendritic spine
Axodendritic
Dendrite
Axodendritic
Soma
Axosomatic
Axon
Axo-axonal


Presynaptic terminals
Postsynaptic elements
Active zones
Neuroscience: Exploring the Brain, 3rd Ed, Bear, Connors, and Paradiso Copyright © 2007 Lippincott Williams & Wilkins

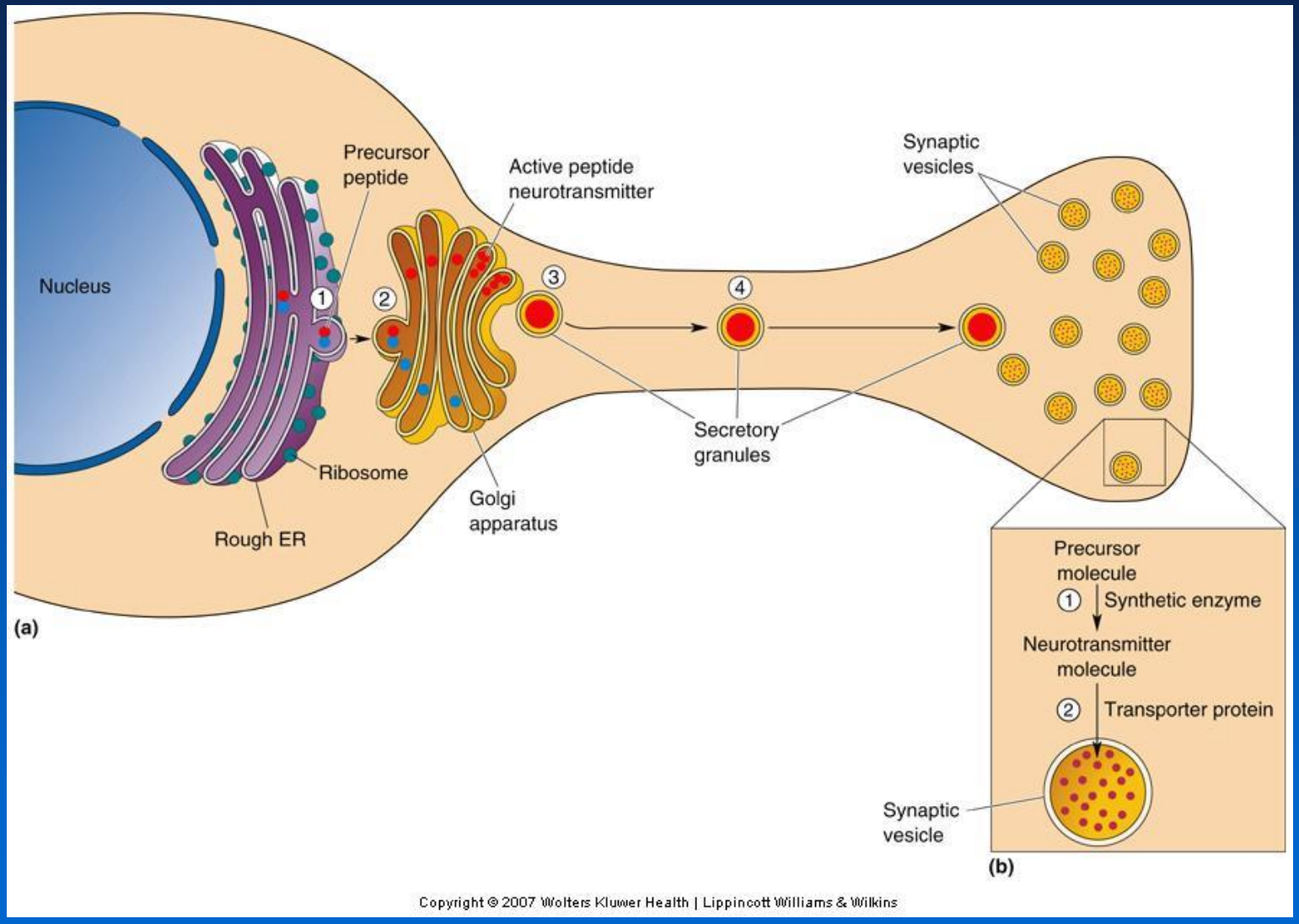
Principles of Chemical Synaptic Transmission

- **Basic Steps**
  - Neurotransmitter synthesis
  - Load neurotransmitter into synaptic vesicles
  - Vesicles fuse to presynaptic terminal
  - Neurotransmitter spills into synaptic cleft
  - Binds to postsynaptic receptors
  - Biochemical/Electrical response elicited in postsynaptic cell
  - Removal of neurotransmitter from synaptic cleft



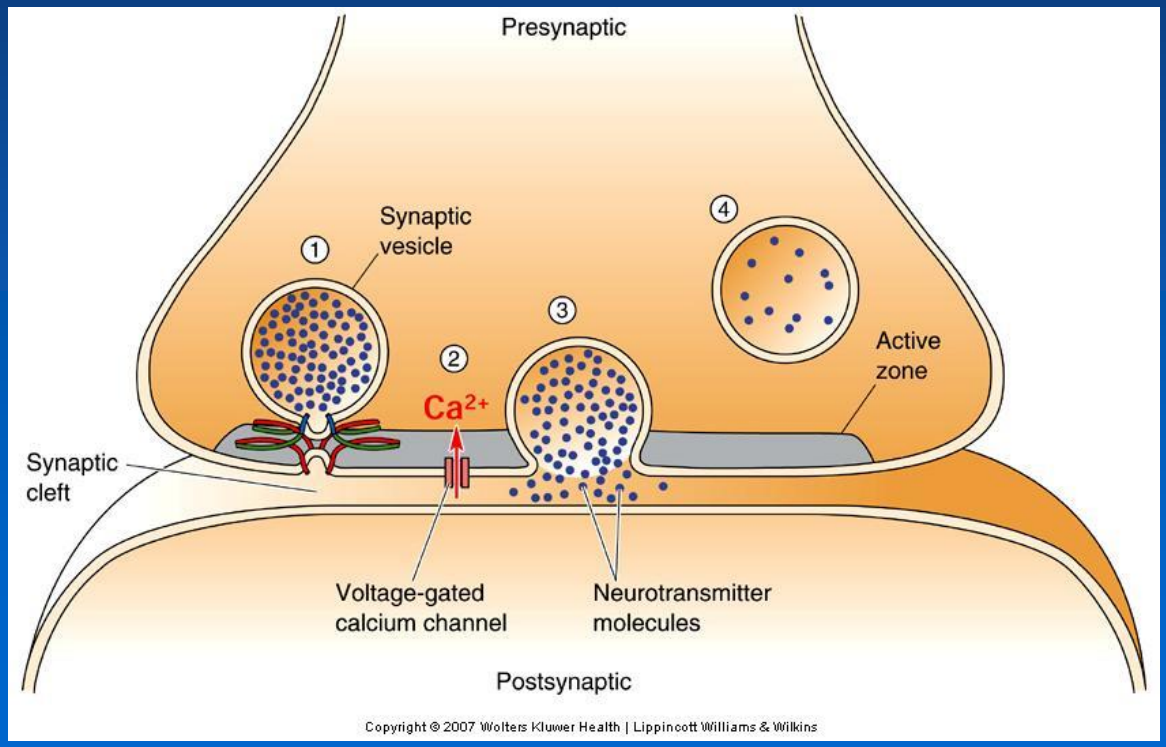


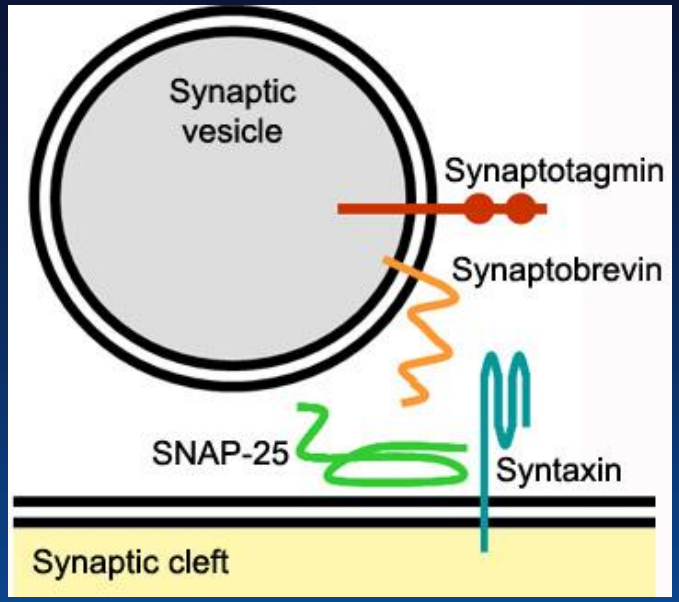
Neurotransmitter Synthesis and Storage



- Neurotransmitter Release
  - Voltage-gated calcium channels open - rapid increase from 0.0002 mM to greater than 0.1 mM
  - Exocytosis can occur very rapidly (within 0.2 msec) because Ca^{2+} enters directly into active zone

- 'Docked' vesicles are rapidly fused with plasma membrane
- Protein-protein interactions regulate the process (SNAREs) of 'docking' as well as Ca^{2+}- induced membrane fusion
- Vesicle membrane recovered by endocytosis

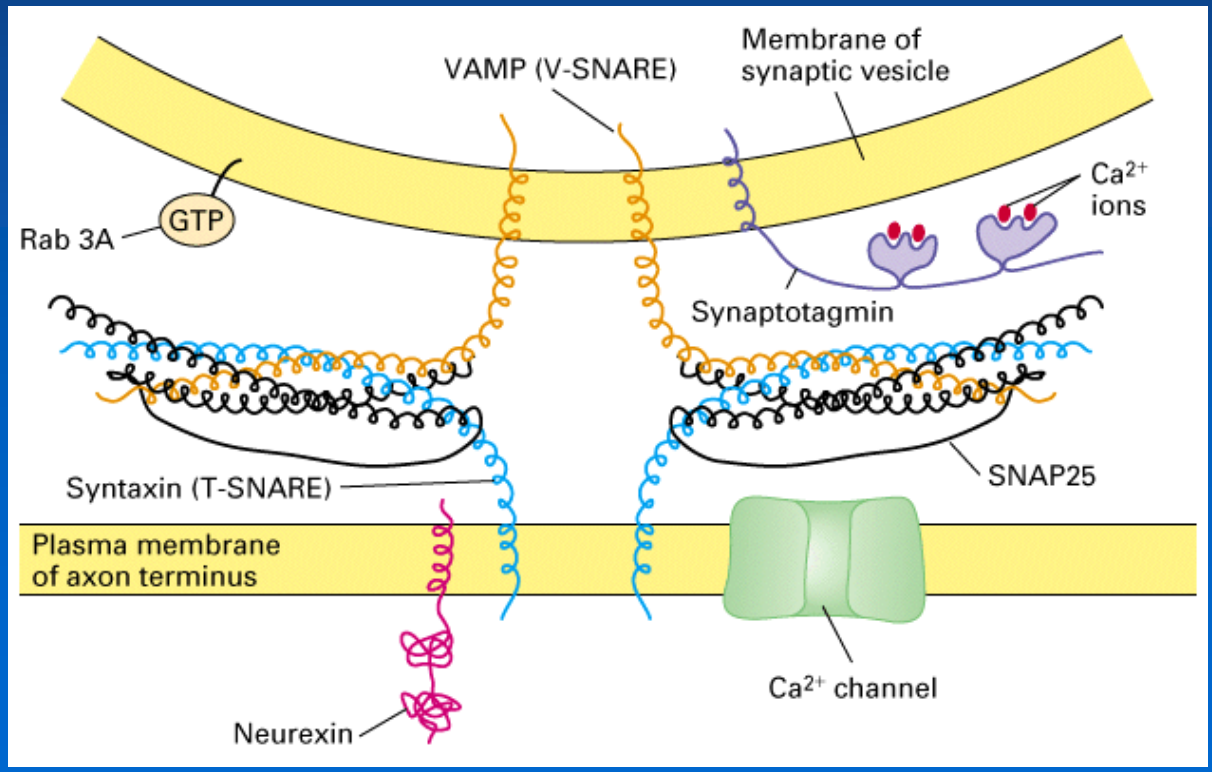




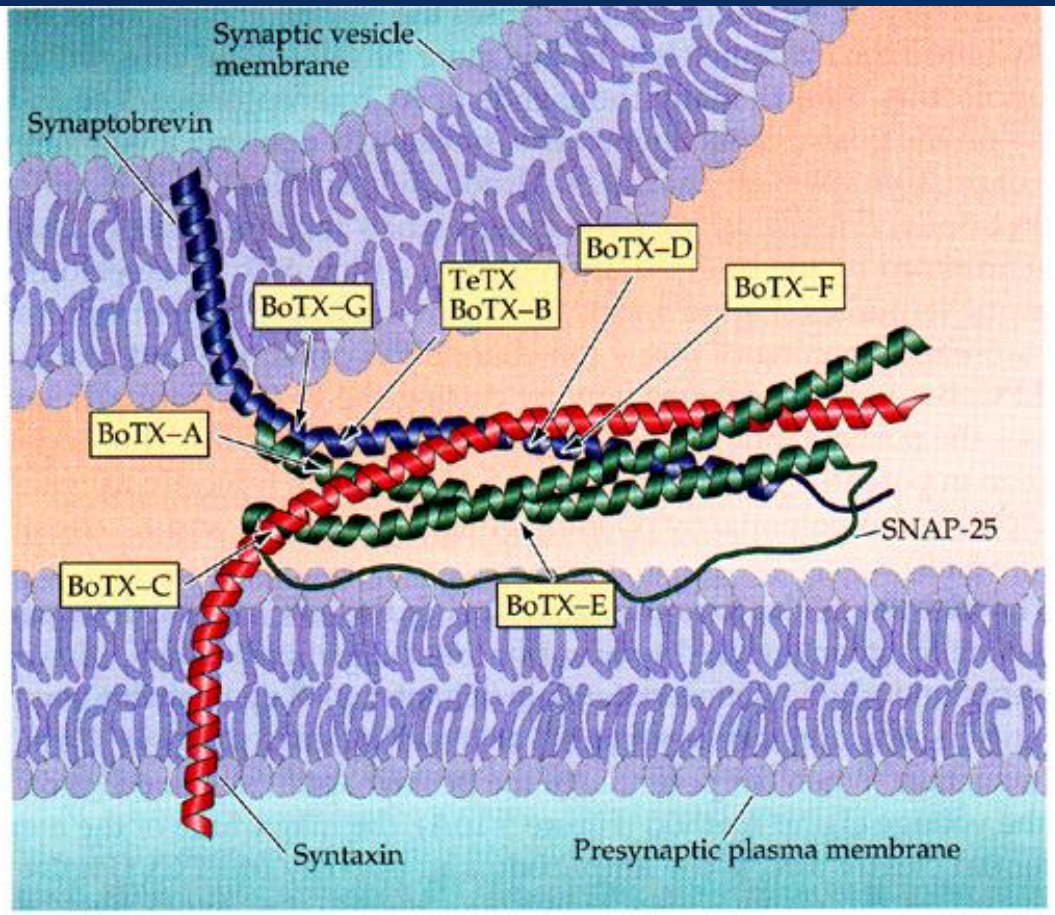
V-SNARES; Synaptobrevin, Synaptotagmin

t-SNARES; SNAP-25, Syntaxin

Synaptotagmin is the Ca^{++} sensor

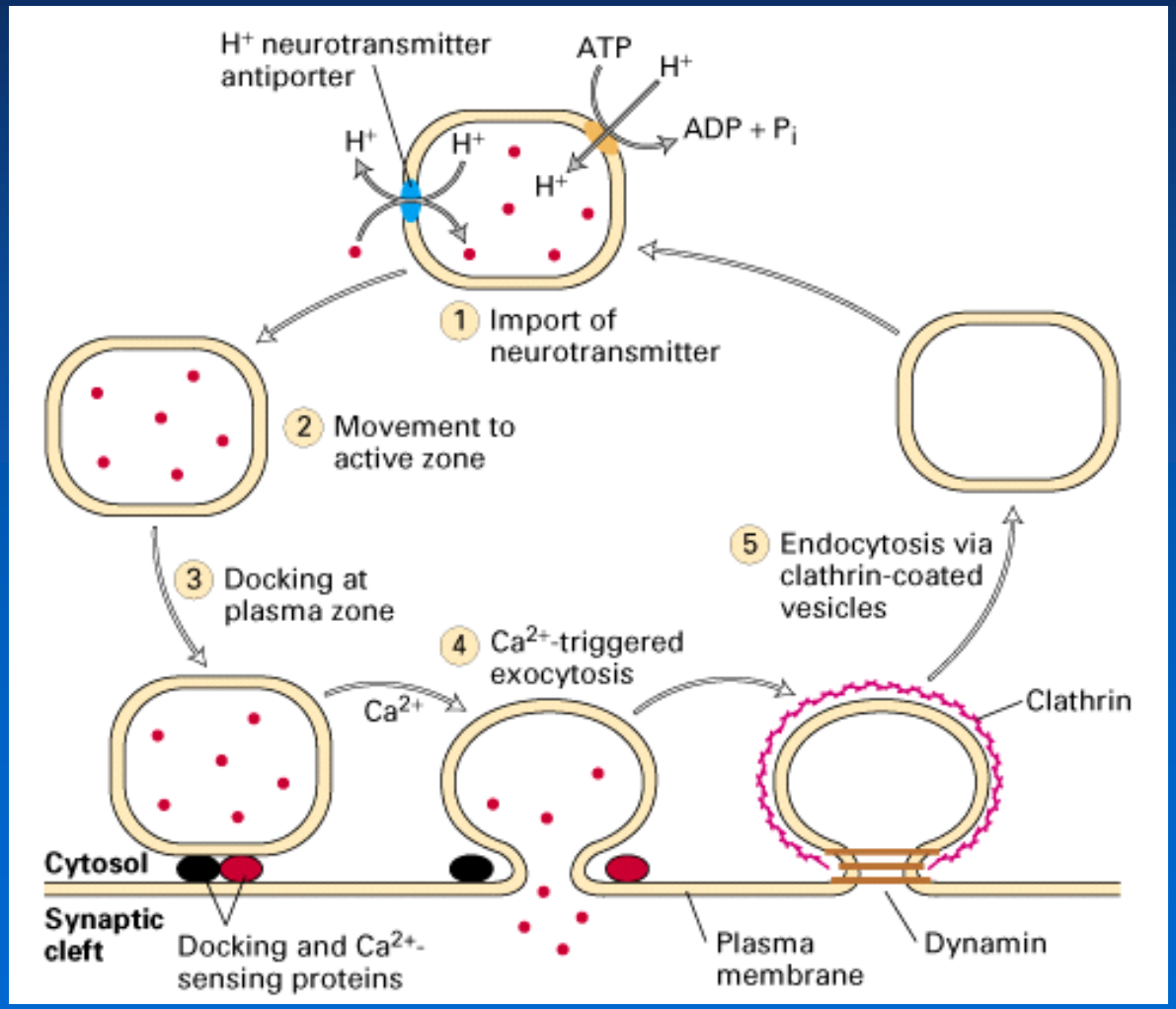


- The SNARE proteins are targets for various **botulinum toxins and tetanus toxin** which disrupt synaptic transmission, thus demonstrating their critical role in this process.



Cleavage of SNARE proteins by clostridial toxins. Indicated are the sites of proteolysis by tetanus toxin (TeTX) and various types of botulinum toxin (BoTX). (After Sutton et al., 1998.)

- Synaptic vesicles are recycled by an endocytotic pathway commonly found in most cell types. Coated pits are formed in the plasma membrane, which then pinch off to form coated vesicles within the cytoplasm of the presynaptic terminal. These vesicles then lose their coat and undergo further transformations to become once again synaptic vesicles ready for release.



- **Neurotransmitter Recovery and Degradation**
  - Clearing of neurotransmitter is necessary for the next round of synaptic transmission
    - Simple Diffusion
      - ✓ Reuptake aids the diffusion
      - ✓ Neurotransmitter re-enters presynaptic axon terminal or enters glial cells through transporter proteins
    - Enzymatic destruction
      - ✓ In the synaptic cleft
      - ✓ Acetylcholinesterase (AchE)
  - Desensitization:
    - Channels close despite the continued presence of ligand
    - Can last several seconds after the neurotransmitter is cleared
    - Nerve gases (e.g. sarin) inhibit AchE --- increased Ach ---- AchR desensitization ---- muscle paralysis

Synaptic Delay

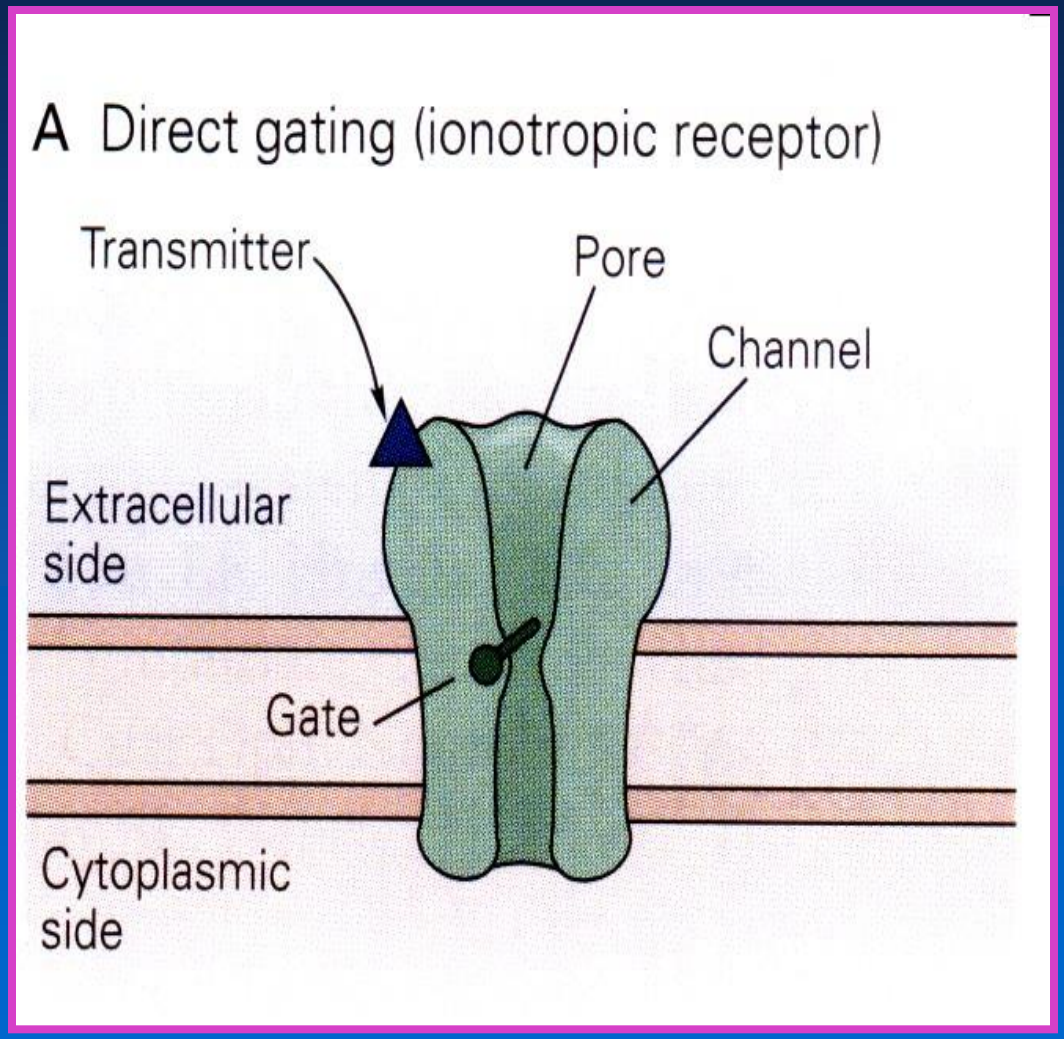
- Neurotransmitter must be released, diffuse across the synapse, and bind to receptor
- Synaptic delay – time needed to do this (0.3-5.0 ms)
- Synaptic delay is the rate-limiting step of neural transmission

Synaptic Receptors

- Ionotropic receptors
- Metabotropic receptors

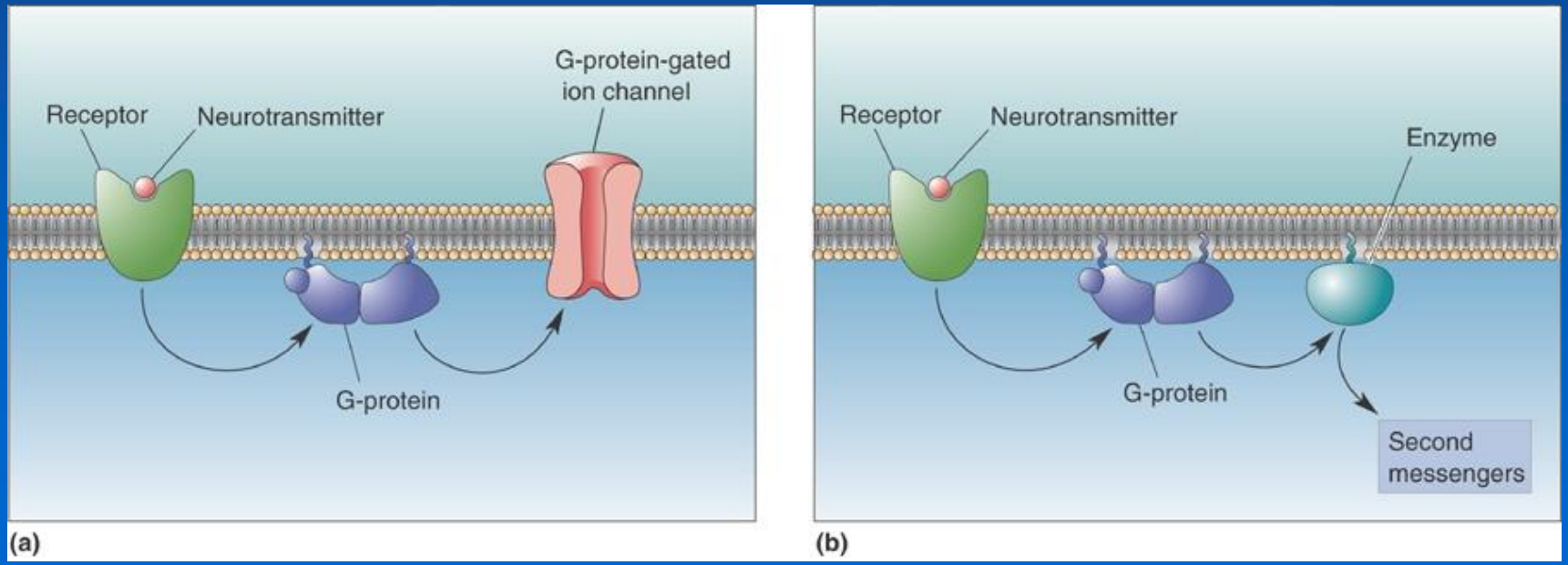
Ionotropic receptors

- ✓ Ligand (Transmitter)-gated ion channels
- ✓ Ligand-binding causes a slight conformational change that leads to the opening of channels
- ✓ Not as selective to ions as voltage-gated channels
- ✓ Depending on the ions that can pass through, channels are either excitatory or inhibitory

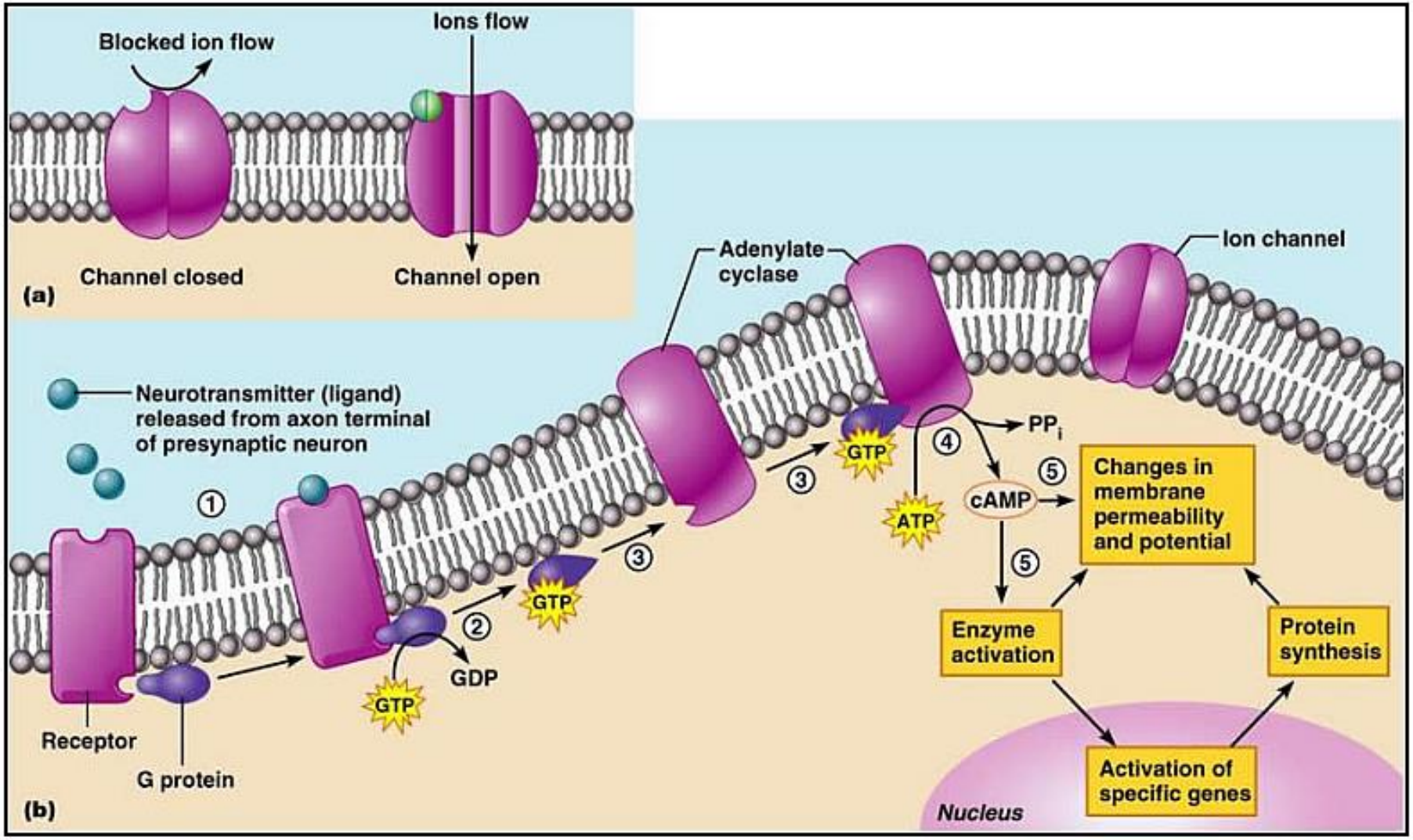


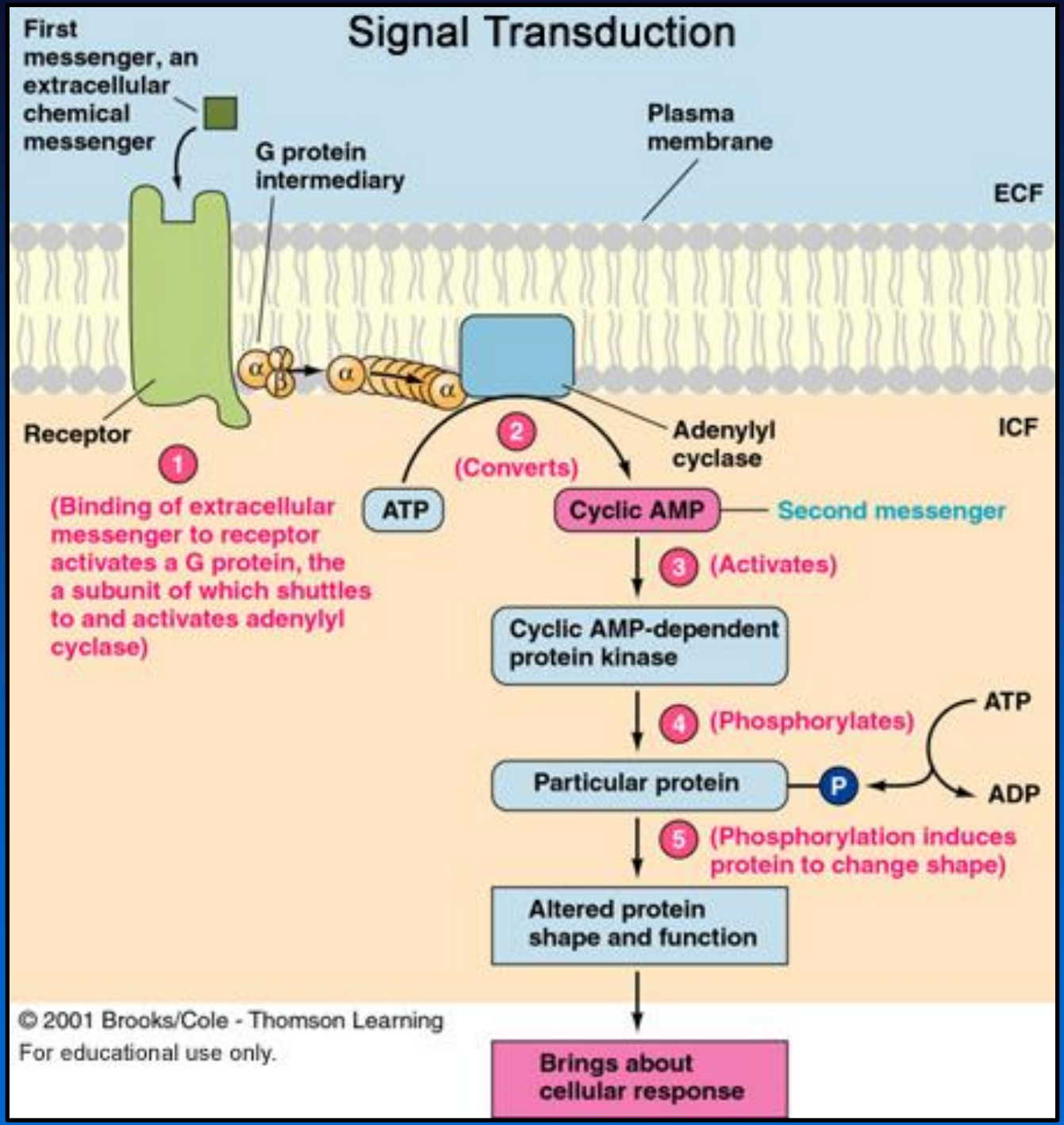
Metabotropic receptors

- G-protein-coupled receptors
- Trigger slower, longer-lasting and more diverse postsynaptic actions
- Same neurotransmitter could exert different actions depending on receptor subtypes



Neurotransmitter Receptor Mechanism




Signal Transduction
First messenger, an extracellular chemical messenger
G protein intermediary
Plasma membrane
ECF
ICF
Receptor
Adenylyl cyclase
1
(Binding of extracellular messenger to receptor activates a G protein, the a subunit of which shuttles to and activates adenylyl cyclase)
2
(Converts)
ATP
Cyclic AMP
Second messenger
3
(Activates)
Cyclic AMP-dependent protein kinase
4
(Phosphorylates)
ATP
ADP
Particular protein
P
5
(Phosphorylation induces protein to change shape)
Altered protein shape and function
Brings about cellular response
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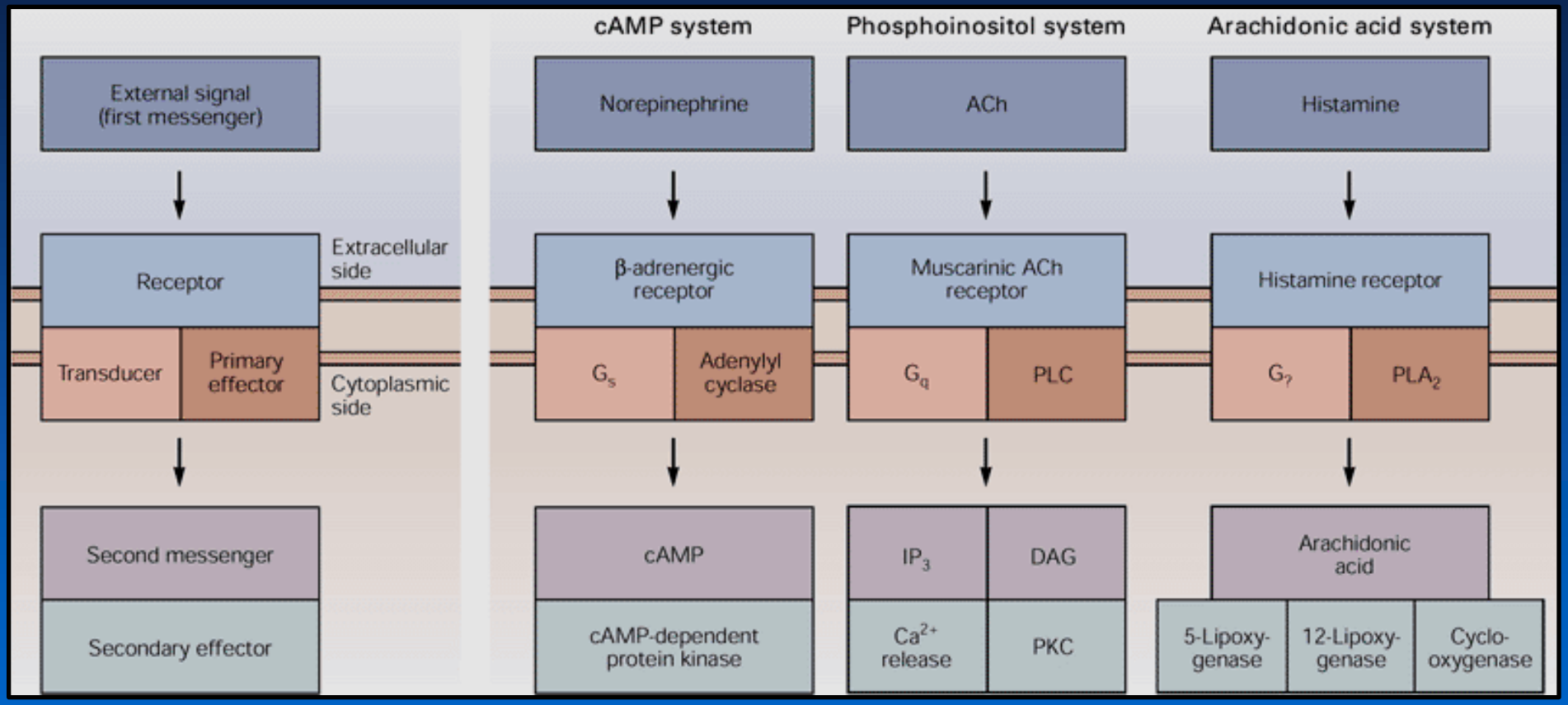
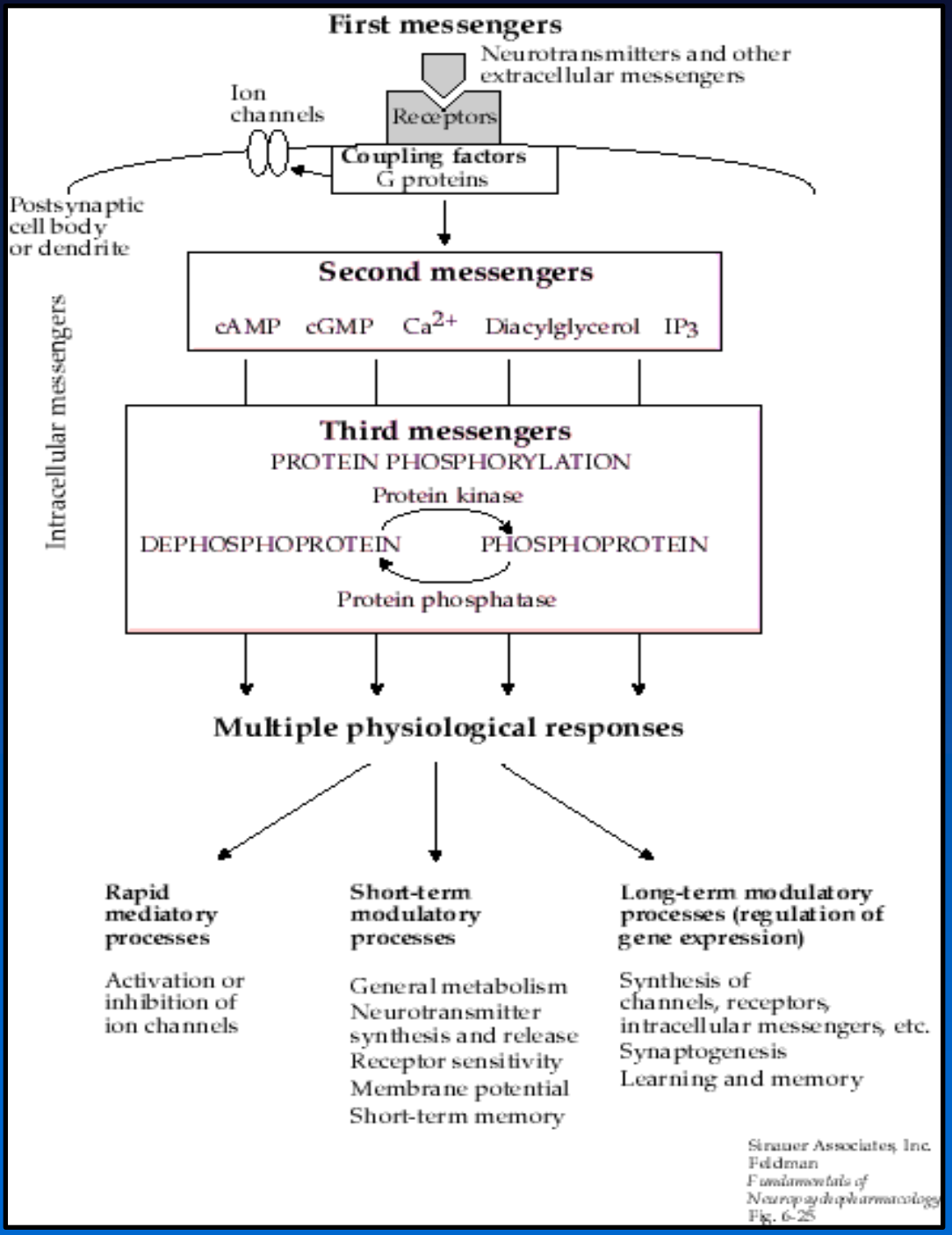
Second Messenger System

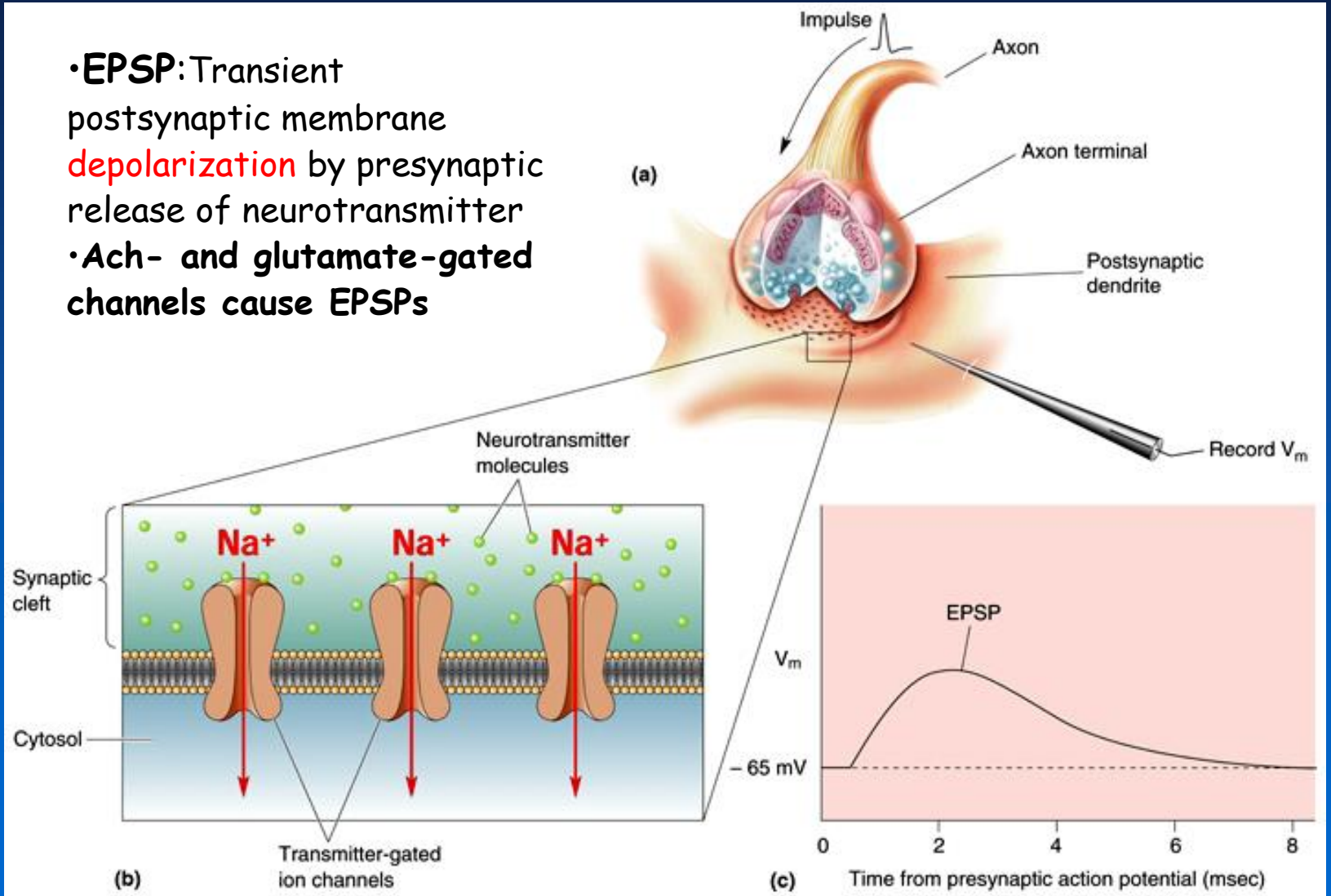



First messengers
Neurotransmitters and other extracellular messengers
Ion channels
Receptors
Coupling factors
G proteins
Postsynaptic cell body or dendrite
Second messengers
cAMP cGMP Ca^{2+} Diacylglycerol IP_3
Intracellular messengers
Third messengers
PROTEIN PHOSPHORYLATION
Protein kinase
DEPHOSPHOPROTEIN PHOSPHOPROTEIN
Protein phosphatase
Multiple physiological responses
Rapid mediatory processes
Activation or inhibition of ion channels
Short-term modulatory processes
General metabolism
Neurotransmitter synthesis and release
Receptor sensitivity
Membrane potential
Short-term memory
Long-term modulatory processes (regulation of gene expression)
Synthesis of channels, receptors, intracellular messengers, etc.
Synaptogenesis
Learning and memory
Sinauer Associates, Inc.
Feldman
Fundamentals of Neuropsychopharmacology
Fig. 6-25

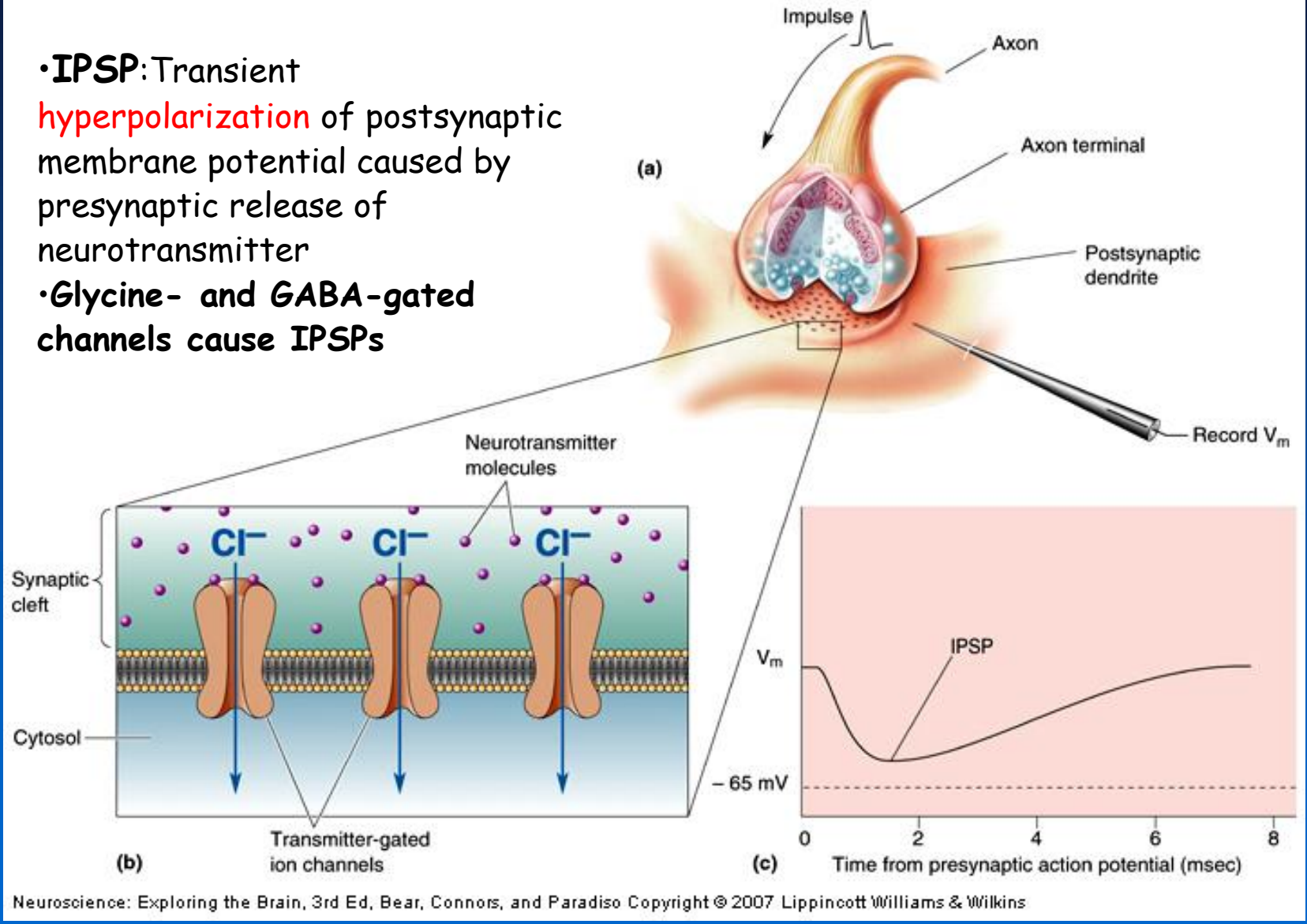
- **Neuropharmacology**
  - The study of effect of drugs on nervous system tissue
  - Receptor antagonists: Inhibitors of neurotransmitter receptors
    - e.g. Curare binds tightly to Ach receptors of skeletal muscle
  - Receptor agonists: Mimic actions of naturally occurring neurotransmitters
    - e.g. Nicotine binds and activates the Ach receptors of skeletal muscle (nicotinic Ach receptors)
  - Toxins and venoms
  - Defective neurotransmission: Root cause of neurological and psychiatric disorders

Excitatory and Inhibitory Postsynaptic Potentials

- **EPSP**: Transient postsynaptic membrane depolarization by presynaptic release of neurotransmitter
- **Ach- and glutamate-gated channels cause EPSPs**



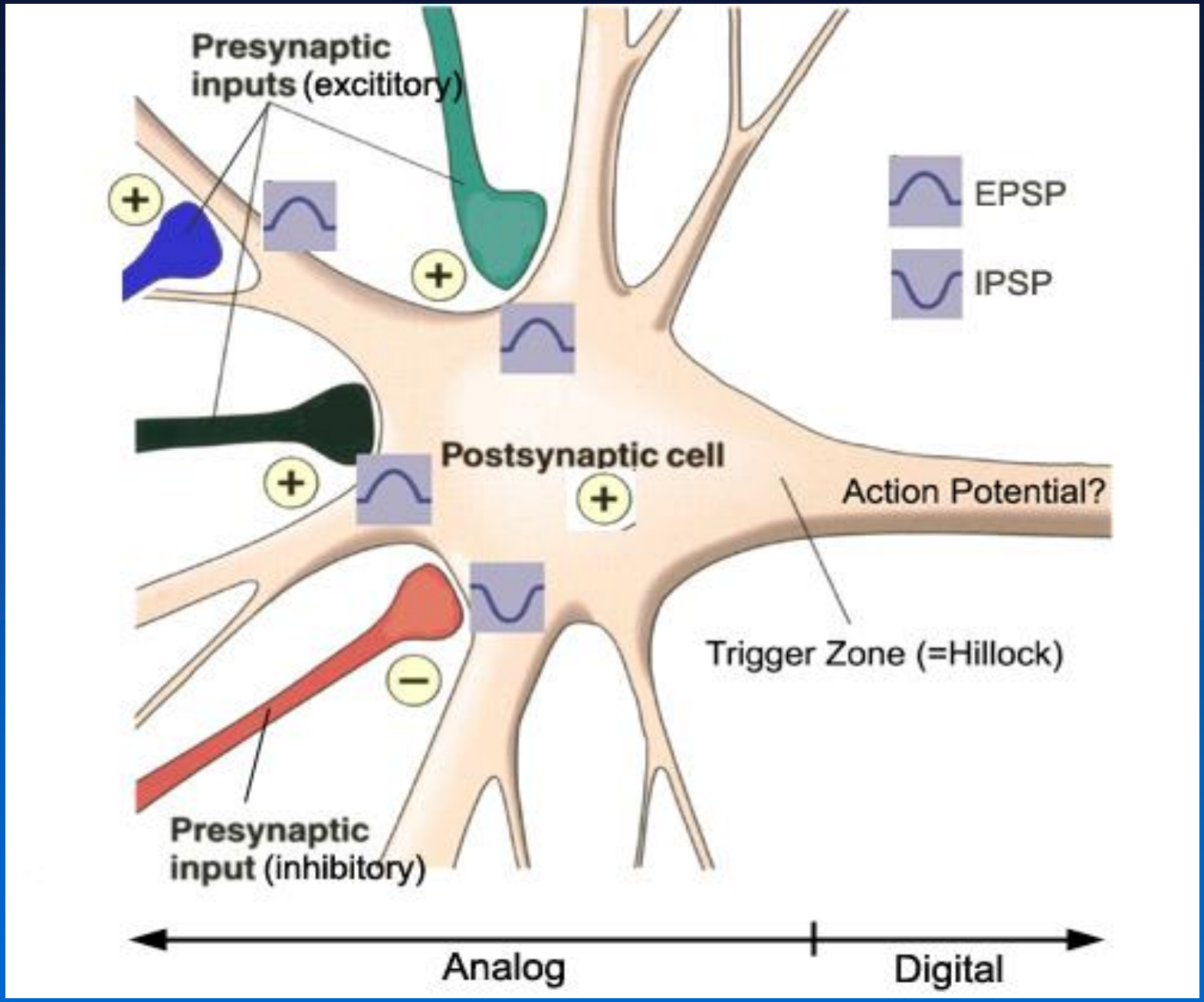
- **IPSP**: Transient hyperpolarization of postsynaptic membrane potential caused by presynaptic release of neurotransmitter
- **Glycine- and GABA-gated channels cause IPSPs**



Synaptic Integration

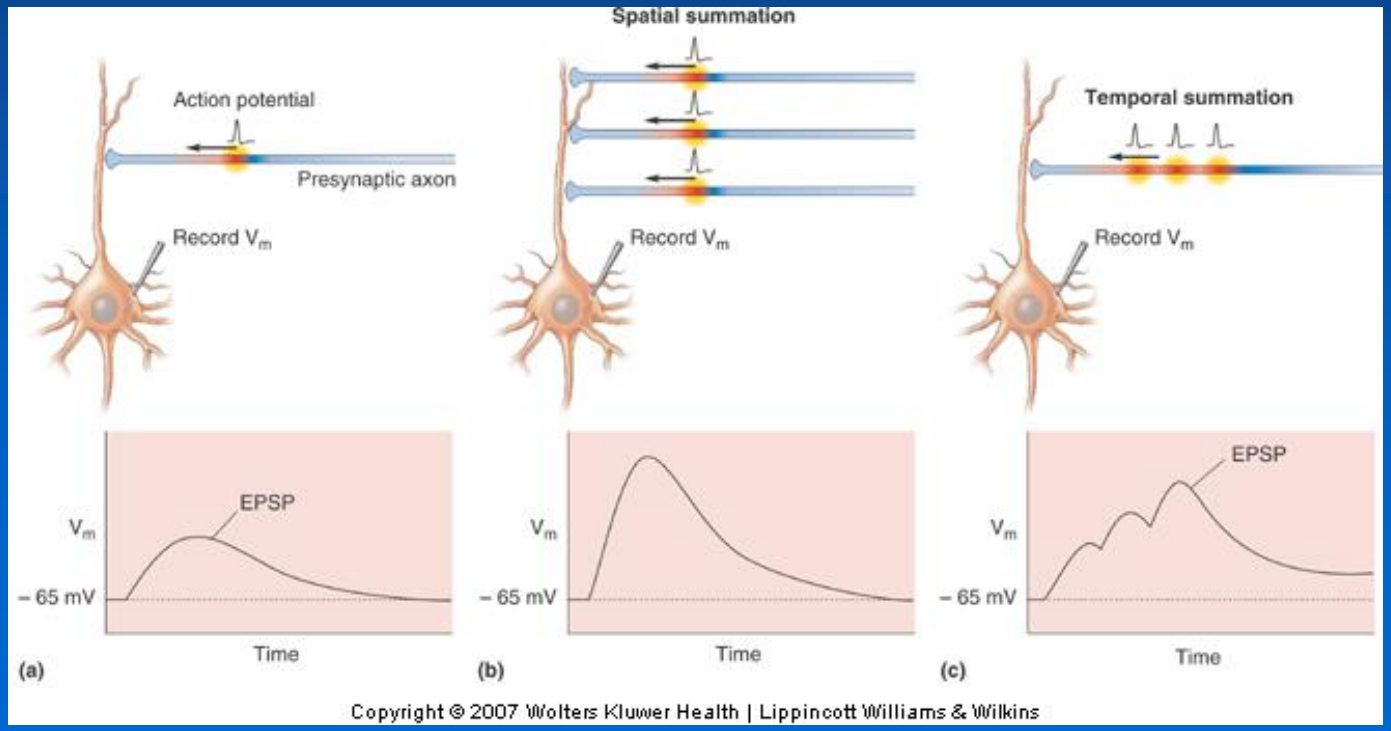
- Basic principle of neural computation
- Process by which multiple synaptic potentials combine within one postsynaptic neuron
  - The combining of excitatory and inhibitory signals acting on adjacent membrane regions of a neuron.
  - In order for an action potential to occur, the sum of excitatory and inhibitory postsynaptic potentials (local responses) must be greater than a threshold value.

- To understand this concept fully, we must first recall that action potentials are typically generated at the axon hillock of the cell because it has the highest density of voltage-gated Na^+ channels and therefore the lowest threshold for initiation of a spike.
- Thus, it is the summed amplitudes of the synaptic potentials at this point, the axon hillock, that is critical for the decision to spike. EPSPs generated by synapses close to the axon hillock (i.e., synapses onto the soma or proximal dendrites) will result in a larger depolarization at the hillock than will EPSPs generated by synapses on distal dendrites.
- Thus, the synapse's spatial location in the dendritic tree is an important determinant of its efficacy.


Presynaptic inputs (excititory)
EPSP
IPSP
Postsynaptic cell
Action Potential?
Trigger Zone (=Hillock)
Presynaptic input (inhibitory)
Analog
Digital

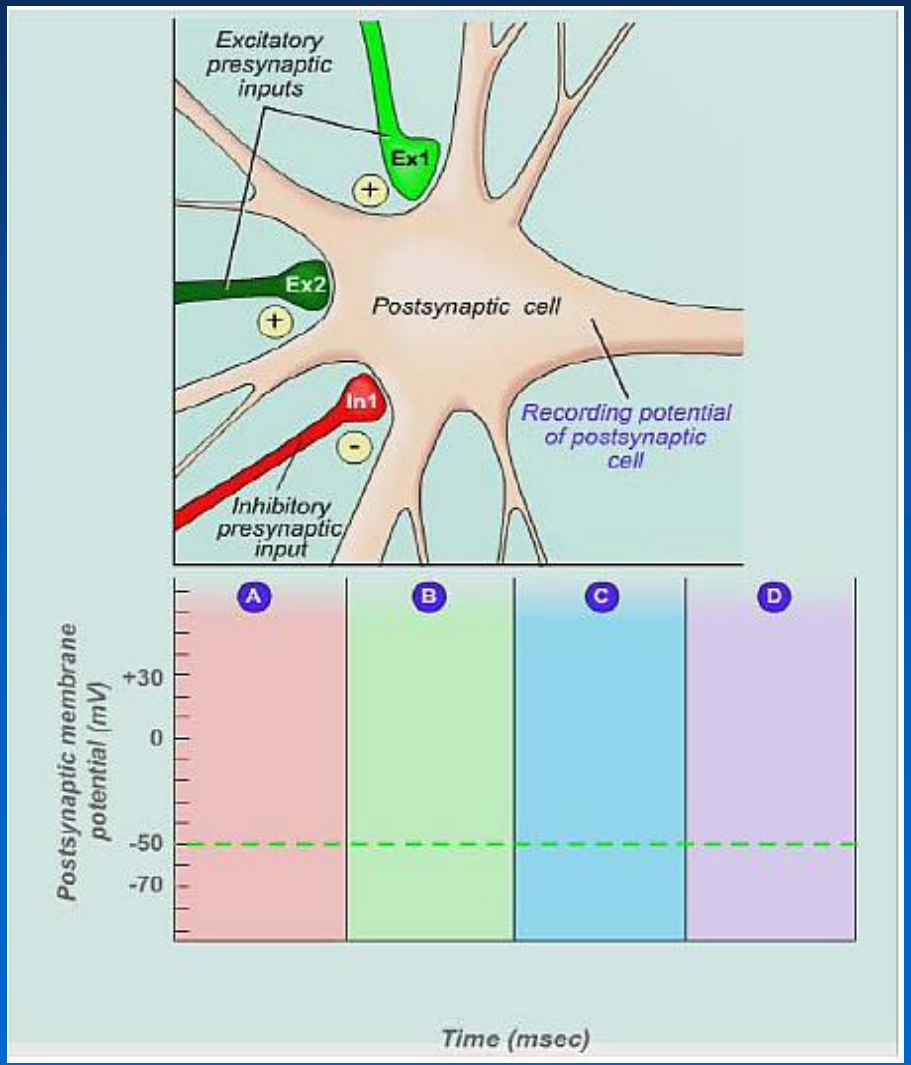
- **EPSP Summation**
  - A single EPSP cannot induce an action potential
  - EPSPs must summate temporally or spatially to induce an action potential
  - ***Spatial* summation :** adding together of EPSPs generated simultaneously at different synapses (postsynaptic neuron is stimulated by a large number of terminals at the same time)

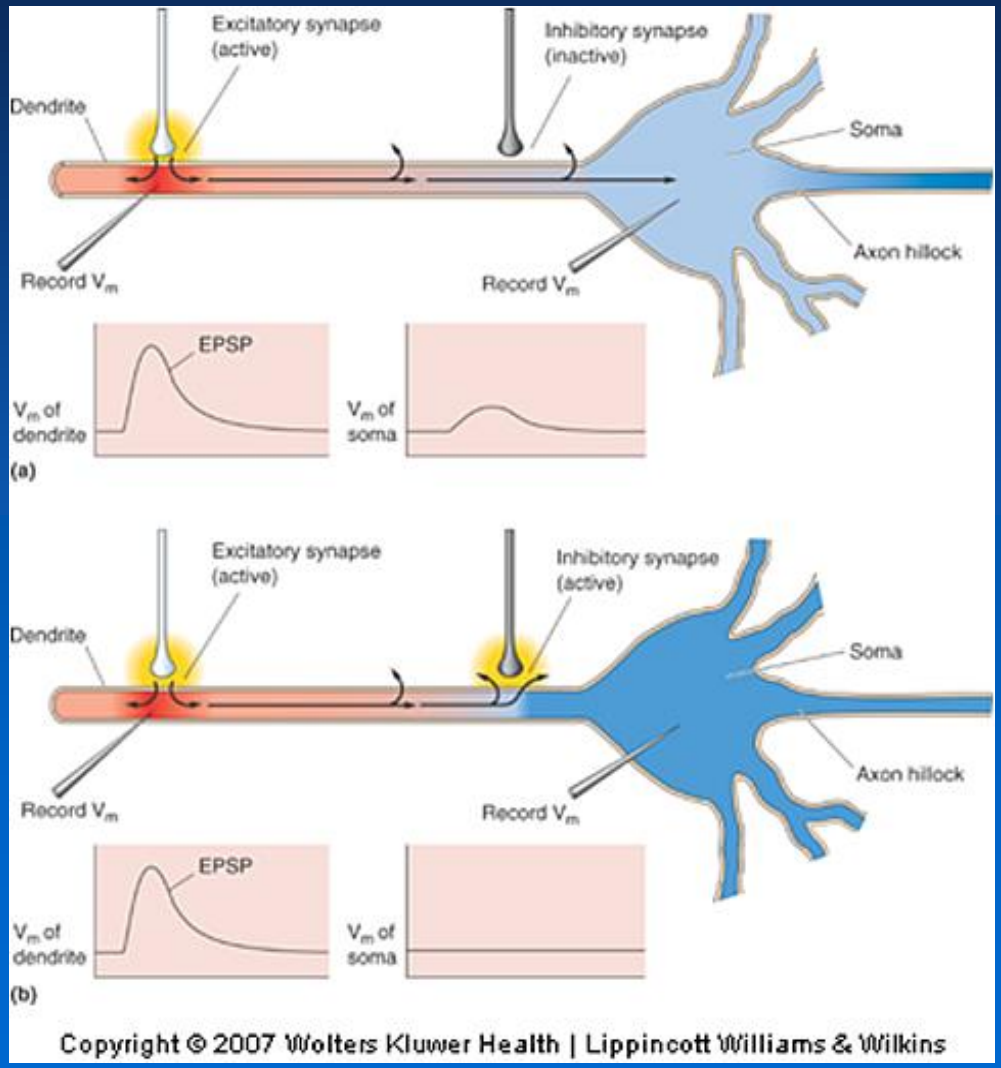
- ***Temporal* summation :** adding together of EPSPs generated at the same synapse in rapid succession (presynaptic neurons transmit impulses in rapid-fire order)



The Geometry of Excitatory and Inhibitory Synapses

- Inhibitory synapses clustered on soma and near axon hillock
- Powerful position to influence the activity of the postsynaptic neuron





- Thousands of synapses from many different presynaptic cells can affect a single postsynaptic cell **(convergence)**.
- A single presynaptic cell can send branches to affect many other postsynaptic cells **(divergence)**.
- Convergence allows information from many sources to influence a cell's activity; divergence allows one information source to affect multiple pathways.
- If the membrane of the postsynaptic neuron reaches threshold, it will generate action potentials that are propagated along its axon to the terminal branches, which influence the excitability of other cells by divergence.

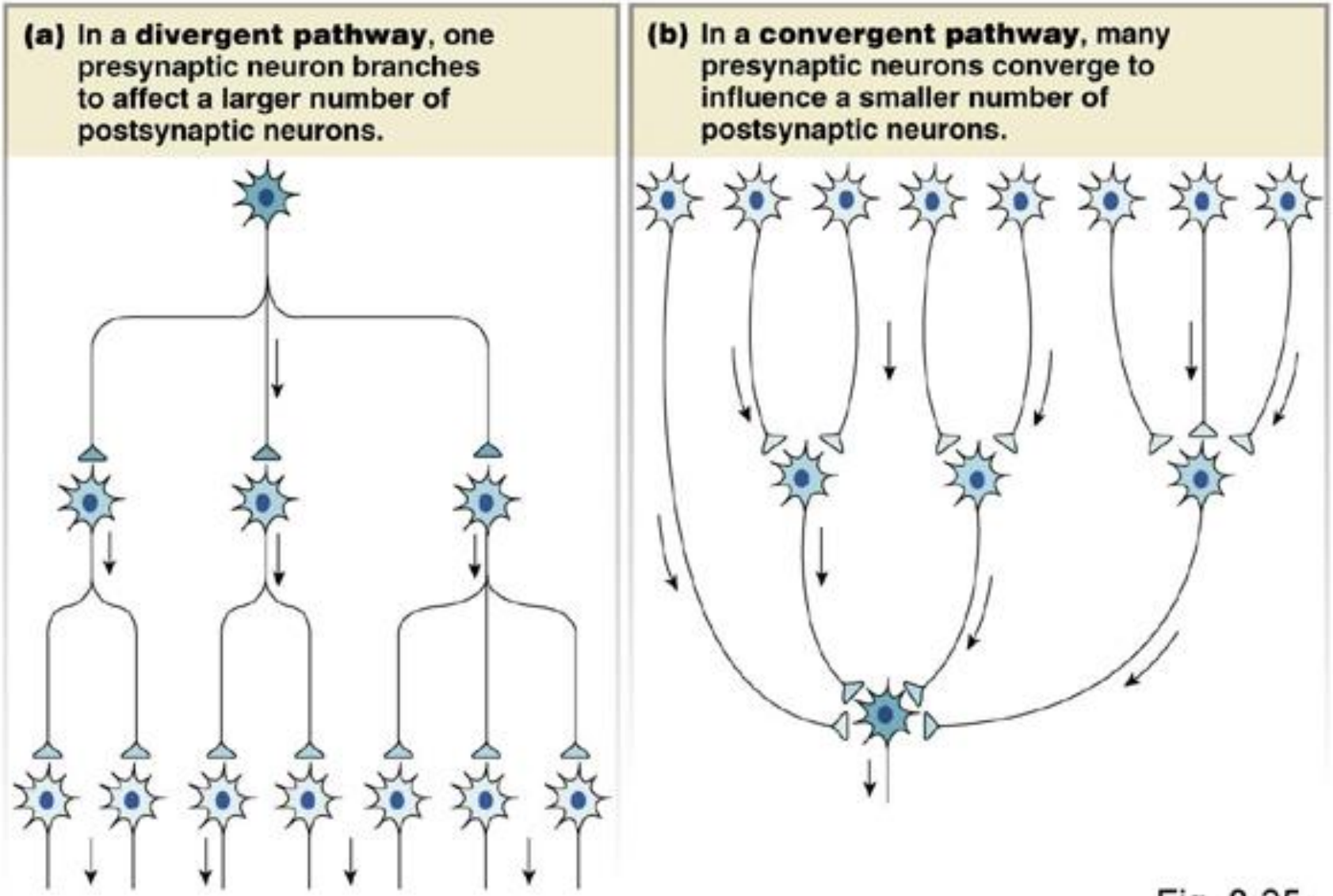
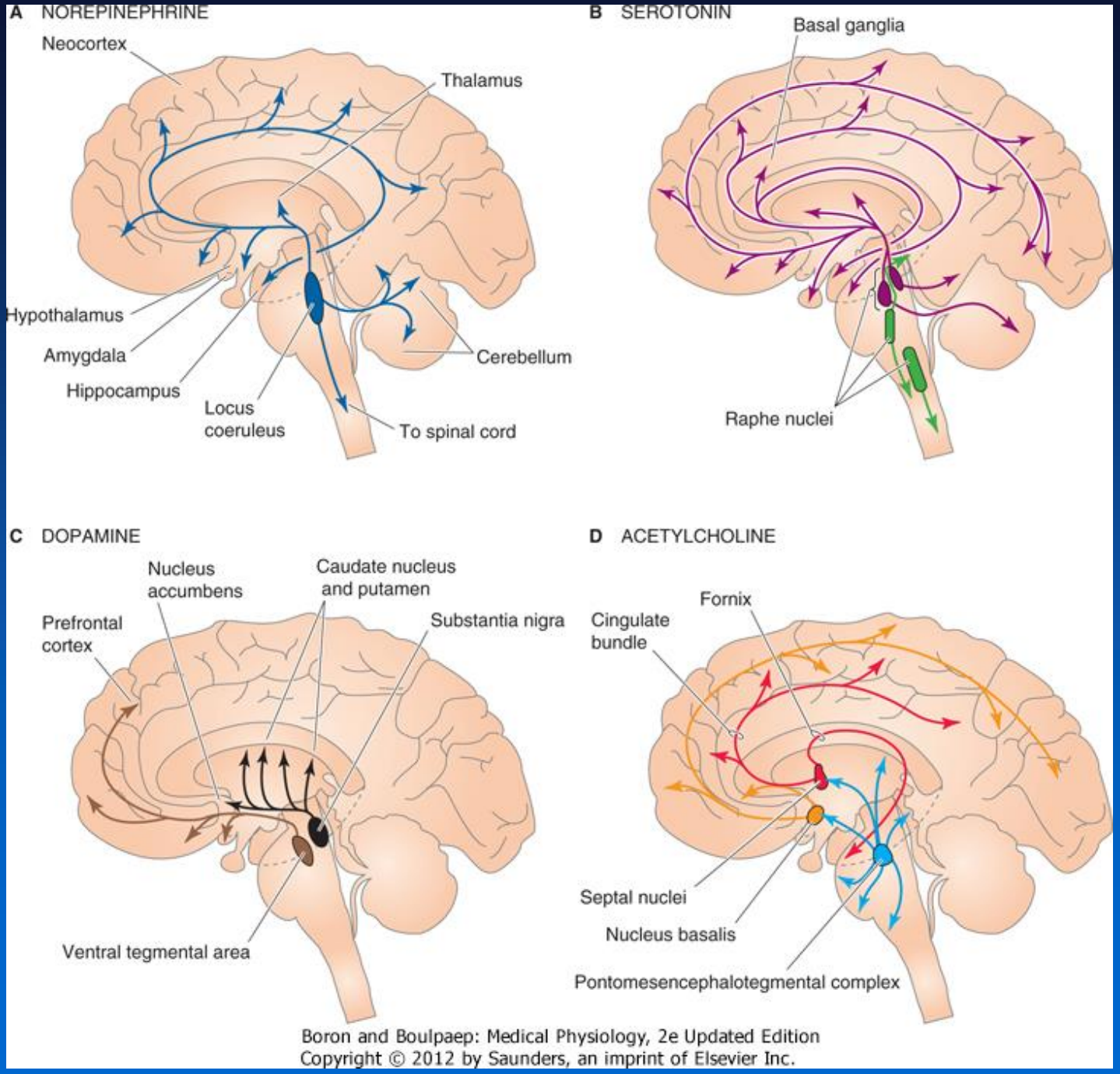


Fig. 8-25

The brain has several modulatory systems with diffuse central connections. Although they differ in structure and function, they have certain similarities:

1. Typically, a small set of neurons (several thousand) forms the center of the system.
2. Neurons of the diffuse systems arise from the central core of the brain, most of them from the brainstem.
3. Each neuron can influence many others because each one has an axon that may contact more than 100,000 postsynaptic neurons spread widely across the brain.
4. The synapses made by some of these systems seem designed to release transmitter molecules into the extracellular fluid so that they can diffuse to many neurons rather than be confined to the vicinity of a single synaptic cleft.



Neurotransmitters

- Amino acids
- Amines
- Peptides

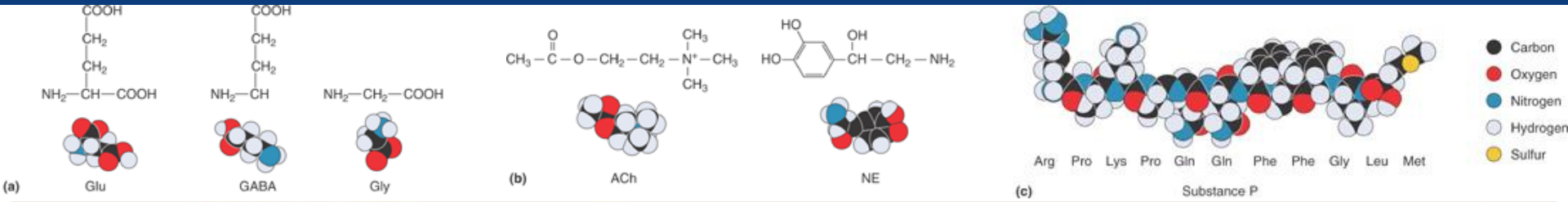
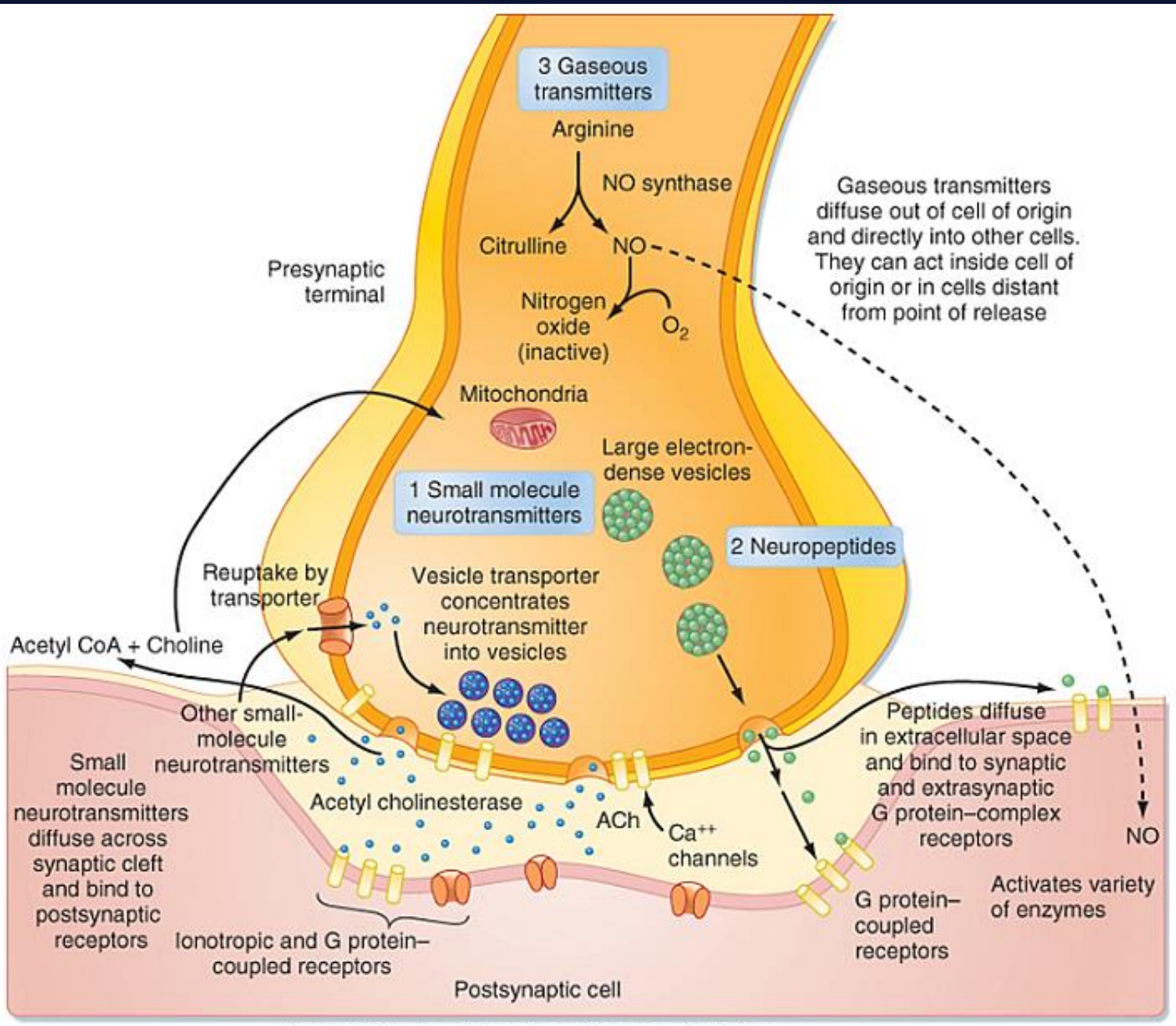


Table 5.1 **The Major Neurotransmitters**

AMINO ACIDS	AMINES	PEPTIDES
Gamma-aminobutyric acid (GABA)	Acetylcholine (ACh)	Cholecystokinin (CCK)
Glutamate (Glu)	Dopamine (DA)	Dynorphin
Glycine (Gly)	Epinephrine	Enkephalins (Enk)
	Histamine	N-acetylaspartylglutamate (NAAG)
	Norepinephrine (NE)	Neuropeptide Y
	Serotonin (5-HT)	Somatostatin
		Substance P
		Thyrotropin-releasing hormone
		Vasoactive intestinal polypeptide (VIP)

Table 6-1. Distinctions between Classic Nonpeptide Neurotransmitters and Peptide Neurotransmitters

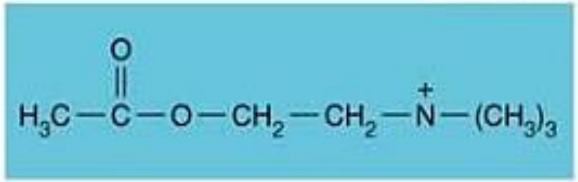
Nonpeptide Transmitters	Peptide Transmitters
Synthesized and packaged in the nerve terminal	Synthesized and packaged in the cell body; transported to the nerve terminal by fast axonal transport
Synthesized in active form	Active peptide formed when it is cleaved from a much larger polypeptide that contains several neuropeptides
Usually present in small, clear vesicles	Usually present in large, electron-dense vesicles
Released into a synaptic cleft	May be released some distance from the postsynaptic cell There may be no well-defined synaptic structure
Action of many terminated because of uptake by presynaptic terminals via Na^+-powered active transport	Action terminated by proteolysis or by the peptide diffusing away
Typically, action has short latency and short duration (msec)	Action may have long latency and may persist for many seconds



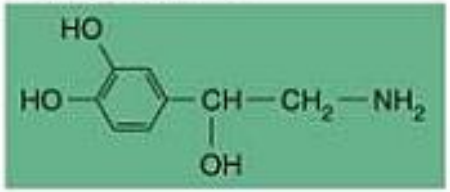
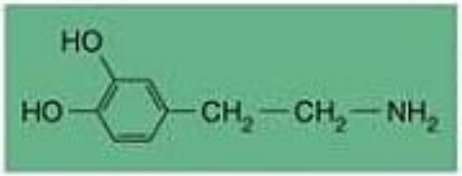
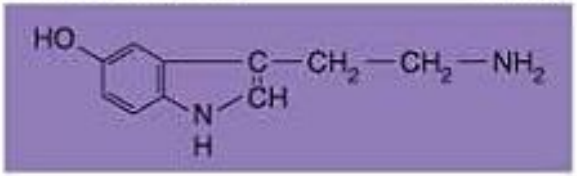
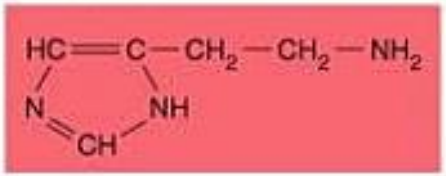
http://classes.midlandstech.edu/carterp/Courses/bio210/chap11/lecture1.html

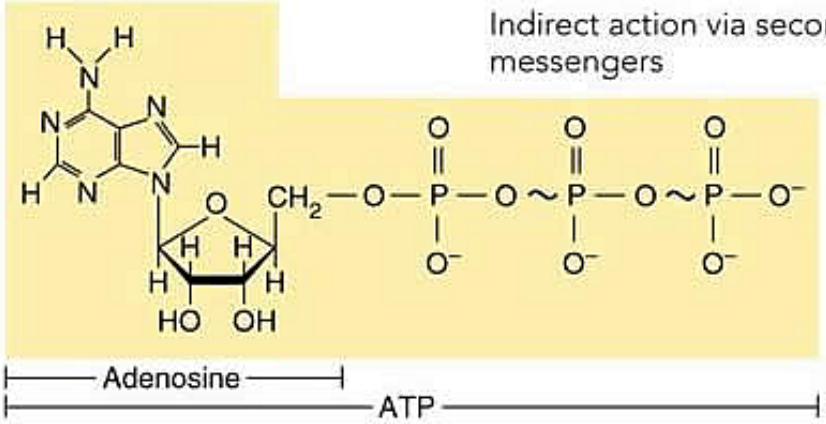
TABLE 11.3 Neurotransmitters and Neuromodulators

NEUROTRANSMITTER	FUNCTIONAL CLASSES	SITES WHERE SECRETED	COMMENTS
ACETYLCHOLINE			
▪ At *nicotinic ACh receptors* (on skeletal muscles, autonomic ganglia, and in the CNS)	Excitatory Direct action	CNS: widespread throughout cerebral cortex, hippocampus, and brain stem	Effects prolonged, leading to tetanic muscle spasms, when AChE blocked by nerve gas and organophosphate insecticides (malathion). Release inhibited by botulinum toxin; binding to nicotinic ACh receptors inhibited by curare (a muscle paralytic agent) and some snake venoms, and to muscarinic ACh receptors by atropine. ACh levels decreased in certain brain areas in Alzheimer's disease; nicotinic ACh receptors destroyed in myasthenia gravis. Binding of nicotine to nicotinic receptors in the brain enhances dopamine release, which may account for the behavioral effects of nicotine in smokers
▪ At *muscarinic ACh receptors* (on visceral effectors and in the CNS)	Excitatory or inhibitory depending on subtype of muscarinic receptor Indirect action via second messengers	PNS: all neuromuscular junctions with skeletal muscle; some autonomic motor endings (all preganglionic and parasympathetic postganglionic fibers)	

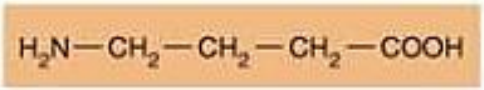
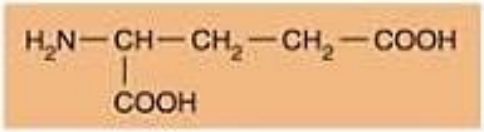
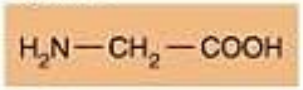


BIOGENIC AMINES

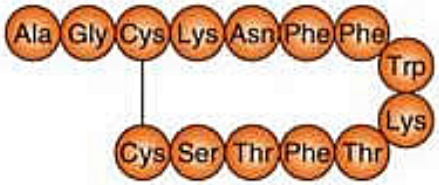
Norepinephrine 	Excitatory or inhibitory, depending on receptor type bound Indirect action via second messengers	CNS: brain stem, particularly in the locus coeruleus of the midbrain; limbic system; some areas of cerebral cortex PNS: main neurotransmitter of ganglion neurons in the sympathetic nervous system	A "feeling good" neurotransmitter; release enhanced by amphetamines; removal from synapse blocked by tricyclic antidepressants [amitriptyline (Elavil) and others] and cocaine; brain levels reduced by reserpine (an antihypertensive drug), leading to depression
Dopamine 	Excitatory or inhibitory depending on the receptor type bound Indirect action via second messengers	CNS: substantia nigra of midbrain; hypothalamus; is the principal neurotransmitter of extrapyramidal system PNS: some sympathetic ganglia	A "feeling good" neurotransmitter; release enhanced by L-dopa and amphetamines; reuptake blocked by cocaine; deficient in Parkinson's disease; may be involved in pathogenesis of schizophrenia
Serotonin (5-HT) 	Mainly inhibitory Indirect action via second messengers; direct action at 5-HT_3 receptors	CNS: brain stem, especially midbrain; hypothalamus; limbic system; cerebellum; pineal gland; spinal cord	Activity blocked by LSD and enhanced by ecstasy (MDMA); may play a role in sleep, appetite, nausea, migraine headaches, and regulation of mood; drugs that block its uptake [fluoxetine (Prozac)] relieve anxiety and depression
Histamine 	Indirect action via second messengers	CNS: hypothalamus	Increases acid secretion in the stomach; acid secretion blocked by histamine H_2 receptor blockers (cimetidine); also released by mast cells during inflammation and acts as powerful vasodilator

PURINES			
ATP	Excitatory or inhibitory depending on receptor type bound	CNS: basal nuclei, induces Ca^{2+} wave propagation in astrocytes	ATP released by sensory neurons (as well as that released by injured cells) provokes pain sensation
	Direct and indirect actions via second messengers	PNS: dorsal root ganglion neurons	
Adenosine	Inhibitory neuromodulator	Throughout CNS	
	Indirect action via second messengers		Caffeine (coffee), theophylline (tea), and theobromine (chocolate) stimulate by blocking brain adenosine receptors; may be involved in sleep-wake cycle and terminating seizures. Dilates arterioles, increasing blood flow to heart and other tissues as needed

AMINO ACIDS

GABA (γ-aminobutyric acid) 	Generally inhibitory Direct and indirect actions via second messengers	CNS: cerebral cortex, hypothalamus, Purkinje cells of cerebellum, spinal cord, granule cells of olfactory bulb, retina	Principal inhibitory neurotransmitter in the brain; important in presynaptic inhibition at axoaxonic synapses. GABA-dependent neural communication declines with age in visual and auditory systems. Inhibitory effects augmented by alcohol, antianxiety drugs of the benzodiazepine class (e.g., Valium), and barbiturates, resulting in impaired motor coordination. Substances that block its synthesis, release, or action induce convulsions
Glutamate 	Generally excitatory Direct action	CNS: spinal cord; widespread in brain where it represents the major excitatory neurotransmitter	Important in learning and memory. The "stroke neurotransmitter": excessive release produces excitotoxicity—neurons literally stimulated to death; most commonly caused by ischemia (oxygen deprivation, usually due to a blocked blood vessel). When released by gliomas, aids tumor advance
Glycine 	Generally inhibitory Direct action	CNS: spinal cord and brain stem, retina	Principal inhibitory neurotransmitter of the spinal cord. Strychnine blocks glycine receptors, resulting in uncontrolled convulsions and respiratory arrest

PEPTIDES

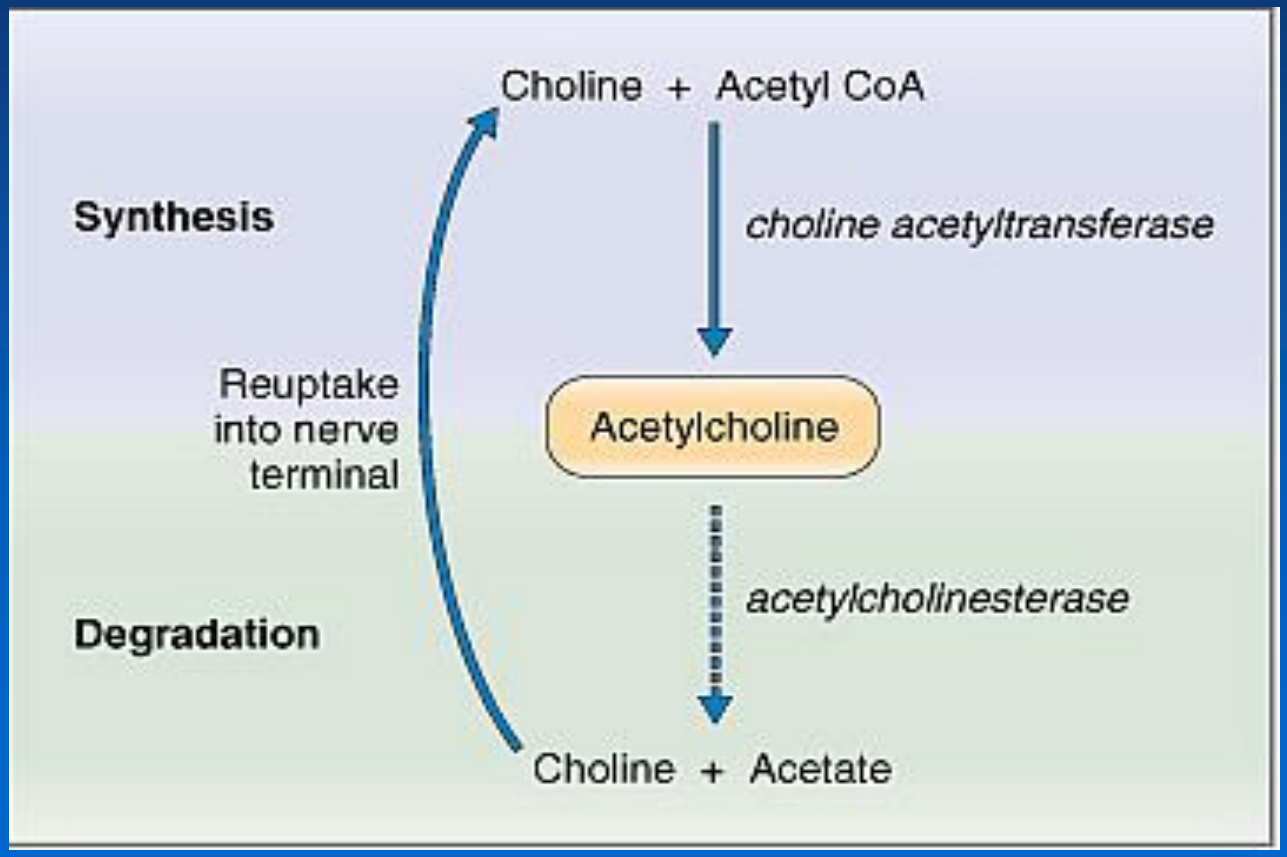
Endorphins, e.g., dynorphin, enkephalins (illustrated) 	Generally inhibitory Indirect action via second messengers	CNS: widely distributed in brain; hypothalamus; limbic system; pituitary; spinal cord	Natural opiates; inhibit pain by inhibiting substance P; effects mimicked by morphine, heroin, and methadone
Tachykinins: Substance P (illustrated), neurokinin A (NKA) 	Excitatory Indirect action via second messengers	CNS: basal nuclei, midbrain, hypothalamus, cerebral cortex PNS: certain sensory neurons of dorsal root ganglia (pain afferents)	Substance P mediates pain transmission in the PNS; in the CNS tachykinins are involved in respiratory and cardiovascular controls and in mood
Somatostatin 	Generally inhibitory Indirect action via second messengers	CNS: hypothalamus, retina, and other parts of brain Pancreas	Inhibits release of growth hormone; a gut-brain peptide
Cholecystokinin (CCK) 	Possible neurotransmitter	Cerebral cortex Small intestine	May be related to feeding behaviors; a gut-brain peptide

DISSOLVED GASES

Nitric oxide (NO)	Excitatory Indirect action via second messengers	CNS: brain; spinal cord PNS: adrenal gland; nerves to penis	Its release potentiates stroke damage; some types of male impotence treated by enhancing NO action [e.g., with sildenafil (Viagra)]
Carbon monoxide (CO)	Excitatory Indirect action via second messengers	Brain and some neuromuscular and neuroglandular synapses	

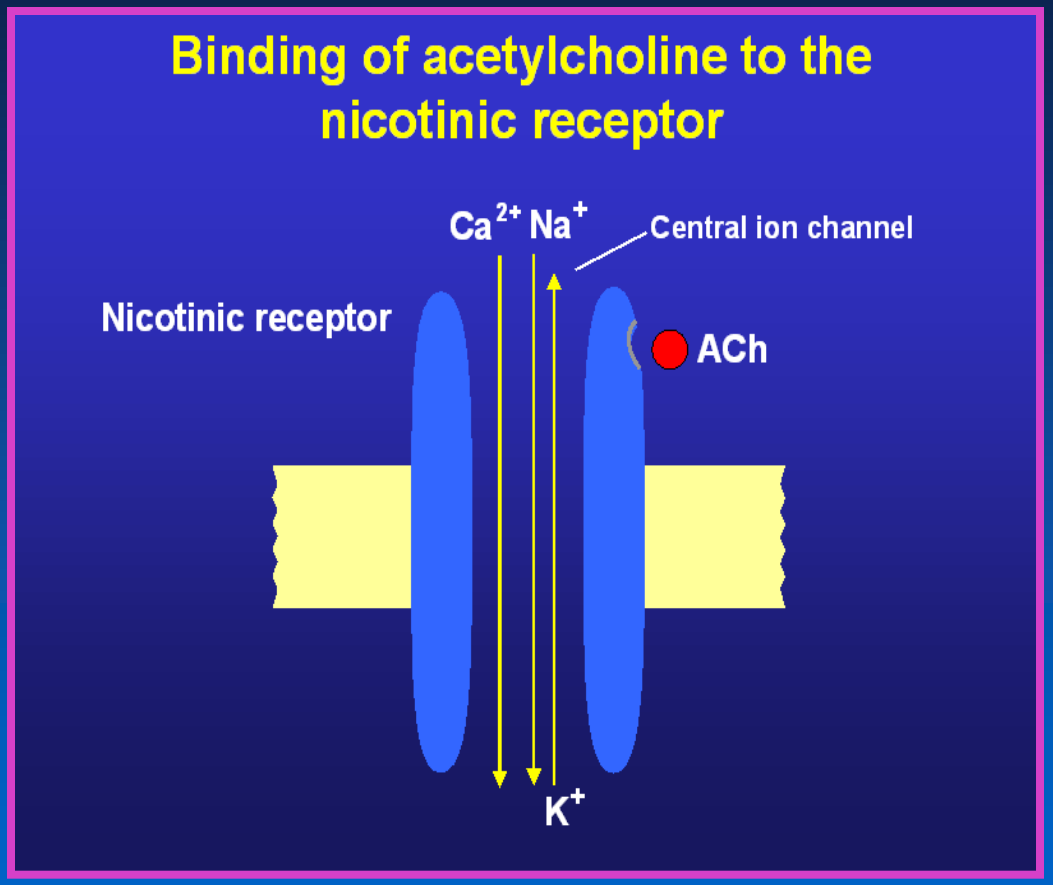
Acetylcholine (ACh)

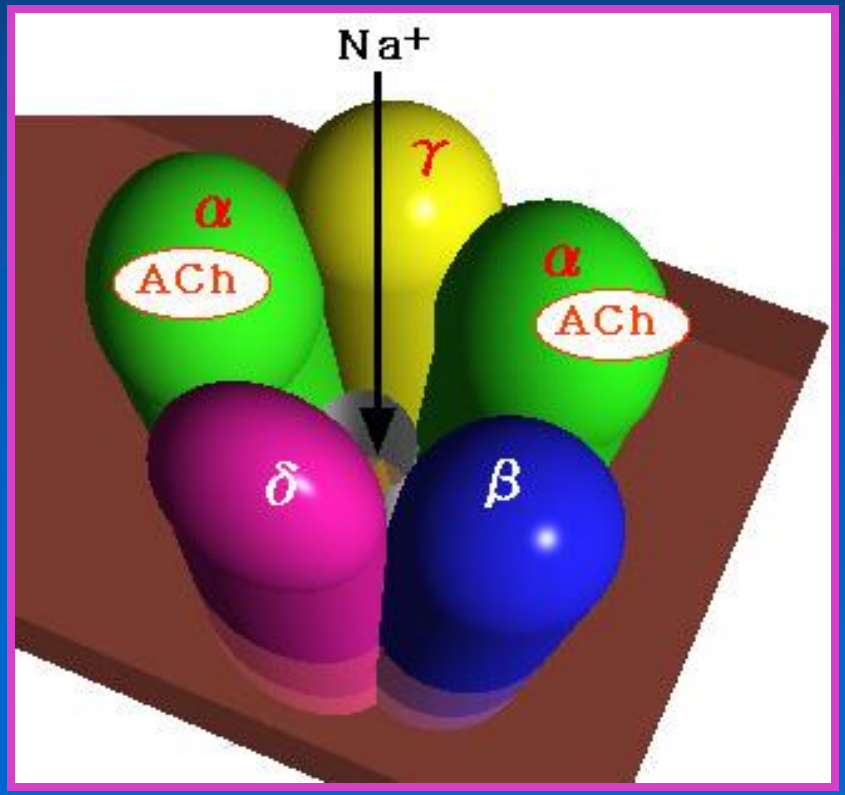
- Releases from all preganglionic and most postganglionic neurons in the parasympathetic nervous system and from all preganglionic neurons in the sympathetic nervous system.
- It is also the neurotransmitter that is released from presynaptic neurons of the adrenal medulla.



Nicotinic ACh receptors

Ionotrophic; nonselective cationic channel





Muscarinic ACh receptors

- There are five known muscarinic subtypes of ACh receptors (M_1 to M_5).
- All are metabotropic receptors; however, they are coupled to different G proteins and can thus have distinct effects on the cell
- M_1, M_3, and M_5 are coupled to pertussis toxin-insensitive G proteins, whereas M_2 and M_4 are coupled to pertussis toxin-sensitive G proteins
- Each set of G proteins is coupled to different enzymes and second messenger pathways

Receptor Type	Agonists*	Antagonists	G Protein	Linked Enzyme	Second Messenger
N_1 nicotinic ACh	ACh (nicotine, decamethonium)	*d*-Tubocurarine, α-bungarotoxin	-	-	-
N_2 nicotinic ACh	ACh (nicotine, TMA)	Hexamethonium	-	-	-
M_1, M_3, M_5 muscarinic ACh	ACh (muscarine)	Atropine, pirenzepine (M_1)	$G\alpha_q$	PLC	IP_3 and DAG
M_2, M_4 muscarinic ACh	ACh (muscarine)	Atropine, methoctramine (M_2)	$G\alpha_i$ and $G\alpha_o$	Adenylyl cyclase	↓ $[cAMP]_i$

Distribution and Functions of Muscarinic Receptors

M1; EPSP in autonomic ganglia
Secretion from salivary glands and stomach
In CNS

M2; Slow heart rate
Reduce contractile forces of atrium
Reduce conduction velocity of AV node
In CNS

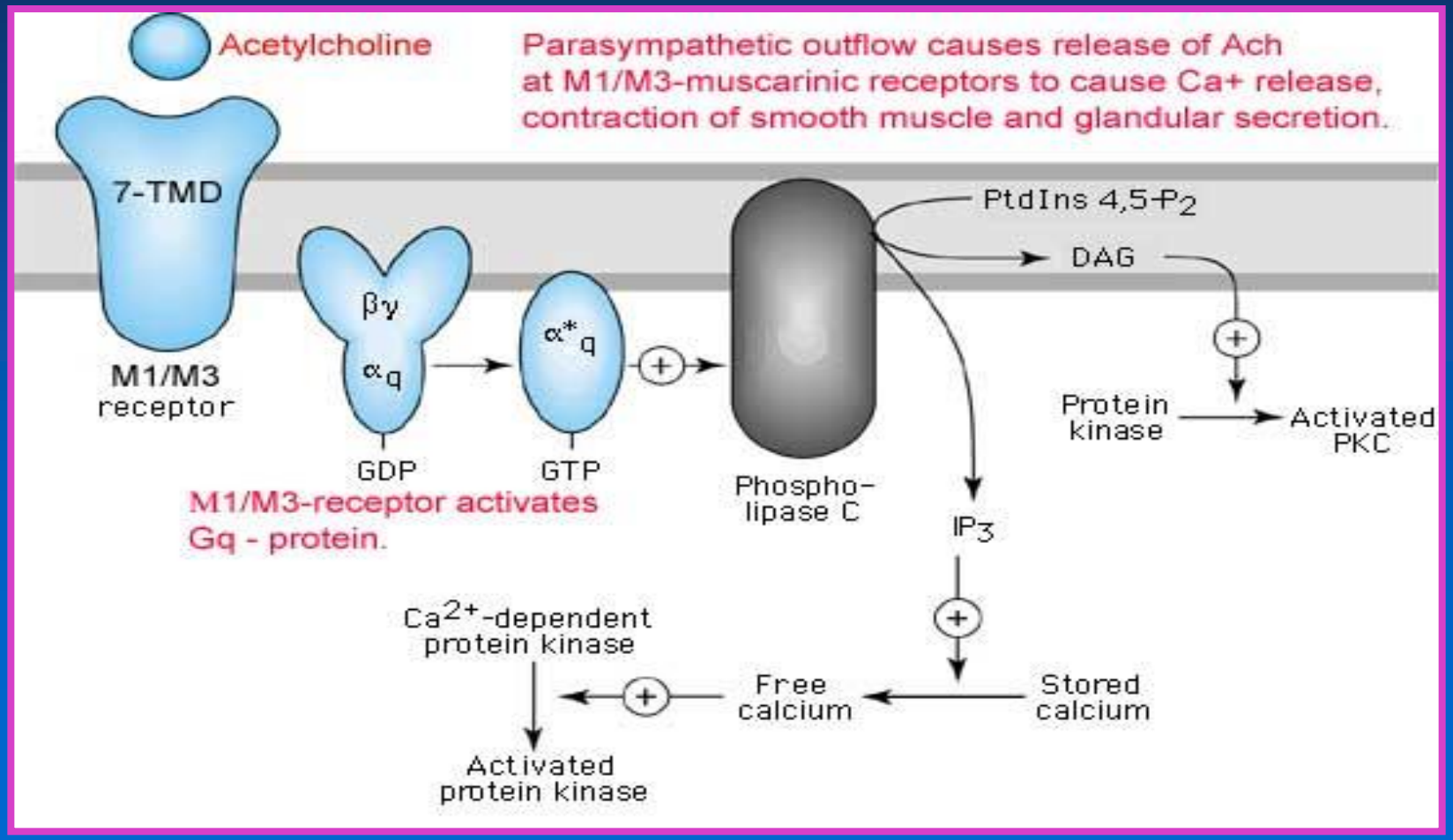
M3; Smooth muscle contraction
Bronchoconstriction
Increase intracellular calcium in vascular endothelium
Increased endocrine and exocrine gland secretions,
(e.g. salivary glands and stomach)
In CNS
Eye accommodation
Vasodilation
Induce emesis

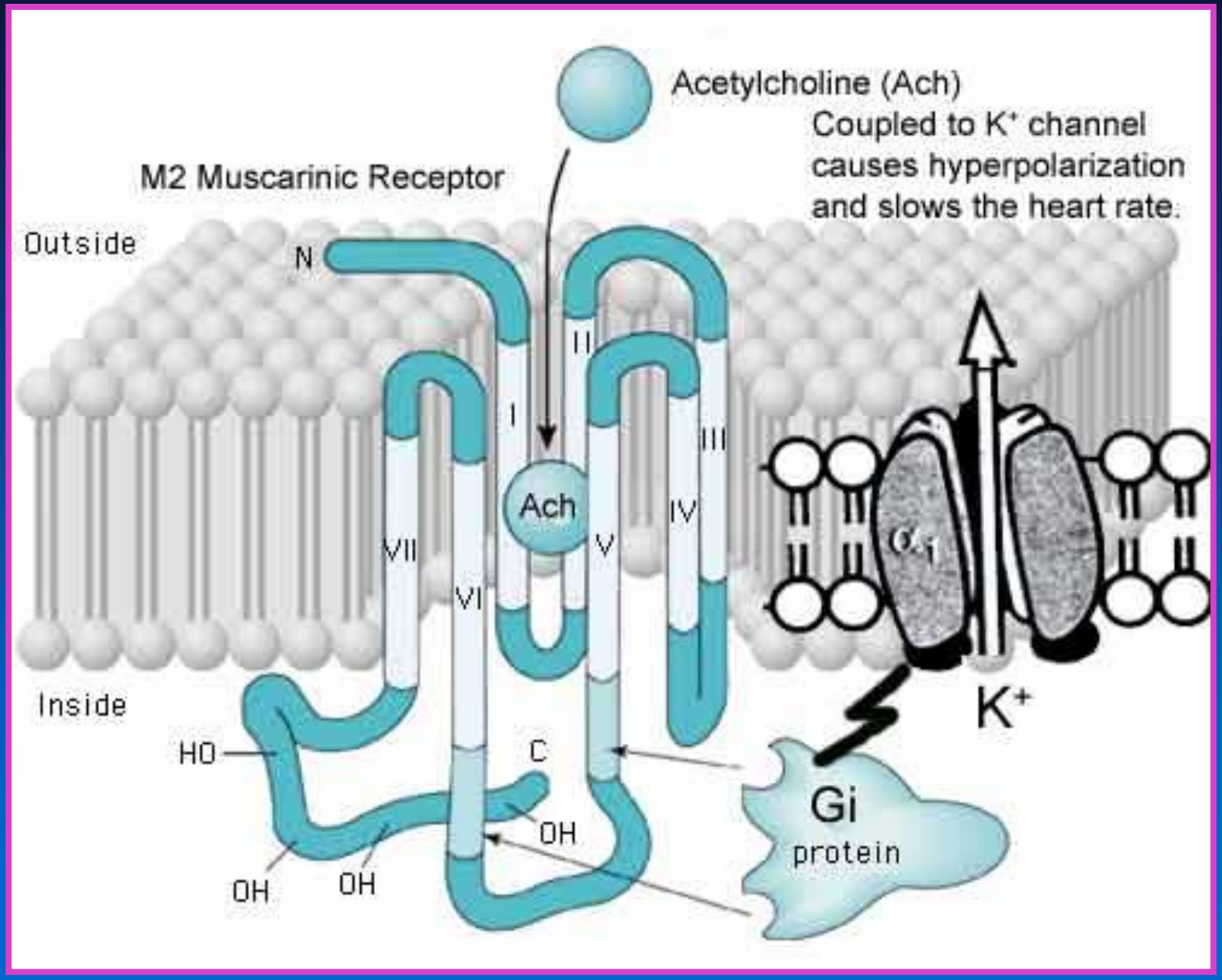
M4; In CNS

Produce generally inhibitory effects

M5; In CNS

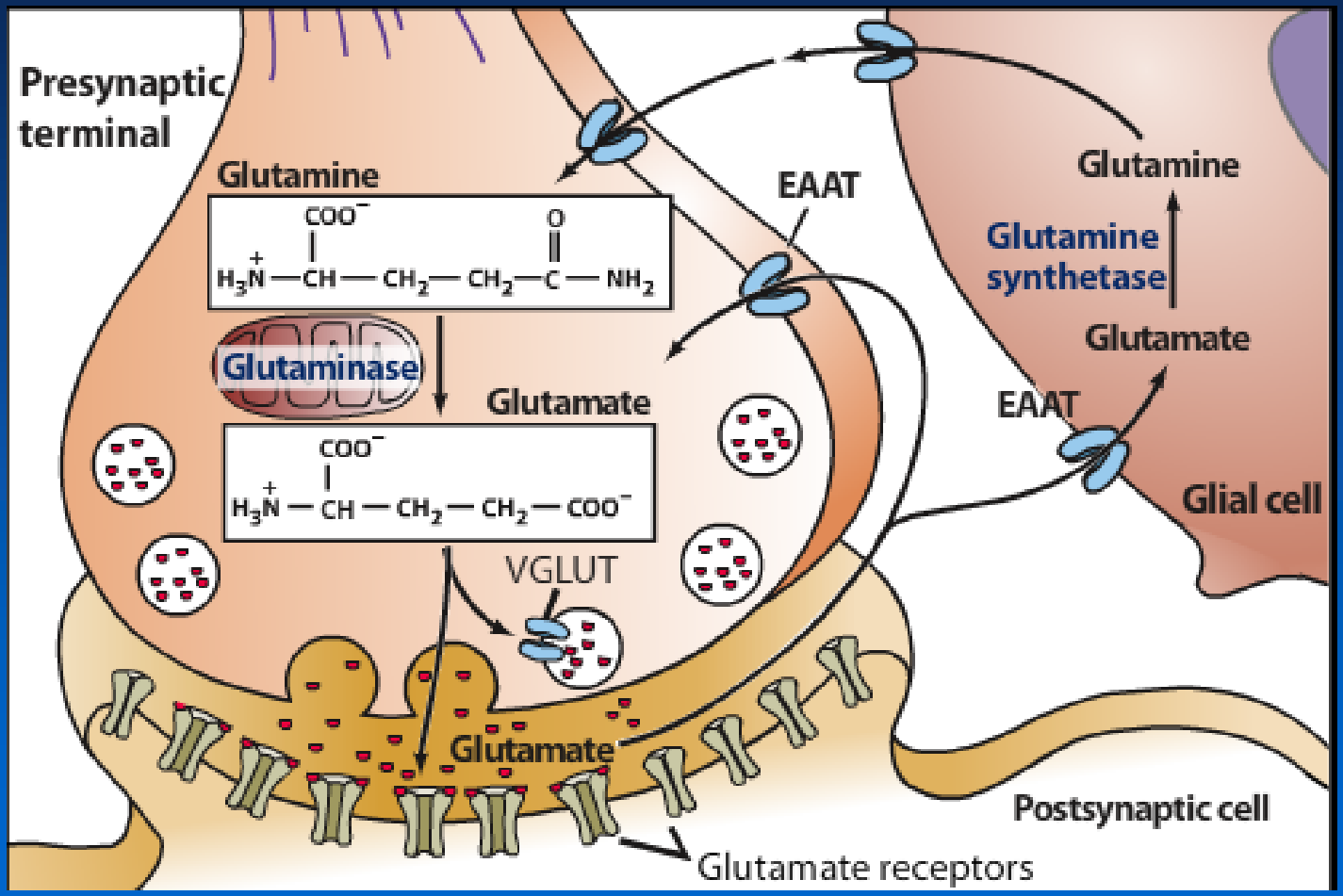
Location of M_5 receptors is not well known




Acetylcholine (Ach)
Coupled to K⁺ channel
causes hyperpolarization
and slows the heart rate.
M2 Muscarinic Receptor
Outside
N
I
II
III
IV
V
VI
VII
Ach
Inside
HO
C
OH
OH
OH
α_i
K⁺
Gi
protein

Glutamate

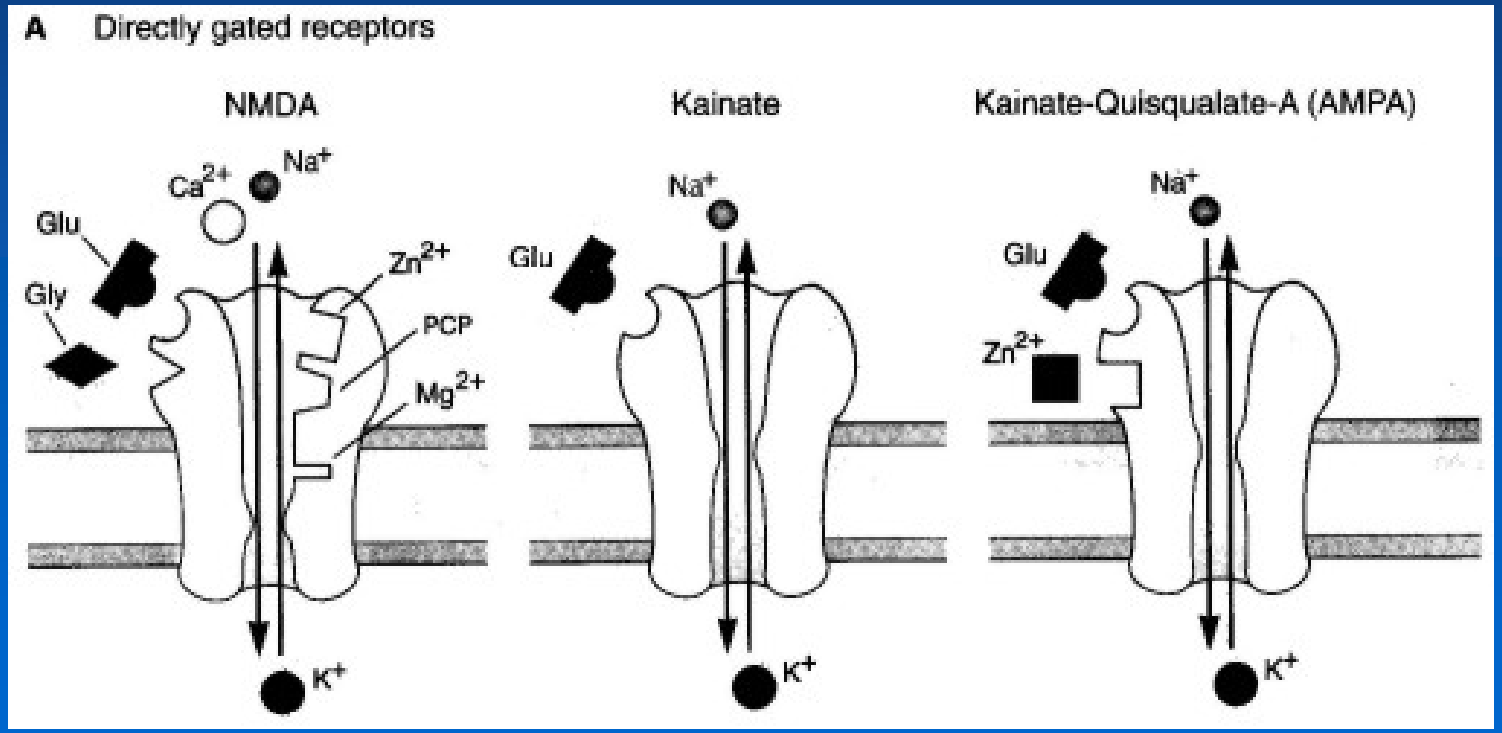
- Glutamate, an amino acid, is the major **excitatory** neurotransmitter in the central nervous system

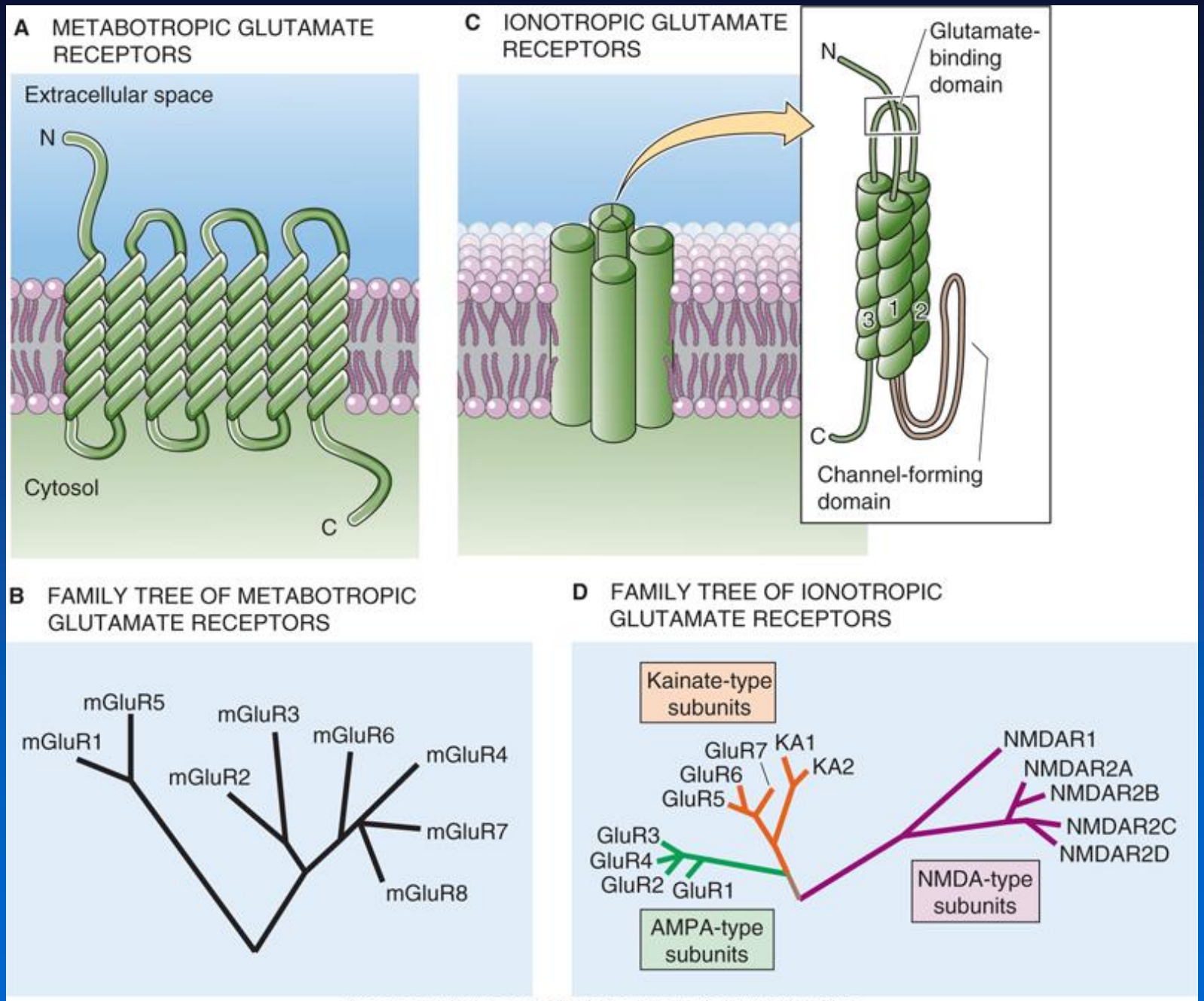


glutamate-glutamine cycle

- Glutamate has both ionotropic and metabotropic receptors
- Based on pharmacological properties and subunit composition, several distinct **ionotropic receptor** subtypes are recognized:

AMPA, Kainate and NMDA





AMPA-gated channels are found in most excitatory synapses in the brain, and they mediate fast excitation

NMDA-gated channels have more complex behavior. The ion selectivity of NMDA channels is the key to their functions: permeability to Na^+ and K^+ causes depolarization and thus excitation of a cell, but their high permeability to Ca^{2+} allows them to influence $[Ca^{2+}]_i$

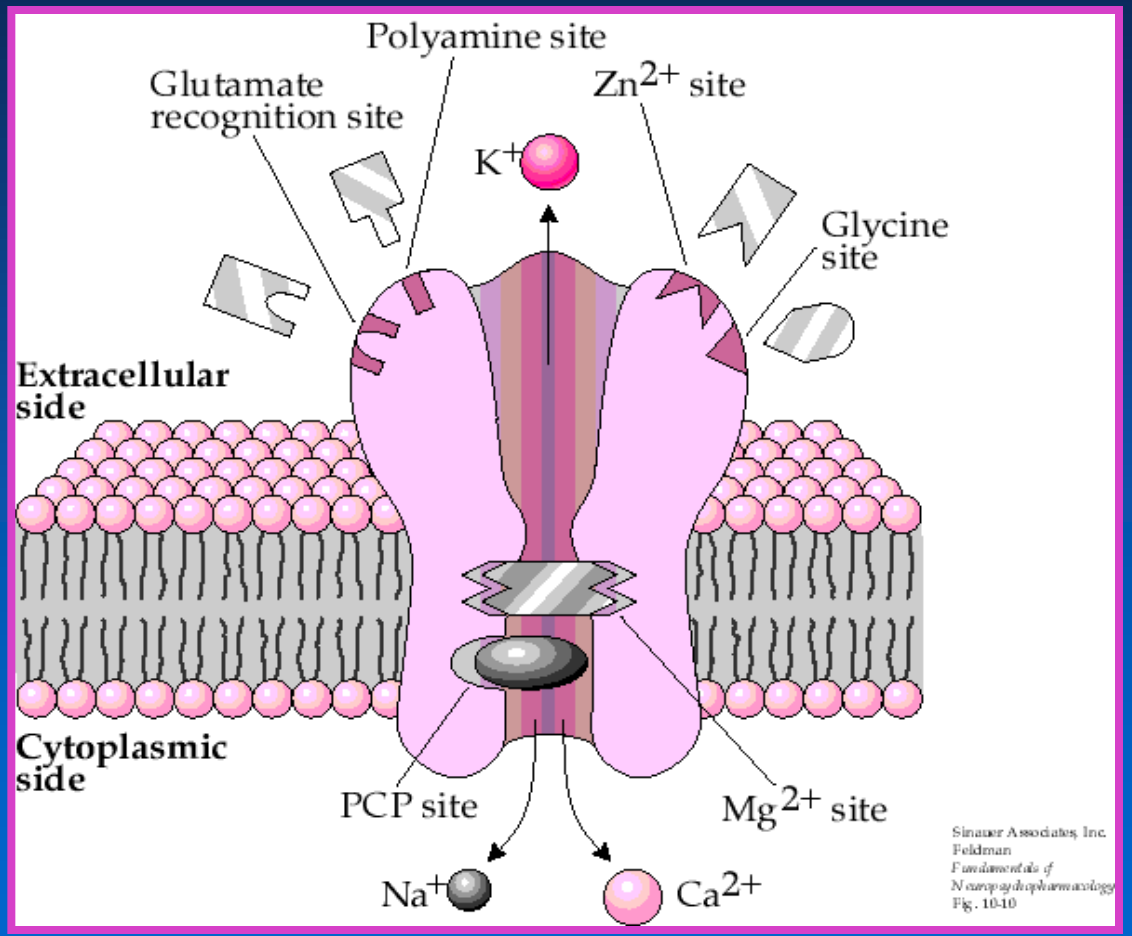
Ca^{2+} can activate many enzymes, regulate the opening of a variety of channels, and affect the expression of genes. Excess Ca^{2+} can even precipitate the death of a cell

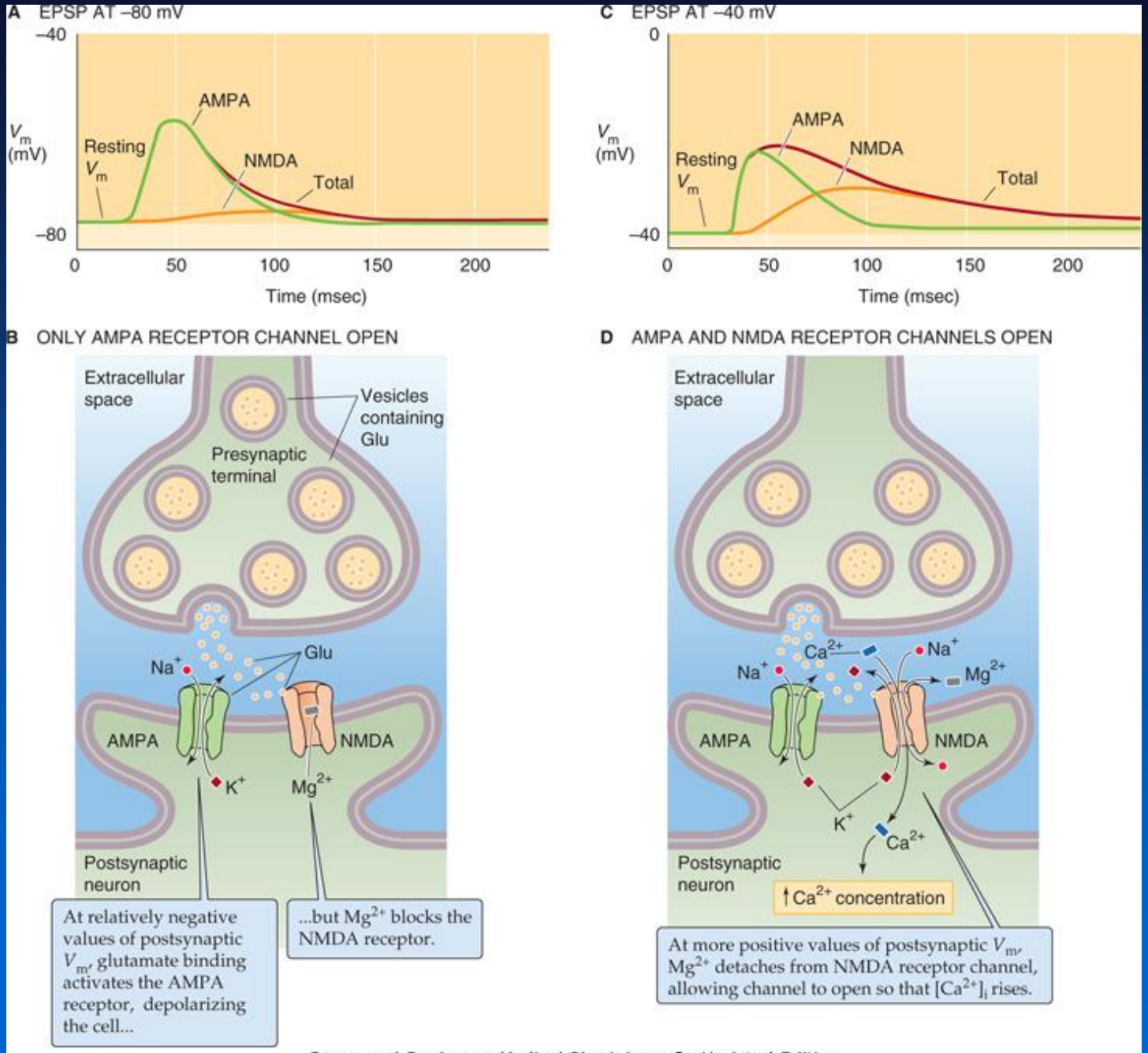
Table 13-2. Ionotropic Glutamate Receptors

Class of Receptor	Agonist	Antagonist	Kinetics	Permeability
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid	CNQX (6-cyano-7-nitroquinoxaline-2,3-dione)	Fast	Na^+, K^+ (Ca^{2+} in a few cases)
		GYKI53655 (2,3-benzodiazepine derivatives)		
NMDA	*N*-Methyl-D-aspartate	APV (2-amino-5-phosphonovaleric acid)	Slow	Na^+, K^+, Ca^{2+}
Kainate	Kainic acid	CNQX	Fast	Na^+, K^+
	Domoic acid	UBP296 ((*RS*)-1-(2-amino-2-carboxyethyl)-3-(2-carboxybenzyl) pyrimidine-2,4-dione)		

- The combination of voltage sensitivity and Ca^{2+} permeability of the NMDA channels has led to hypotheses concerning their role in learning and memory-related functions

- NMDA channel is **voltage dependent** in addition to being **ligand gated**; both glutamate and a relatively positive V_m are necessary for the channel to open.
  - NMDA-gated channels coexist with AMPA-gated channels in many synapses of the brain.
  - When the postsynaptic cell is at a relatively negative resting potential, the glutamate released from a synaptic terminal can open the AMPA-gated channel. When the postsynaptic cell is more depolarized because of the action of other synapses the larger depolarization of the postsynaptic membrane now allows the NMDA-gated channel to open by relieving its Mg^{2+} block.

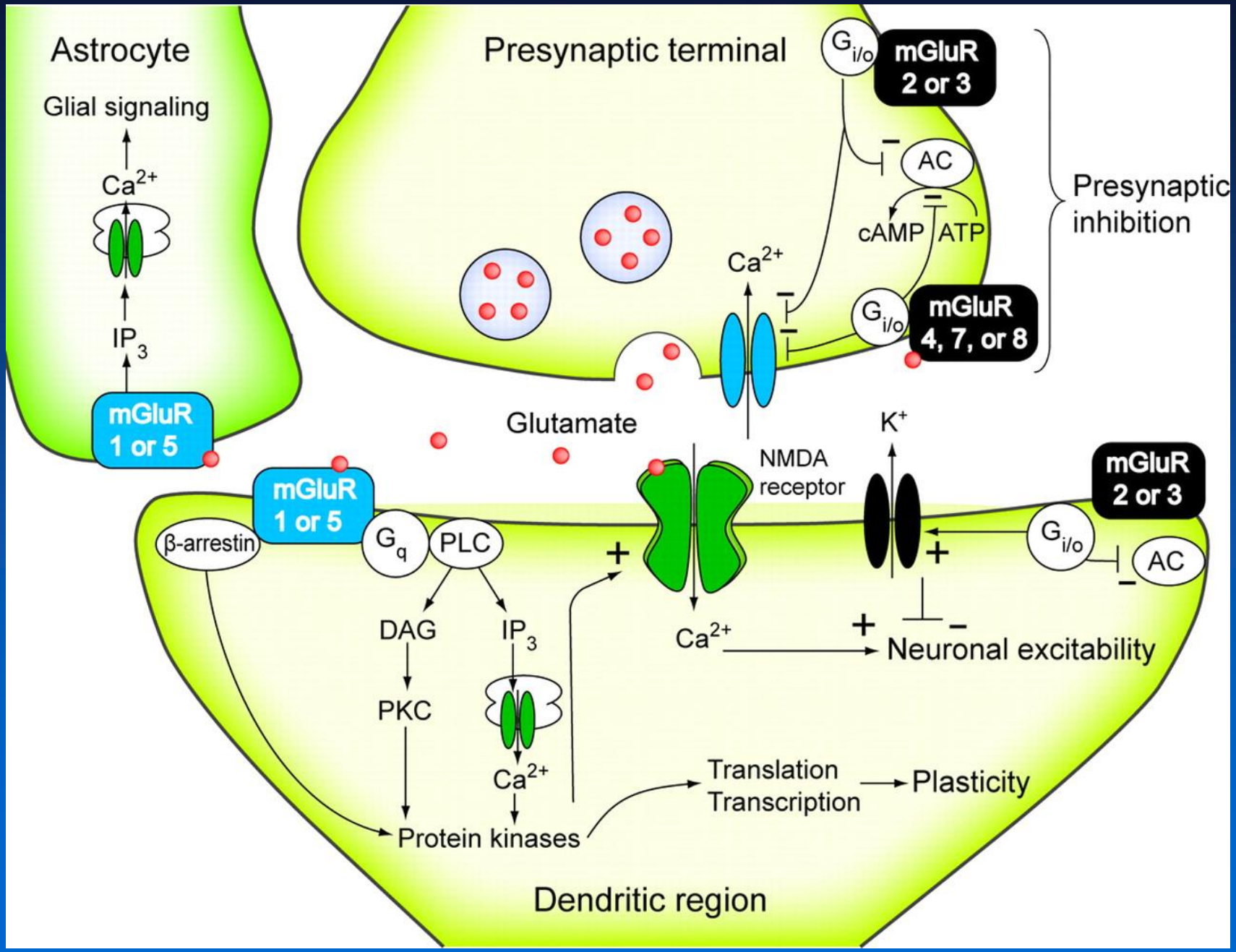




- Eight genes coding for **metabotropic glutamate receptors** have been identified and classified into three groups. **Group I receptors are found postsynaptically, whereas groups II and III are found presynaptically.**

Table 1. **'Group' classification of metabotropic glutamate receptors.**

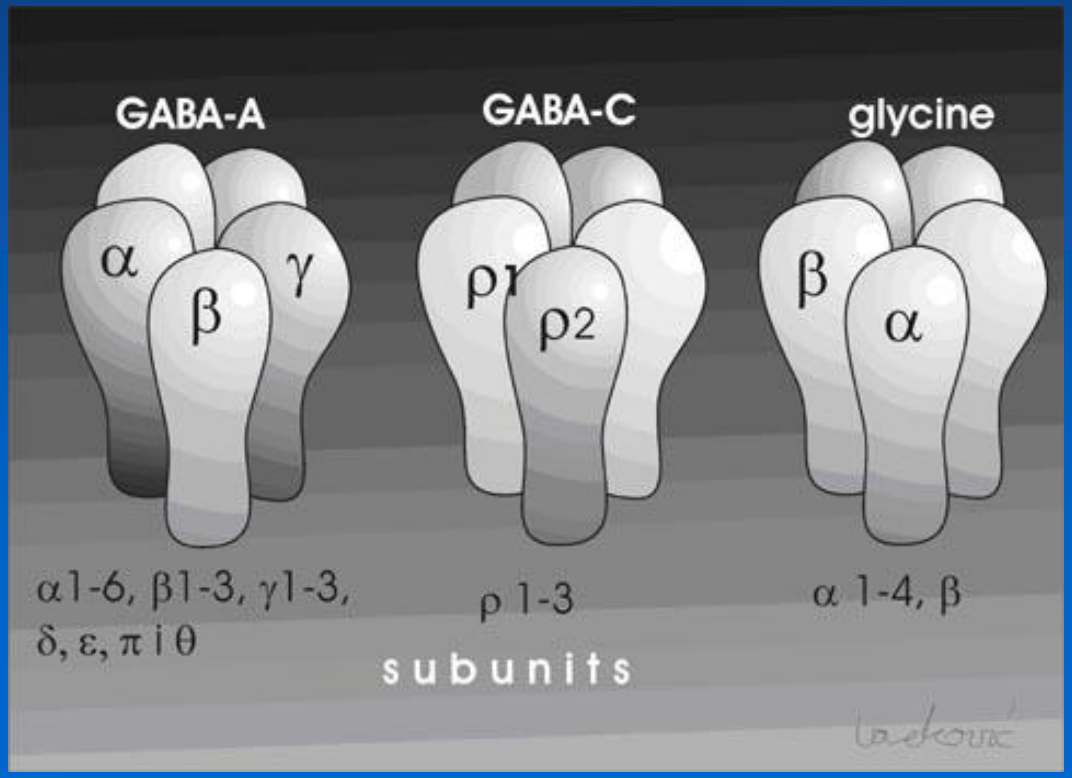
	Receptor	Transduction mechanism	Prototypic agonists
Group I	$mGlu_1$ $mGlu_5$	activation of PLC	quisqualate 3,5-DHPG
Group II	$mGlu_2$ $mGlu_3$	inhibition of adenylate cyclase	DCG-IV 2R,4R-APDC LY354740 LY379268
Group III	$mGlu_4$ $mGlu_6$ $mGlu_7$ $mGlu_8$	inhibition of adenylate cyclase	L-AP4 L-AP4 (RS)PPG


Astrocyte
Glial signaling
Ca2+
IP3
mGluR 1 or 5
Presynaptic terminal
Gi/o
mGluR 2 or 3
AC
cAMP
ATP
Presynaptic inhibition
Ca2+
Gi/o
mGluR 4, 7, or 8
Glutamate
K+
NMDA receptor
mGluR 1 or 5
β-arrestin
Gq
PLC
mGluR 2 or 3
Gi/o
AC
DAG
IP3
Ca2+
Neuronal excitability
PKC
Ca2+
Translation
Transcription
Plasticity
Protein kinases
Dendritic region

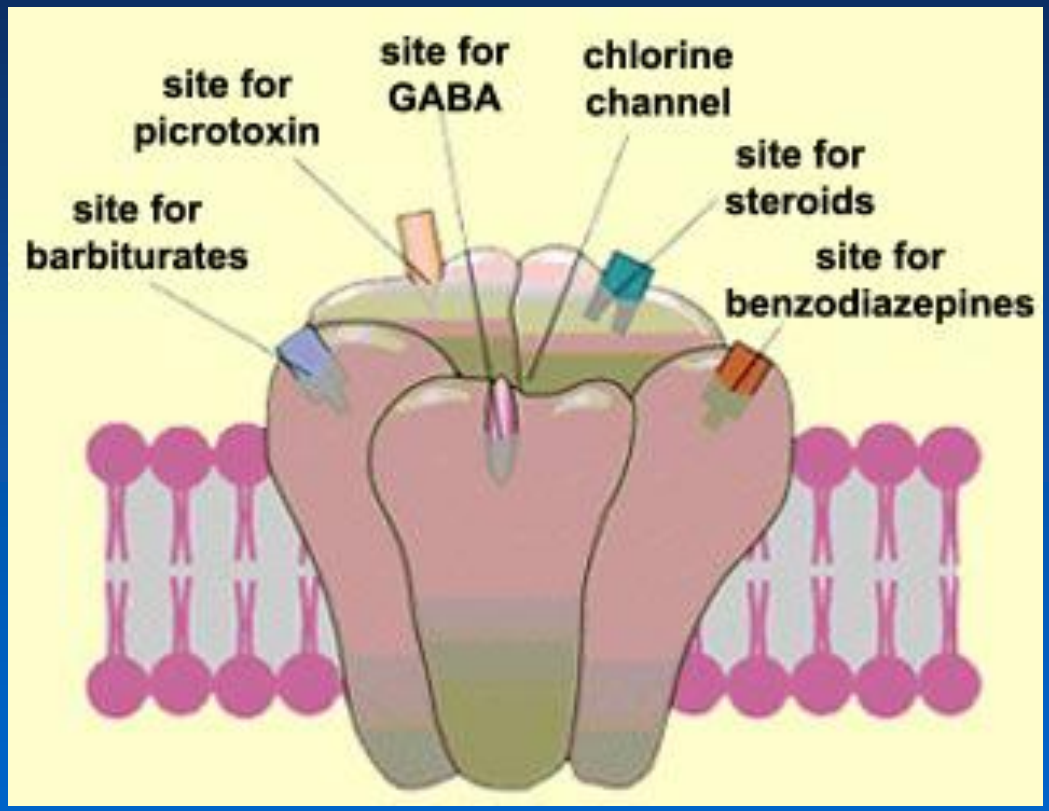
Inhibitory Amino Acid Receptors: GABA and Glycine

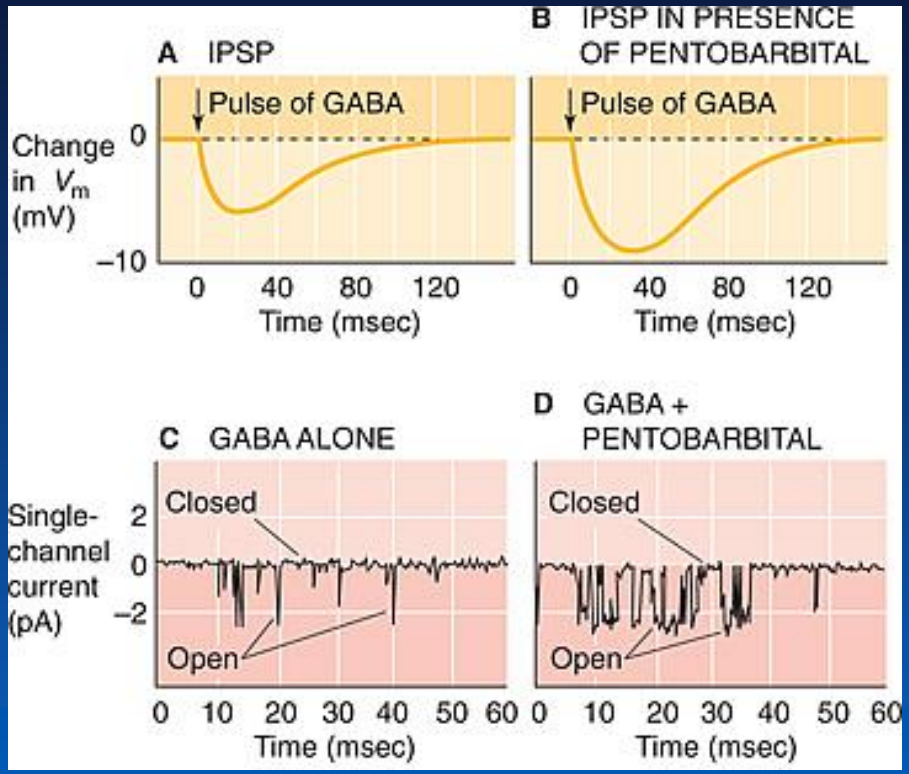
- Both glycine and GABA (**$GABA_A$ and $GABA_C$**) have ionotropic receptors
- Each of these receptors has a **Cl^- channel**
- Probability of these channels opening and the average time that a channel stays open are controlled by the concentration of the neurotransmitter for which the receptor is specific.

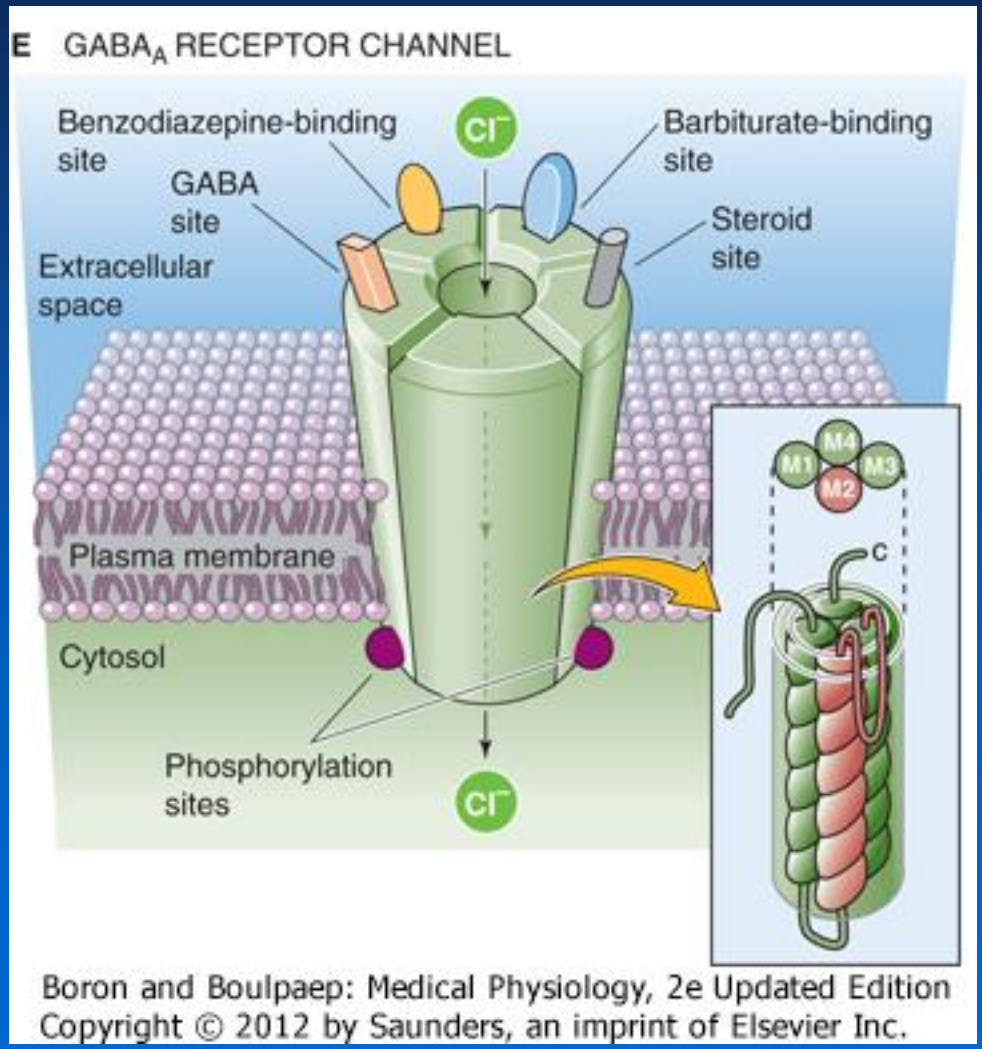
✓ Glycine-mediated inhibitory synapses predominate in the spinal cord, whereas GABAergic synapses make up the majority of inhibitory synapses in the brain



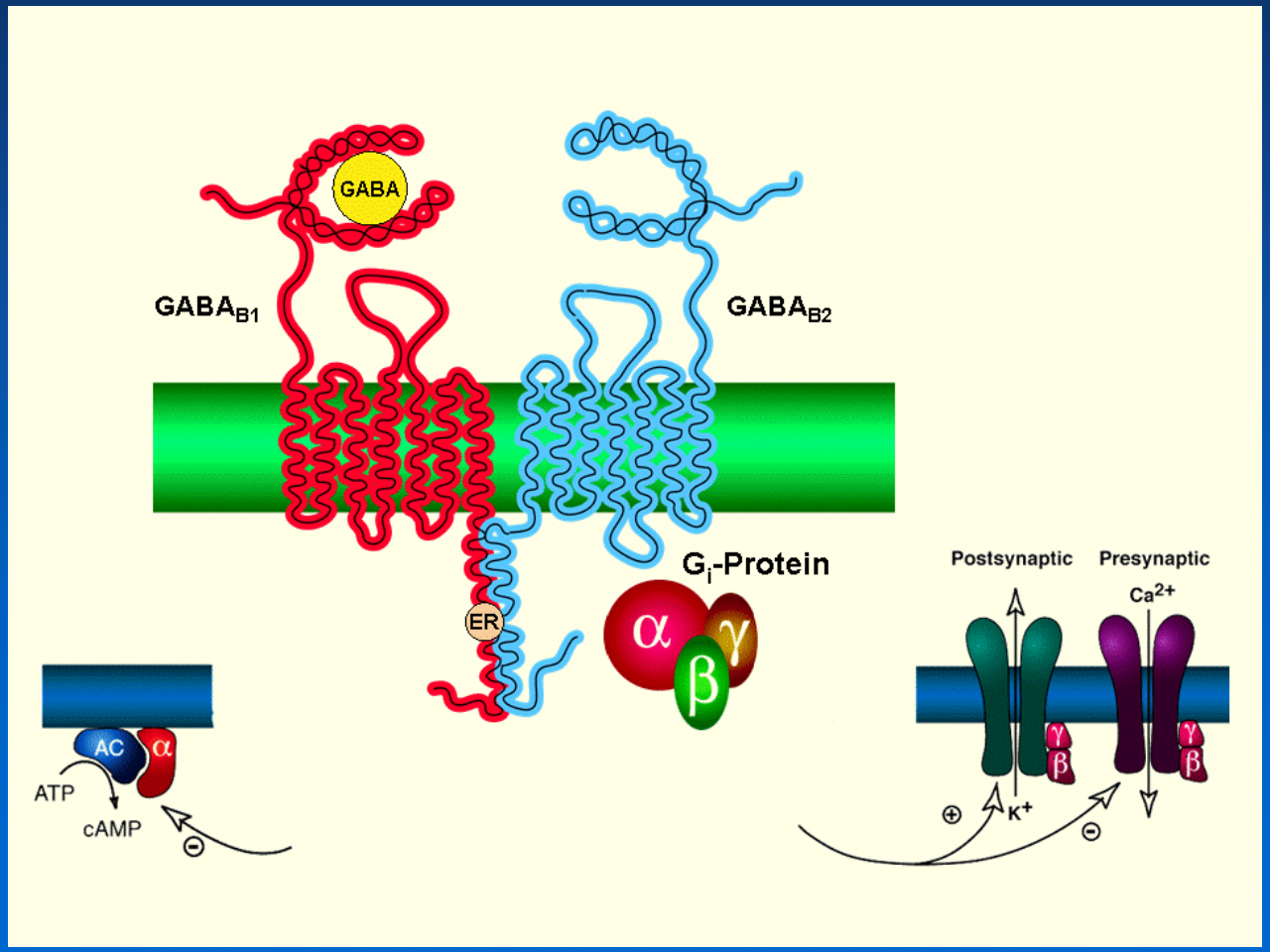
- $GABA_A$ receptors are the targets of two major classes of drugs: **benzodiazepines and barbiturates.**
  - Benzodiazepines are widely used antianxiety and relaxant drugs
  - Barbiturates are used as sedatives and anticonvulsants
  - Both classes of drugs bind to distinct sites on the a subunits of $GABA_A$ receptors and enhance opening of the receptors' Cl^- channels in response to GABA




A IPSP
B IPSP IN PRESENCE OF PENTOBARBITAL
Pulse of GABA
Pulse of GABA
Change in V_m (mV)
0
−10
0 40 80 120
Time (msec)
0 40 80 120
Time (msec)
C GABA ALONE
D GABA + PENTOBARBITAL
Single-channel current (pA)
2
0
−2
Closed
Open
Closed
Open
0 10 20 30 40 50 60
Time (msec)
0 10 20 30 40 50 60
Time (msec)


E GABA$_A$ RECEPTOR CHANNEL
Benzodiazepine-binding site
GABA site
Extracellular space
Cl^-
Barbiturate-binding site
Steroid site
Plasma membrane
Cytosol
Phosphorylation sites
Cl^-
M4
M1
M3
M2
C
Boron and Boulpaep: Medical Physiology, 2e Updated Edition
Copyright © 2012 by Saunders, an imprint of Elsevier Inc.

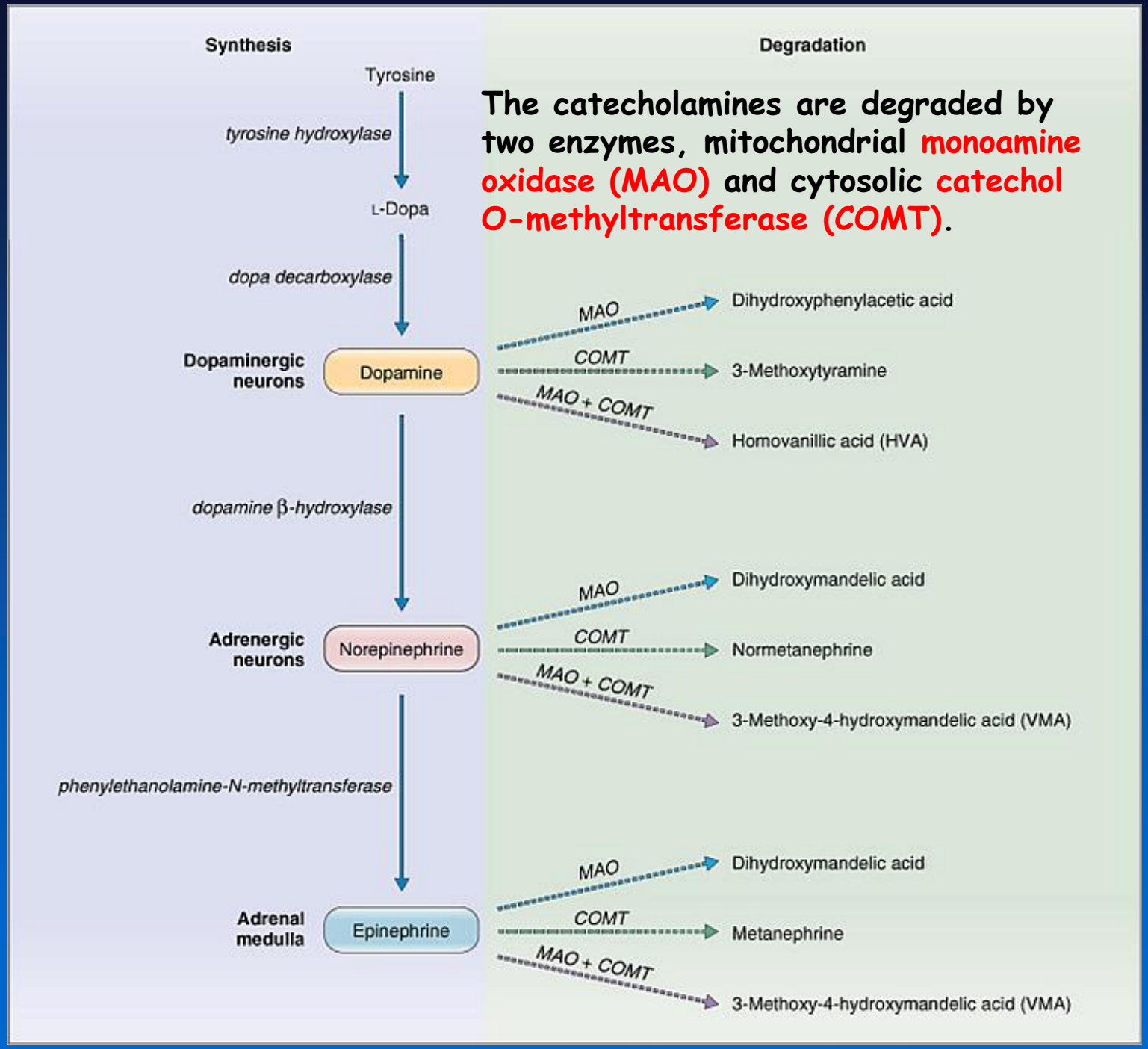
• **The $GABA_B$ receptor** is a **metabotropic receptor**. Binding of GABA to this receptor activates a heterotrimeric GTP-binding protein which leads to activation of K^+ channels and hence hyperpolarization of the postsynaptic cell, as well as inhibition of Ca^{++} channels (when located presynaptically) and thus a reduction in release of transmitter.



Biogenic Amines

- Among the amines known to act as neurotransmitters are;
  - **Dopamine**
  - **Norepinephrine** (noradrenaline),
  - **Epinephrine** (adrenaline),
  - **Serotonin** (5-hydroxytryptamine [5-HT])
  - **Histamine**

✓ Dopamine, norepinephrine, and epinephrine are **catecholamines**, and they share a common biosynthetic pathway that starts with the amino acid tyrosine.



The catecholamines are degraded by two enzymes, mitochondrial monoamine oxidase (MAO) and cytosolic catechol O-methyltransferase (COMT).

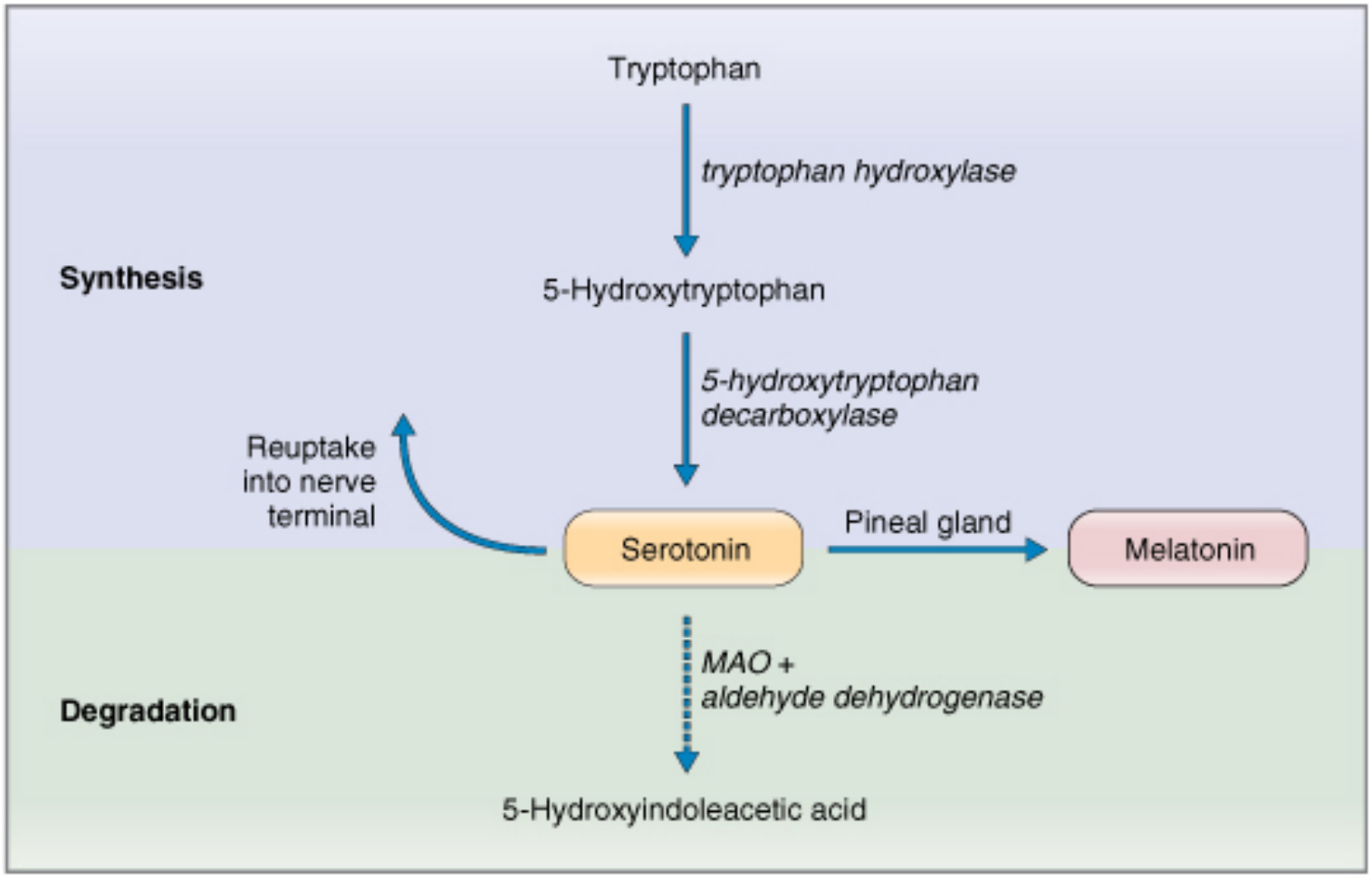


Figure 1-19 **Synthesis and degradation of serotonin.** MAO, Monoamine oxidase.

Biogenic Amine Receptors

- With the exception of one class of serotonin receptors (5-HT_3), the receptors for the various biogenic amines are all metabotropic-type receptors.
- Thus, these neurotransmitters tend to act on relatively long time scales by generating slow synaptic potentials and by initiating second messenger cascades.
- Agonists and blockers of many of these receptors are important clinical tools for treating various neurological and psychiatric disorders.

Serotonin receptors (5-hydroxytryptamine; 5-HT receptors)

Receptor[a]	Distribution	Effector mechanism
5-HT_{1A}	Hippocampus, amygdala, septum, entorhinal cortex, hypothalamus, raphe nuclei	Inhibition of adenylyl cyclase, opening of K^+ channels
$5\text{-HT}_{1D\alpha}$	Not distinguishable from $5\text{-HT}_{1D\beta}$	Inhibition of adenylyl cyclase
$5\text{-HT}_{1D\beta}$	Substantia nigra, basal ganglia, superior colliculus	Inhibition of adenylyl cyclase
5-ht_{1E}	?	Inhibition of adenylyl cyclase
5-ht_{1F}	Cerebral cortex, striatum, hippocampus, olfactory bulb	Inhibition of adenylyl cyclase
5-HT_{2A}	Claustrum, cerebral cortex, olfactory tubercle, striatum, nucleus accumbens	Stimulation of phosphoinositide-specific phospholipase C, closing of K^+ channels
5-HT_{2B}	?	Stimulation of phosphoinositide-specific phospholipase C
5-HT_{2C}	Choroid plexus, globus pallidus, cerebral cortex, hypothalamus, septum, substantia nigra, spinal cord	Stimulation of phosphoinositide-specific phospholipase C
5-HT_{3}	Hippocampus, entorhinal cortex, amygdala, nucleus accumbens, solitary tract nerve, trigeminal nerve, motor nucleus of the dorsal vagal nerve, area postrema, spinal cord	Ligand-gated cation channel
5-HT_{4}	Hippocampus, striatum, olfactory tubercle, substantia nigra	Stimulation of adenylyl cyclase
5-ht_{5A}	?	Inhibition of adenylyl cyclase
5-HT_{5B}	?	?
5-ht_{6}	?	Stimulation of adenylyl cyclase
5-HT_{7}	Cerebral cortex, septum, thalamus, hypothalamus, amygdala, superior colliculus	Stimulation of adenylyl cyclase

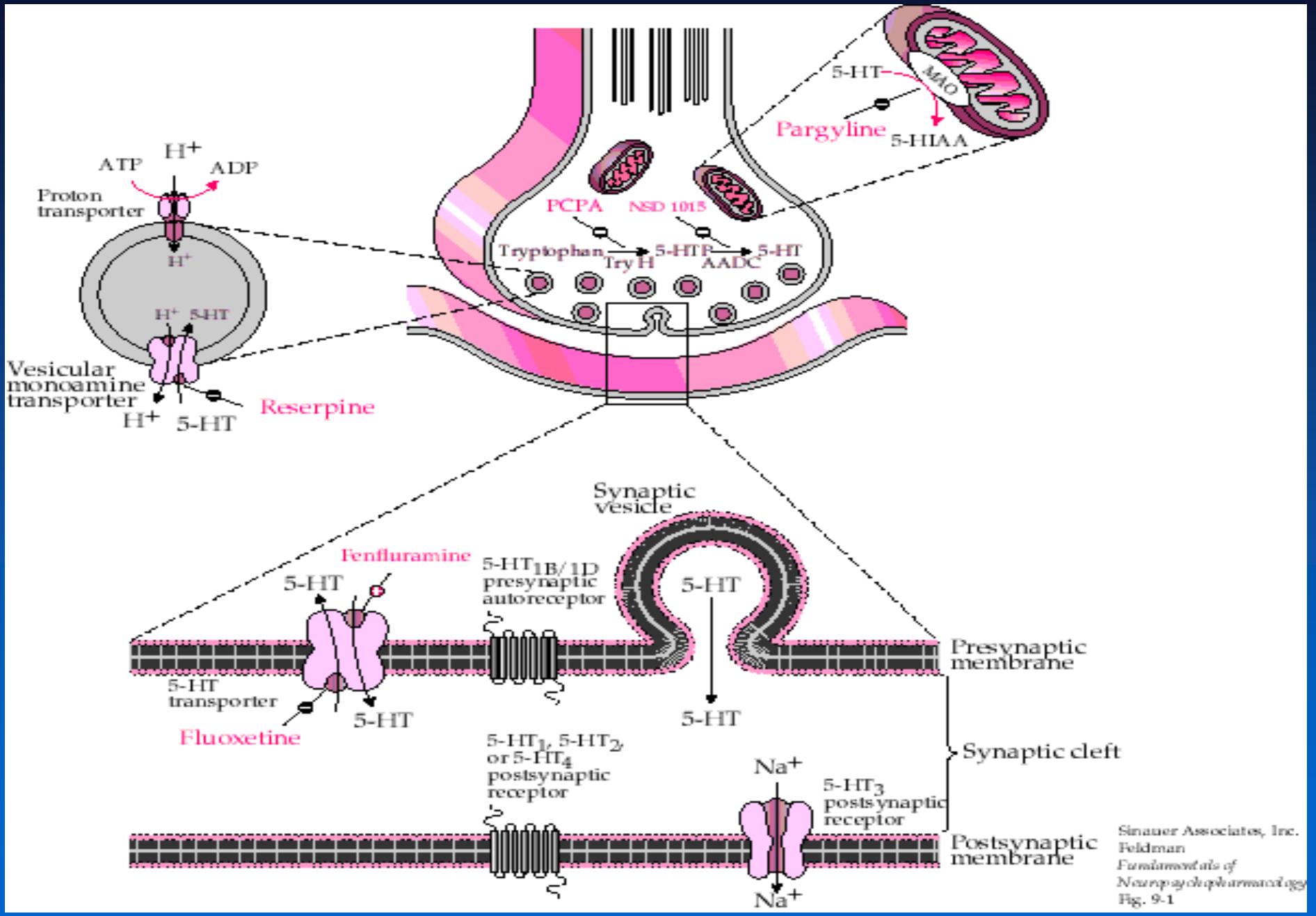


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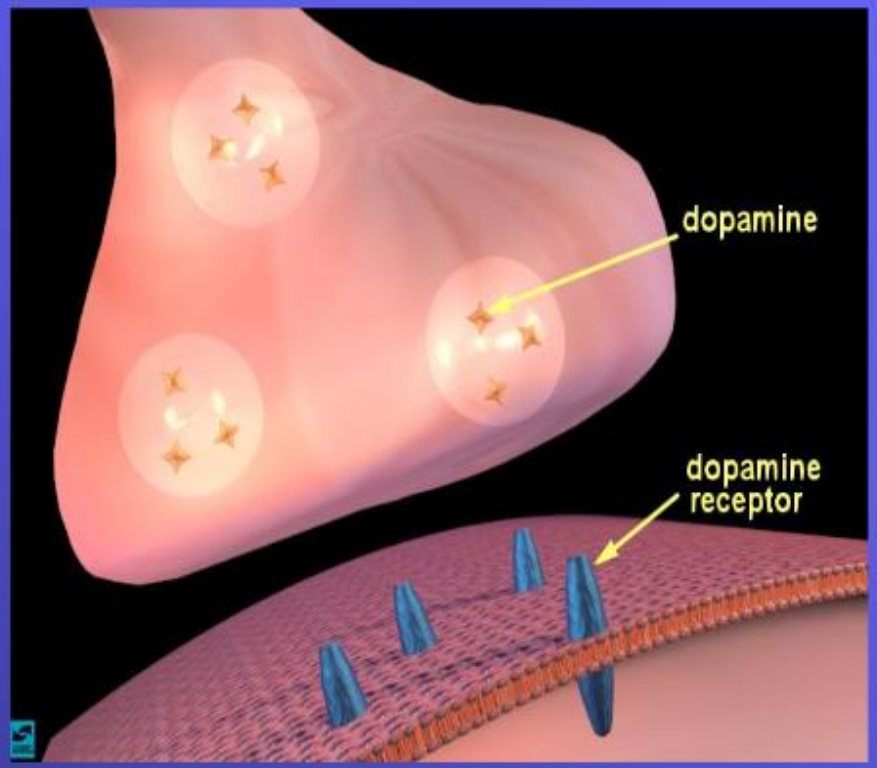
Fig. 9-1

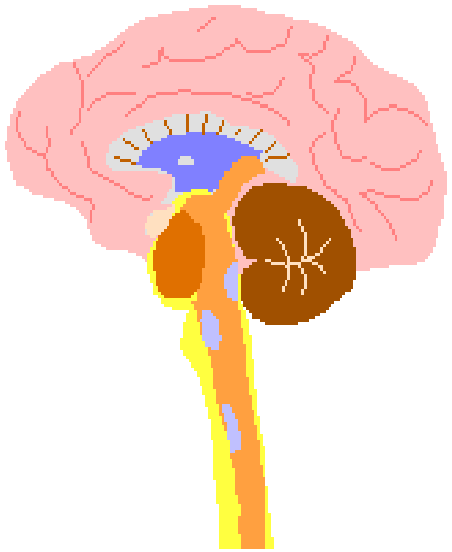
Dopamine Receptors

- Five subtypes of dopamine receptor have been cloned. The D1 and D5 receptors are closely related, and couple to Gs alpha and stimulate adenylyl cyclase activity. In contrast, the D2, D3 and D4 receptors couple to Gi alpha and inhibit the formation of cAMP.



striatum
D_1, D_2

limbic/cortex
D_1, D_2, D_3, D_4, D_5



pituitary
D_2

Localisation of dopamine receptors

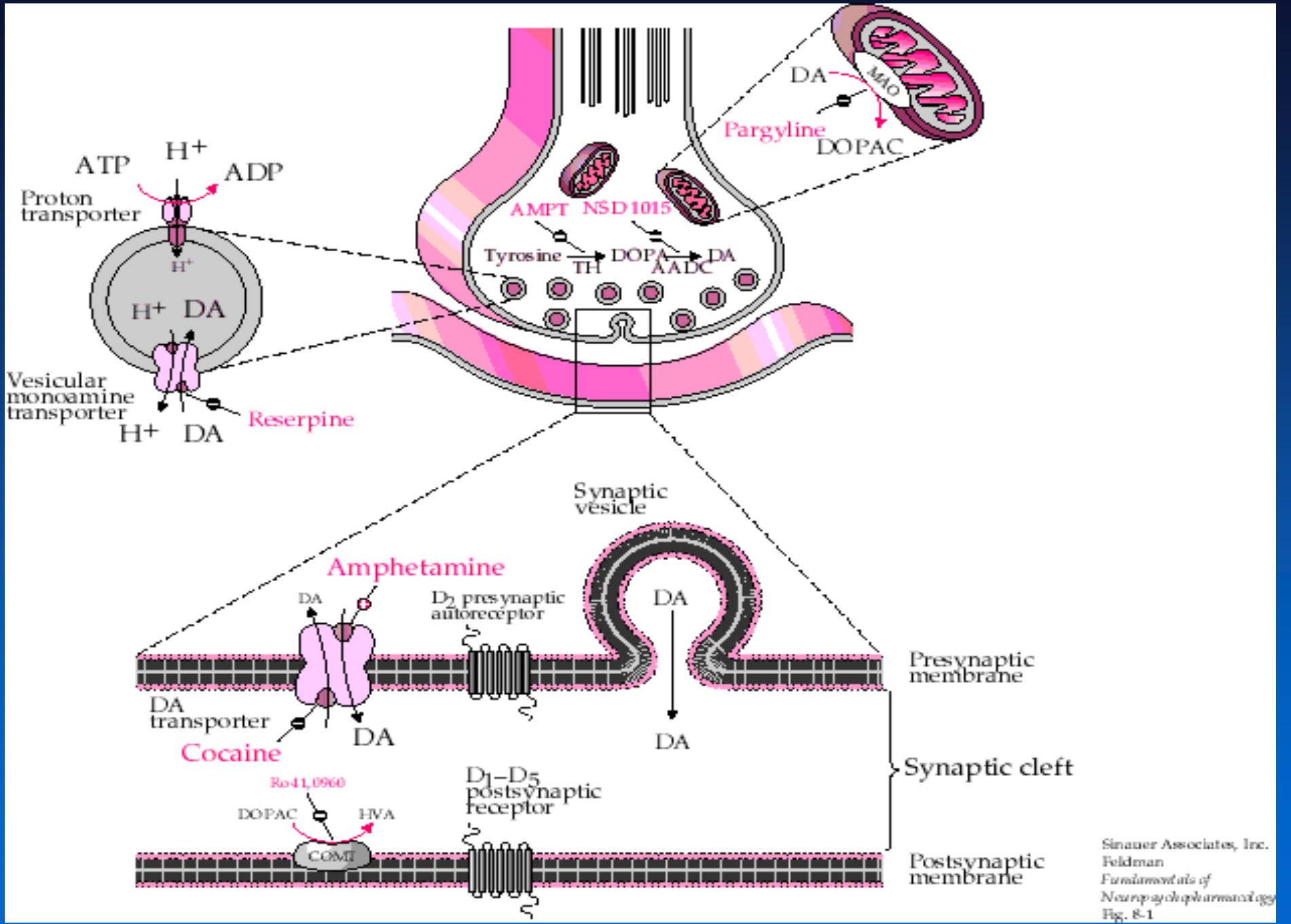


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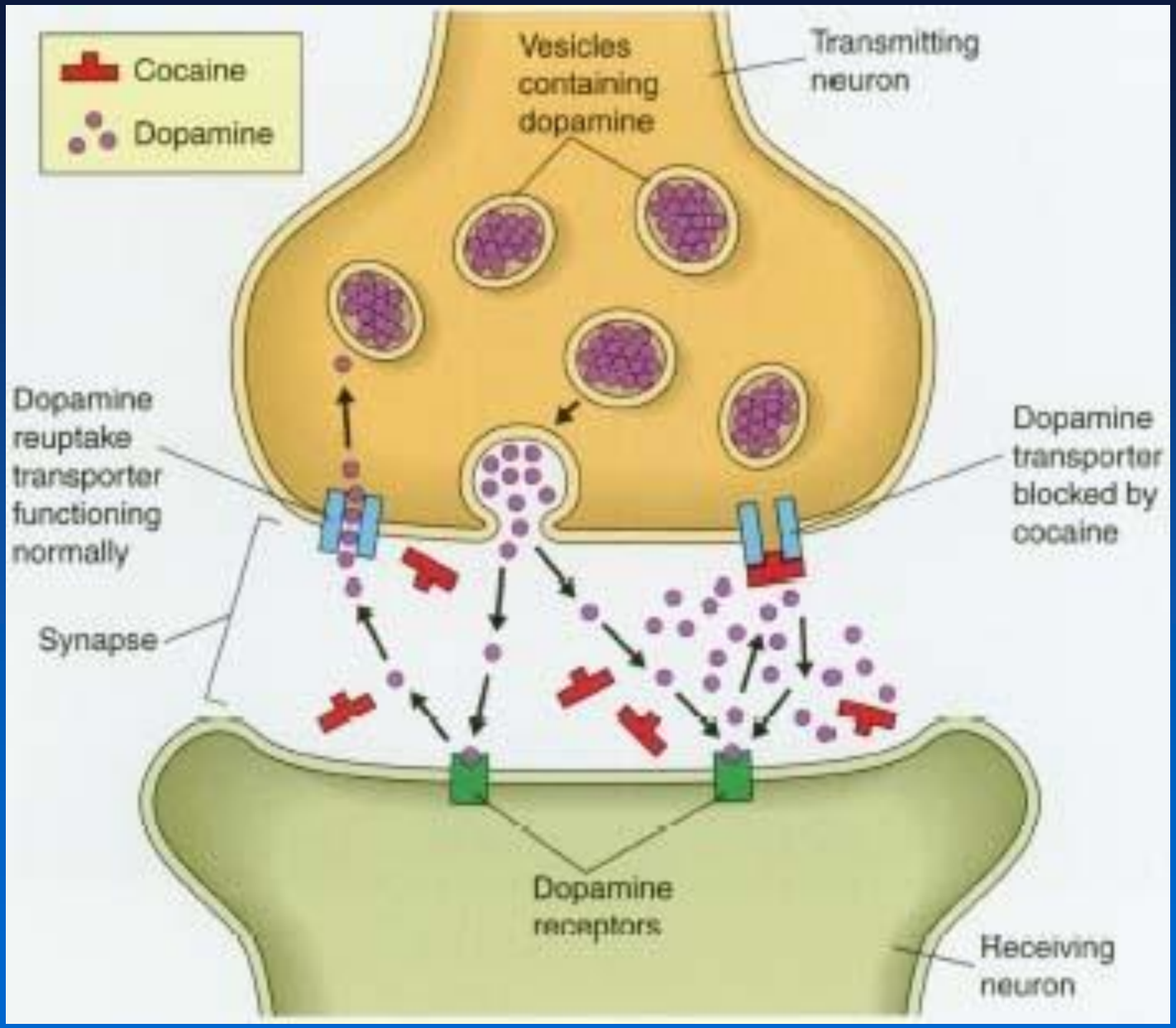
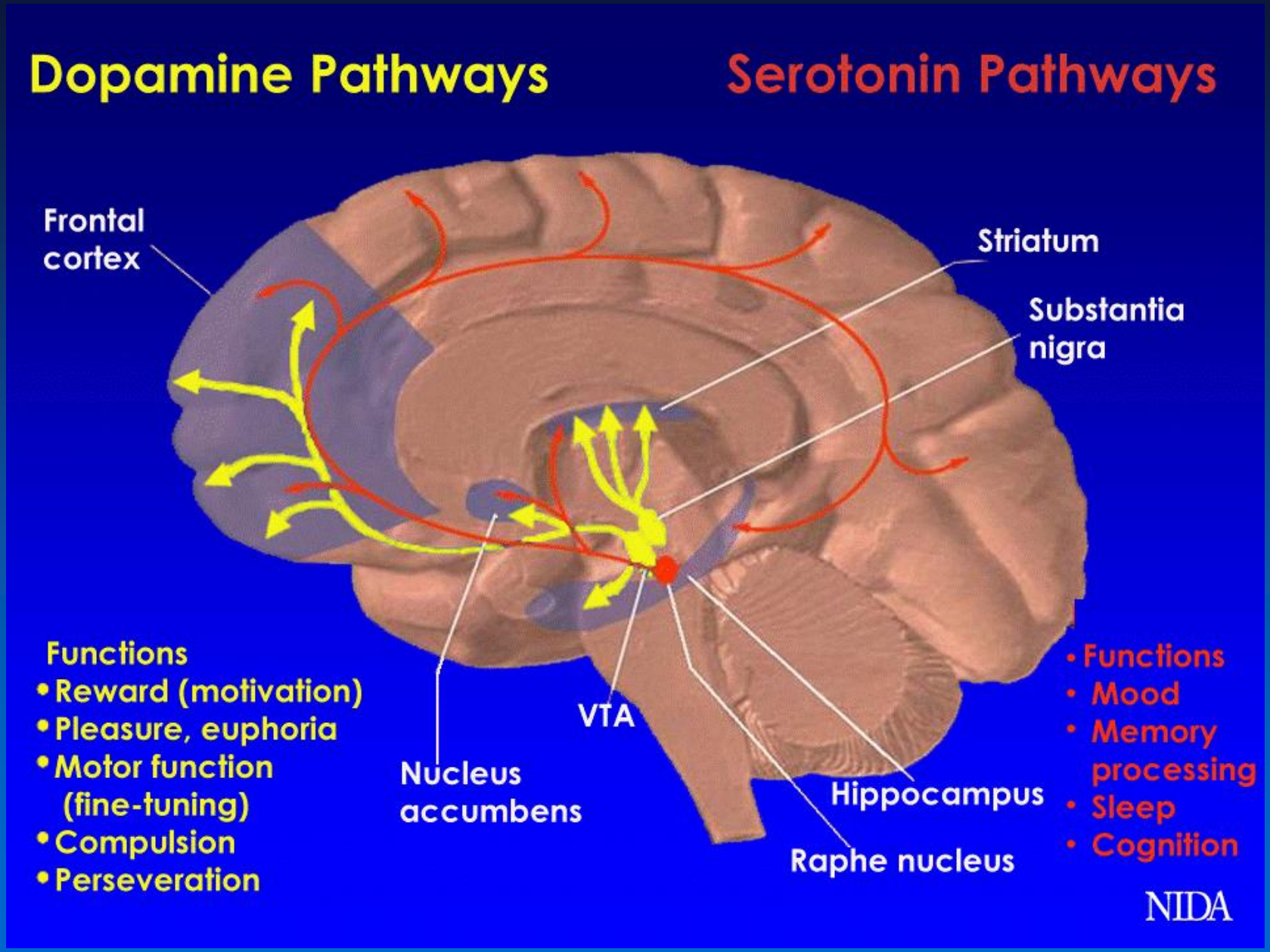
Fig. 8-1


Cocaine
Dopamine
Vesicles containing dopamine
Transmitting neuron
Dopamine reuptake transporter functioning normally
Dopamine transporter blocked by cocaine
Synapse
Dopamine receptors
Receiving neuron


Dopamine Pathways
Serotonin Pathways
Frontal cortex
Striatum
Substantia nigra
Functions
• Reward (motivation)
• Pleasure, euphoria
• Motor function (fine-tuning)
• Compulsion
• Perseveration
VTA
Nucleus accumbens
Hippocampus
Raphe nucleus
• Functions
• Mood
• Memory processing
• Sleep
• Cognition
NIDA