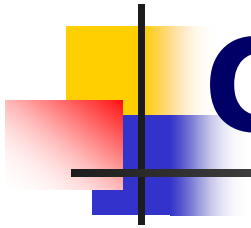
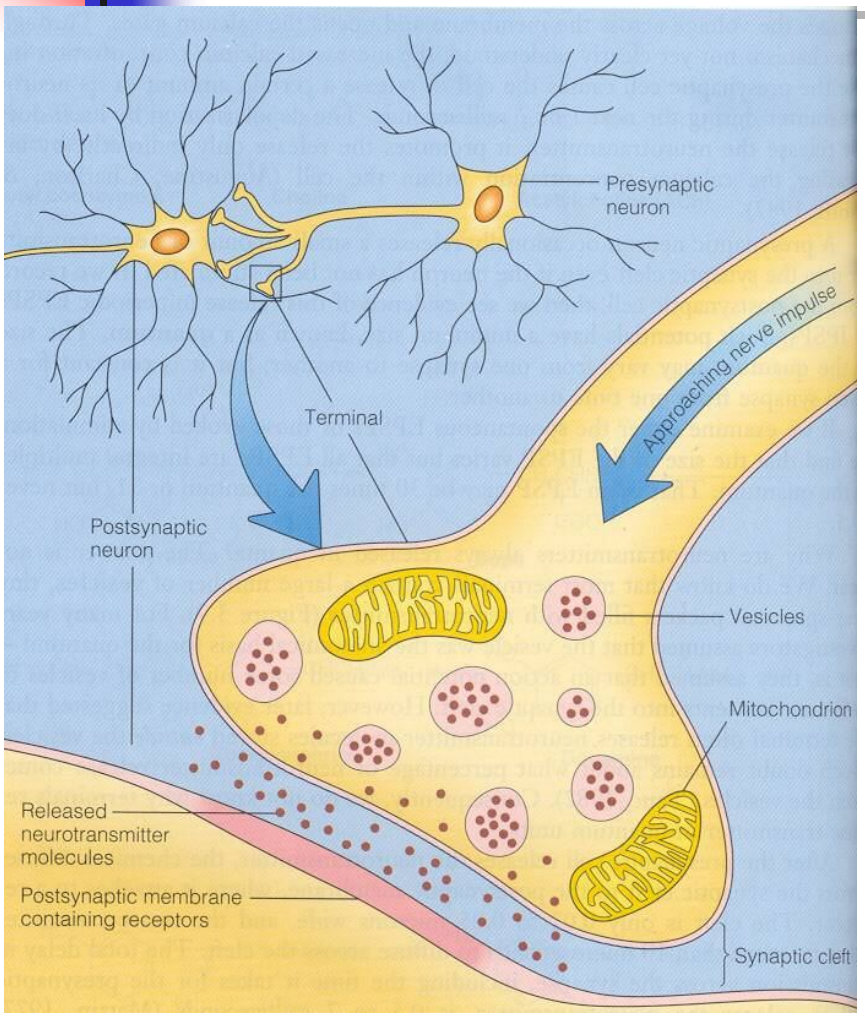


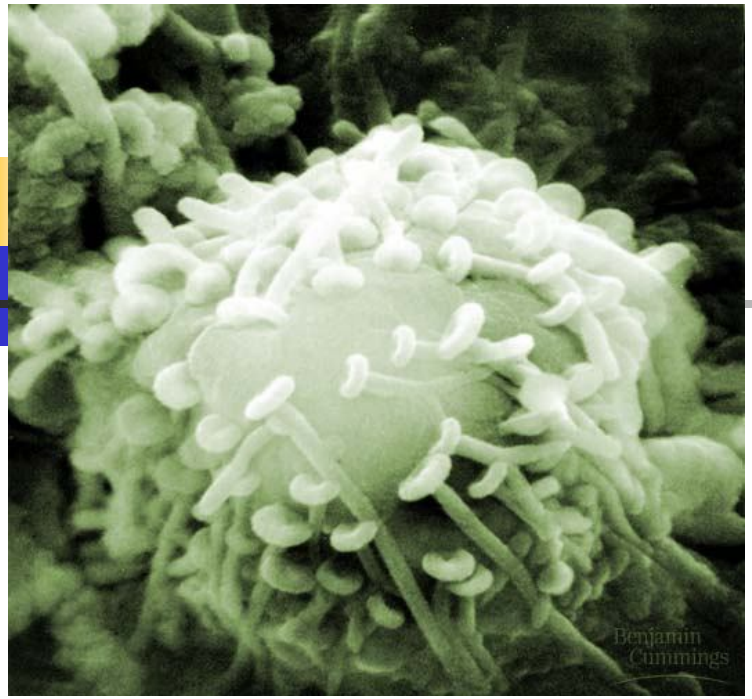
Chapter 30

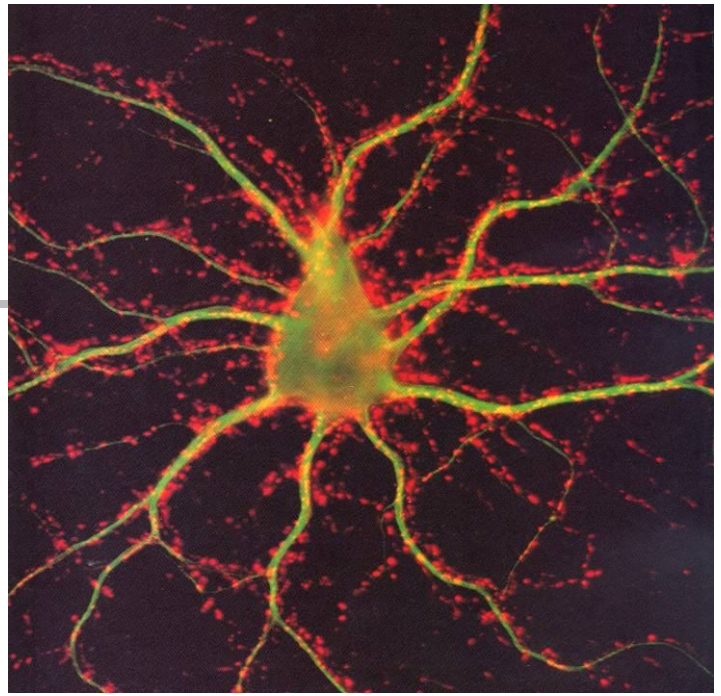
Basic principles of nervous system activity and functions

1. Introduction



Synapse **is a specialized junction at which a nerve cell communicates with another.**





On average, each neuron divides to form over 2000 synaptic endings, and since the human CNS has 10^{11} neurons, it follows that there are about 2×10^{14} synapses. Obviously, therefore, the communications between neurons are extremely complex.
It has been calculated that in the cerebral cortex, 98% of the synapses are on dendrites and only 2% are on cell bodies.

Types of synapse

On the basis of connecting area of synapses

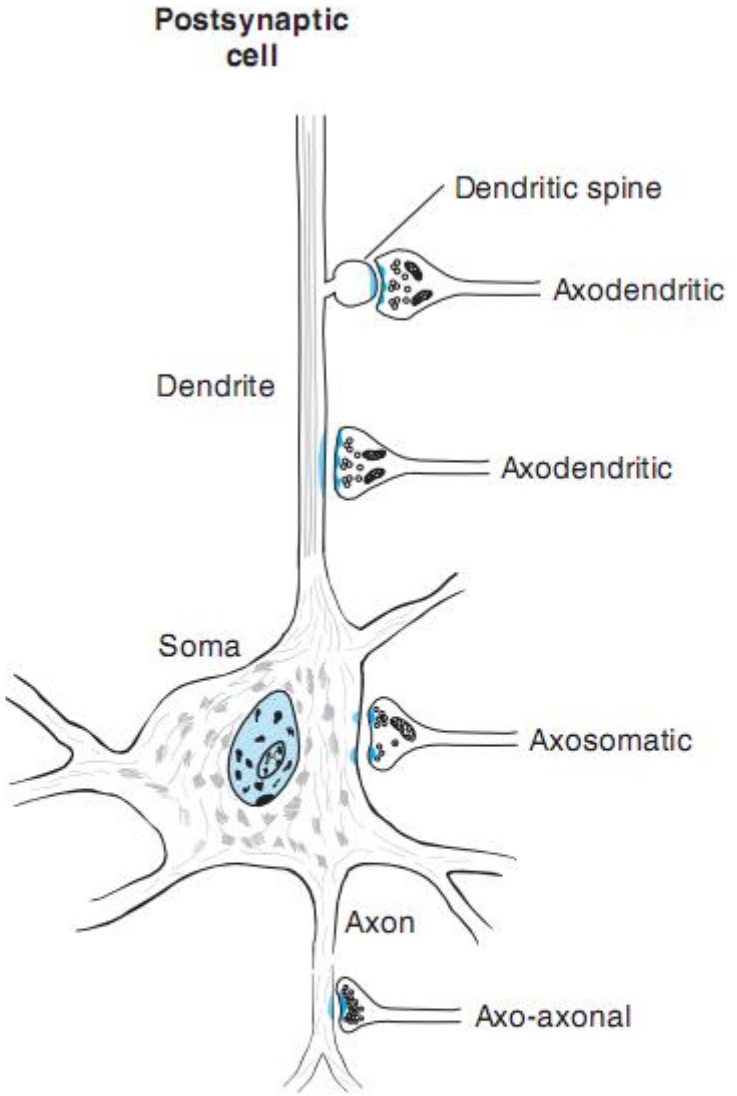
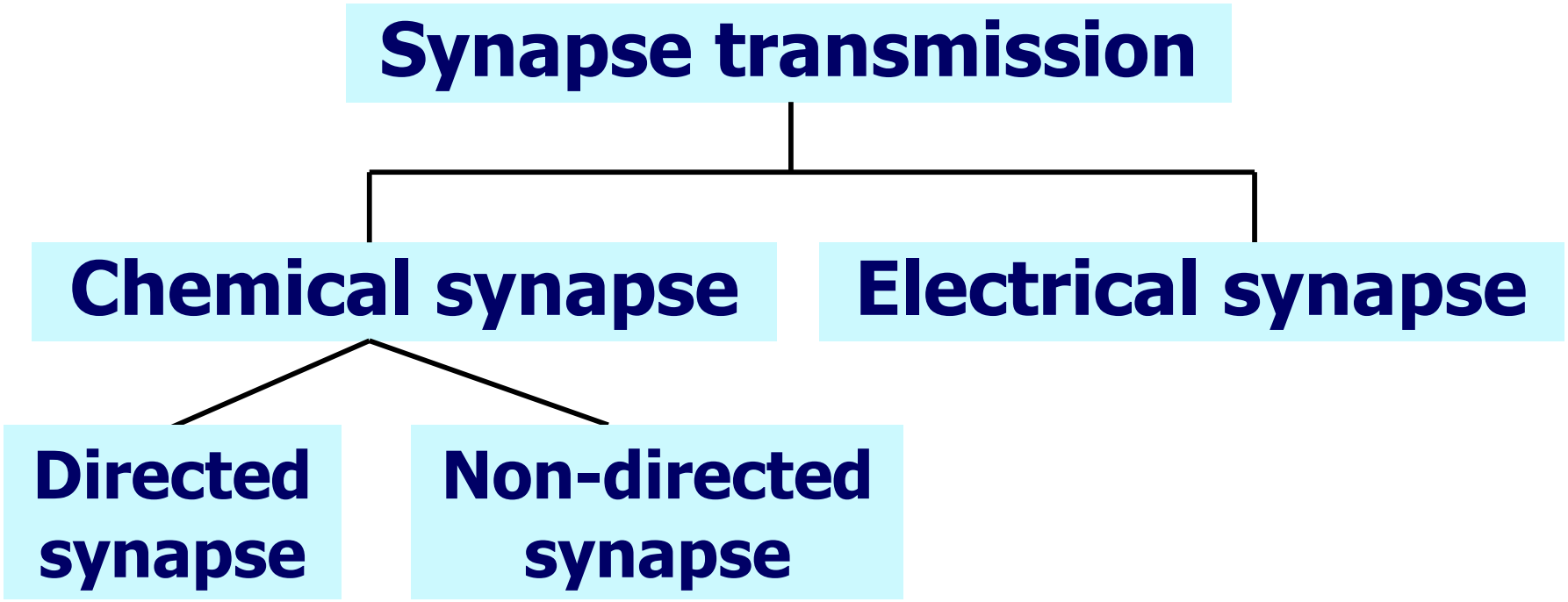
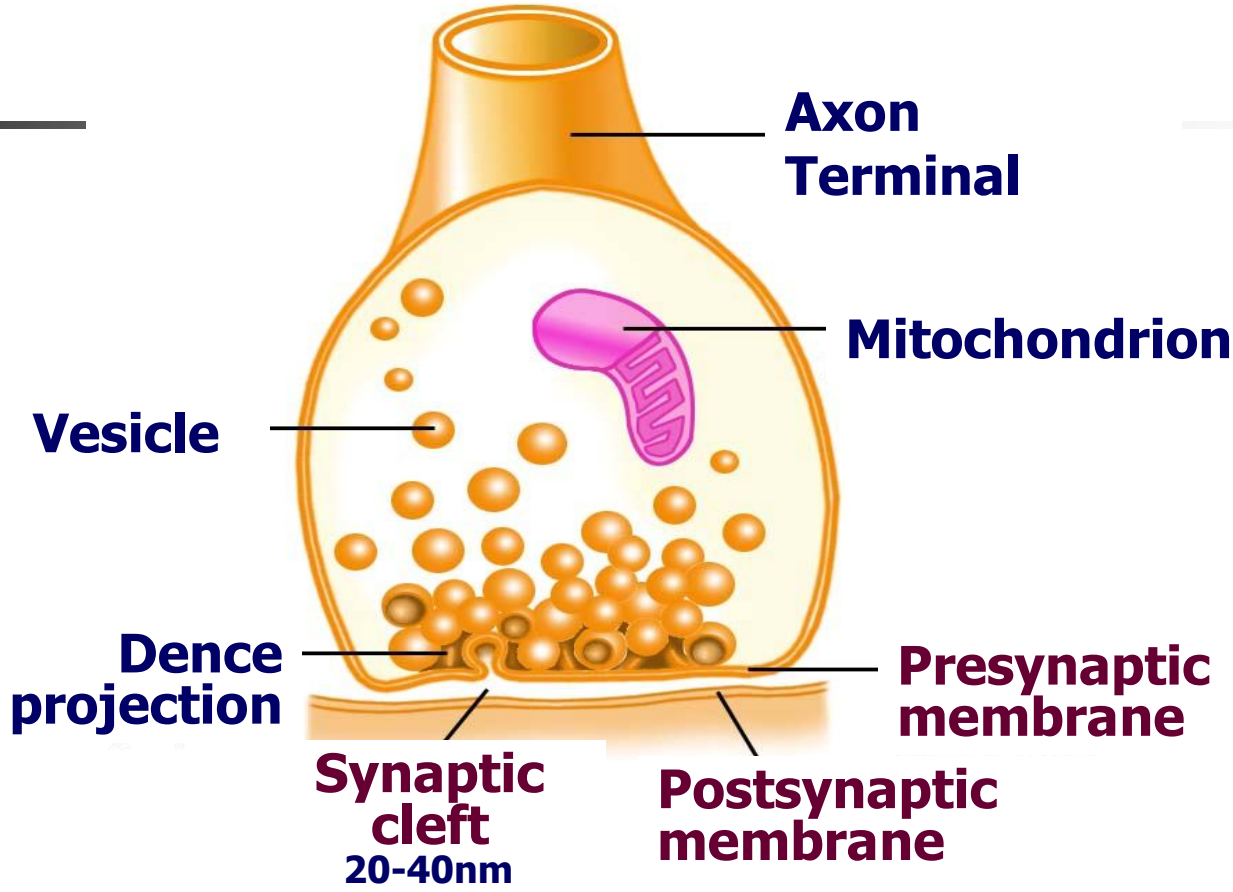


Figure 4–3. Axodendritic, axoaxonal, and axosomatic synapses. Many presynaptic neurons terminate on dendritic spines, as shown at the top, but some also end directly on the shafts of dendrites. Note the presence of clear and granulated synaptic vesicles in endings and clustering of clear vesicles at active zones.

Types of synapse transmission



Chemical synapse

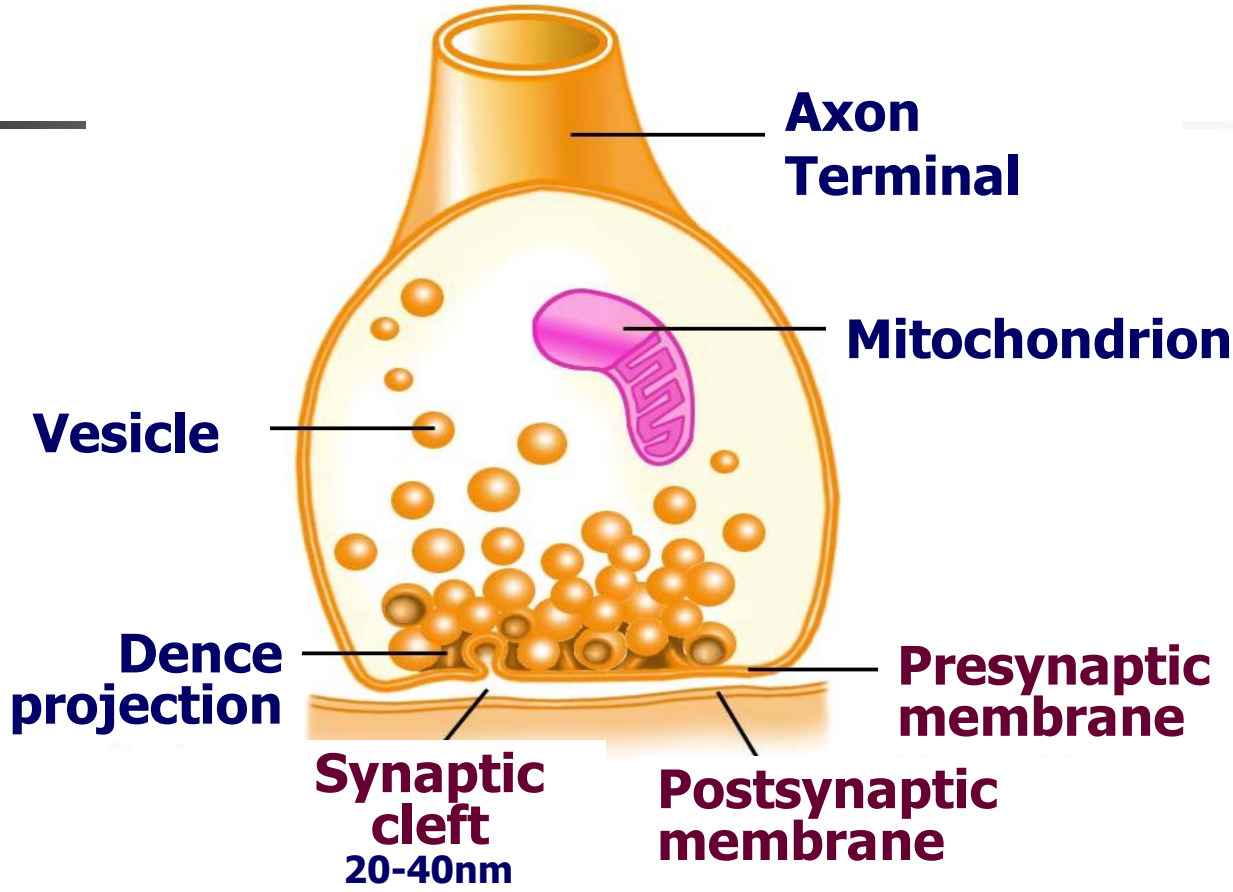


Synaptic Structure

Synaptic Delay

- An interval of at least 0.5 ms occurs.
- The delay is due to the time it takes for the neurotransmitter to be released and to act on the membrane of the postsynaptic cell.
- Since the minimum time for transmission across one synapse is 0.5 ms, it is also possible to determine whether a given reflex pathway is monosynaptic or polysynaptic.

Chemical synapse



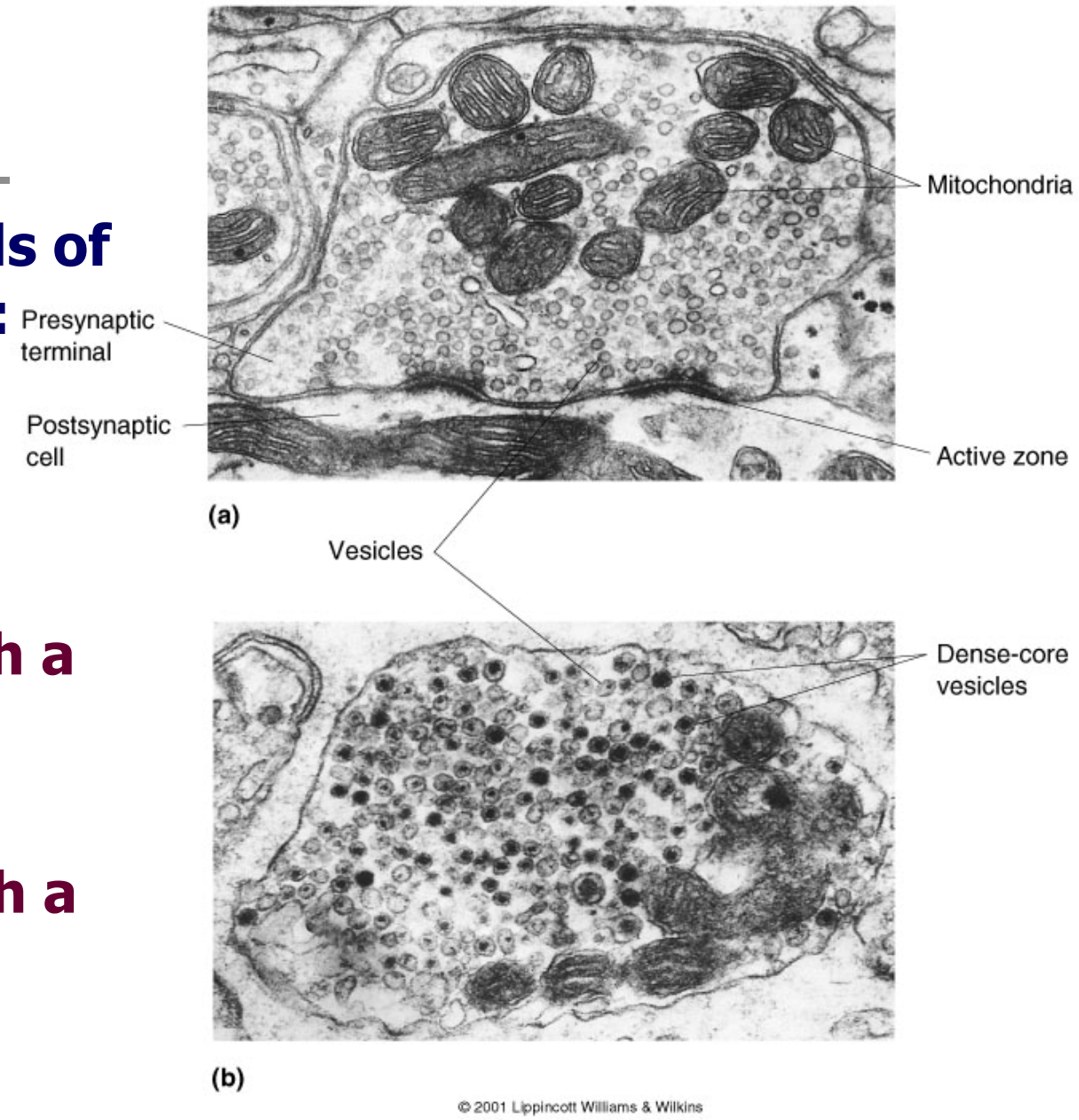
Synaptic Structure

Vesicles

There are three kinds of synaptic vesicles:

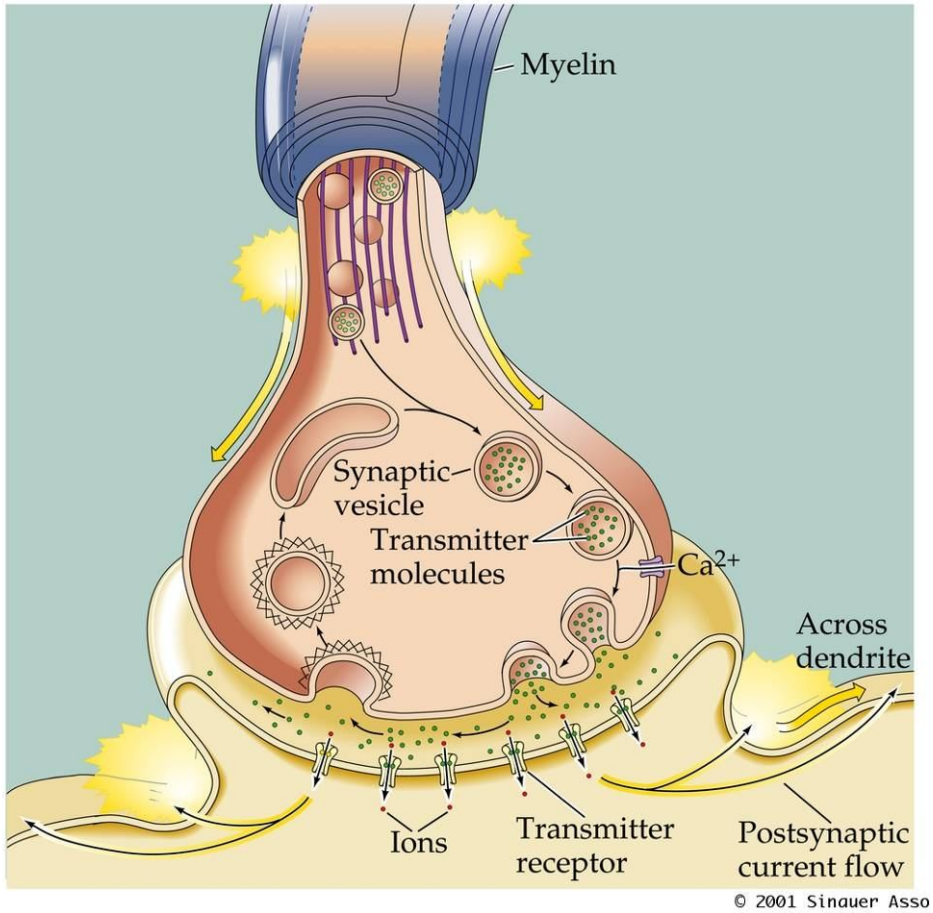
1. **Small clear: Ach, glycine, GABA or glutamate**
2. **Small vesicle with a dense core: catecholamines**
3. **Large vesicle with a dense core: neuropeptide**

Figure 5.3
Chemical synapses, as seen with the electron microscope. (a) Fast excitatory synapse in the CNS. (Source: Adapted from Heuser and Reese, 1977, p. 262.) (b) A synapse in the PNS, with numerous dense-core vesicles. (Source: Adapted from Heuser and Reese, 1977, p. 278.)



Process of chemical synapse transmission

electric-chemical-electric process



Vesicles bud off the early endosome and fill with NT

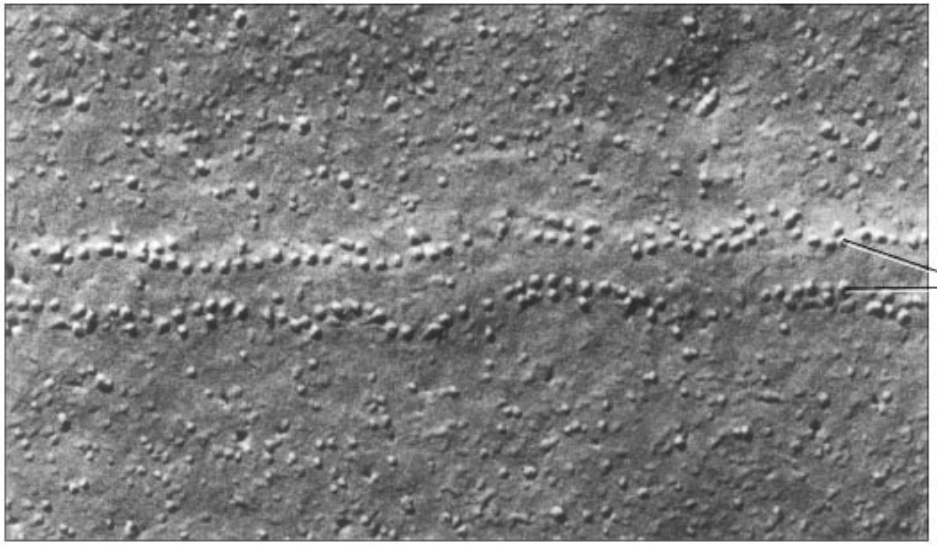
→ move to the plasma membrane

→ docking & become primed

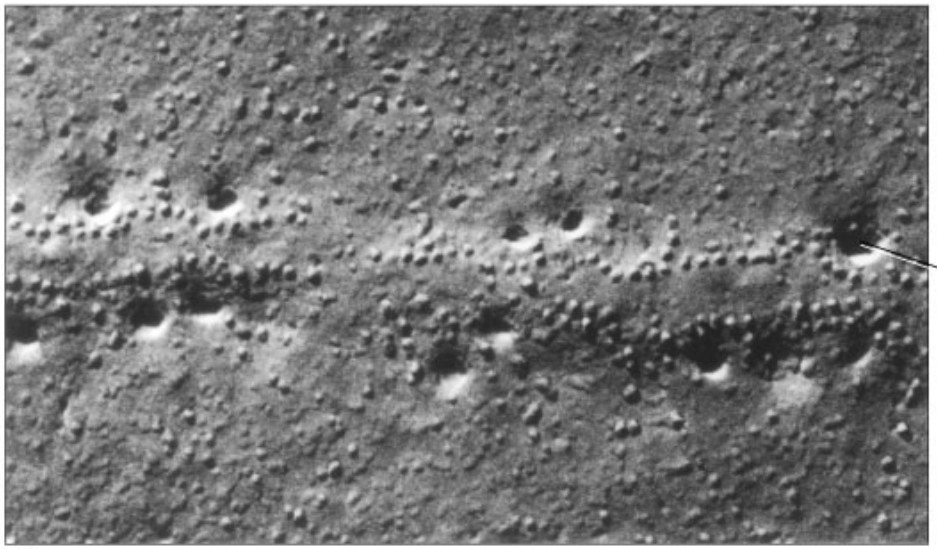
→ AP arrives at the ending

→ Ca^{2+} influx triggers fusion and exocytosis

Figure 5.11
A "receptor's eye" view of neurotransmitter release. (a) Extracellular surface of the active zone at the frog neuromuscular junction. The particles are believed to be calcium channels. (b) The presynaptic terminal has been stimulated to release neurotransmitter. The exocytotic fusion pores are where synaptic vesicles have fused with the presynaptic membrane and released their contents. (Source: Heuser and Reese, 1973.)



(a)



(b)

Electrical events in postsynaptic neurons

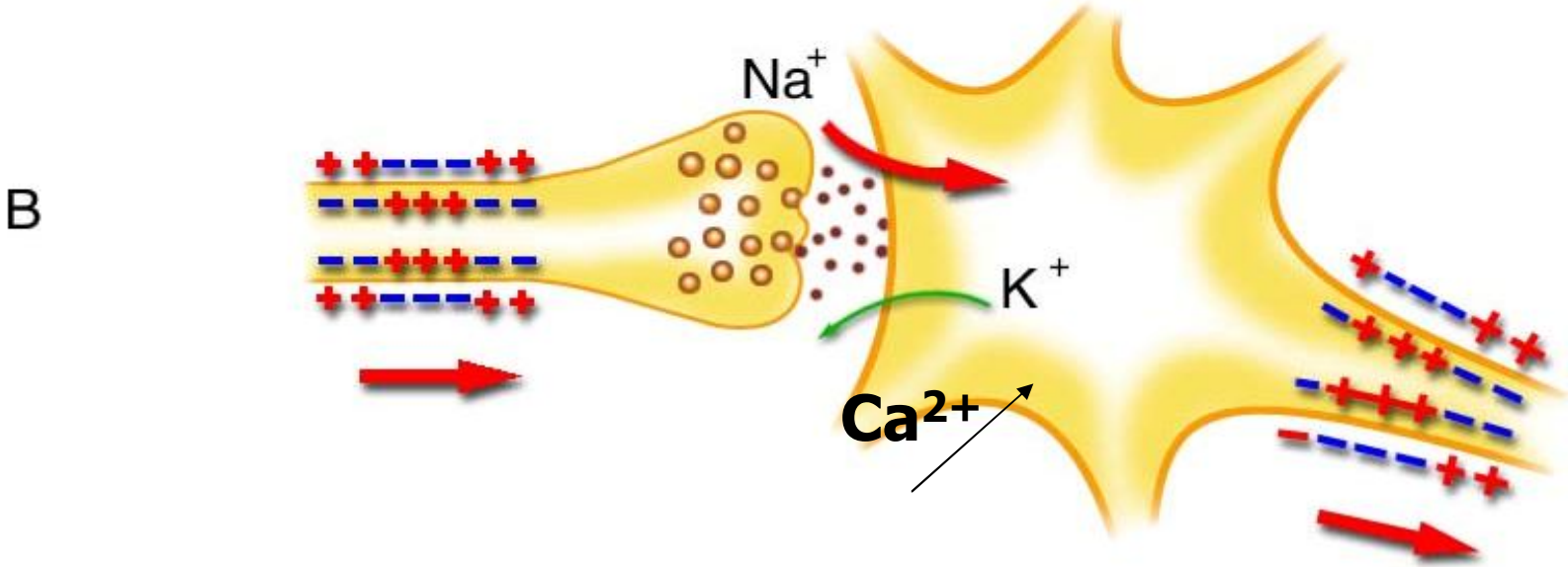
- **EPSP:**

  excitatory postsynaptic potential

- **IPSP:**

  inhibitory postsynaptic potential

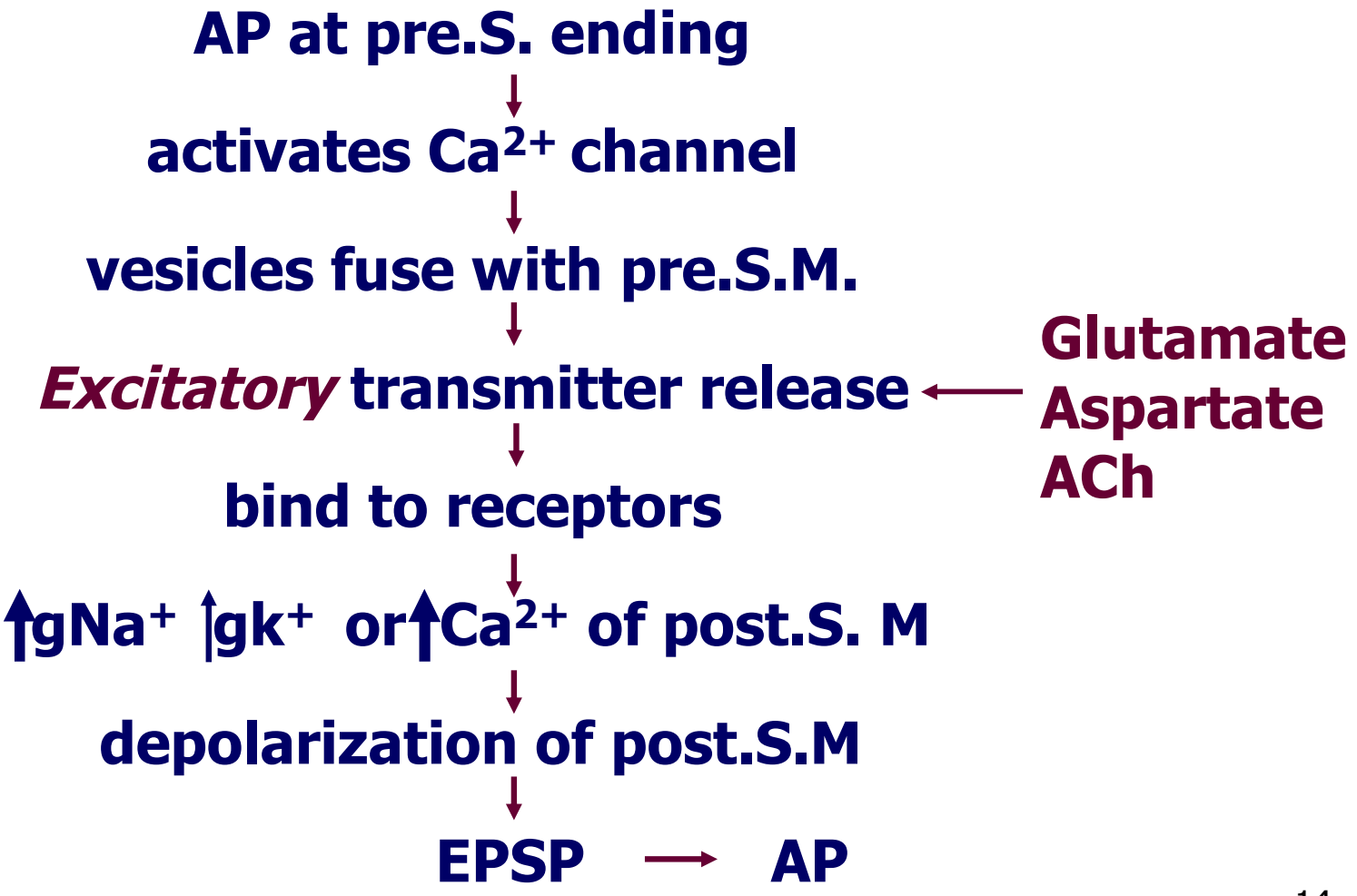
Action potential EPSP Action potential

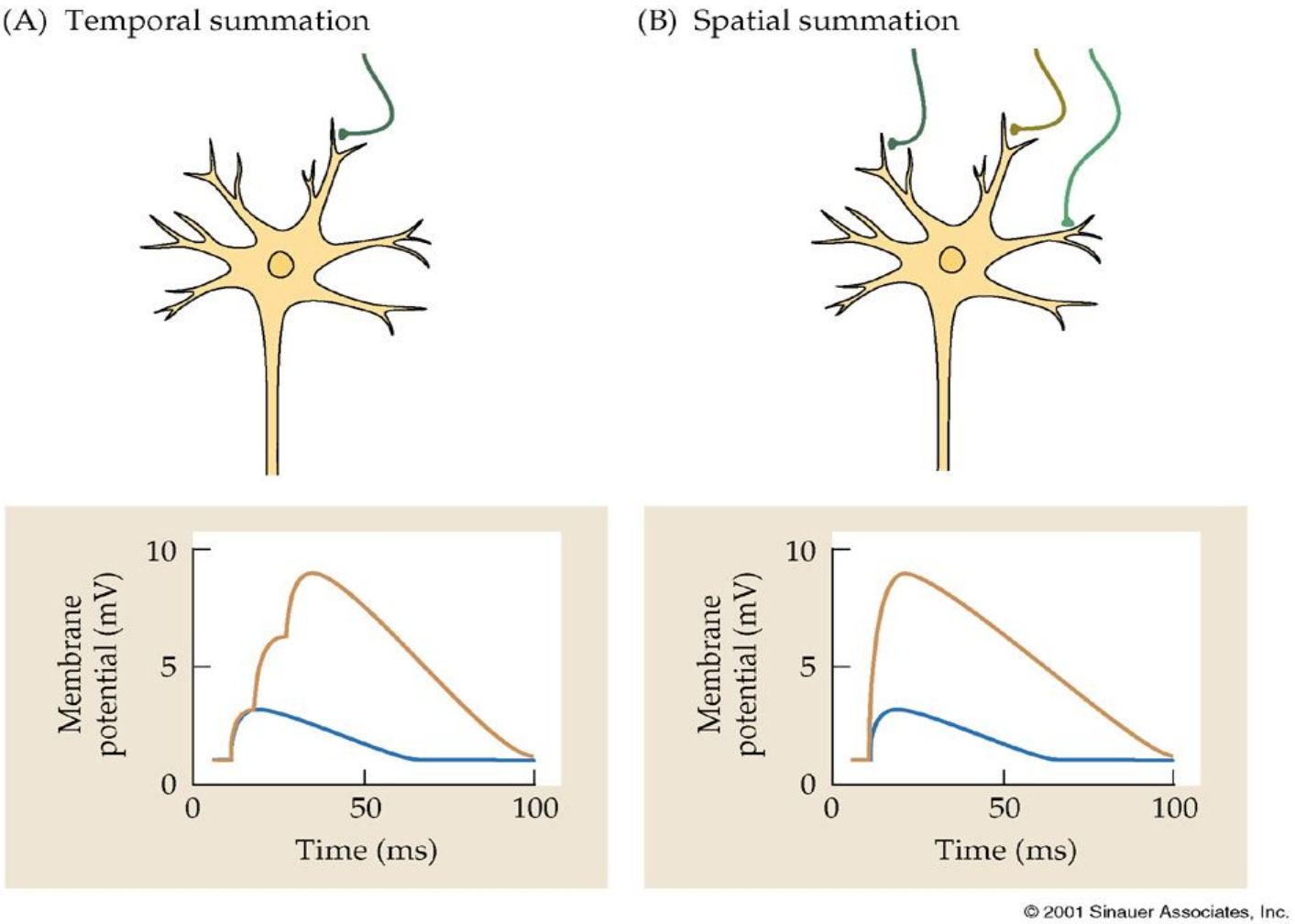


excitatory postsynaptic potential

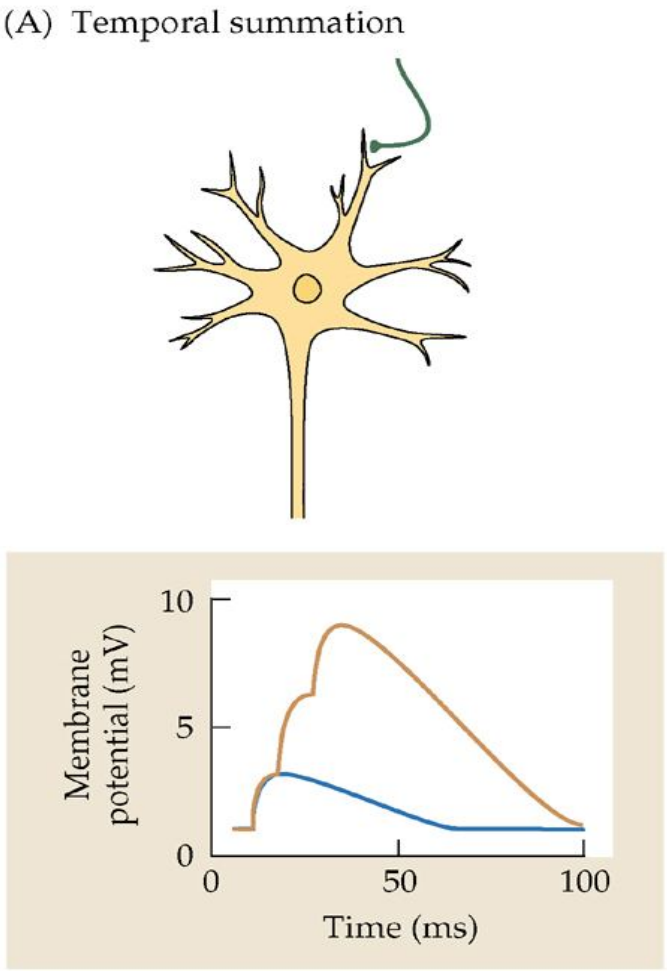
The EPSP is produced by depolarization of the postsnaptic cell membrane immediately under the presyaptic ending.

The process of excitatory postsynaptic potential (EPSP)

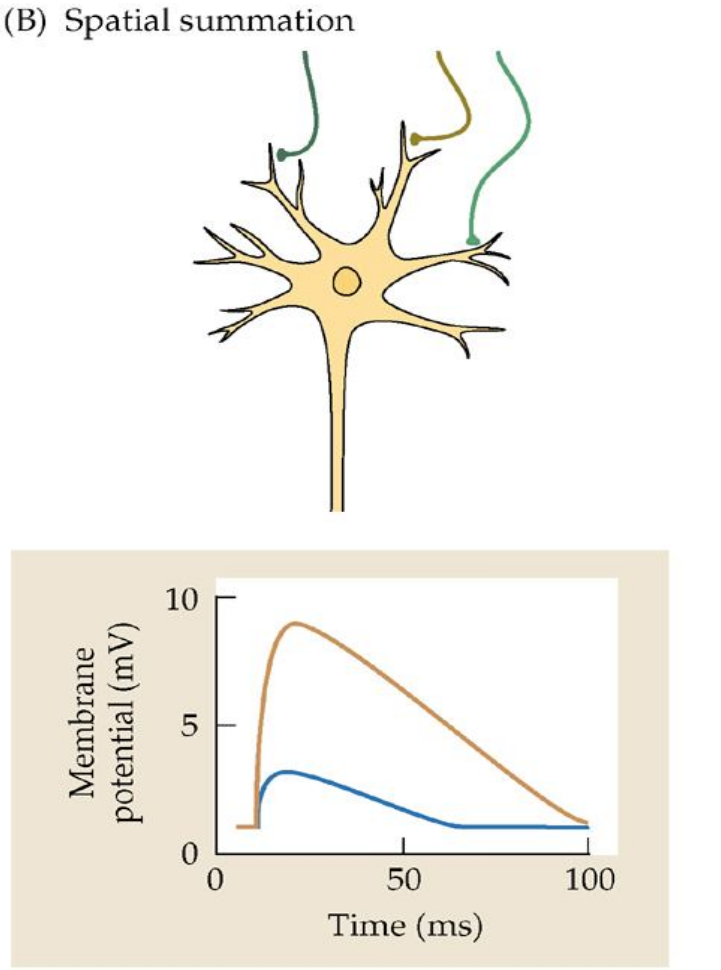




The EPSP due to activity in one synaptic knob is small, but the depolarizations produced by each of the active knobs summate. Summation may be temoral or spatial.

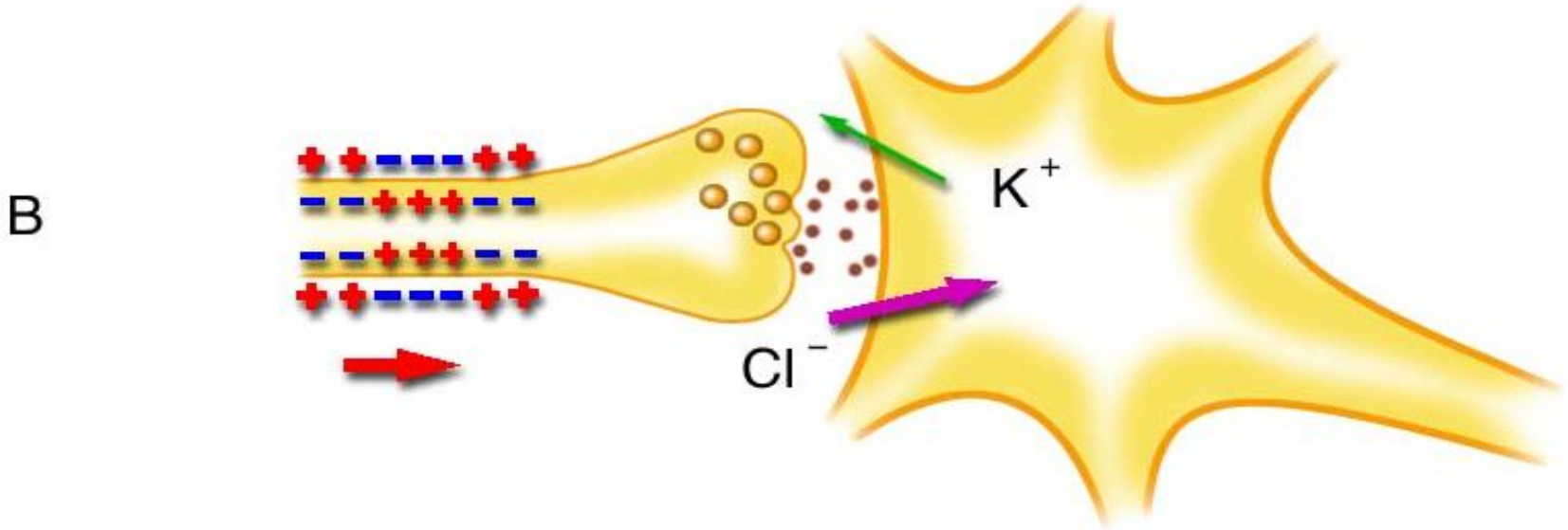


Temporal summation occurs if repeated afferent stimuli cause new EPSPs before previous EPSPs have decayed.



When activity is present in more than one synaptic knob at the same time, spatial summation occurs.

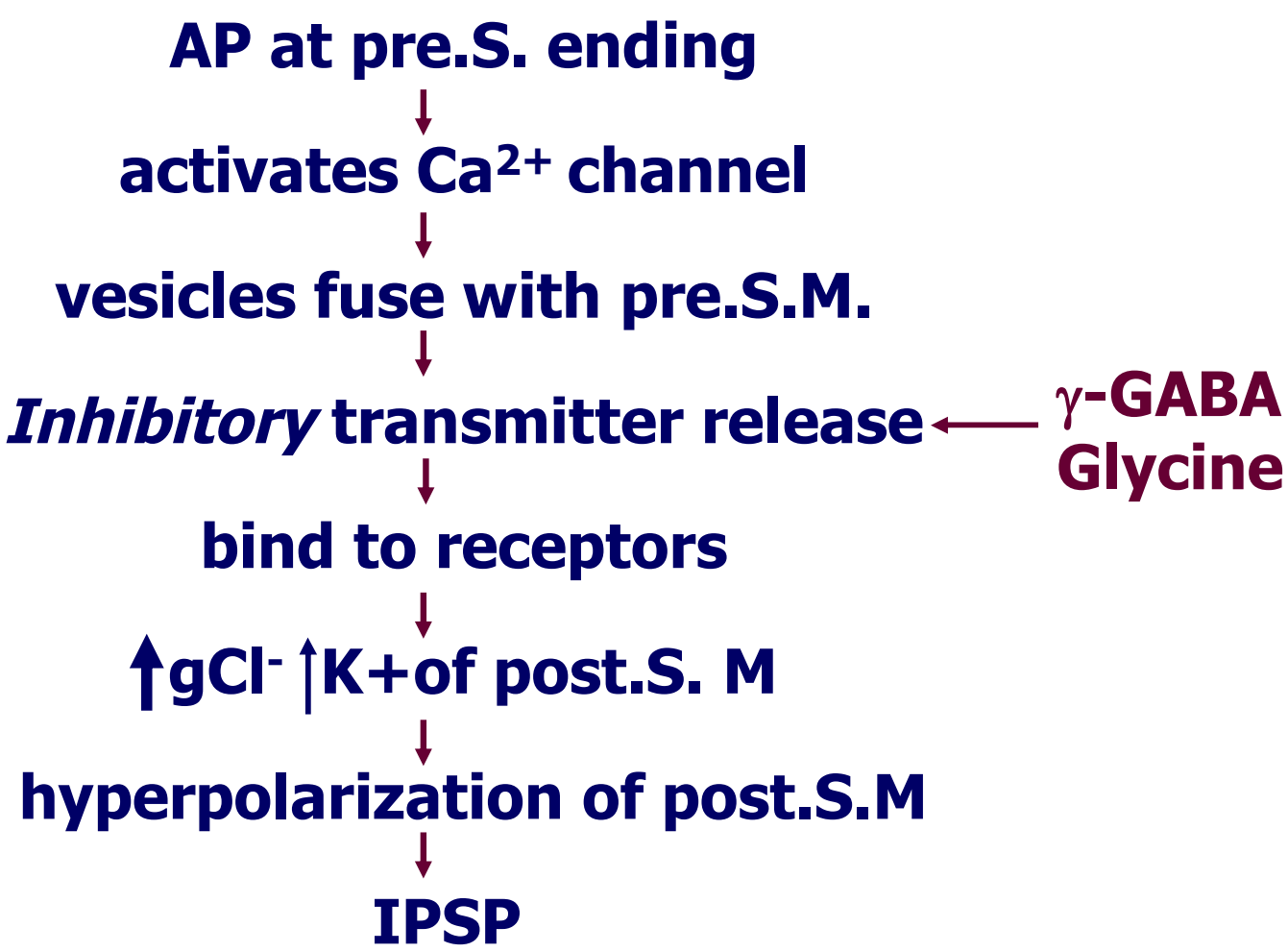
The EPSP is therefore not an all-or-none response but is proportionate in size to the strength of the afferent stimulus.

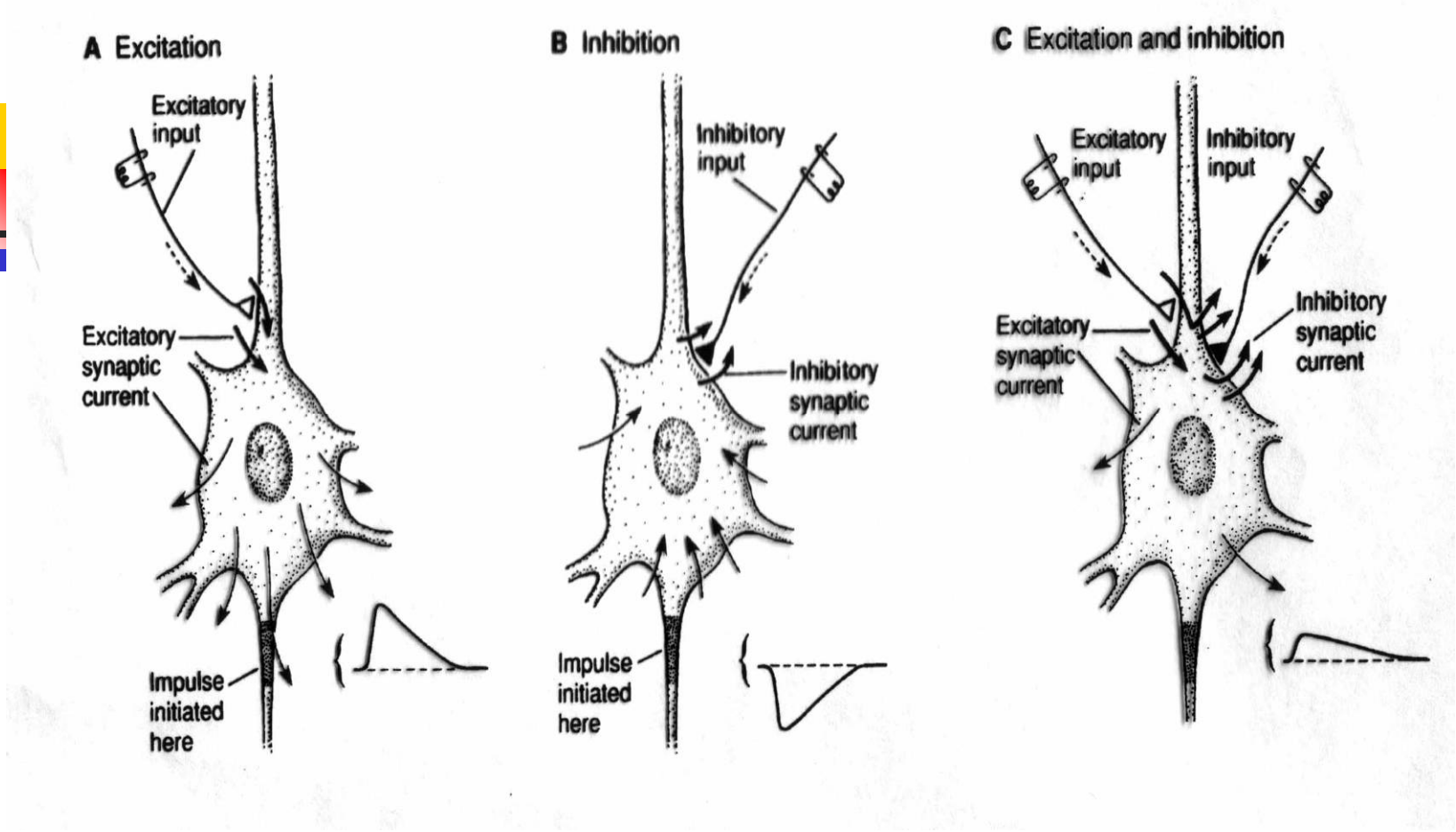


inhibitory postsynaptic potential

The EPSP is produced by hyperpolarization of the postsnaptic cell membrane immediately under the presyaptic ending.

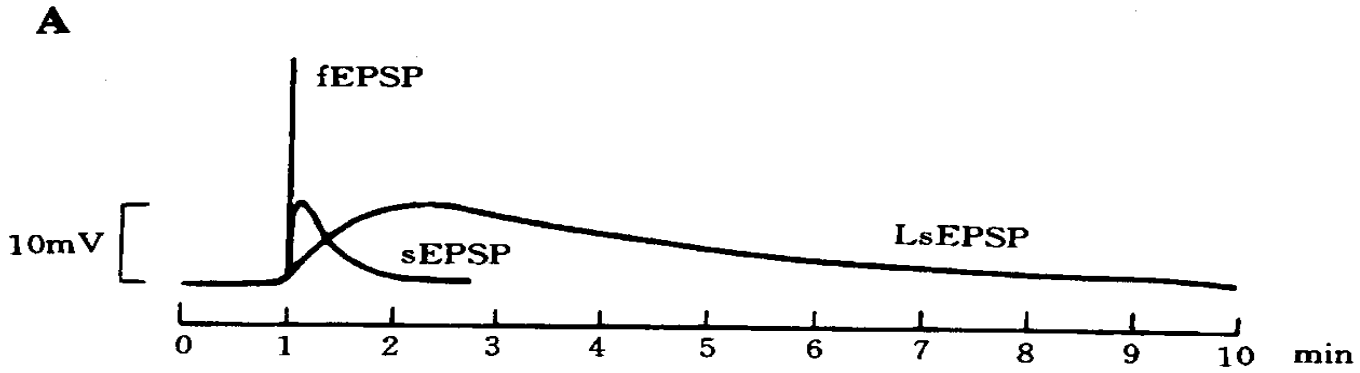
The process of inhibitory postsynaptic potential (IPSP)





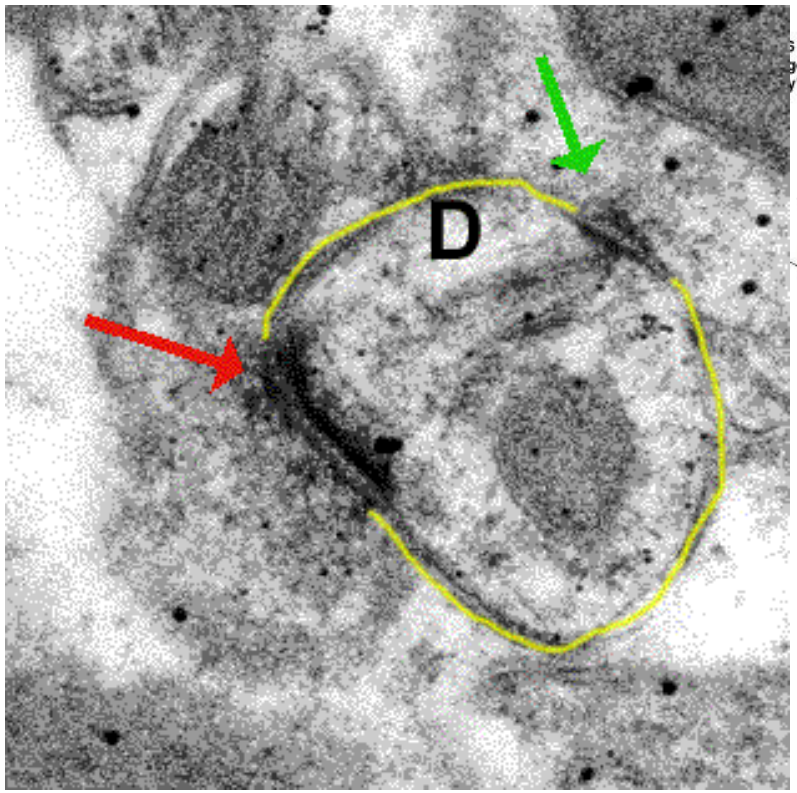
When the 10–15 mV of depolarization sufficient to reach the firing level, a propagated spike results.

Fast EPSP, Slow EPSP, late slow EPSP

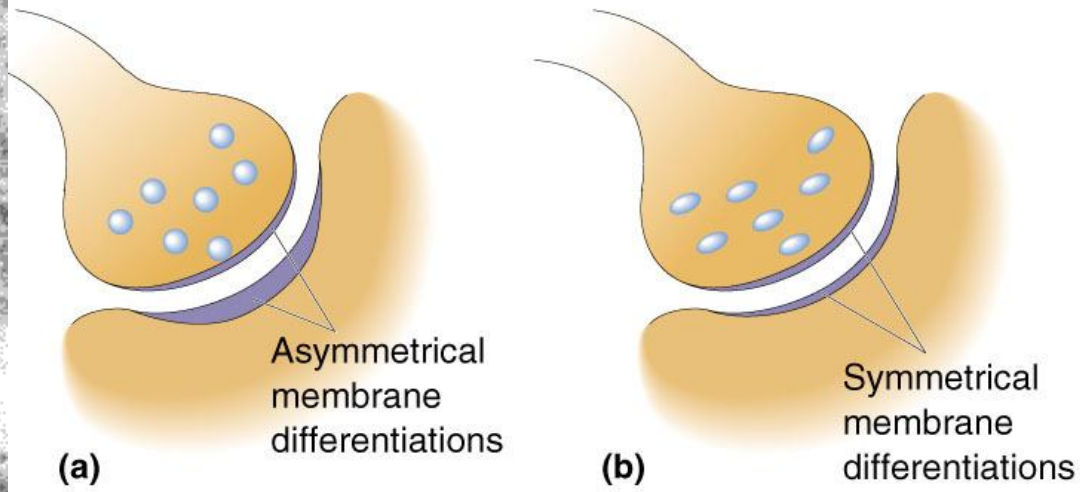


- The slow EPSP have a latency of 100–500 ms and last several seconds. The slow EPSPs are generally due to decreases in K+ conductance.
- In sympathetic ganglia, there is also a late slow EPSP that has a latency of 1–5 s and lasts 10–30 min.

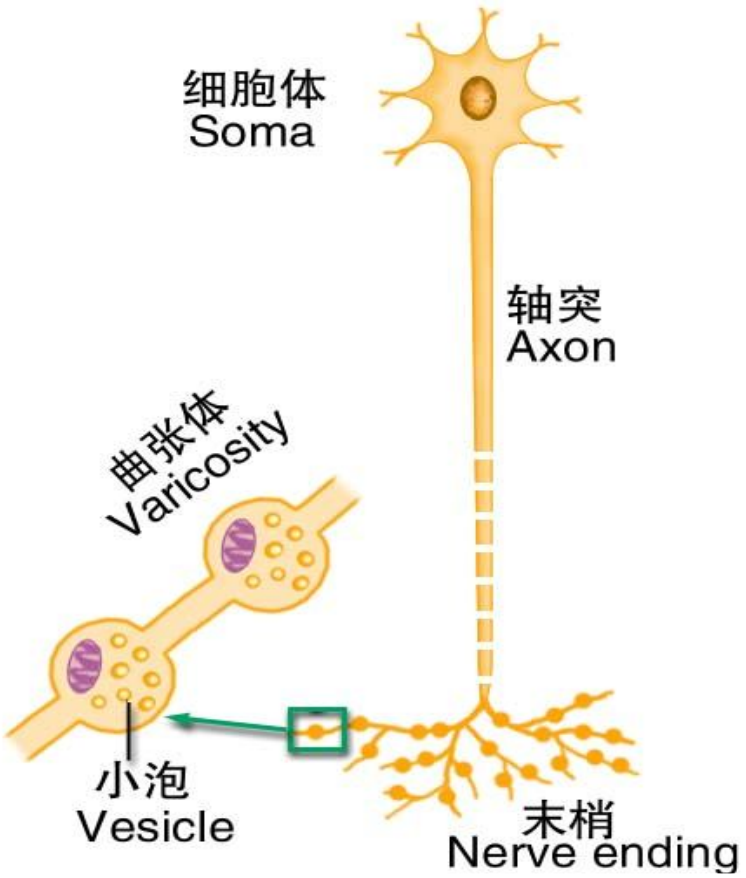
Excited or inhibited?



gories of CNS synaptic membrane differentiations. (a) A Gray's type I synapse is asymmetrical and usually excitatory.
y's type II synapse is symmetrical and usually inhibitory.



Non-direct synaptic chemical transmission



The multiple branches of these neurons are beaded with enlargements (varicosities).

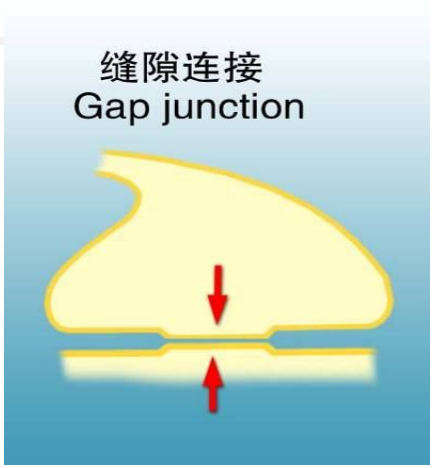
Some of these varicosities contain ACh, whereas others contain norepinephrine or DA.

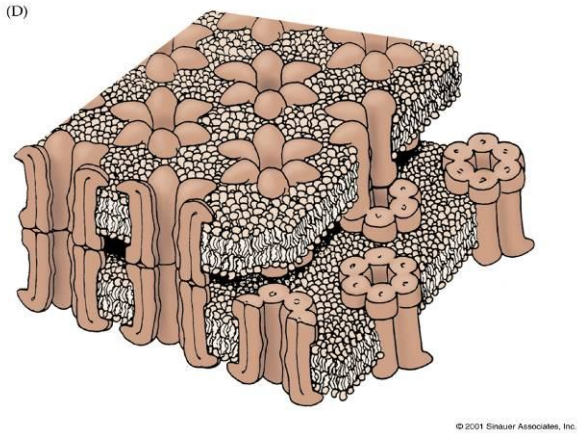
This arrangement permits one neuron to innervate many effector cells.

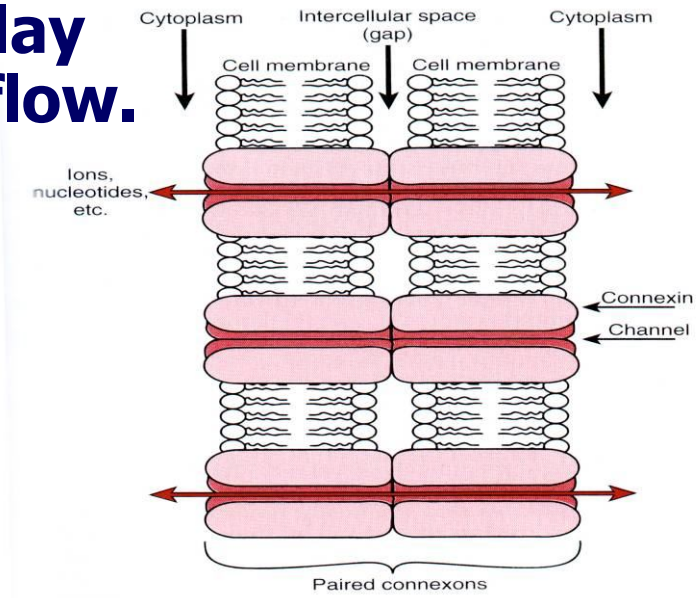
Electrical synapse transmission

- Distance between Pre- and Post, 2~4nm.
- Gap-junction :

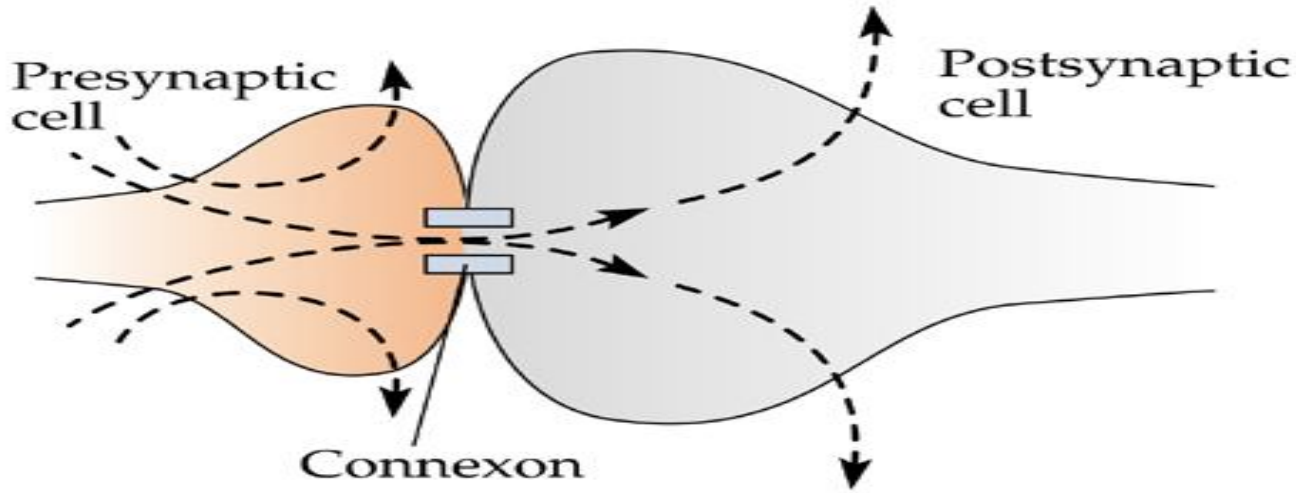
  each hemichannel or connexon is made up of 6 connexin.
- Low–resistance, little synaptic delay (<0.1ms) , bidirectional current flow.



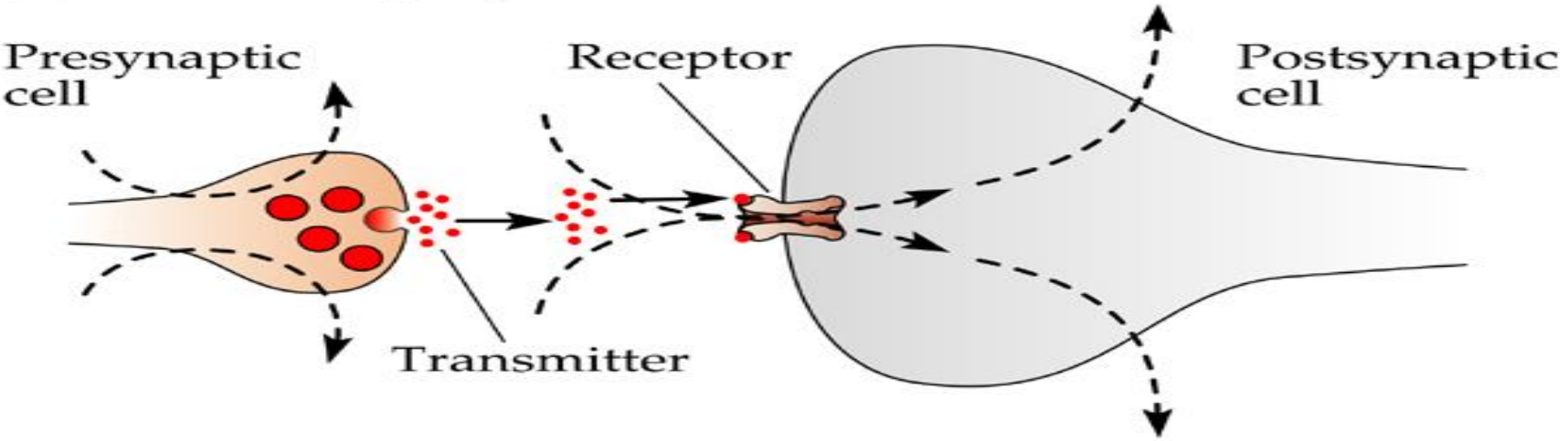




(A) **Electrical synapse**



(B) **Chemical synapse**



Summary

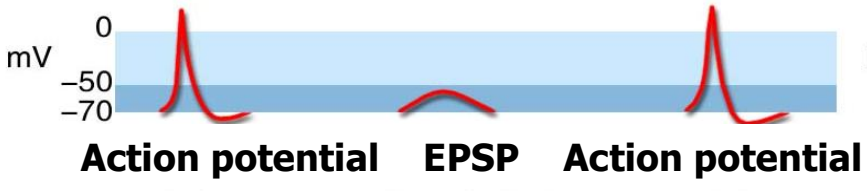
- **Definition of synapse:**
  Synapse is a specialized junction at which a nerve cell communicates with another.

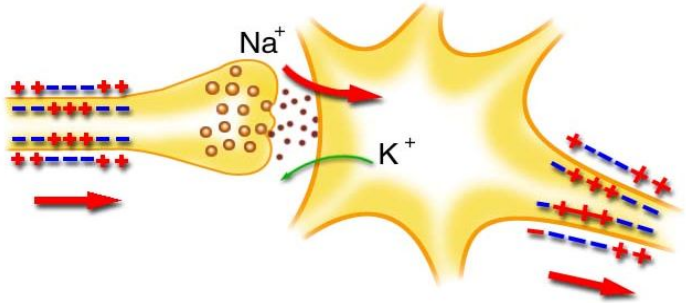
- **The structure of synapse includes**
  presynaptic membrane
  synaptic cleft
  postsynaptic membrane

Summary

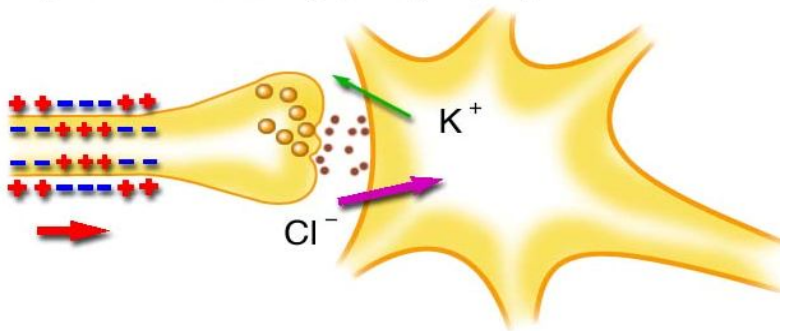
✦Types of postsynaptic potential：

EPSP





IPSP

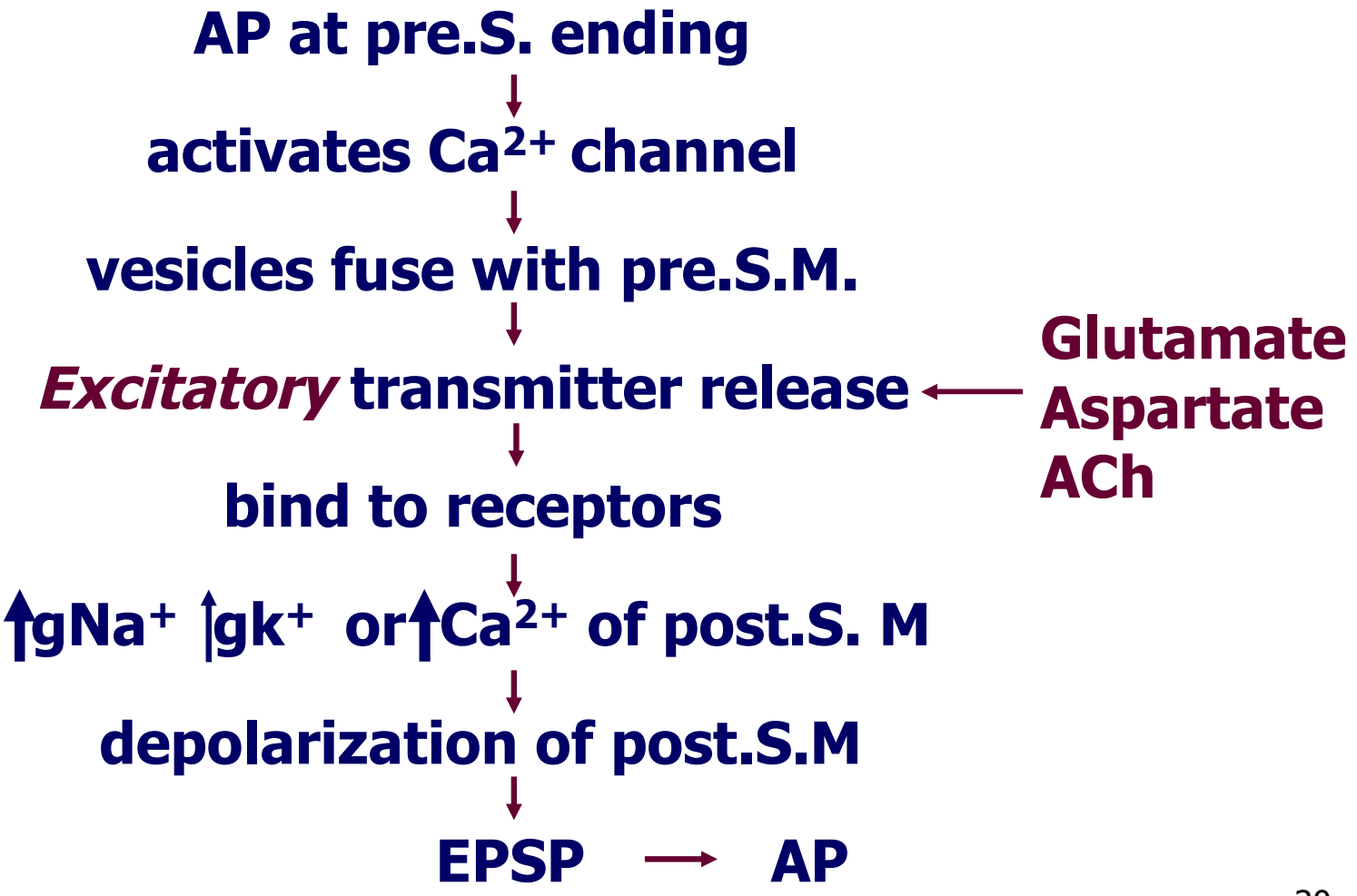


Summary

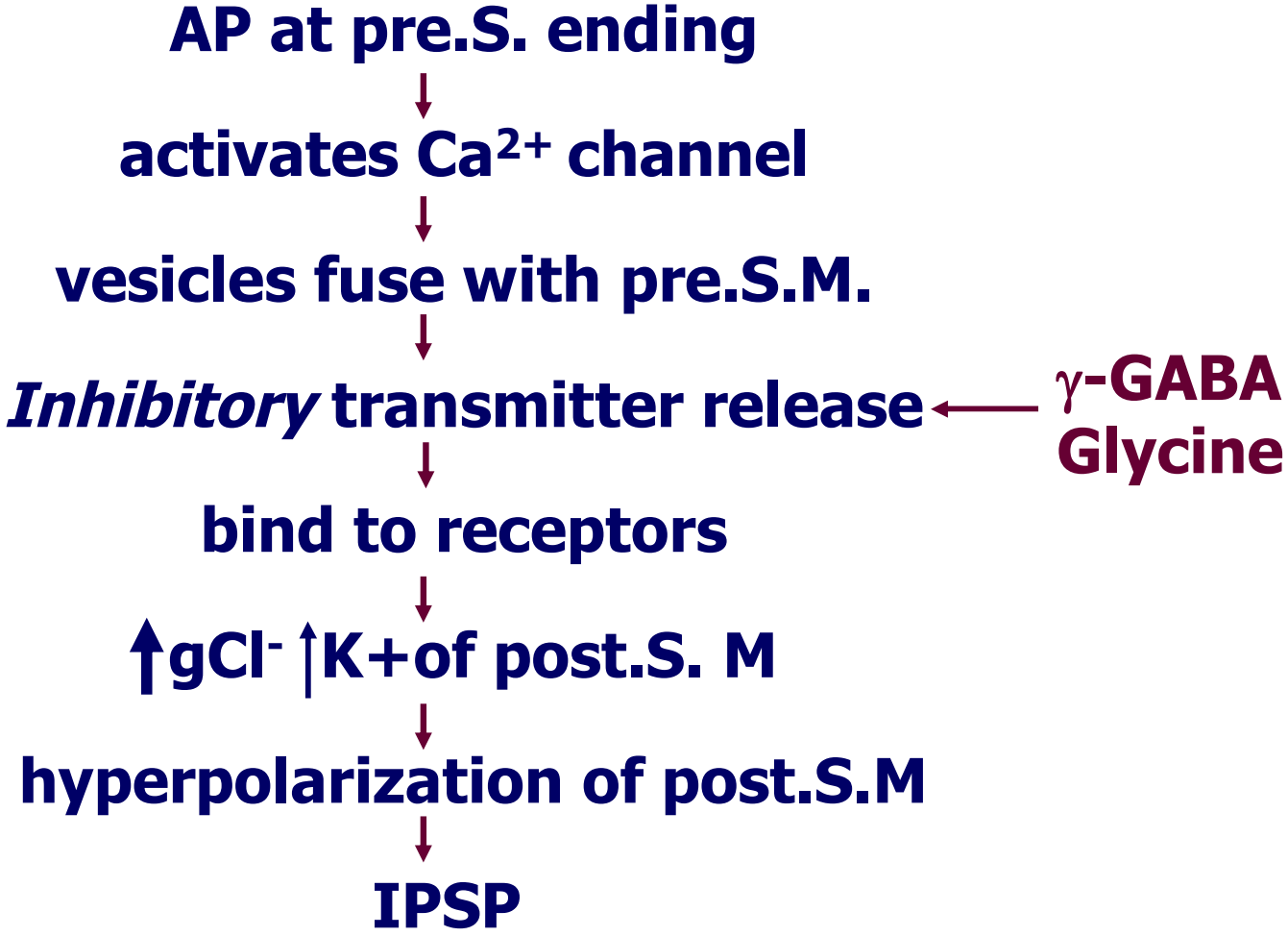
- **Definition of EPSP:**
  The EPSP is produced by depolarization of the postsnaptic cell membrane immediately under the presyaptic ending.

- **Definition of IPSP:**
  The IPSP is produced by hyperpolarization of the postsnaptic cell membrane immediately under the presyaptic ending.

The process of excitatory postsynaptic potential (EPSP)

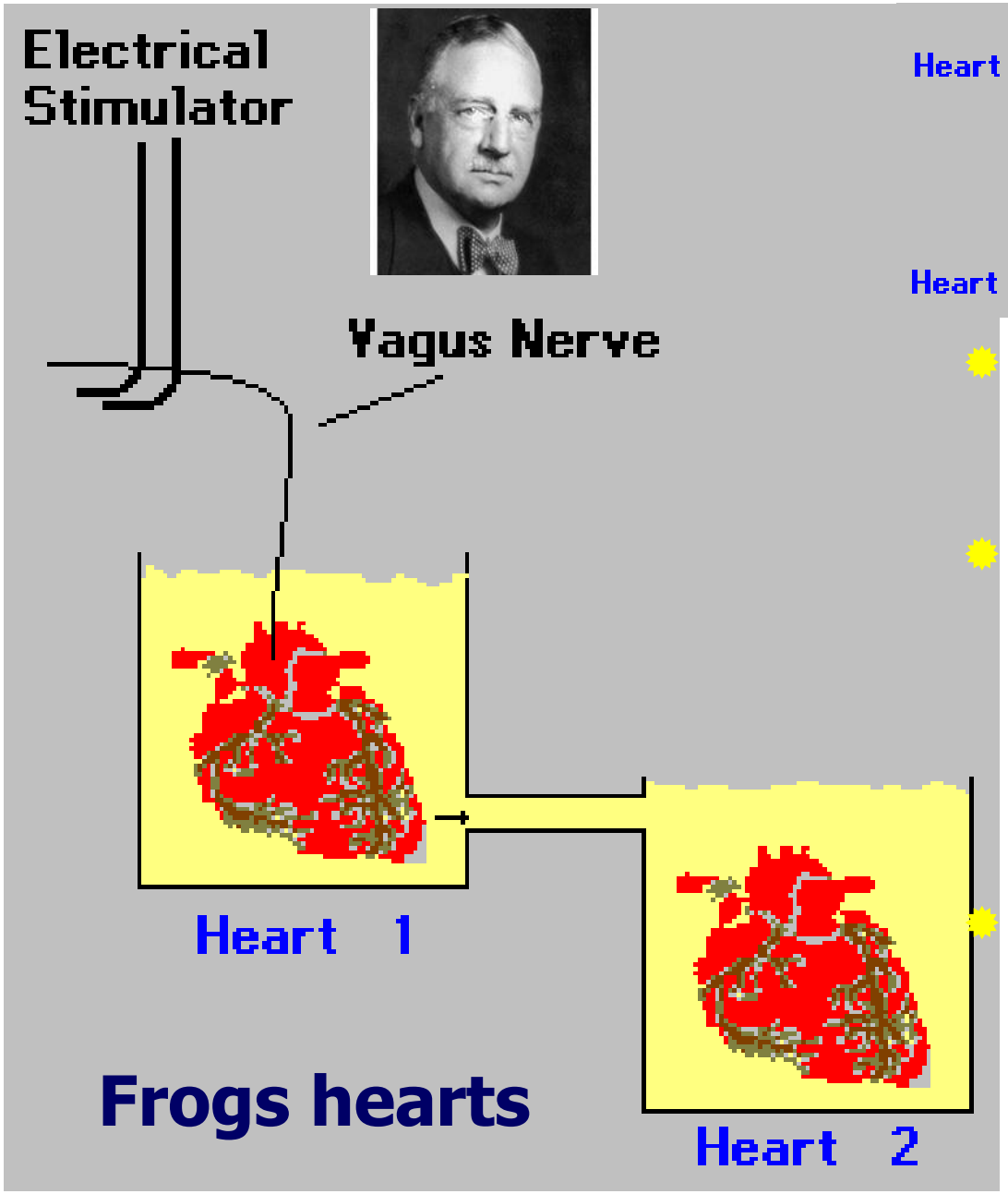


The process of inhibitory postsynaptic potential (IPSP)



Neurotransmitter and receptor

* Awarded 1936 Nobel Prize in Physiology or Medicine



- He connected two frogs hearts by a solution
- The electrical stimulation of the first heart affected the second through the solution
- Concluded that there was a chemical released that affected the second heart

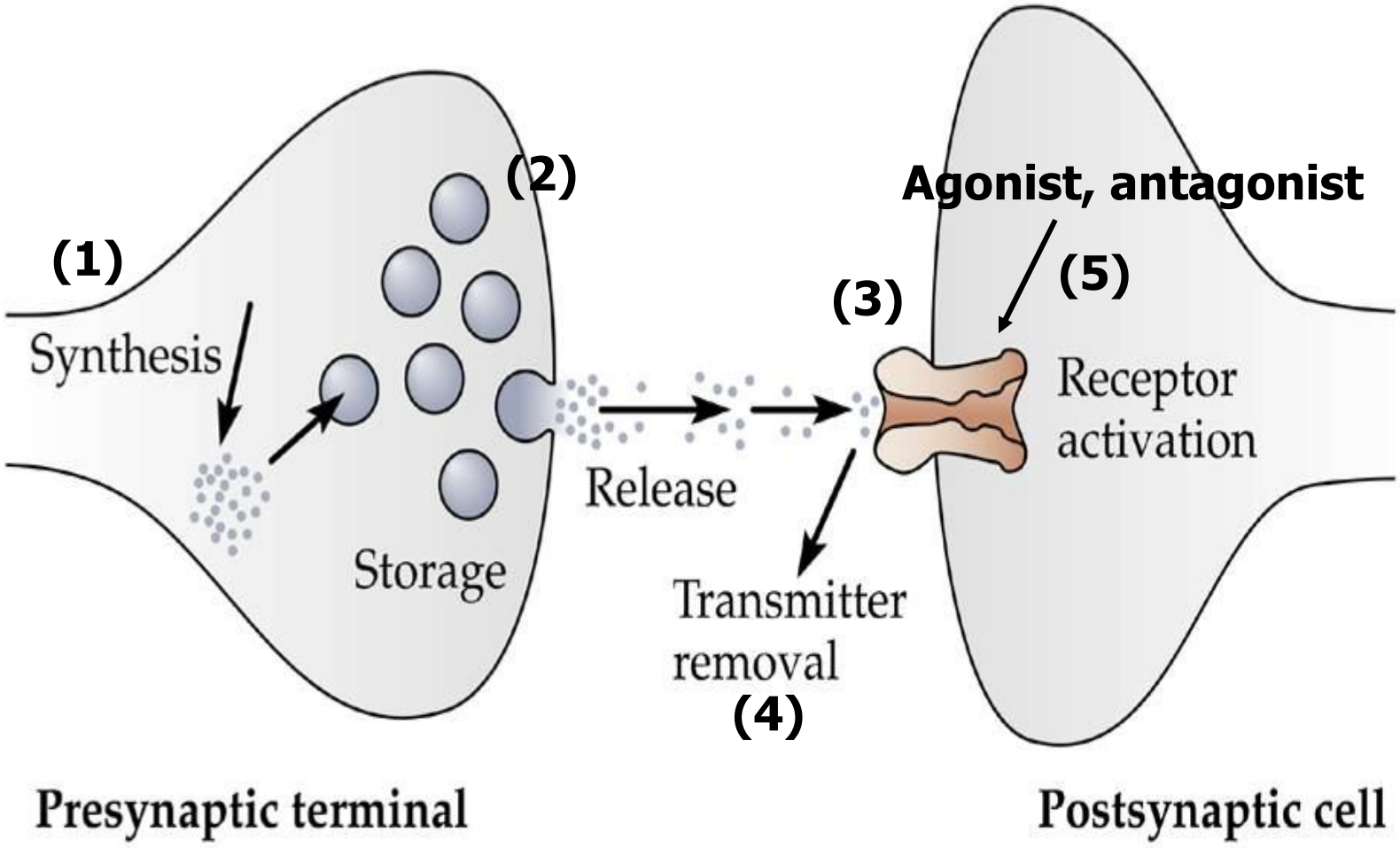
一. Neurotransmitter

(一) Definition and Identification Standard of Neurotransmitter

1. Definition :

A chemical released from a nerve ending diffuses to the postsynapic receptor where it causes postsynaptic potential.

2. Identification Standard for a classical neurotransmitter



Identification Standard

1.Synthesizing and catalyzed enzymes.

2. After synthesis, the chemical can be stored in synaptic vesicle. When the nerve impulse arrive at the axon terminal, the chemical can be released into the synaptic cleft.

3. The released neurotransmitters can act on the postsynaptic receptor and exert it's biological effect.

4. The chemical can be removed from synaptic cleft by diffusion, metabolism or reuptake into the presynaptic neuron.

5. There are agonist and antagonist to mimic or block the effect.

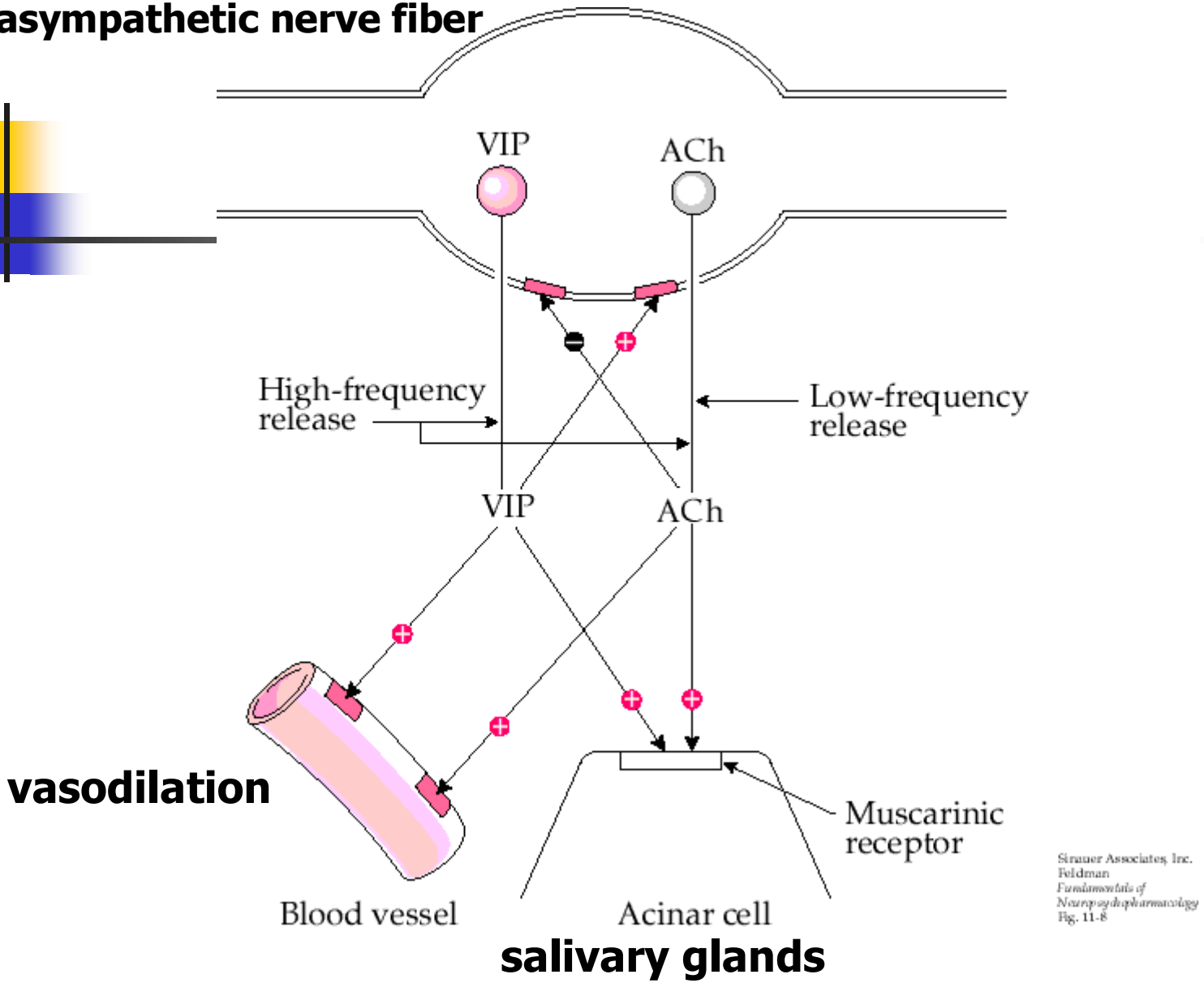
With the development of neuroscience, further research has shown that some chemicals (NO, CO) also exert their biological effect just like a neurotransmitter, even though they do not fit to the classical standard.

(二) Definition of Neuromodulator

A chemical substance that potentiates or inhibits the transmission of a nerve impulse but is not the actual means of transmission itself.

It should be emphasized that a neurotransmitter sometimes plays a role of a neuromodultor, sometimes vice versa.

Parasympathetic nerve fiber



vasodilation

salivary glands

Coexistence of acetylcholine and vasoactive intestinal peptide

(三) Neurotransmitter coexistence

- **Dale' principle (Eccles, 1954)**

A neuron contains only one neuro-transmitter and releases only one neuro-transmitter at all of their synapses.

- **Neurotransmitter coexistence**

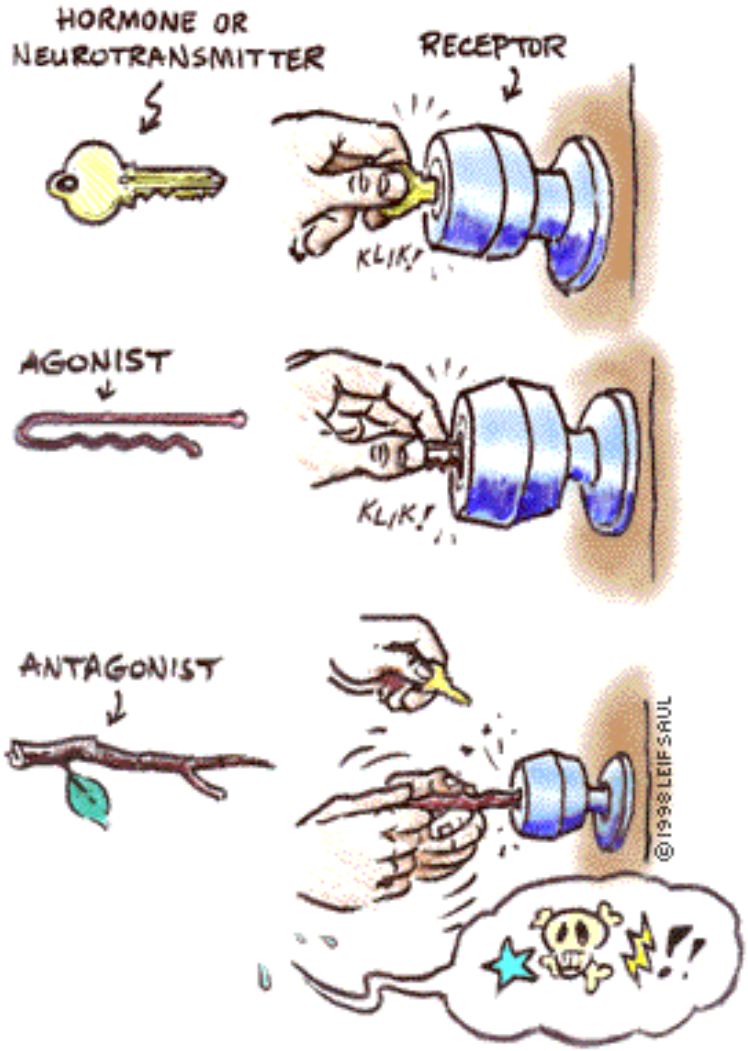
二. Receptor

1. Definition

A structure on the surface of a cell (or inside a cell) that selectively receives and binds a specific substance.

Agonists and Antagonists

- **Agonists**
  - **Structurally similar to neurotransmitter to activate receptor**
- **Antagonists**
  - **Antagonists block receptor**
  - **Diverse structures often unrelated to neurotransmitter**



Classification of Receptors

- **Acetycholine receptor**
  (muscarinic receptor, nicotinic receptor)
- **Adrenergic receptors**
  (α receptor and β receptor)
- **Amino acids neurotransmitter receptor**
  (Glu receptor, GABA receptor, Gly receptor)

Classification of Receptors

- **G-protein-coupled receptors**

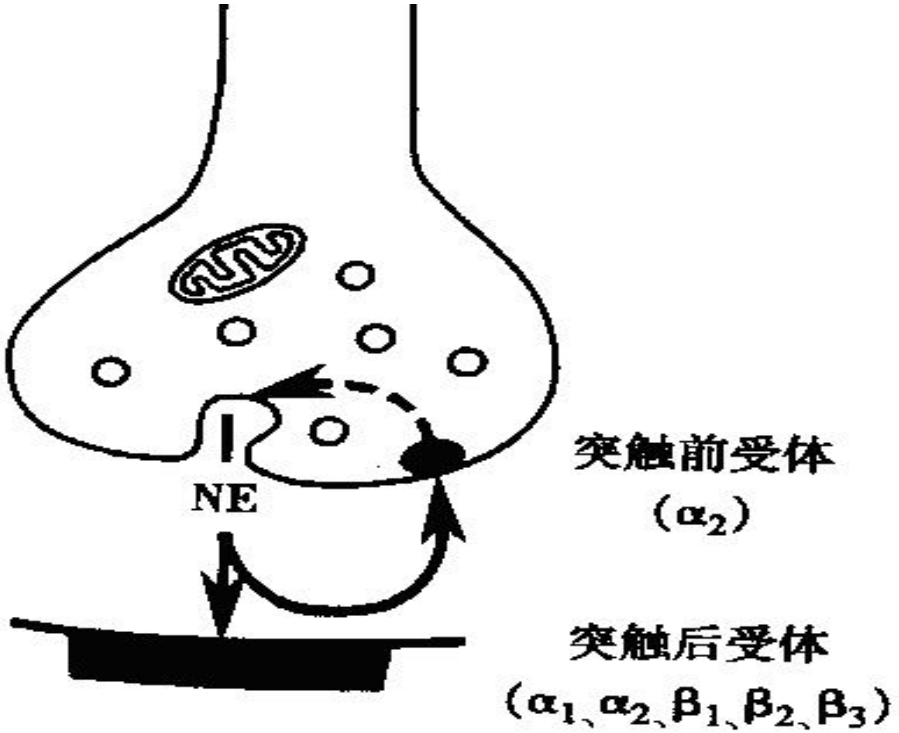
  M-ACh R, Adrenergic R, R of Peptide, $GABA_B$ R, DA R, 5-HT(except 5-HT3) R mGLU R

- **Ion-channel-coupled receptors**

  N-ACh R, $GABA_A$ R, Gly R, NMDA, $5\text{-}HT_3$

Classification of Receptors

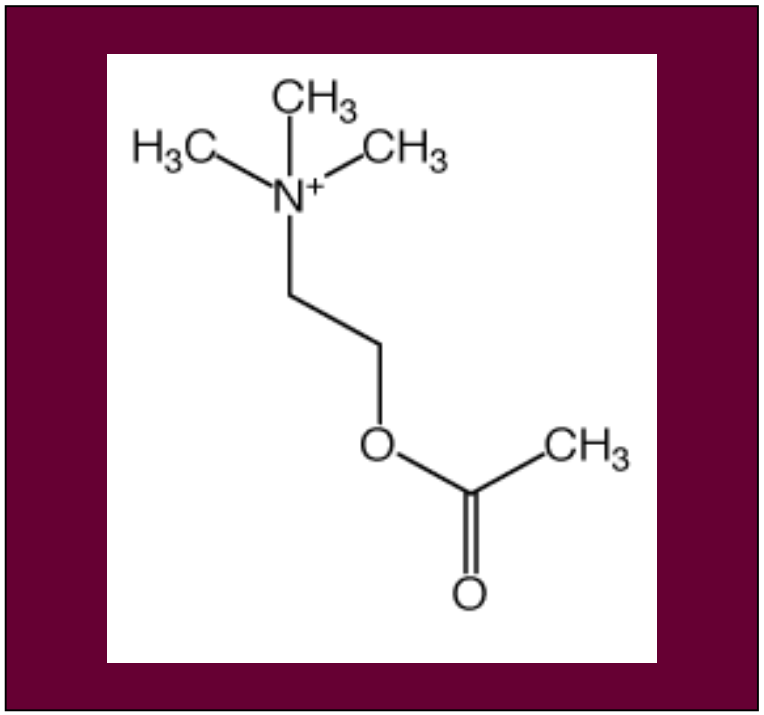
Presynaptic receptor/Autoreceptor
Postsynaptic receptor



三. Principal Neurotransmitters Systems

- Acetylcholine (Ach)
- Monoamine neurotransmitter
  (NE, E, DA, 5-HT, histamine)
- Amino acids neurotransmitter
  (Glu, GABA, Gly)
- Peptides neurotransmitter
  (tachykinin, opioid peptide, HRP et al.)
- Purines Neurotransmitter
- Gas (NO and CO)

(—) Acetylcholine



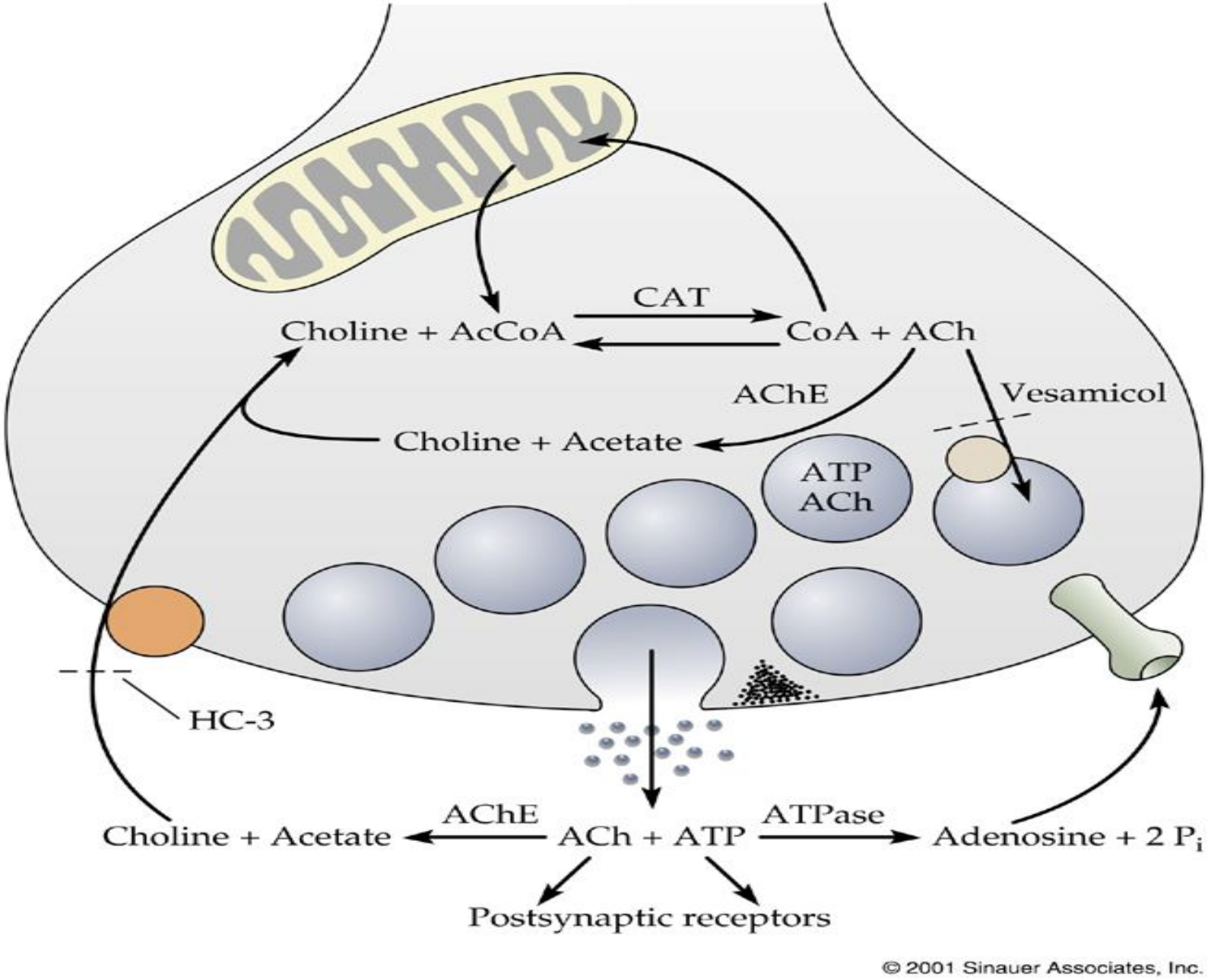
Acetylcholine, ACh

Acetyl ester of choline

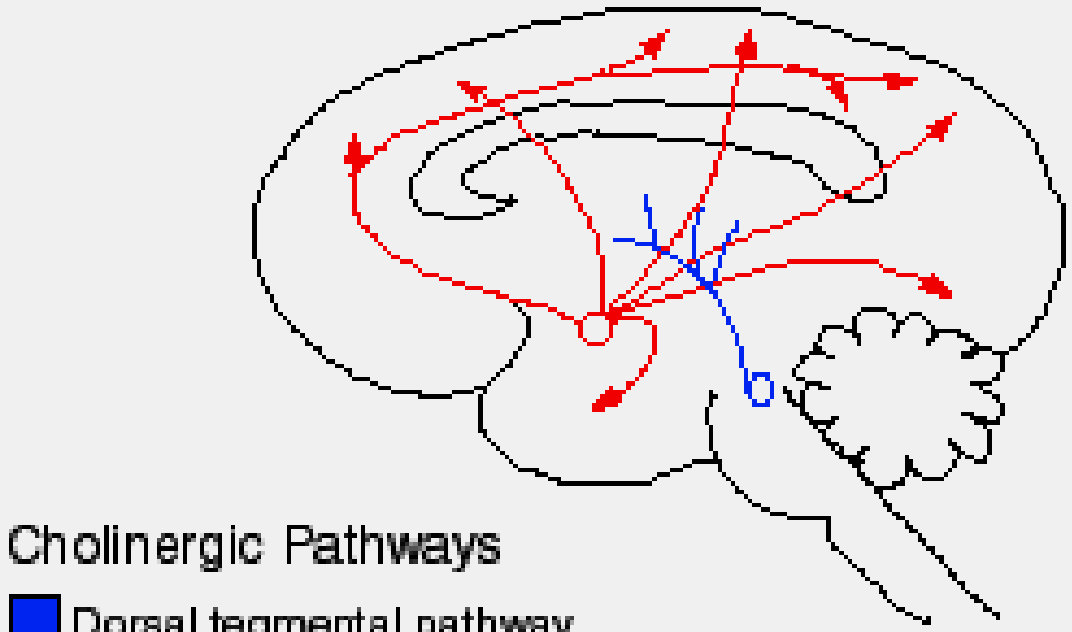
Cholinergic neuron

Cholinergic fiber

Metabolism of ACh



Cholinergic Neuron in CNS



Adapted from reference 1.

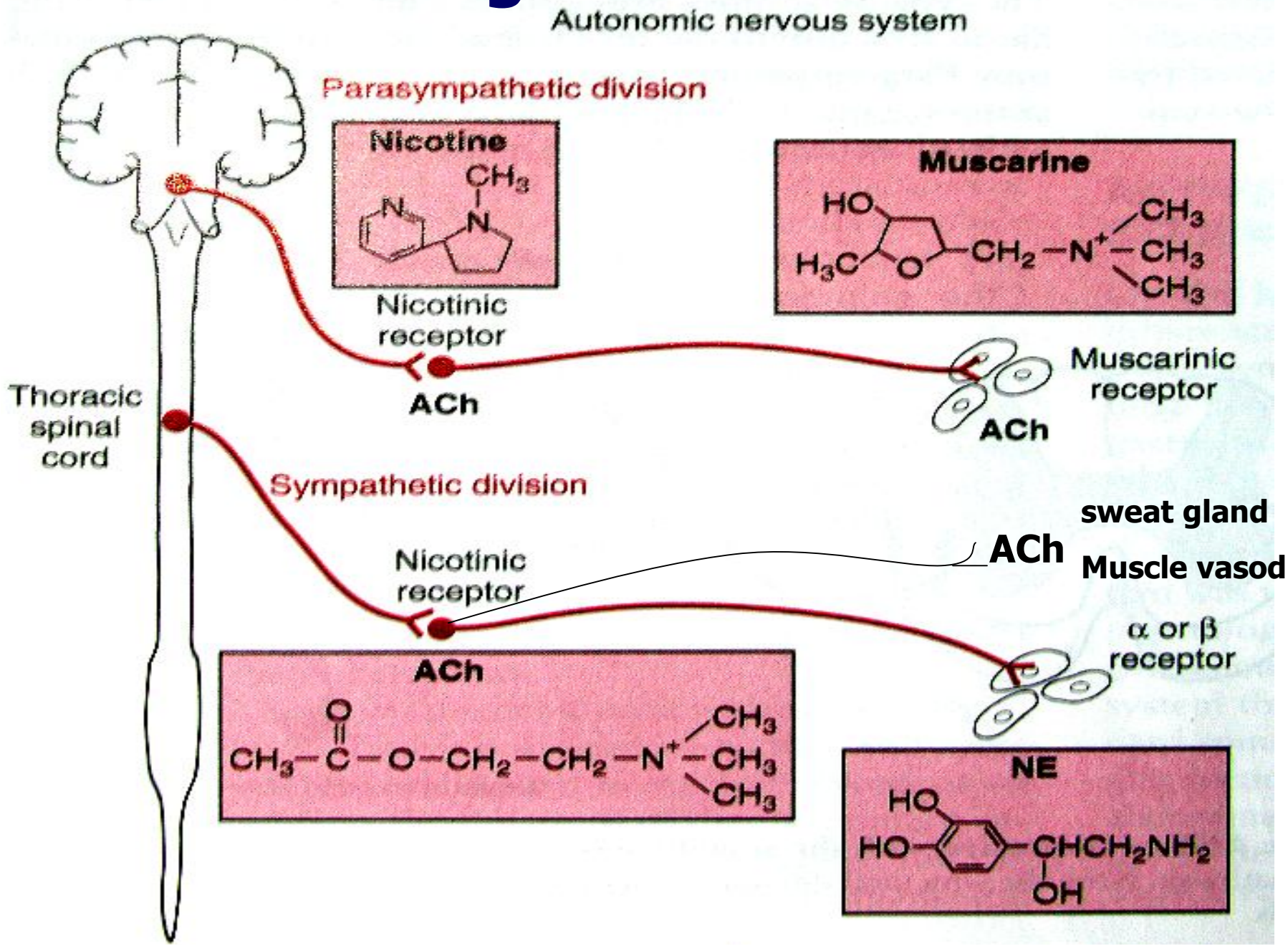
Many parts of the brain:

Spinal motor neuron

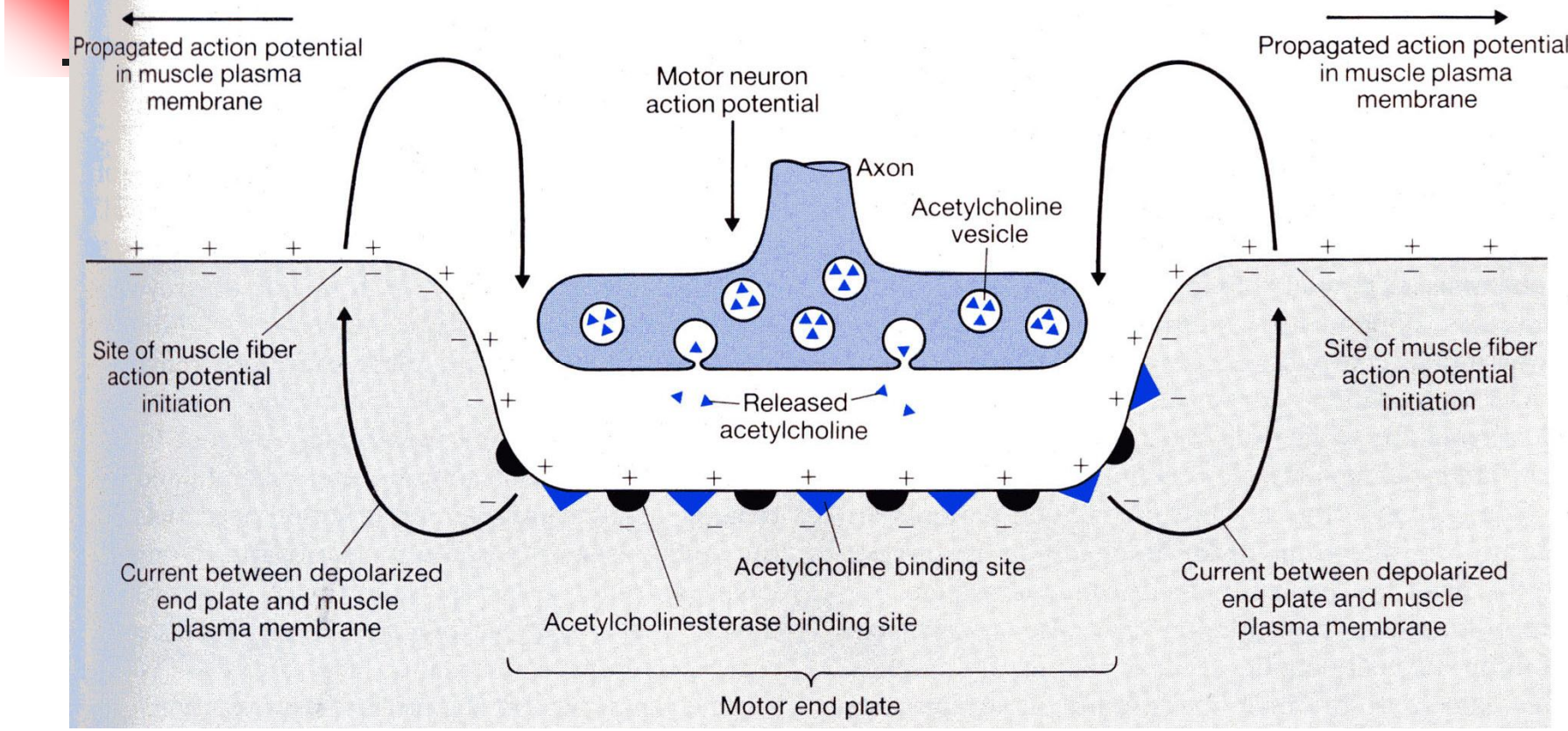
hippocampus

Striatum et al.

Cholinergic fiber in PNS



Somatic nervous system



Neuromuscular junction

Cholinergic fiber in PNS

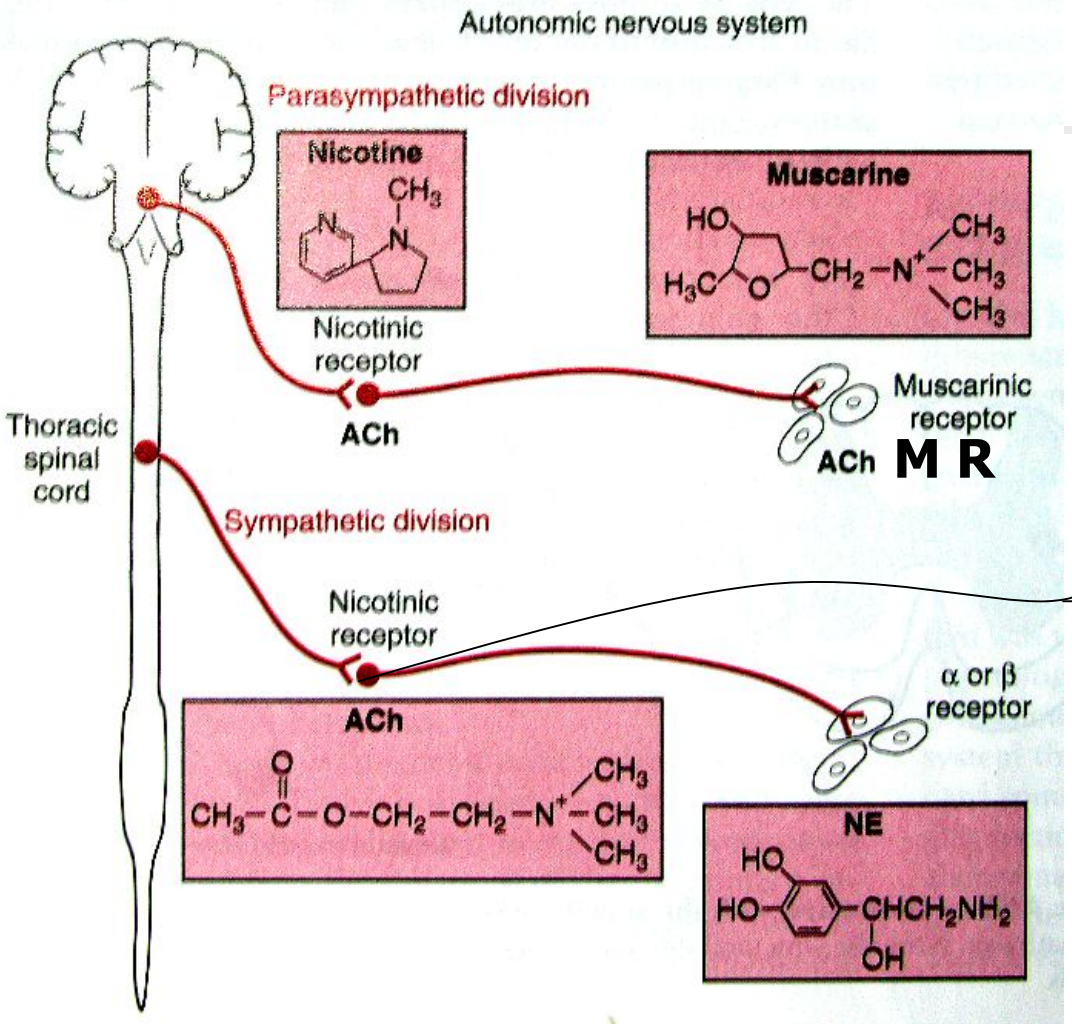
1. Preganglionic autonomic endings
2. Parasympathetic postganglionic endings
3. Sympathetic postganglionic endings that innervate sweat glands and sympathetic vasodilator endings
4. Motor nerve endings

Cholinergic Receptors

- **Muscarinic receptor（M1R~M5R）:**
  Muscarine, the alkaloid responsible for the toxicity of toadstools, mimics the stimulatory action of ACh on smooth muscle and glands.
- **Nicotinic Receptor（N1, N2）:**

  Ionotropic receptor

Distribution of Muscarinic receptors



ACh M R

sweat gland

muscle vasodilator

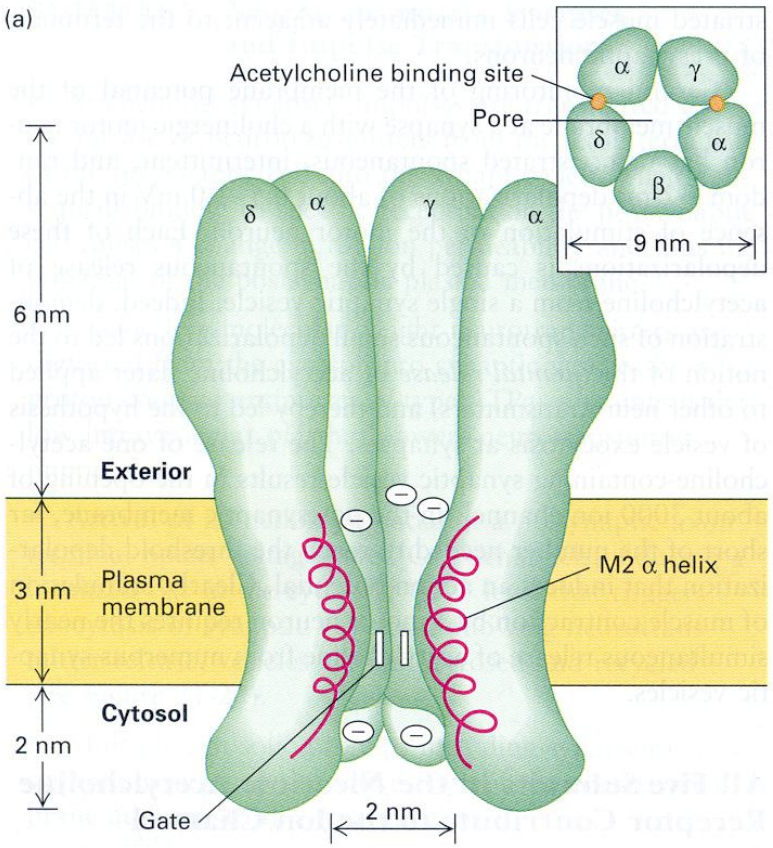
Brain: M_1 R

Cholinergic Receptors

Muscarinic receptor: metabotropic

- $M_1R \rightarrow Gq \rightarrow IP_3/DAG\uparrow$ (brain)
- $M_2R \rightarrow Gi \rightarrow cAMP\downarrow$ (heart)
- $M_3R \rightarrow Gq \rightarrow IP_3/DAG\uparrow$ (smooth muscle)
- $M_4R \rightarrow Gi \rightarrow cAMP\downarrow$ (gland, smooth muscle)
- $M_5R \rightarrow Gq \rightarrow IP_3/DAG\uparrow$

Distribution of nicotinic receptors

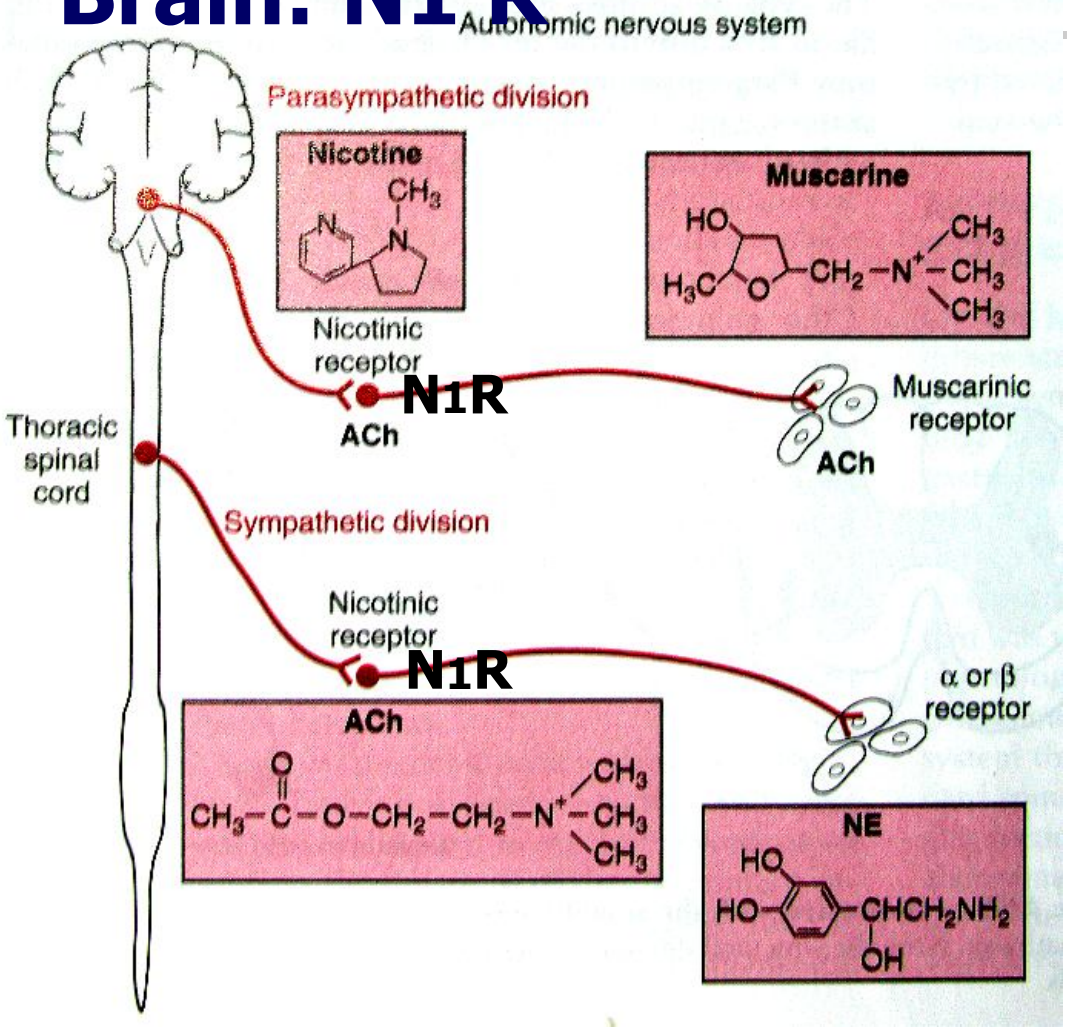


N1: neuronal-type nicotinic R

N2: muscle-type nicotinic R

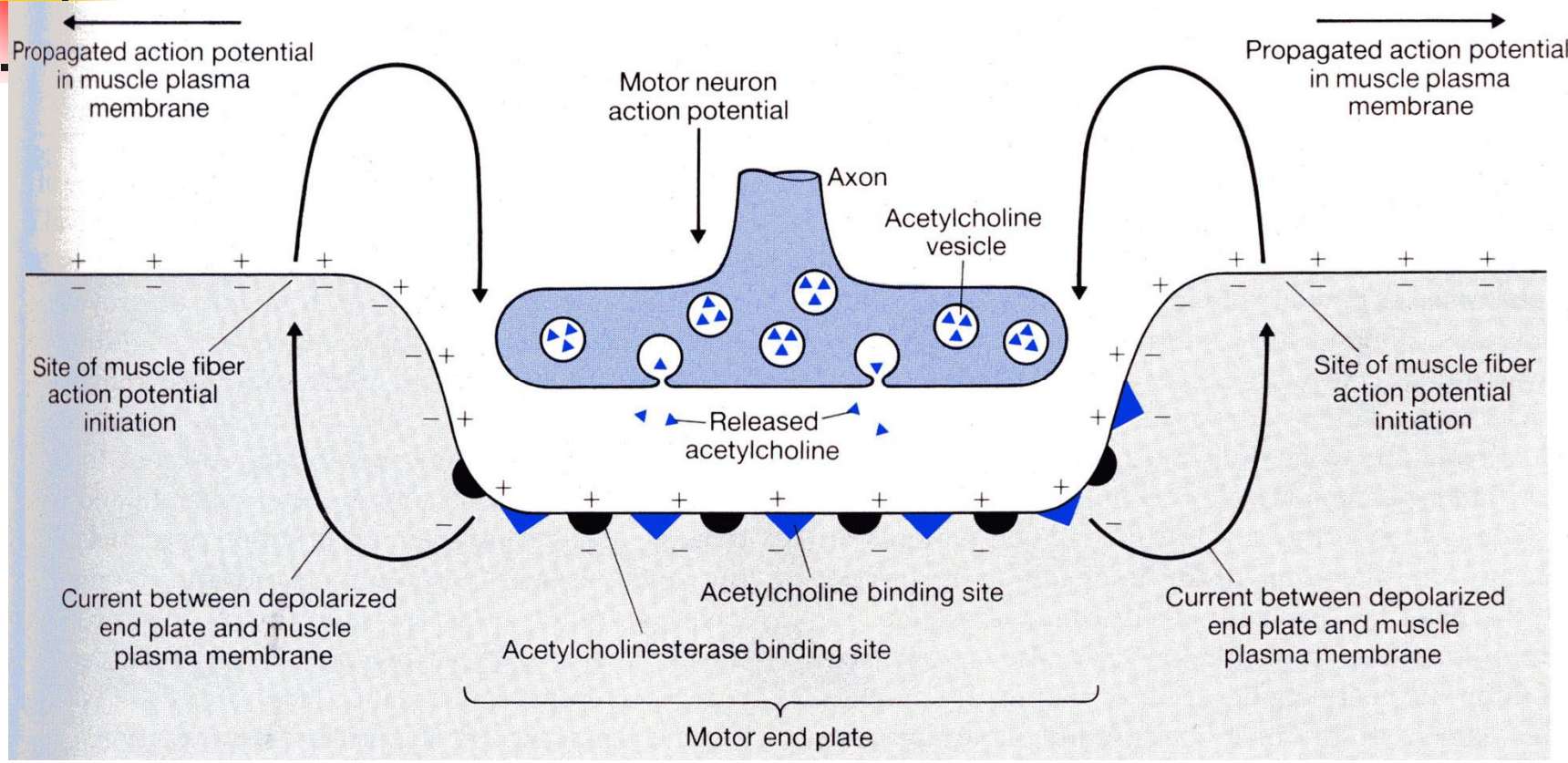
Neuronal-type nicotinic receptor, N1

Brain: N1 R



- Located at postsynaptic membrane of both sympathetic and parasympathetic ganglia.

Neuromuscular junction



N_2 AChR: muscle-type nicotinic receptor

Blocker or antagonist of ACh R

Types of receptor	antagonist
M AChR	Atropine
Muscle-type or neuronal type N AChR	Tubocurarine
Muscle-type N AChR (N_2)	Docamethonium
Neuron- type N AChR (N_1)	Hexamethonium

(二) Monoamine Neurotransmitter

- **Noradrenalin,NA → Noadrenergic neuron**
- **Adrenalin, A → Adrenergic neuron**
- **Dopamine, DA → Dopaminergic neuron**
- **Serotonin, 5-HT → Serotonergic neuron**
- **Histamine → Histaminergic neuron**

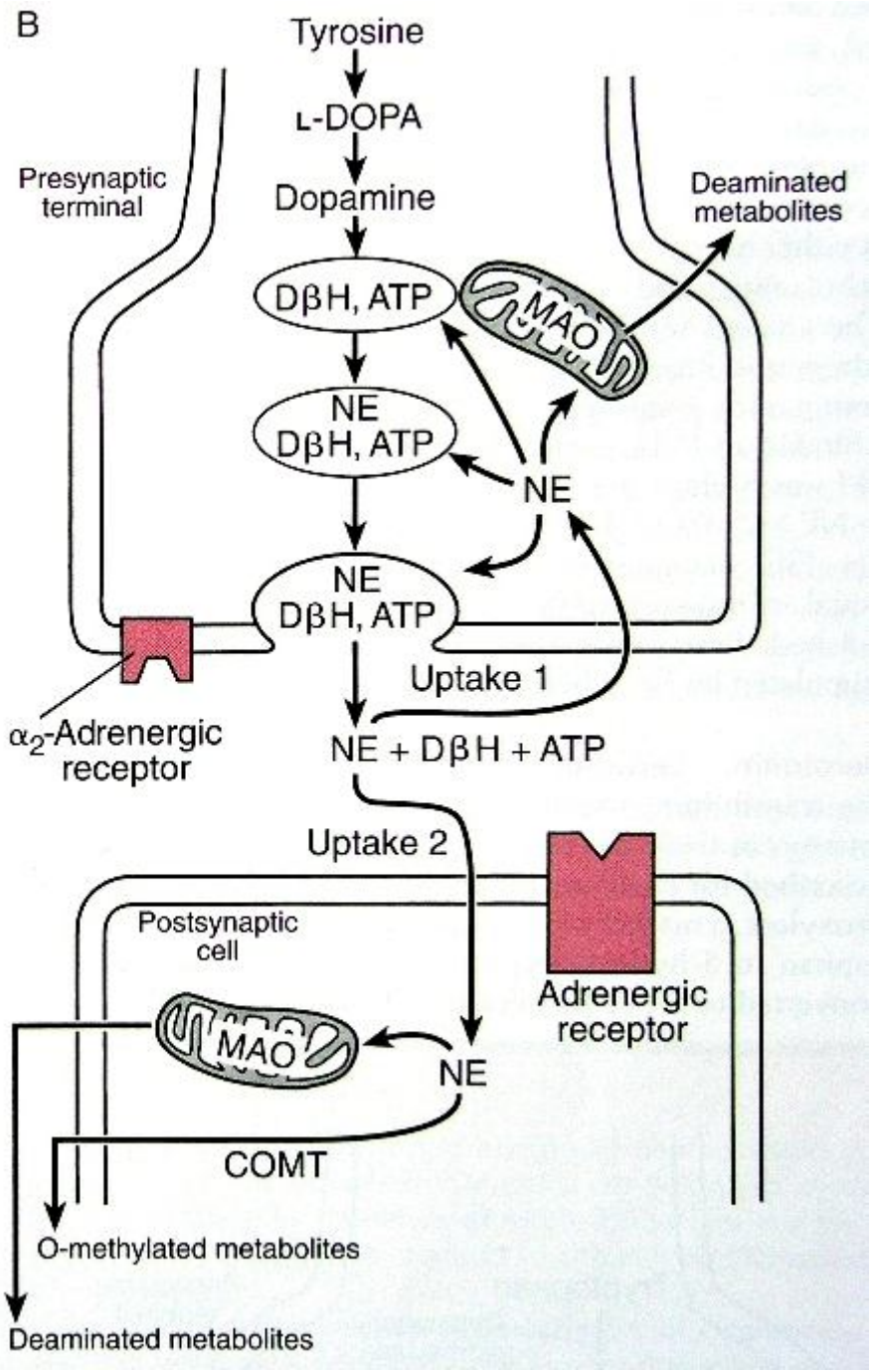
Metabolism of Catecholamine

NA,NE

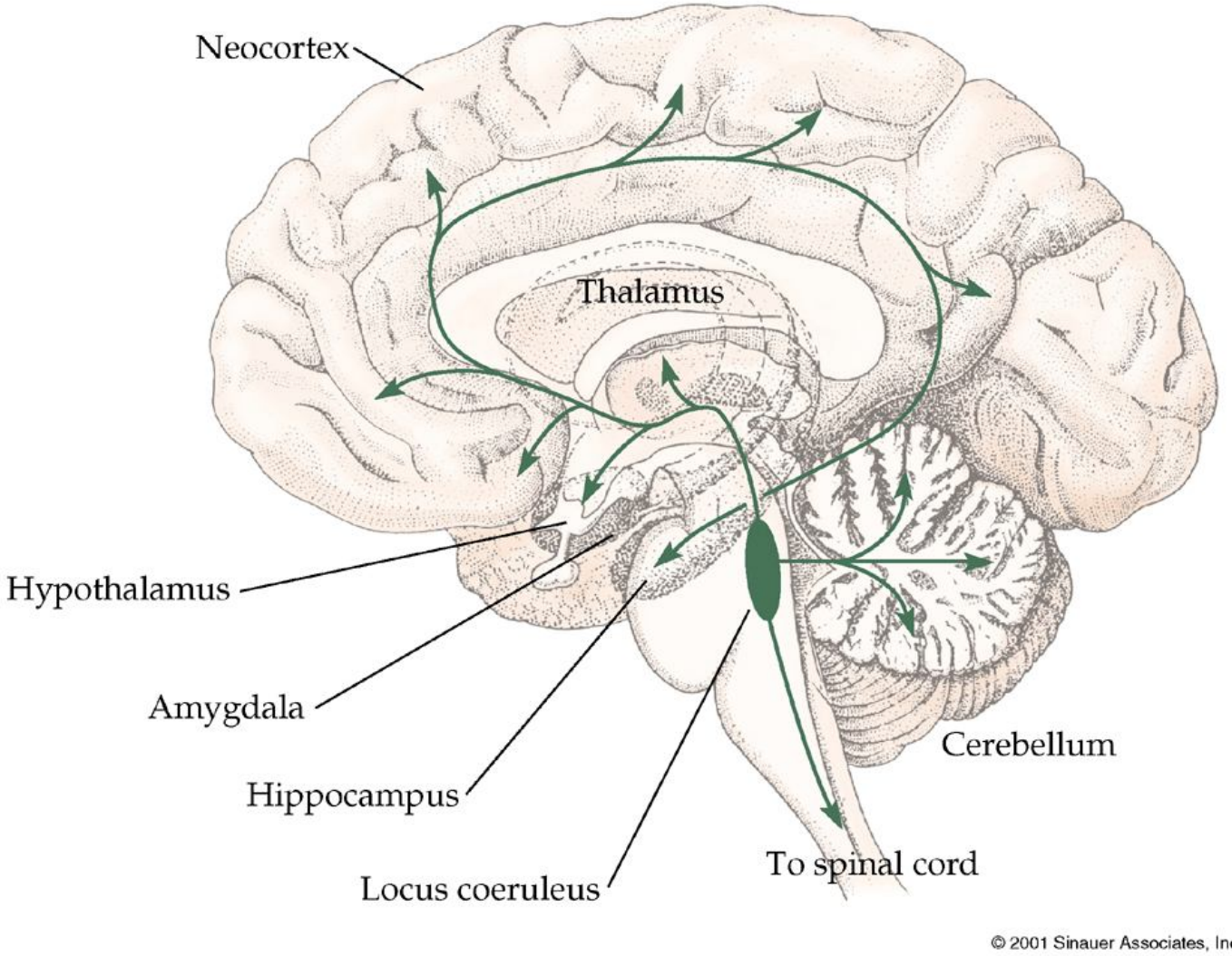
↓ **PNMT**

(phenylethanolamine-N-Methyltransferase)

A, E

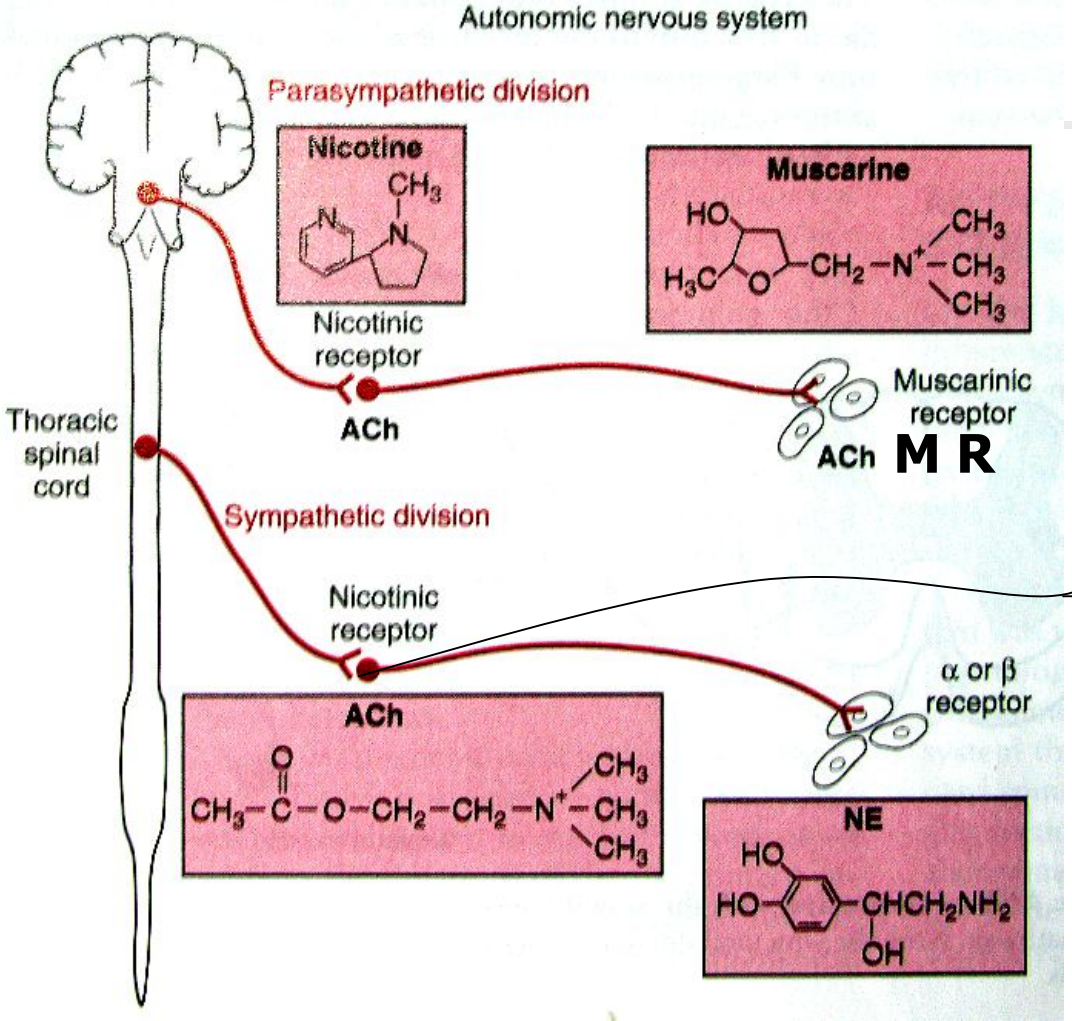


1. Noadrenergic neuron and adrenergic neuron



Cerebral cortex, hypothalamus, brain stem, cerebellum, spinal cord

Adrenergic fiber in PNS

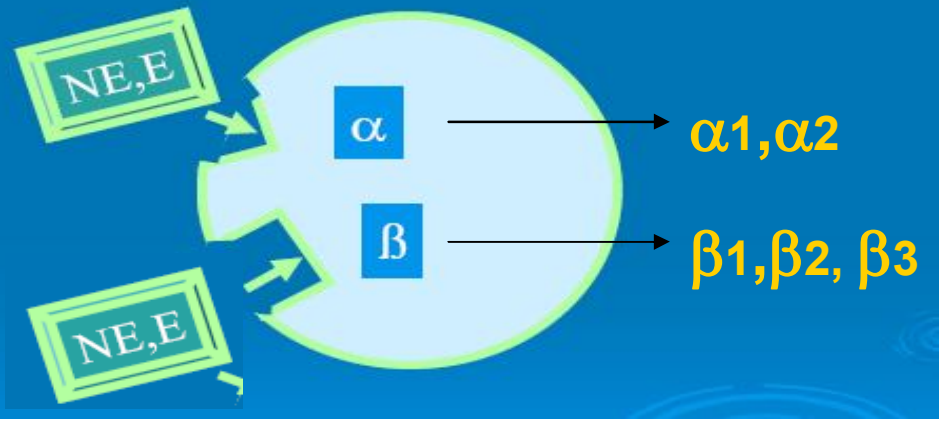


ACh M R

Most postganglionic sympathetic endings

Adrenergic Receptors

- Two main families of adrenergic receptors
  - Alpha (α)
  - Beta (ß)



Receptor	Agonists	Second Messenger	G protein
alpha$_1$ (α_1)	E>NE	IP_3/Ca^{2+}; DAG	G_q
alpha$_2$ (α_2)	NE>E	↓ cyclic AMP	G_i
beta$_1$ (β_1)	E=NE	↑ cyclic AMP	G_s
beta$_2$ (β_2)	E>>NE	↑ cyclic AMP	G_s

DISTRIBUTION AND PHYSIOLOGIC EFFECTS OF DIFFERENT ADRENERGIC RECEPTORS

TISSUE	RECEPTOR TYPE	EFFECT
Blood vessels	α_1 and α_2	Constriction
	β_2	Dilatation
Heart	β_1	Tachycardia; increased contractility
	α_1	Increased contractility
Bronchi	β_2	Relaxation
Thrombocytes	α_2	Aggregation
Kidneys	α_1 and α_2	Vasoconstriction
	β_1 and β_2	Renin release; inhibition tubular sodium reabsorption
Adipocytes	α_2	Inhibition lipolysis
	β_1, β_2, and β_3 (?)	Lipolysis

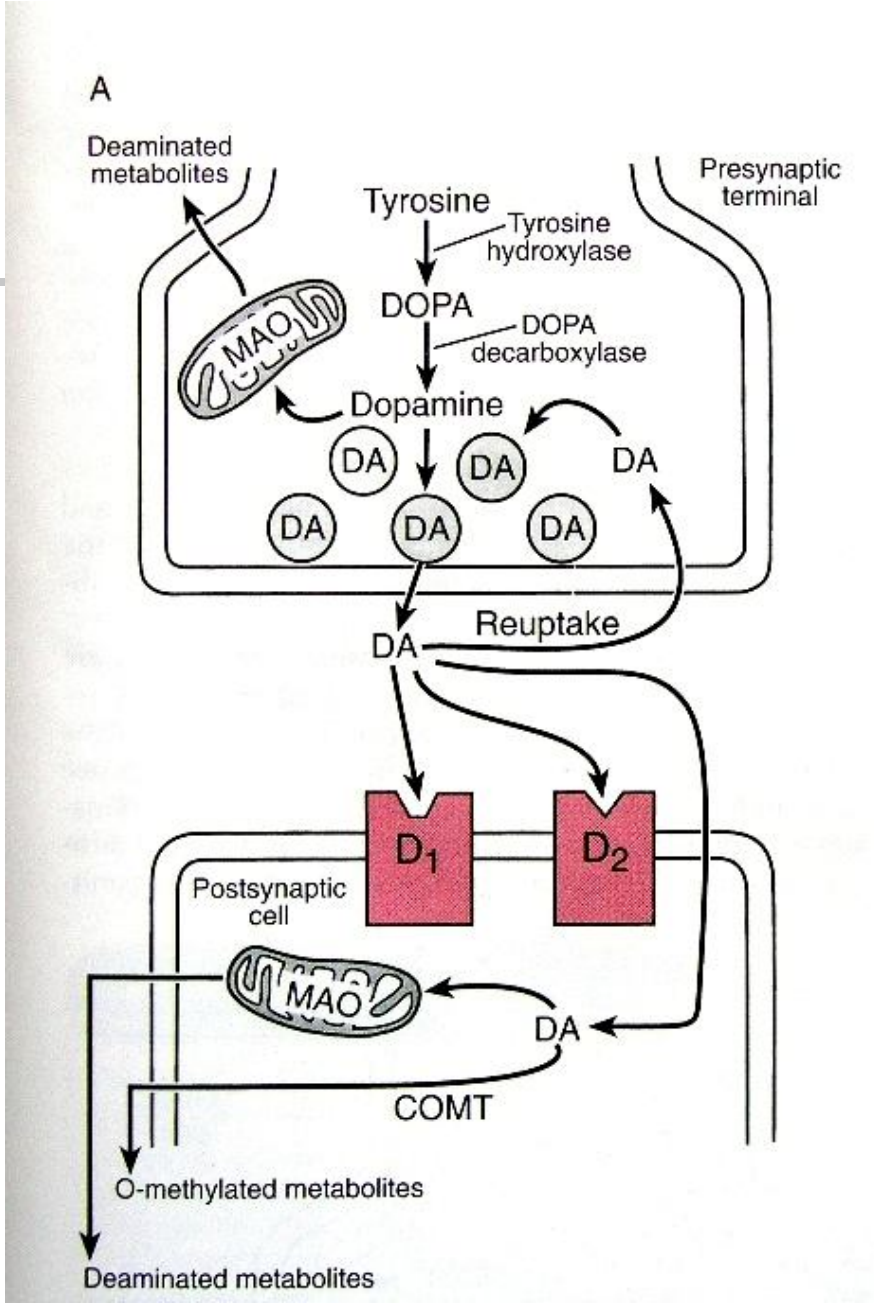
Functions of NE and E

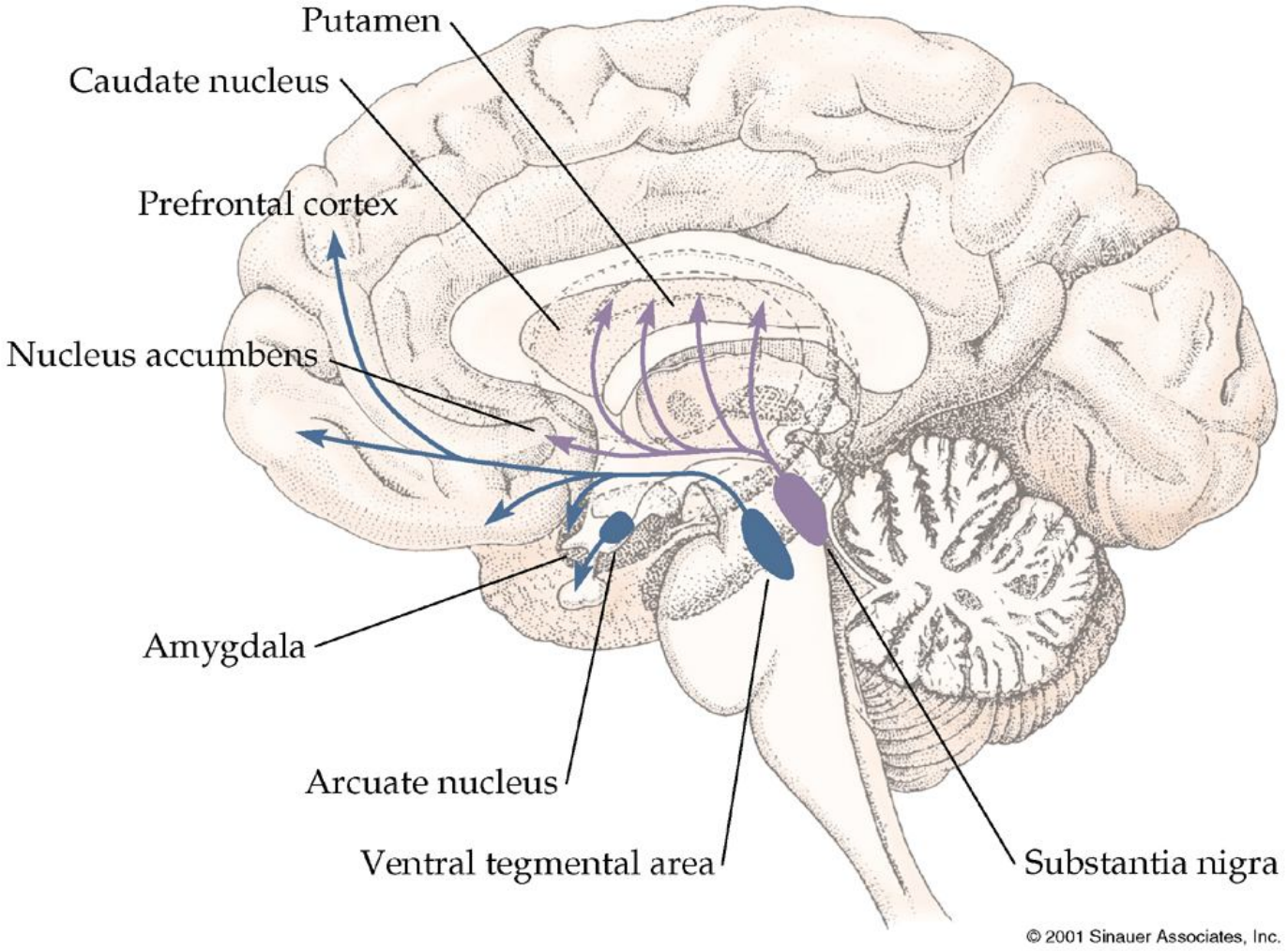
- NE in CNS plays a role in cardiovascular activity, mood, food intake, body temperature et al.
- E in CNS plays a role in cardiovascular.
- Inhibitors of NE neuronal reuptake are antidepressants.

Blocker or antagonist of Adrenergic R

receptor	antagonist
α R	phentolamine
α1 R	prazosine
α2 R	yohimbine
β R	propranolol
β1 R	atenolol metoprolol
β2 R	butoxamine

2. Dopamine (DA)





substantia nigra-striatum system

ventral tegmental area-limbic system

nodules - infundibular dopamine system (arcuate nucleus)

DA Receptors

- All DA receptors are metabotropic receptor
- D1,D5 → Gs → ↑AC → ↑cAMP
- D2,3,4 → Gi → ↓AC → ↓cAMP
- D1 D2 postsynaptic on striatum.
- D2, autoreceptors in SN, ventral tegmental area, regulate DA synthesis.

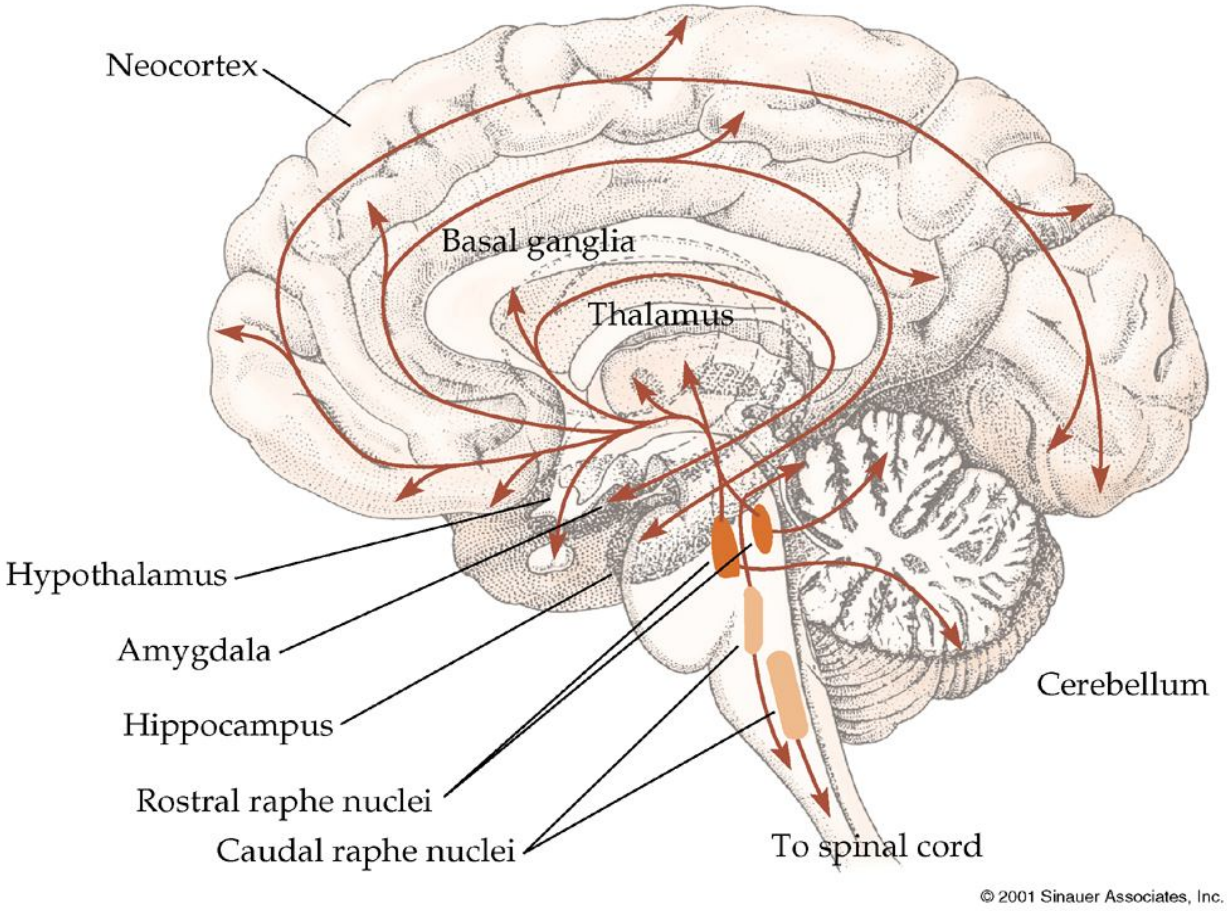
Functions of DA

- DA plays a role in movement

  Parkinson disease: degeneration of Dopaminerginc neurons in SNc→ behavioral disorders
- Mental and mood activity;
- Endocrine of pituitary
- Cardiovascular activity

Romantic Love Gives a Dopamine High!

3. Distribution of serotonin neuron

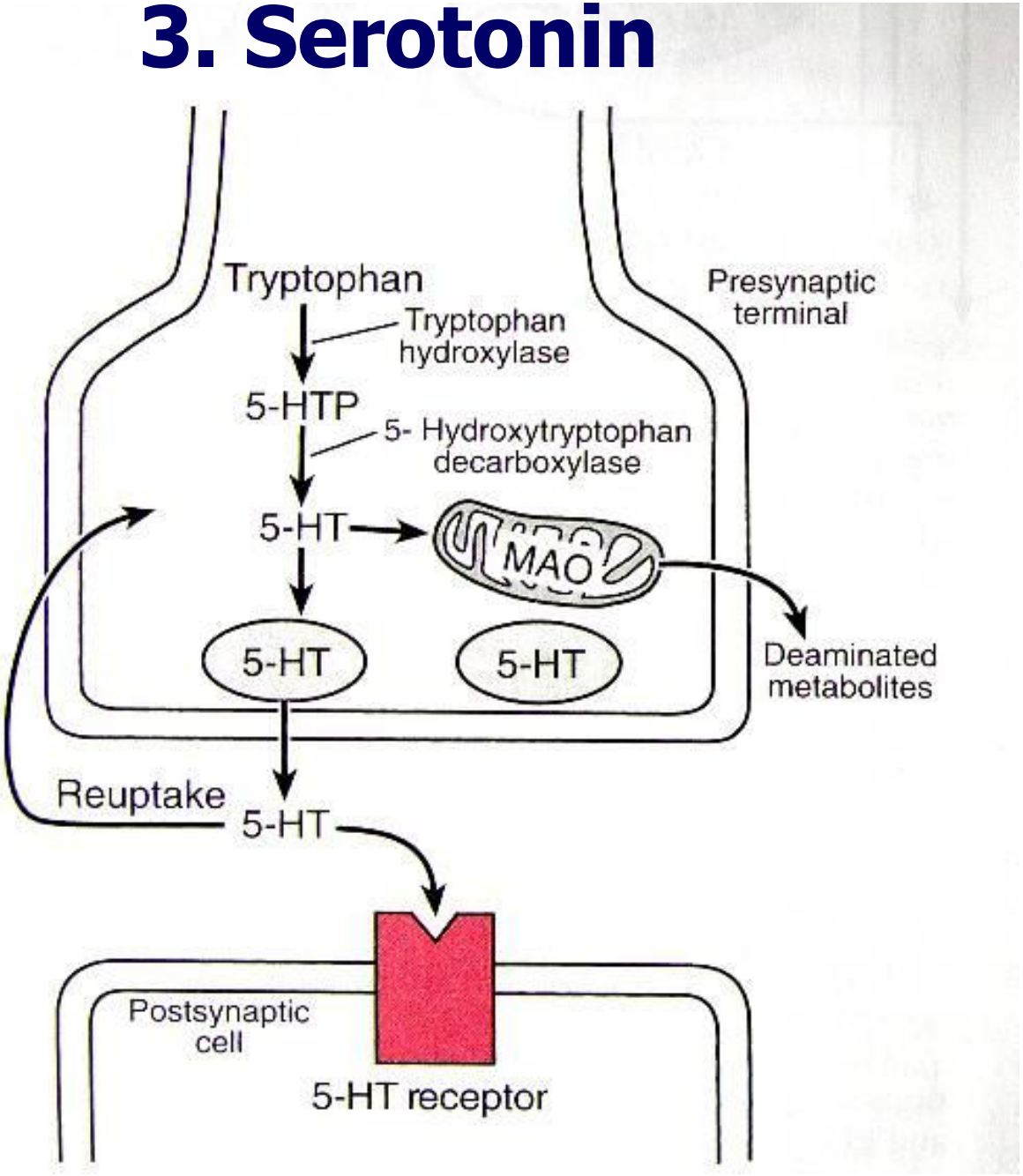


Raphe nuclei,

Functions of serotonin

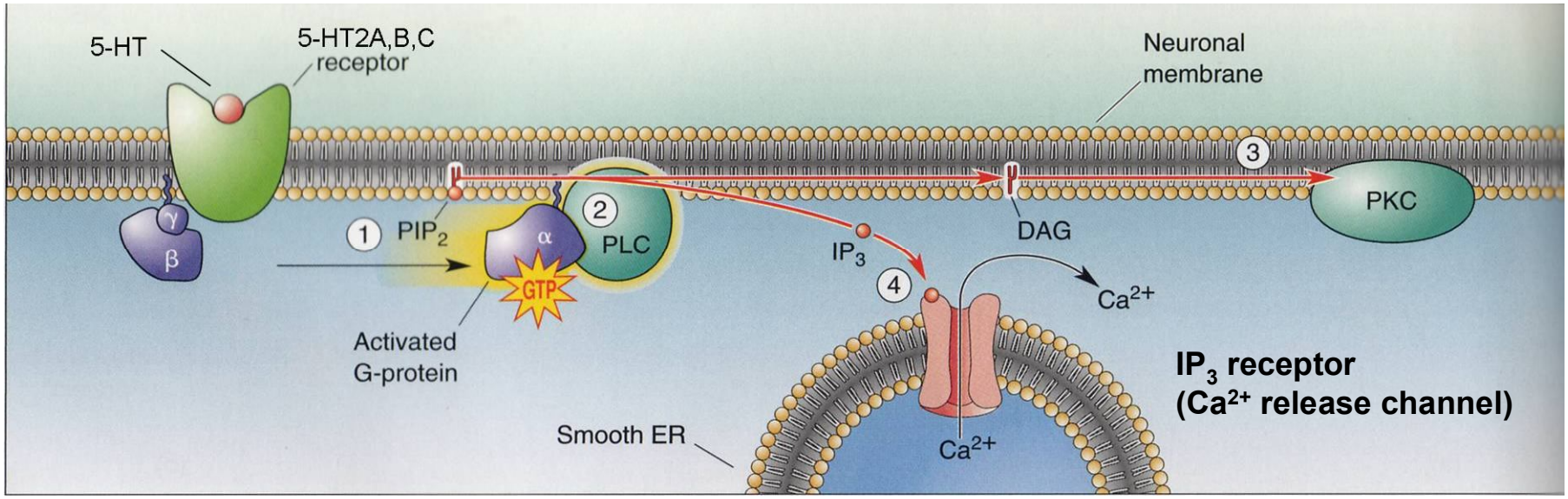
- Pain
- Mood
- Sleep
- Body temperature
- Endocrine of pituitary
- Cardiovascular activity

3. Serotonin


Tryptophan
Tryptophan hydroxylase
5-HTP
5- Hydroxytryptophan decarboxylase
5-HT
MAO
5-HT
5-HT
Presynaptic terminal
Deaminated metabolites
Reuptake
5-HT
Postsynaptic cell
5-HT receptor

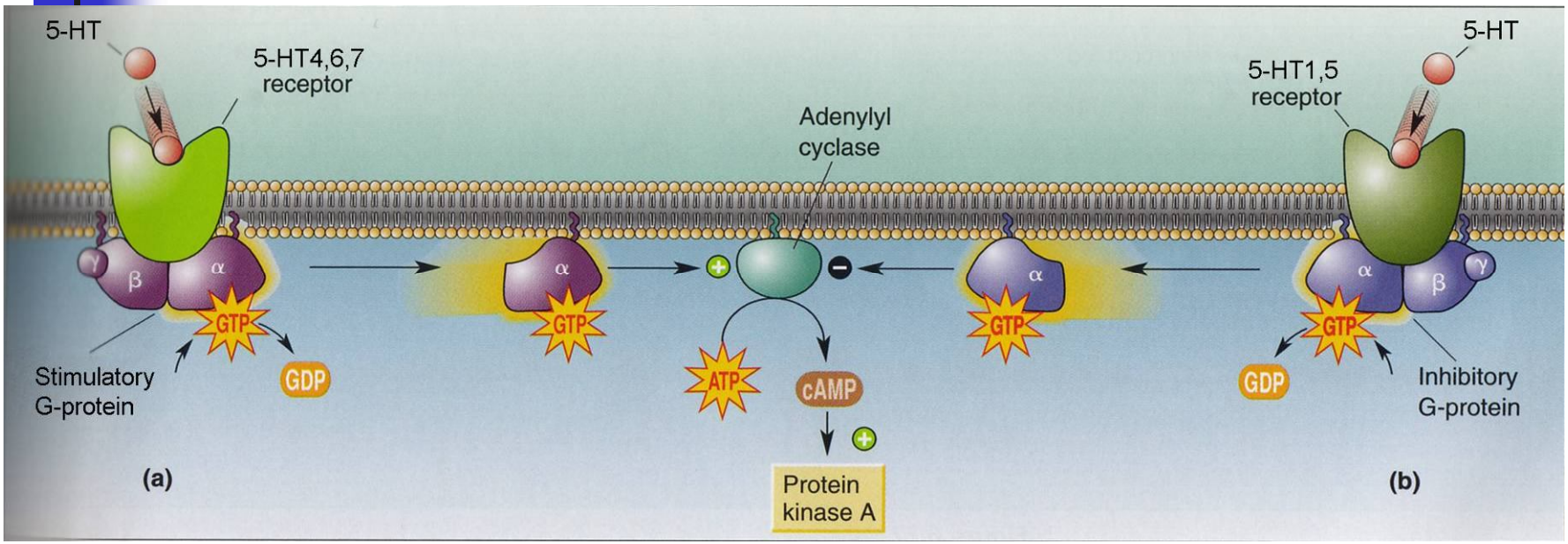
5-HT Receptors

5-H1~5-H7 receptor

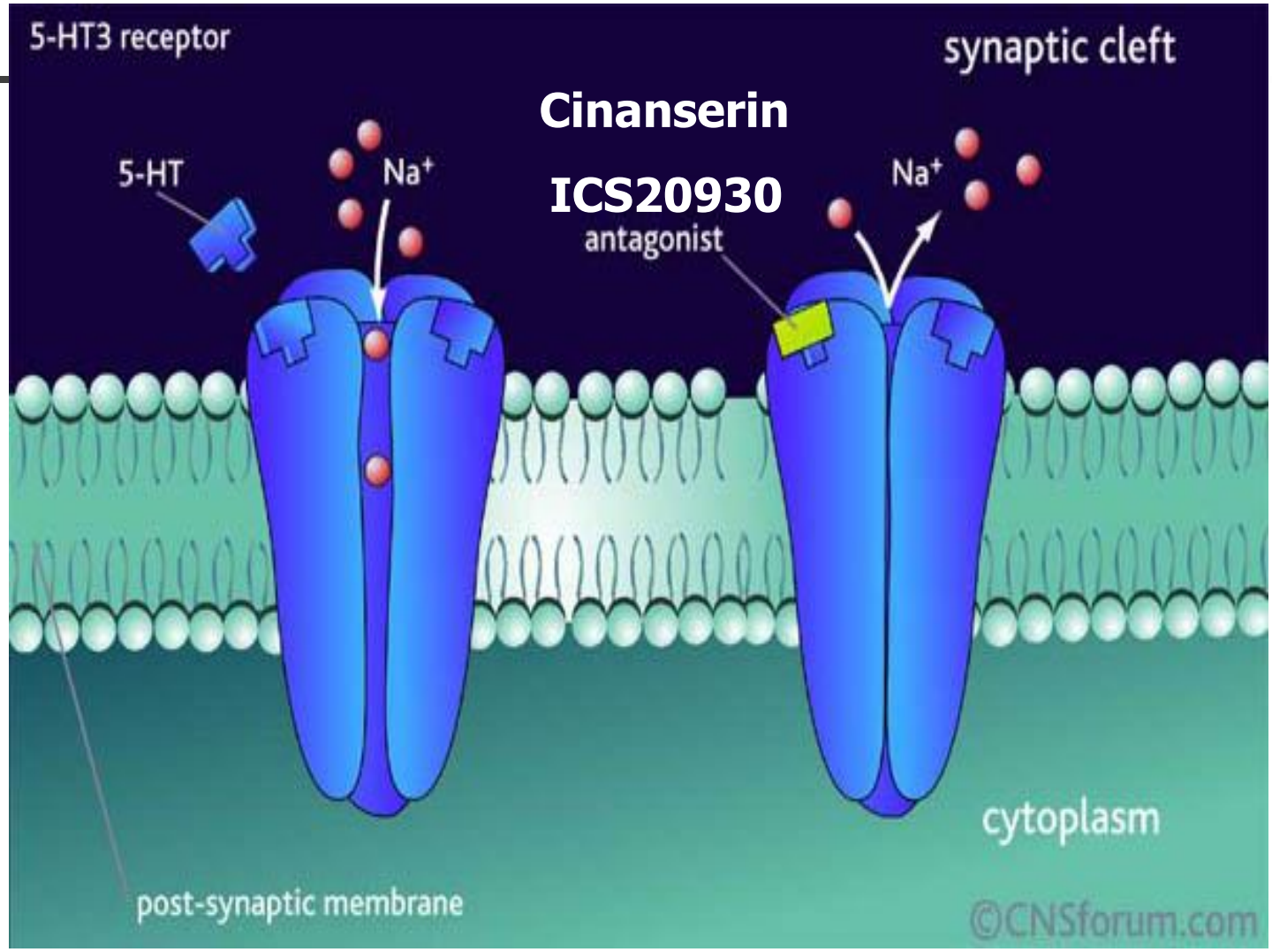


5-HT2: 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}

5-HT Receptors



5-HT3 Receptors

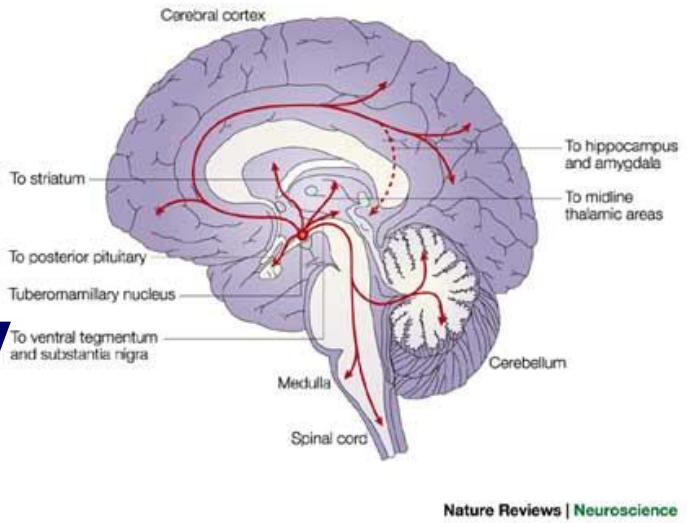


4. Histaminergic neuron

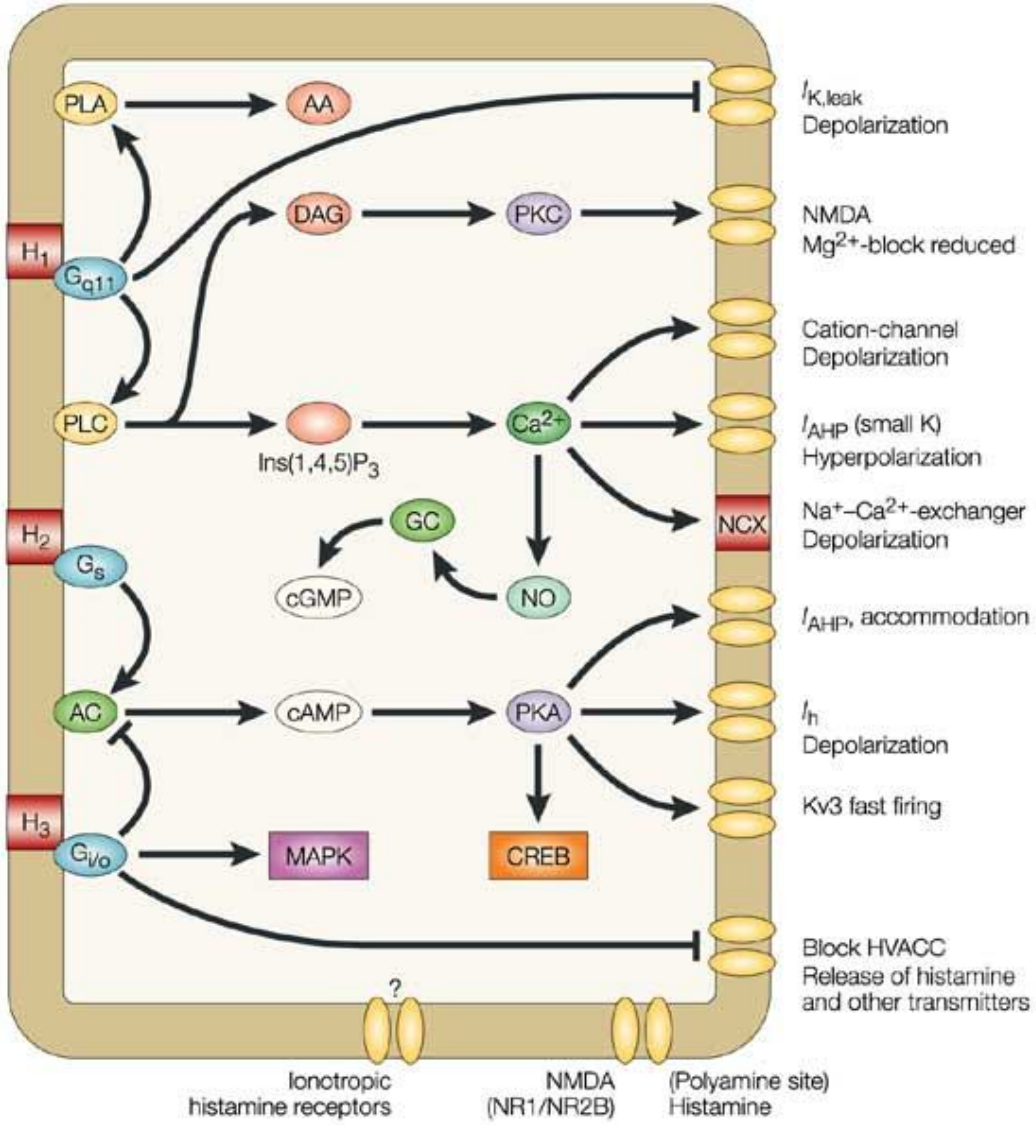
tuberomammillary nucleus

Function in CNS

- wakefulness
- Sexual behavior
- Endocrine of pituitary
- Blood pressure
- Drinking
- Pain thresholds
- The sensation of itch



4. Histaminergic neuron



Nature Reviews | Neuroscience

(三) Amino acids neurotransmitters

* EAA	* IAA
Excitatory amino acid	Inhibitory amino acid
↓	↓
Glutamate	Glycin
Aspartate	γ-aminobutyric acid(GABA)

Glutamate

- **Glutamate** is the major excitatory neurotransmitter which plays an important role in learning and memory.

(1) Glutamate Receptor Family

- **Ionotropic-Rs**

  AMPA receptors

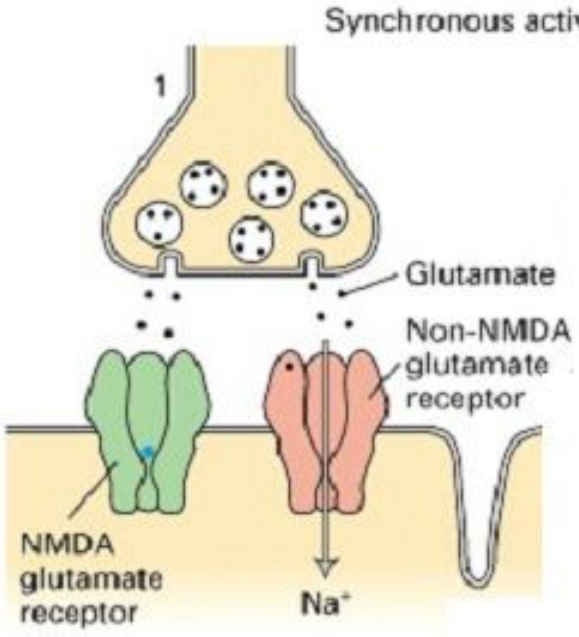
  (α-amino-3-hydroxy-5-methylisoxazole-4-propionate)

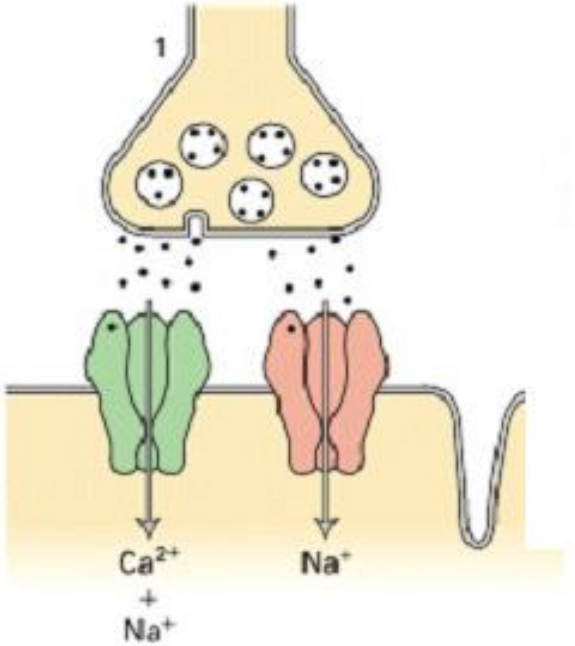
  Kainate receptors

  } **Non-NMDA R**

  NMDA-R (N-methyl-D-aspartate R)

- **Metabotropic-Rs**

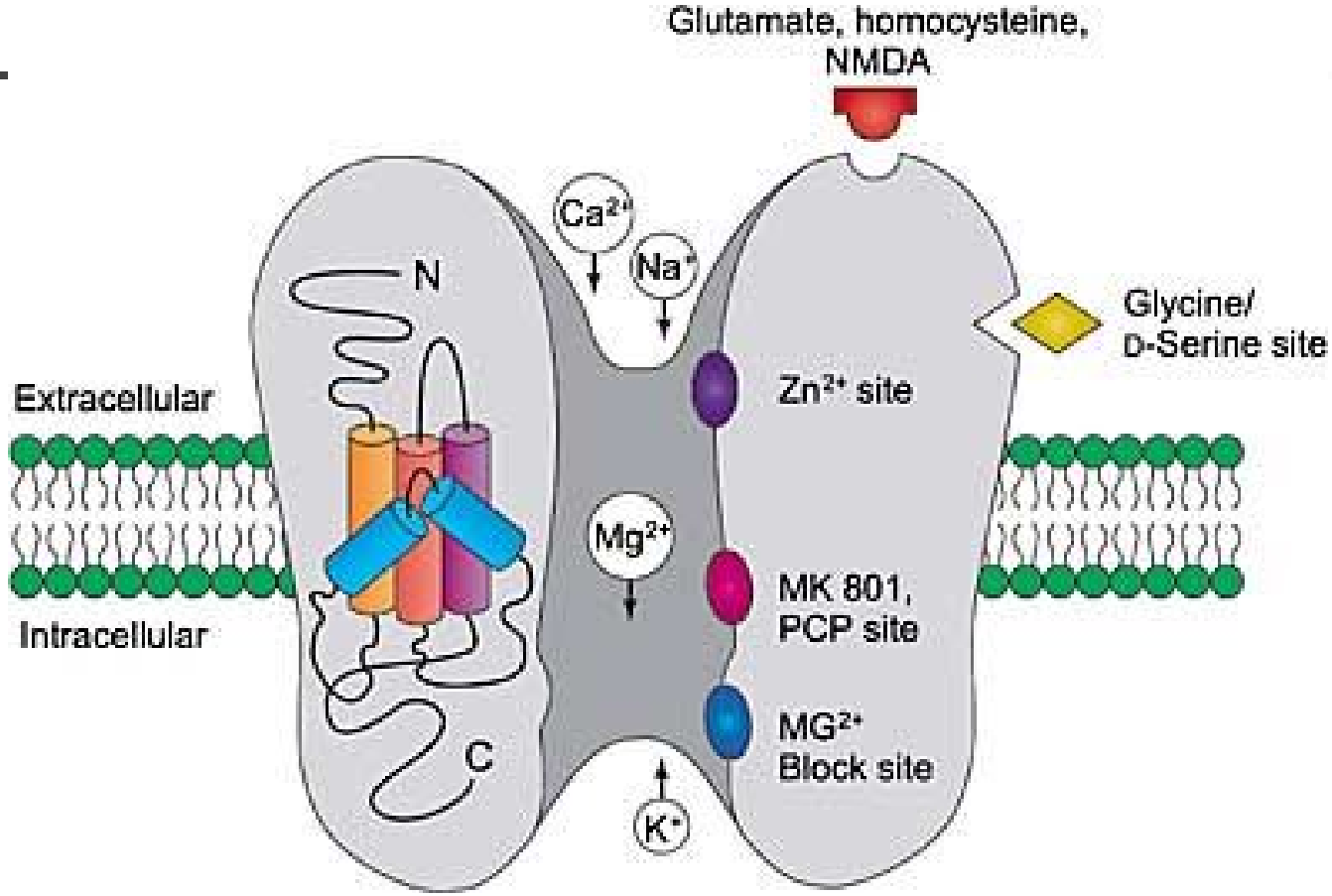




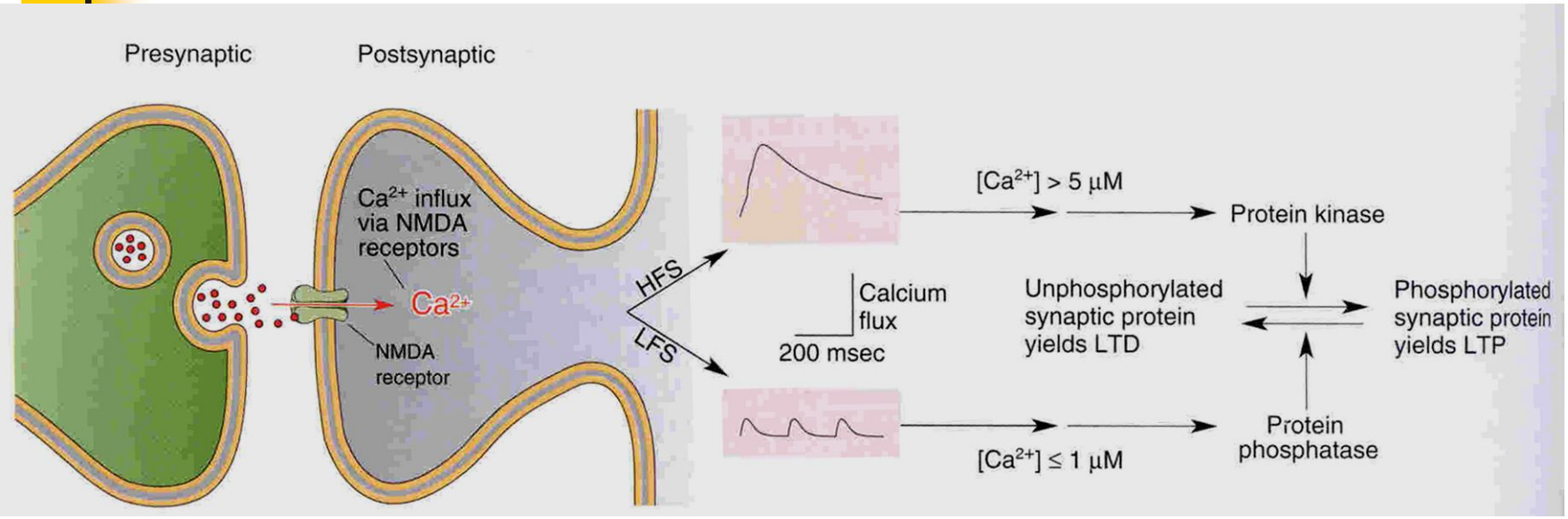
Two types of ionotropic glutamate receptors :

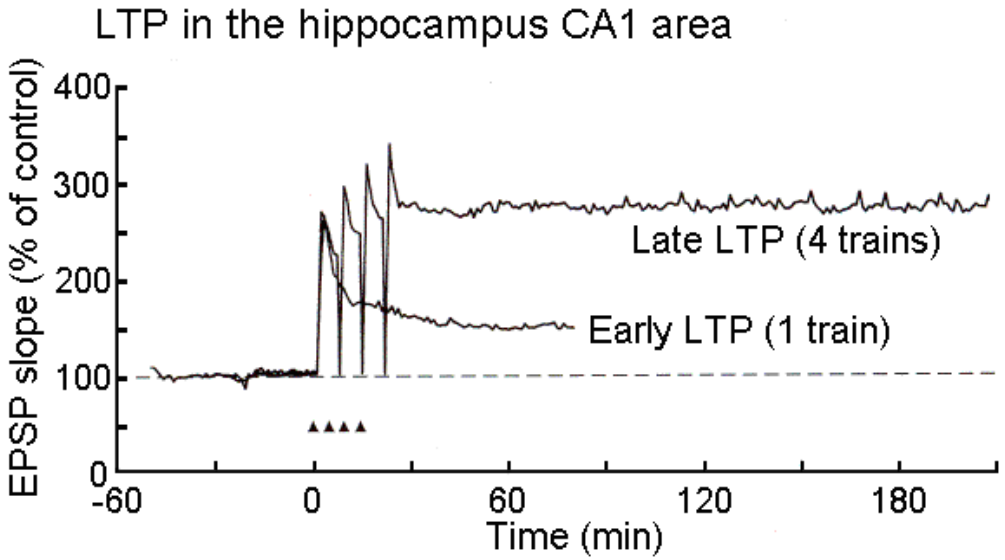
- One that opens when it binds glutamate and the cell is depolarized by Na^+ entry (AMPA/kainate receptor)
- One that opens only when it binds glutamate and the cell is depolarized by Na^+ and Ca^{2+} entry (NMDA receptor) (cortex and H)

NMDA receptor



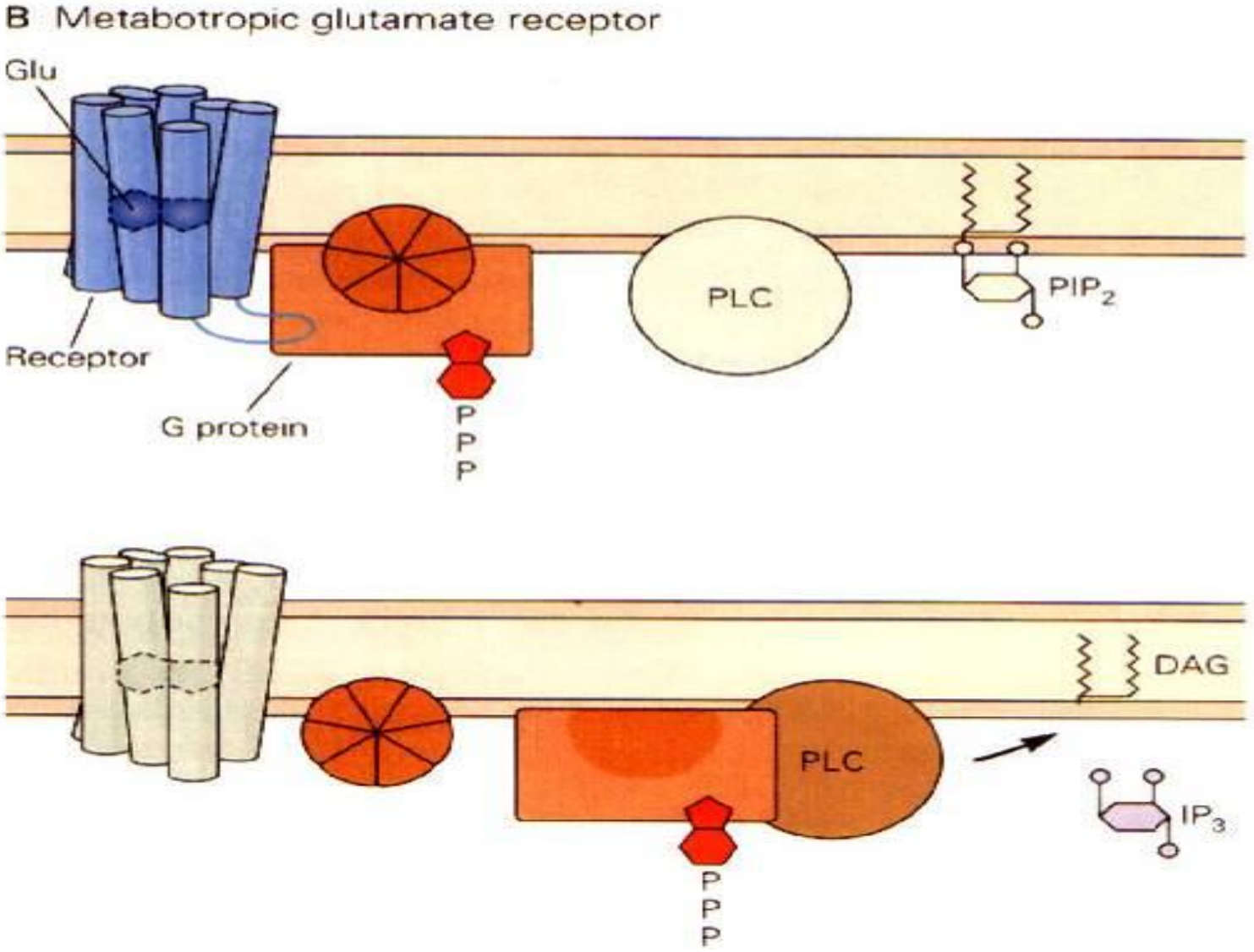
Long-term potentiation (LTP)





Metabotropic Receptors

- mGLU1~mGLU8
- They are both presynaptic and postsynaptic and widely distributed in the brain.


B Metabotropic glutamate receptor
Glu
Receptor
G protein
P
P
P
PLC
PIP2
DAG
PLC
IP3
P
P
P

γ -aminobutyric acid, GABA

- **GABA** is the major inhibitory neurotransmitter which plays anxiolytic, antiepileptic, anticonvulsant and hypnosis effects.

GABA Receptors

- **Ionotropic Rs:**

  $GABA_A$, $GABA_C$

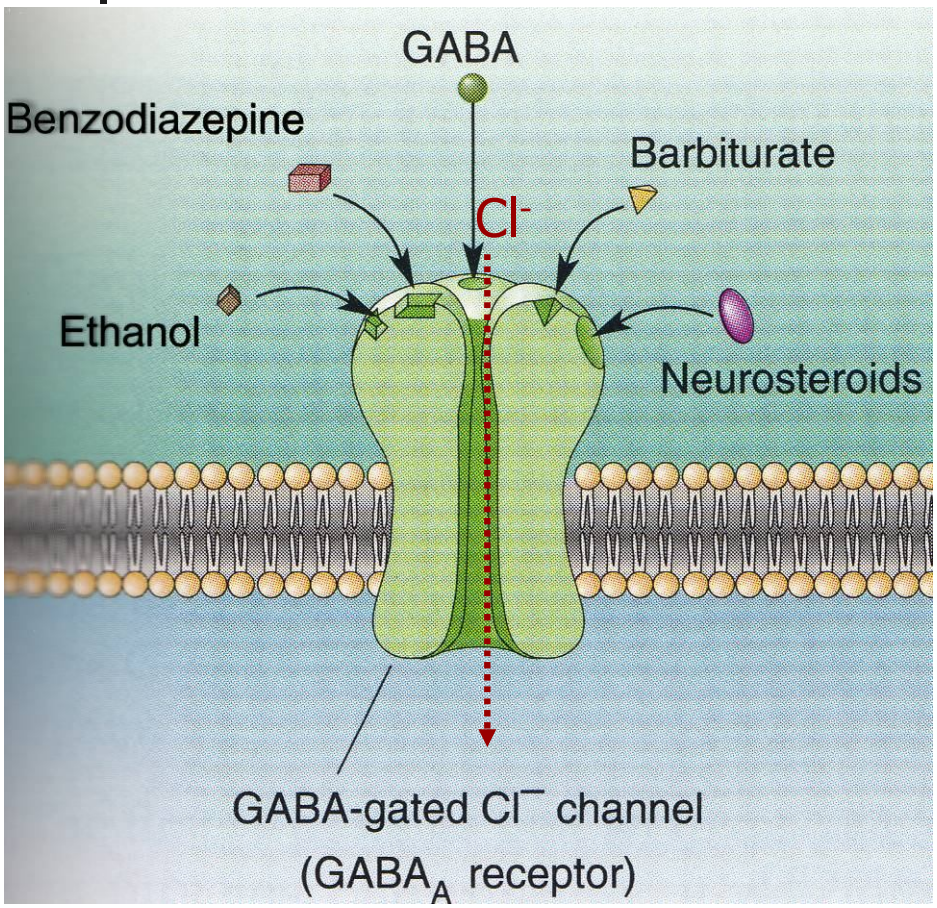
- **Metabotropic R:**

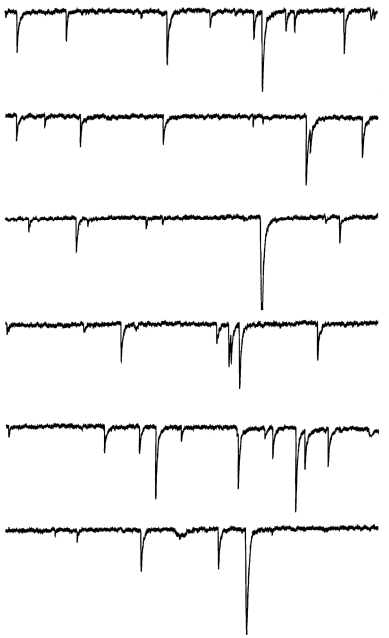
  $GABA_B$

$GABA_A$ & $GABA_B$: CNS

$GABA_C$: Retina & visual pathway

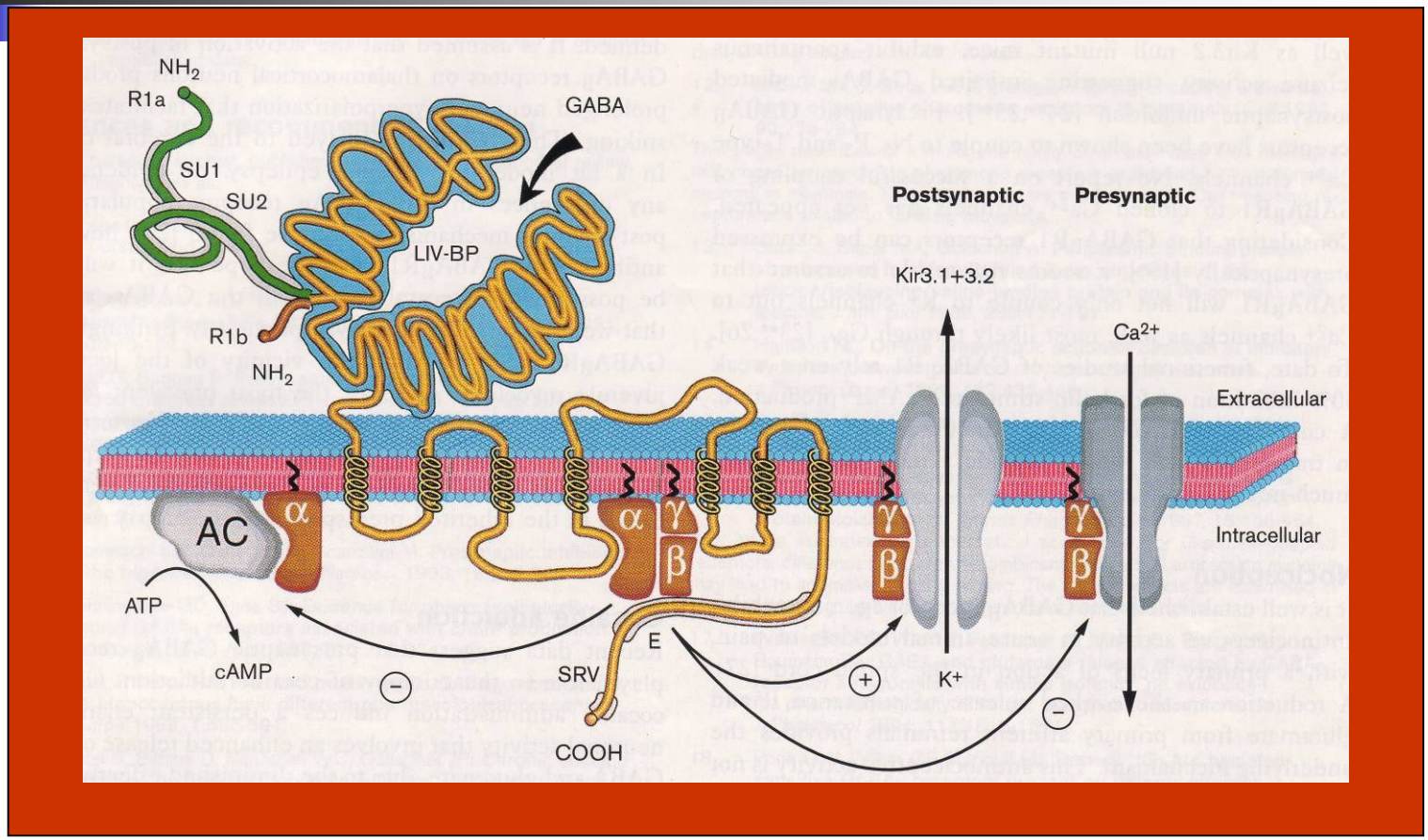
$GABA_A$ receptor





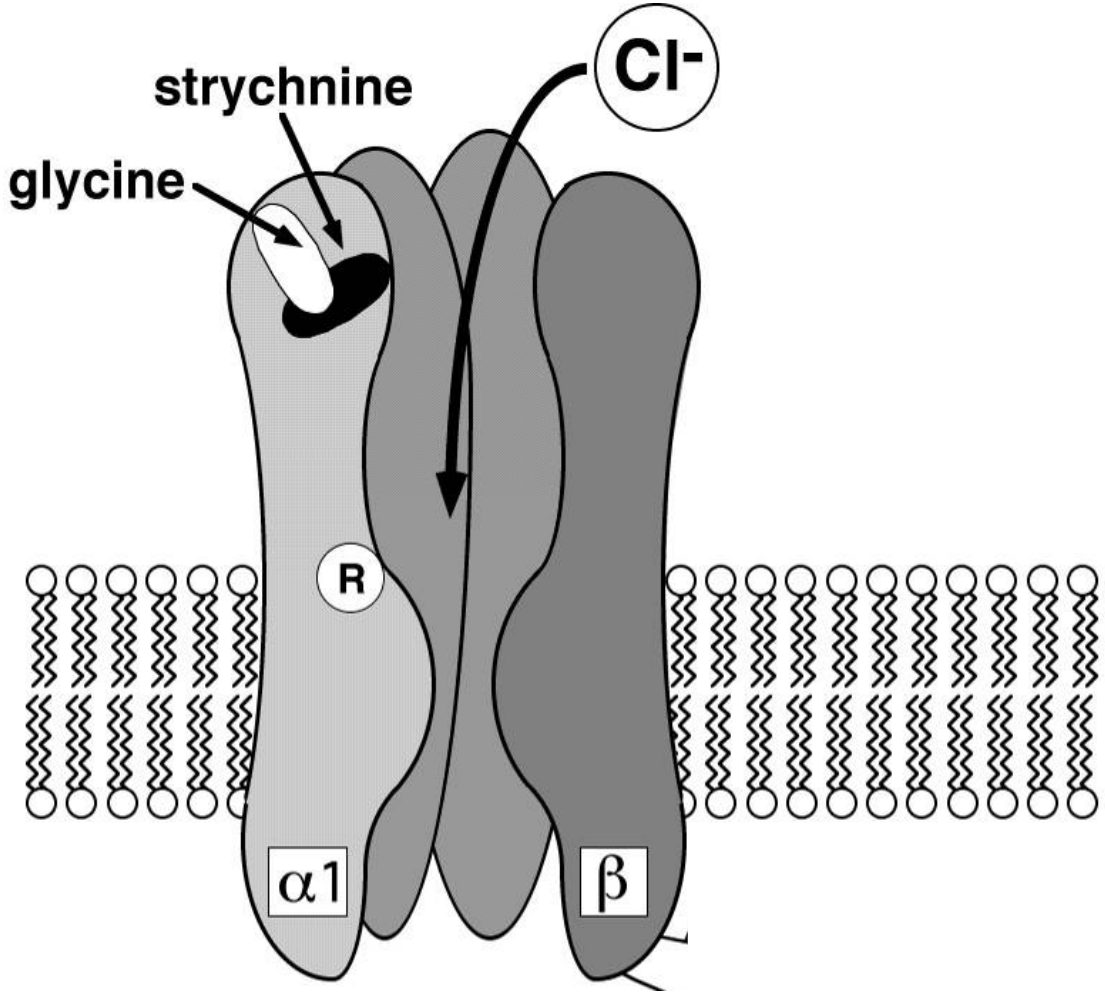
Inhibitory postsynaptic current

$GABA_B$ receptor



Presynaptic and postsynaptic membrane

(3) Glycine receptor



(四) Peptides Neurotransmitter

- Tachykinin: SP, neurokinin A, A(3-10) & B, neuropeptide K & α
- Opioid peptide: β-endophin, enkephalin & dynorphin
- Hypothalamic regulatory peptides & neurohypophysis peptides:
- Brain-gut peptide: CCK, VIP, neurotensin

Receptors of peptide neurotransmitter

① **Receptors of tachykinin**

NK-1, NK-2, NK-3

(SP neuropeptide K neurokinin B)

② **Receptors of opioid peptides**

μ 、 κ 、 δ

Functions: Pain, visceral activity et al.

(五) Purines neurotransmitter

- **Adenosine: inhibitory modulator**

  excitatory modulator

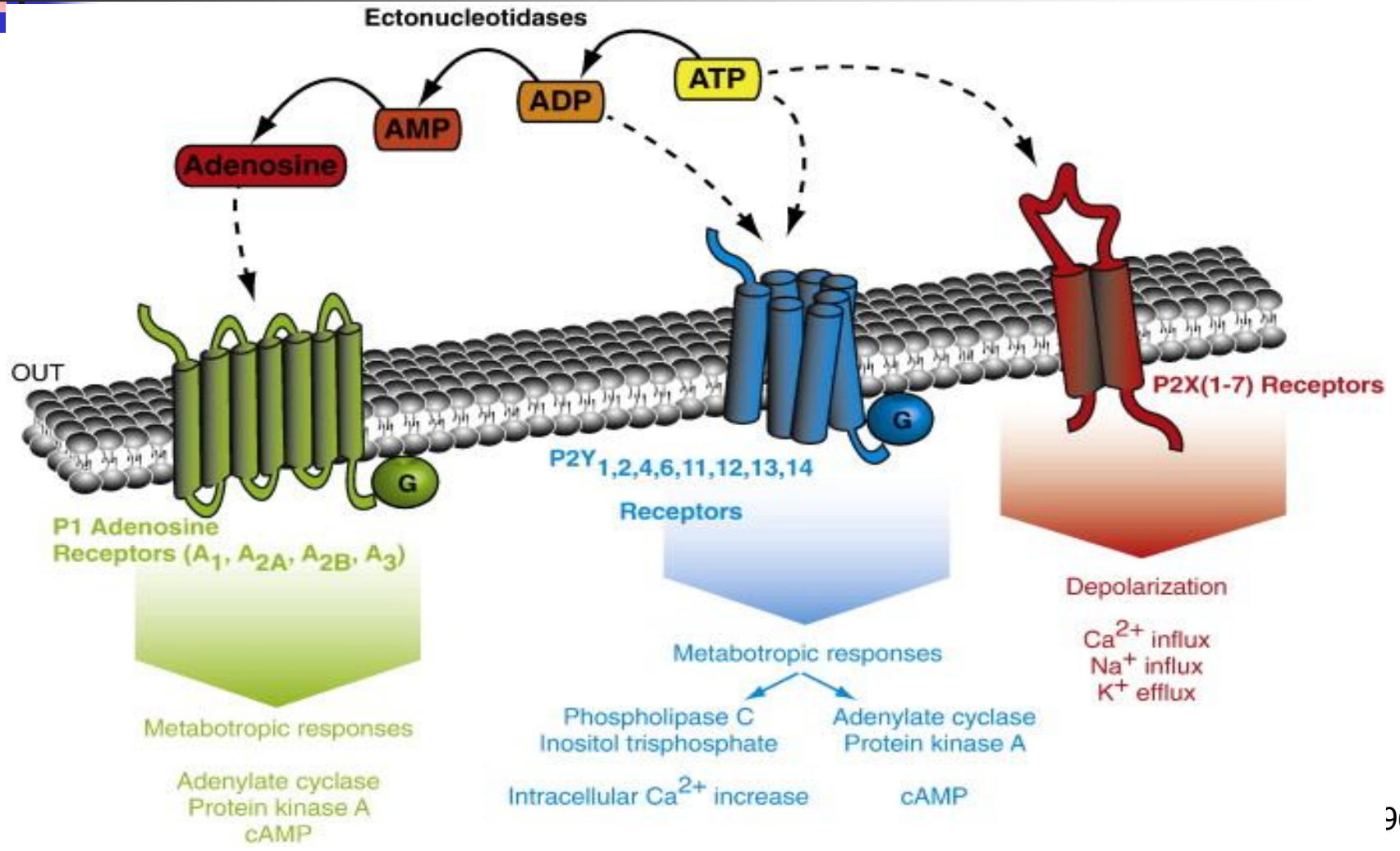
  (ACh, Glu, NE ↑; GABA↓)

- **ATP (adenosine triphosphate)**

(co-exsitence with monoamine or amino acid neurotransmitters)

cardiovascular system, smooth muscle

(五) Purinergic neurotransmitter



(六) Neurotransmitters of other types

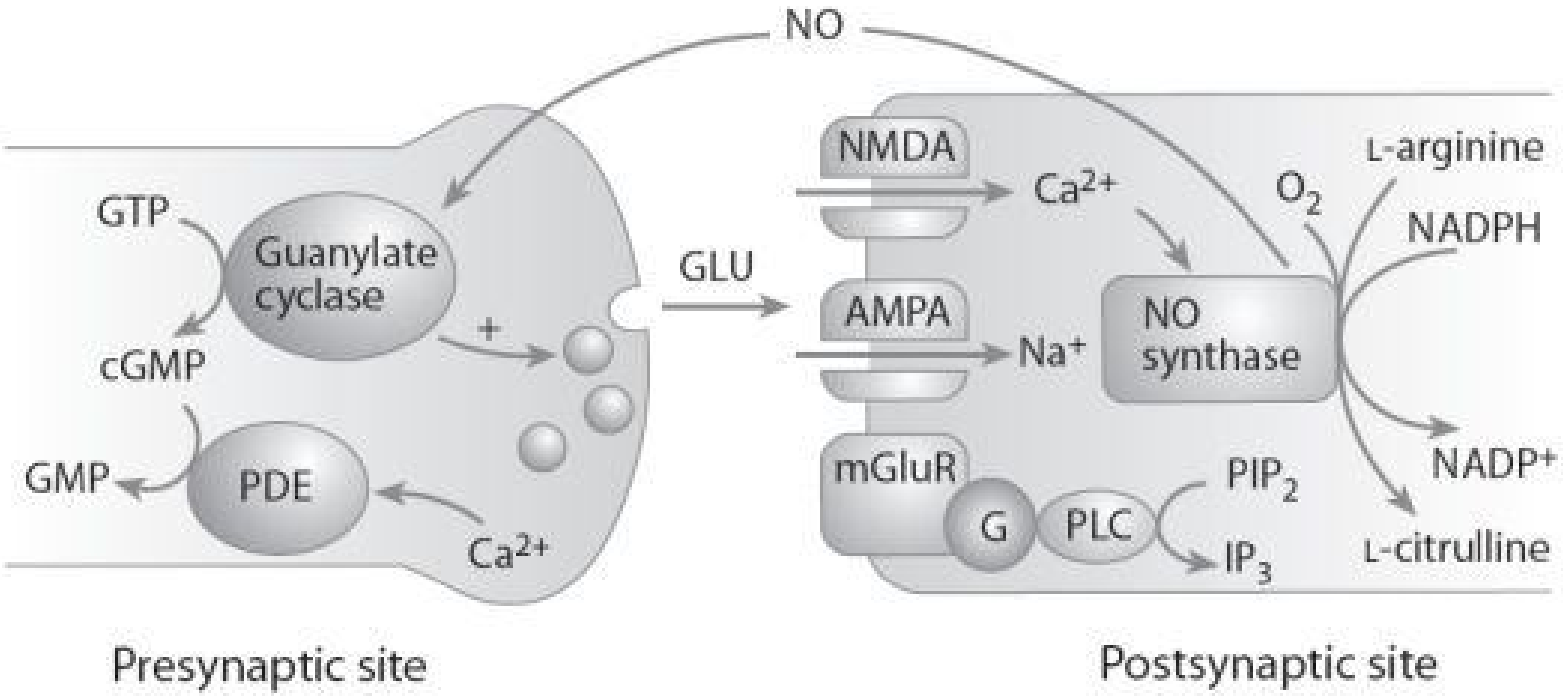
- NO
- CO

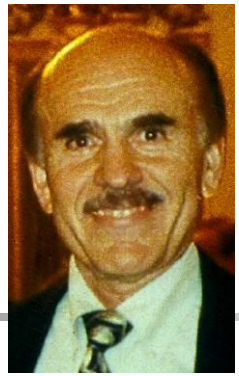
Its synthesis from arginine, a reaction catalyzed in the brain by one of the three forms of NO synthase.

NO Synthase Isoforms

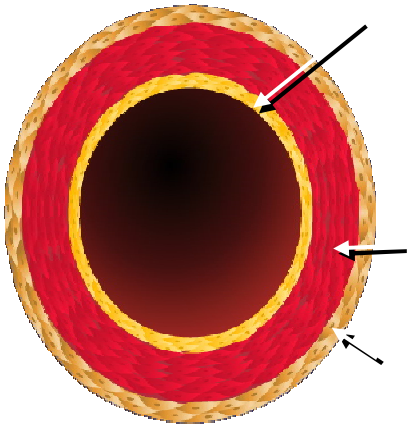
- ✓ **eNOS – Endothelial**
- ✓ **nNOS – Neuronal**
- ✓ **iNOS – inducible**

LTP


NO
GTP
Guanylate cyclase
cGMP
GMP
PDE
Ca2+
+
GLU
NMDA
Ca2+
AMPA
Na+
mGluR
G
PLC
PIP2
IP3
O2
L-arginine
NADPH
NO synthase
NADP+
L-citrulline
Presynaptic site
Postsynaptic site


- **The 1998 Nobel prize was awarded to three U.S. scientists (Bob Furchgott, Lou Ignarro, and Ferid Murad)**



Intima: Endothelial cell layer

Media: Smooth muscel cells

Adventita