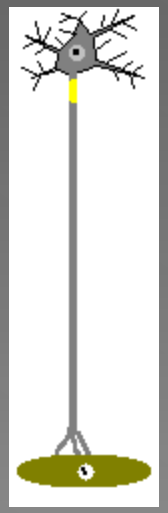
MEDICAL UNIVERSITY – PLEVEN
FACULTY OF MEDICINE
DISTANCE LEARNING CENTER

Lecture №3

Mechanisms of cell-to-cell signaling. Synaptic transmission. Functional anatomy. Chemical transmission of synaptic activity. Chemical substances - synaptic transmitters.



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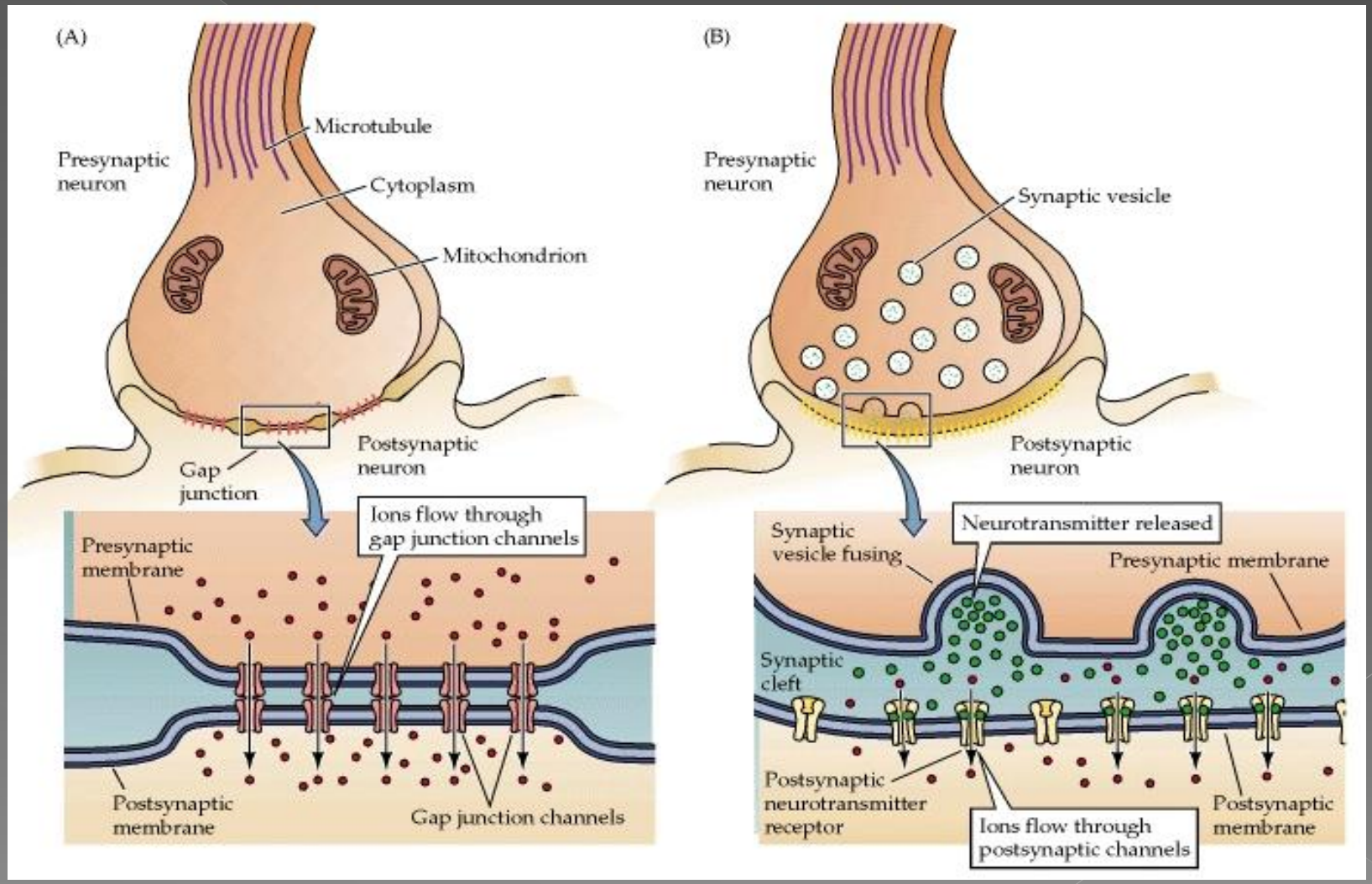
Pleven

Synapses

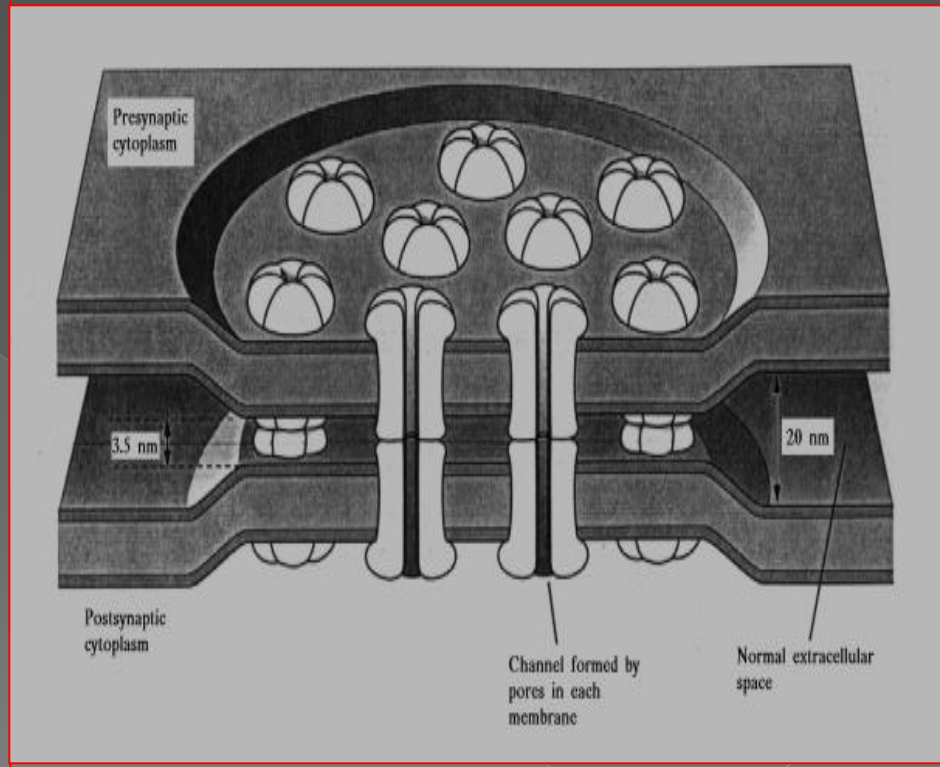
- Synapses are specialized junctions through which cells of the nervous system signal to one another and to non-neuronal cells such as muscles or glands, and the junctions between cardiomyocytes and smooth muscle cells.

There are two major types of synapses: (A) the *electrical synapse* and (B) the *chemical synapse*.

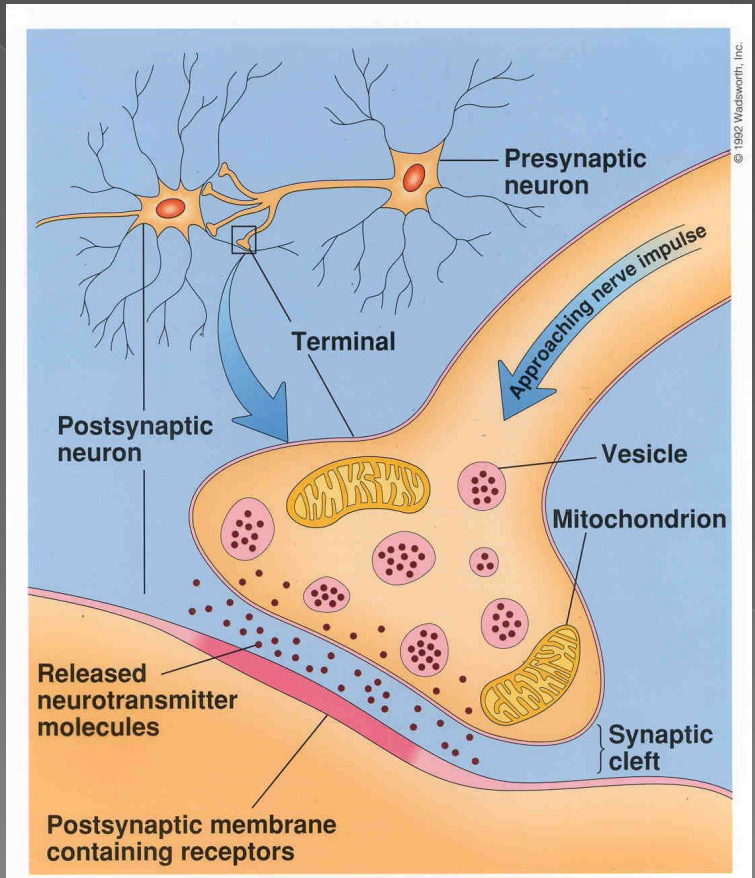


Electrical synapses

- *Electrical synapses* are characterized by direct open fluid channels that conduct electricity from one cell to the next. Most of these consist of small protein tubular structures called *gap junctions* that allow free movement of ions from the interior of one cell to the interior of the next.
- However, it is by way of gap junctions and other similar junctions that action potentials are transmitted from one smooth muscle fiber to the next in visceral smooth muscle and from one cardiac muscle cell to the next in cardiac muscle.
- Electrical synapse transmission has two interesting characteristics:
- First is that ions bidirectional flow is possible.
- The second is the speed with which electrical synapses convey information. Passive flow of ions through channels is nearly instantaneous allowing immediate response to stimulus.

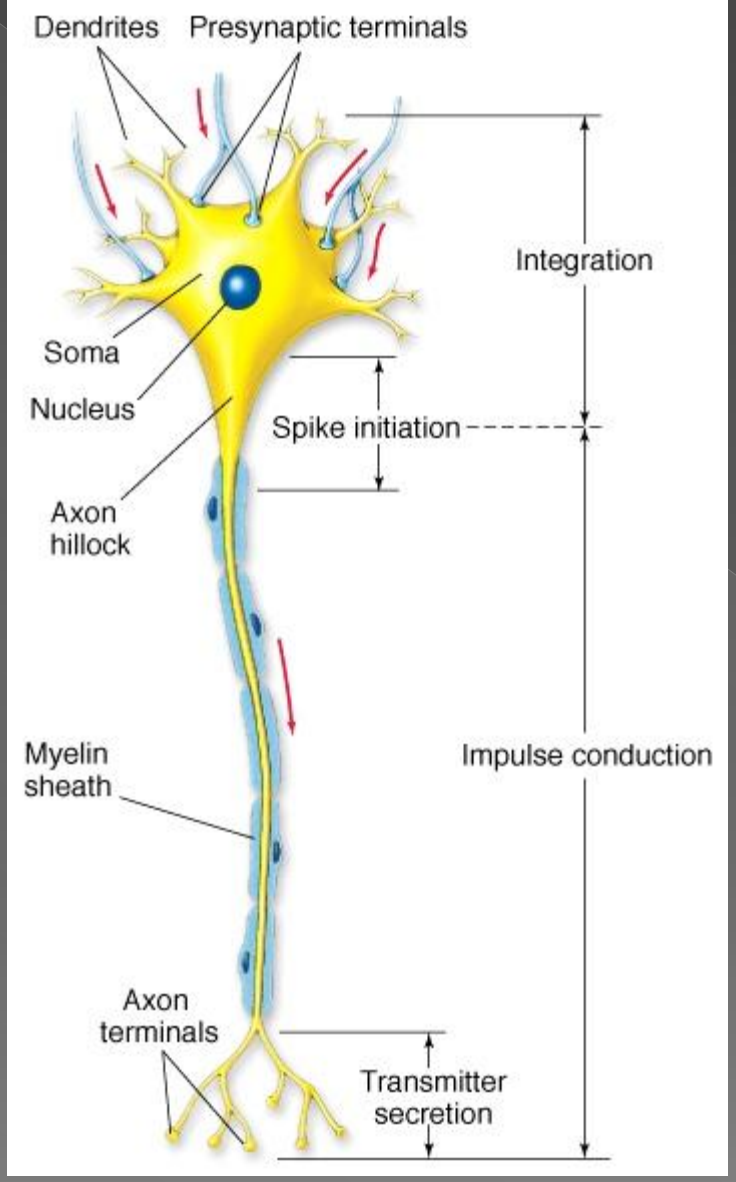


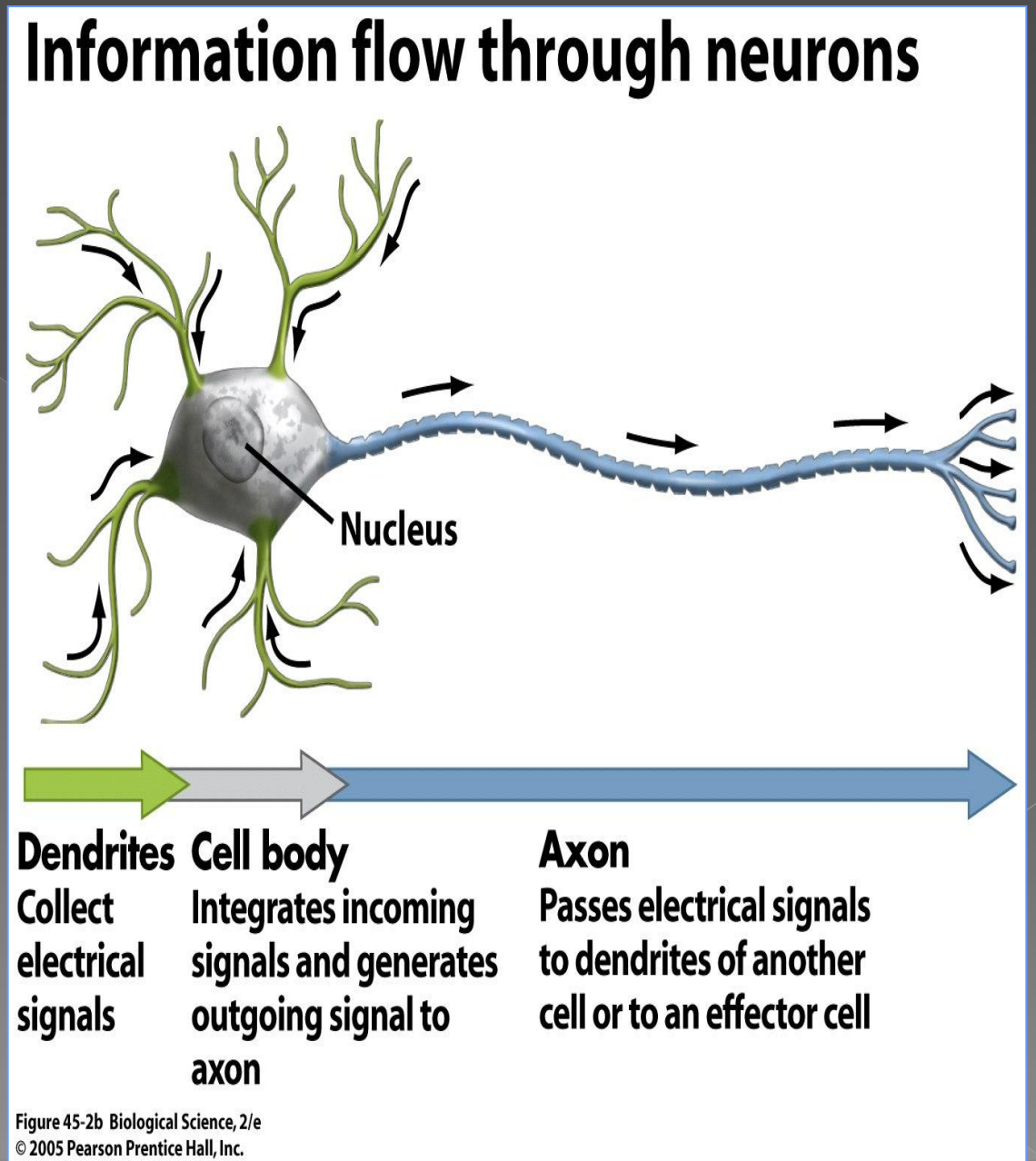
Chemical synapses are specialized junctions through which cells of the nervous system signal to one another and to non-neuronal cells such as muscles or glands.



Physiologic Anatomy of the Synapse

- The next figure shows a typical *anterior motor neuron* in the anterior horn of the spinal cord. It is composed of three major parts: the *soma*, which is the main body of the neuron; a single *axon*, which extends from the soma into a peripheral nerve that leaves the spinal cord; and the *dendrites*, which are great numbers of branching projections of the soma that extend as much as 1 mm into the surrounding areas of the cord.
- As many as 10,000 to 200,000 minute synaptic knobs called *presynaptic terminals* lie on the surfaces of the dendrites and soma of the motor neuron, about 80 to 95% of them on the dendrites and only 5 to 20% on the soma.These presynaptic terminals are the ends of nerve fibrils that originate from many other neurons.


Dendrites
Presynaptic terminals
Integration
Soma
Nucleus
Spike initiation
Axon hillock
Myelin sheath
Impulse conduction
Axon terminals
Transmitter secretion


Information flow through neurons
Nucleus
Dendrites
Collect electrical signals
Cell body
Integrates incoming signals and generates outgoing signal to axon
Axon
Passes electrical signals to dendrites of another cell or to an effector cell
Figure 45-2b Biological Science, 2/e
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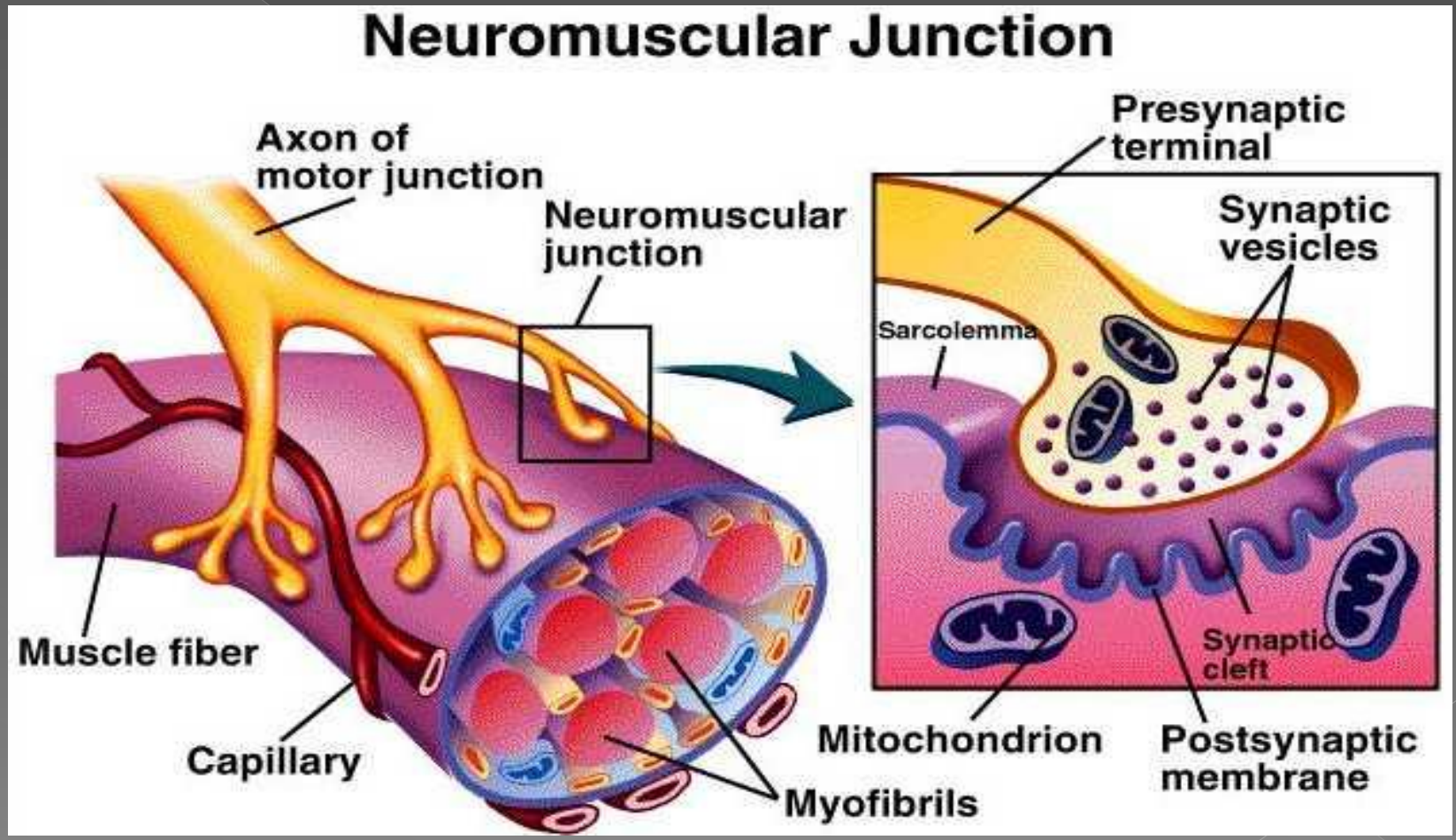
Neuromuscular junction



Presynaptic Terminals

- Electron microscopic studies of the presynaptic terminals show that they have varied anatomical forms, but most resemble small round or oval knobs and, therefore, are sometimes called *terminal knobs*, *boutons*, *end-feet*, or *synaptic knobs*.
- The presynaptic terminal is separated from the postsynaptic neuronal soma by a ***synaptic cleft*** having a width usually of 200 to 300 angstroms.
- The terminal has two internal structures important to the excitatory or inhibitory function of the synapse: the *transmitter vesicles* and the *mitochondria*.

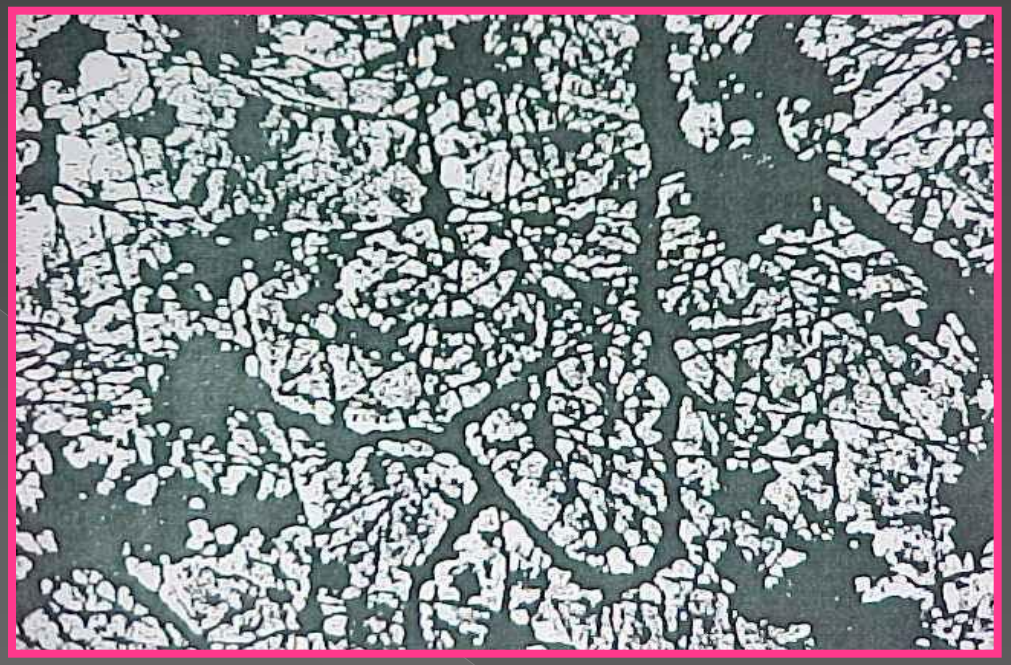
Presynaptic Terminals

- The ***transmitter vesicles*** contain the *transmitter substance* that, when released into the synaptic cleft, either *excites* or *inhibits* the ***postsynaptic neuron*** - excites if the neuronal membrane contains *excitatory receptors*, inhibits if the membrane contains *inhibitory receptors*.
- The ***mitochondria*** provide adenosine triphosphate (ATP), which in turn supplies the energy for synethesizing new transmitter substance.

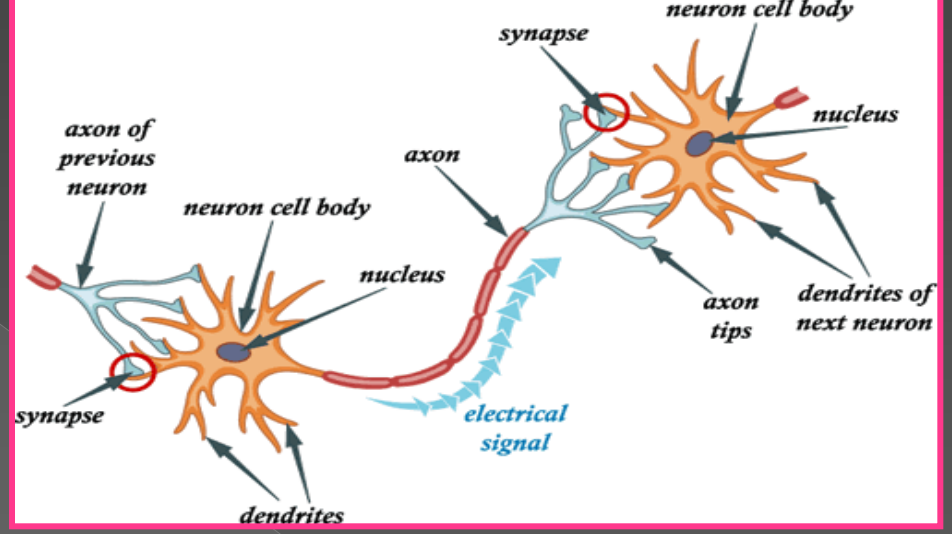
Types of Synapses in CNS

- Almost all the synapses used for signal transmission in the central nervous system of the human being are *chemical synapses*.
- In these, the first neuron secretes at its nerve ending synapse a chemical substance called a *neurotransmitter* (or often called simply *transmitter substance*), and this transmitter in turn acts on receptor proteins in the membrane of the next neuron to excite the neuron, inhibit it, or modify its sensitivity in some other way.

  More than 40 important transmitter substances have been discovered thus far. Some of the best known are acetylcholine, norepinephrine, epinephrine, histamine, gamma-aminobutyric acid (GABA), glycine, serotonin, and glutamate.



- With over a 100 billion cells compromising the human brain and each one needing to communicate information to at least one, if not thousands of other neurons, the importance of effective coding and communication of impulses between cells is vital.
- In order to achieve the complexity of human cognition, perception, and movement electrical stimuli by previous cells needs to convey appropriate information to following neurons.
- An action potential or electrical conduction along a neuron eventually ceases at the terminal ending and requires the propagation of a signal at the site of the post-synaptic terminal across a synapse.



Neuron Anatomy

Neurons have a round shaped **Soma** or **Cell Body** that holds the nucleus and organelles concerned with the synthesis of protein. **Dendrites** are a multitude branched processes that extend from the cell body and are designed to receive signals from other cells. The **Axon** is a single process that carries the action potential from the nerve cell body to a target. The junction of the axon and cell body is referred to as the **Axon Hillock** and is the site where action potentials begin. An action potential is carried along the axon until it reaches the **Terminal Ending**. It is here that the synaptic transmission begins.

Different Types of Synapse

There are 3 different kinds of axons that are determined by where synapse on post-synaptic cell. 1.**Axodendritic** - axons synapse on the dendrites of the post-synaptic cell. These cells are likely to be exhibiting an excitatory influence on the post-synaptic cells. 2.**Axosomatic** - axons synapse directly on the soma/cell body of the post-synaptic cell. These synapses are located closer to the axon hillock and are likely to have an inhibitory influence on the post-synaptic cell in order to "stop" propagation of an action potential. 3.**Axoaxonic** - axons synapse on the axons of the post-synaptic cell.

- Some of presynaptic terminals secrete a transmitter substance that excites the postsynaptic neuron.
- But other presynaptic terminals are *inhibitory* - they secrete a transmitter substance that inhibits the postsynaptic neuron.
- Neurons in other parts of the cord and brain differ from the anterior motor neuron in (1) the size of the cell body; (2) the length, size, and number of dendrites, ranging in length from almost zero to many centimeters; (3) the length and size of the axon; and (4) the number of presynaptic terminals, which may range from only a few to as many as 200,000.
- These differences make neurons in different parts of the nervous system react differently to incoming synaptic signals and, therefore, perform many different functions.

Mechanism by Which an Action Potential Causes Transmitter Release from the Presynaptic Terminals - Role of Calcium Ions

- The *presynaptic membrane* contains large numbers of *voltage-gated calcium channels*.
- When an action potential depolarizes the presynaptic membrane, these calcium channels open and allow large numbers of calcium ions to flow into the terminal.
- The quantity of transmitter substance that is then released from the terminal into the synaptic cleft is directly related to the number of calcium ions that enter.
- The precise mechanism by which the calcium ions cause this release is not known, but it is believed to be the following.

- When the calcium ions enter the presynaptic terminal, it is believed that they bind with special protein molecules on the inside surface of the presynaptic membrane, called *release sites*.
- This binding in turn causes the release sites to open through the membrane, allowing a few transmitter vesicles to release their transmitter into the cleft after each single action potential.
- For those vesicles that store the neurotransmitter acetylcholine, between 2000 and 10,000 molecules of acetylcholine are present in each vesicle, and there are enough vesicles in the presynaptic terminal to transmit from a few hundred to more than 10,000 action potentials.

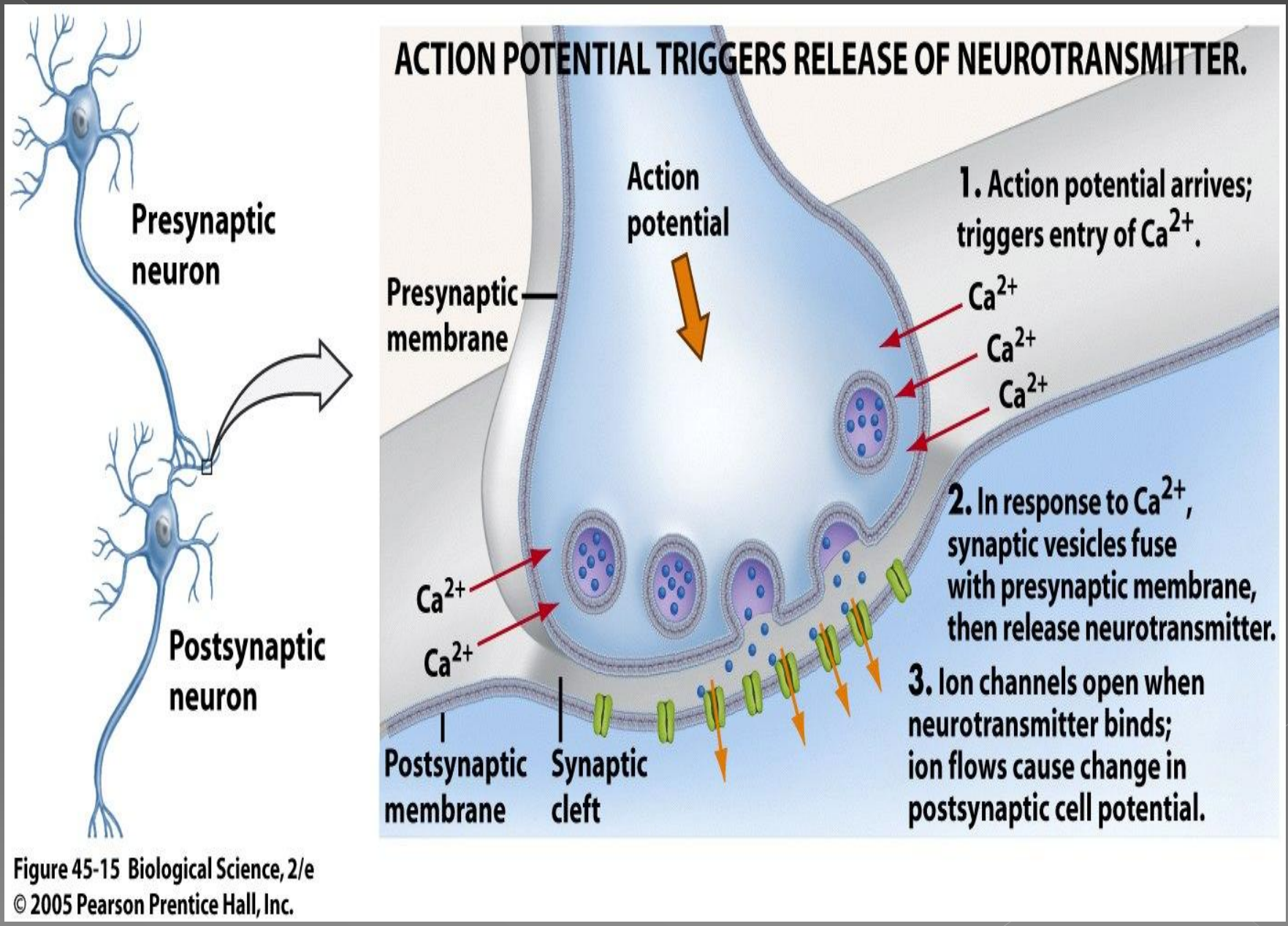


Figure 45-15 Biological Science, 2/e

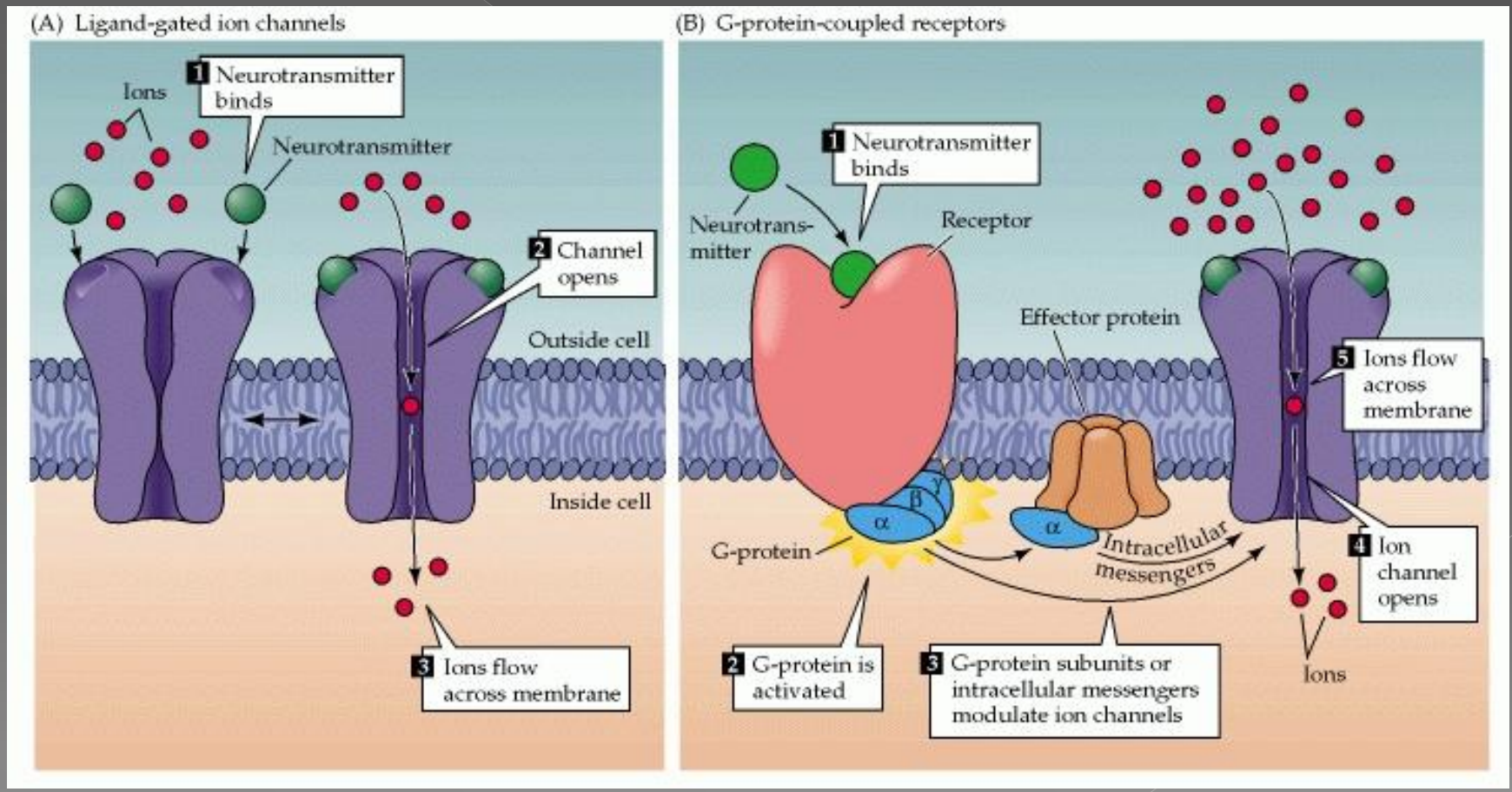
Action of the Transmitter Substance on the Postsynaptic Neuron - Function of "Receptor Proteins"

- The membrane of the postsynaptic neuron contains large numbers of *receptor proteins*.
- The molecules of these receptors have two important components:
  - (1) a *binding component* that protrudes outward from the membrane into the synaptic cleft - here it binds the neurotransmitter coming from the presynaptic terminal, and
  - (2) an *ionophore component* that passes all the way through the postsynaptic membrane to the interior of the postsynaptic neuron.
- The ionophore in turn is one of two types:
  - (1) an *ion channel* that allows passage of specified types of ions through the membrane or
  - (2) a "*second messenger" activator* that is not an ion channel but instead is a molecule that protrudes into the cell cytoplasm and activates one or more substances inside the postsynaptic neuron. These substances in turn serve as "second messengers" to increase or decrease specific cellular functions.

Postsynaptic receptors create an EPSP or IPSP by:

Ligand-Gated/Direct Gating, the transmitter reconfigures the channel when it attaches allowing for the movement of ions either in or out of the cell.

Indirect Gating/Secondary Messengers, when the transmitter binds to the receptor a GTP-binding protein activates a second-messenger cascade that modulates channel activity.



Ion Channels

- The ion channels in the postsynaptic neuronal membrane are usually of two types:
- (1) *cation channels* that most often allow sodium ions to pass when opened, but sometimes allow potassium and/or calcium ions as well, and
- (2) *anion channels* that allow mainly chloride ions to pass but also minute quantities of other anions.
- The *cation channels* that conduct sodium ions are lined with negative charges. These charges attract the positively charged sodium ions into the channel when the channel diameter increases to a size larger than that of the hydrated sodium ion. But those same negative charges *repel chloride ions and other anions* and prevent their passage.

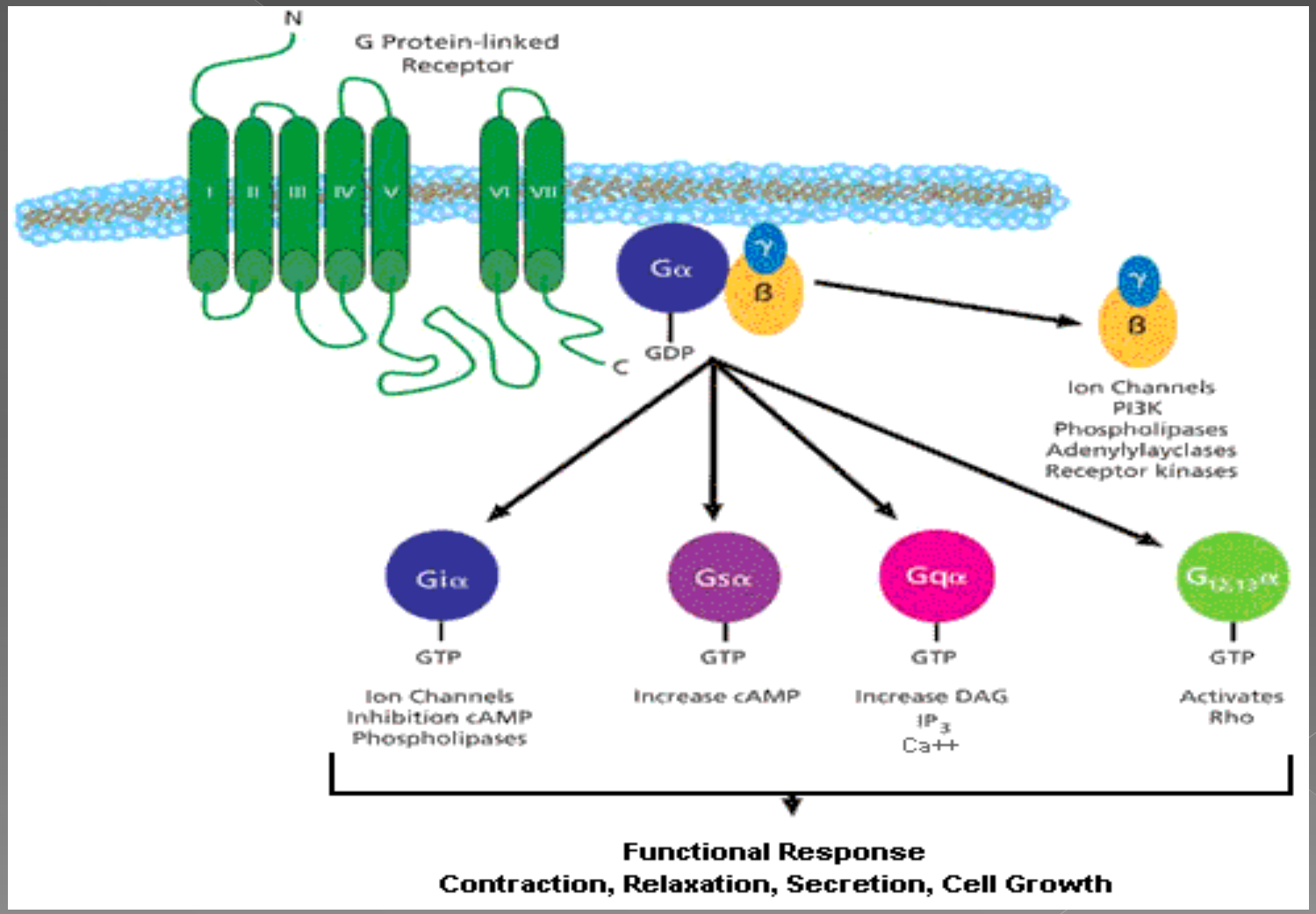
- For the *anion channels*, when the channel diameters become large enough, chloride ions pass into the channels and on through to the opposite side, whereas sodium, potassium, and calcium cations are blocked, mainly because their hydrated ions are too large to pass.
- We discussed that when cation channels open and allow positively charged sodium ions to enter, the positive electrical charges of the sodium ions will in turn excite this neuron.
- Therefore, a transmitter substance that opens cation channels is called an *excitatory transmitter*.
- Conversely, opening anion channels allows negative electrical charges to enter, which inhibits the neuron.
- Therefore, transmitter substances that open anion channels are called *inhibitory transmitters*.

"Second Messenger" System in the Postsynaptic Neuron

- There are several types of second messenger systems. One of the most common types uses a group of proteins called ***G-proteins***.
- A G-protein is attached to the portion of the receptor that protrudes into the interior of the cell.
- The G-protein in turn consists of three components: an alpha (α) component that is the *activator* portion of the G-protein, and beta (β) and gamma (γ) components that are attached to the alpha component and also to the inside of the cell membrane adjacent to the receptor protein.

- On activation by a nerve impulse, the alpha portion of the G-protein separates from the beta and gamma portions and then is free to move within the cytoplasm of the cell.
- Inside the cytoplasm, the separated alpha component performs one or more of multiple functions, depending on the specific characteristic of each type of neuron.

- Nobel laureates in Physiology or Medicine 1994 Alfred G. Gilman and Martin Rodbell (United States) "for their discovery of G-proteins and the role of these proteins in signal transduction in cells"



- Four changes can occur.

1. *Opening specific ion channels through the postsynaptic cell membrane*.
   - These channels often stay open for a prolonged time, in contrast to rapid closure of directly activated ion channels that do not use the second messenger system.
2. *Activation of cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP) in the neuronal cell*.
   - Recall that either cyclic AMP or cyclic GMP can activate highly specific metabolic machinery in the neuron and, therefore, can initiate any one of many chemical results, including long-term changes in cell structure itself, which in turn alters long-term excitability of the neuron.

3. *Activation of one or more intracellular enzymes.*

- The G-protein can directly activate one or more intracellular enzymes. In turn the enzymes can cause any one of many specific chemical functions in the cell.

4. *Activation of gene transcription.*

- This is one of the most important effects of activation of the second messenger systems because gene transcription can cause formation of new proteins within the neuron, thereby changing its metabolic machinery or its structure.
- Indeed, it is well known that structural changes of appropriately activated neurons do occur, especially in long-term memory processes.

Excitatory or Inhibitory Receptors in the Postsynaptic Membrane

- **Excitation**

1. *Opening of sodium channels to allow large numbers of positive electrical charges to flow to the interior of the postsynaptic cell.* This raises the intracellular membrane potential in the positive direction up toward the threshold level for excitation. It is by far the most widely used means for causing excitation.
2. *Depressed conduction through chloride or potassium channels, or both.* This decreases the diffusion of negatively charged chloride ions to the inside of the postsynaptic neuron or decreases the diffusion of positively charged potassium ions to the outside. In either instance, the effect is to make the internal membrane potential more positive than normal, which is excitatory.
3. *Various changes in the internal metabolism of the postsynaptic neuron* to excite cell activity or, in some instances, to increase the number of excitatory membrane receptors or decrease the number of inhibitory membrane receptors.

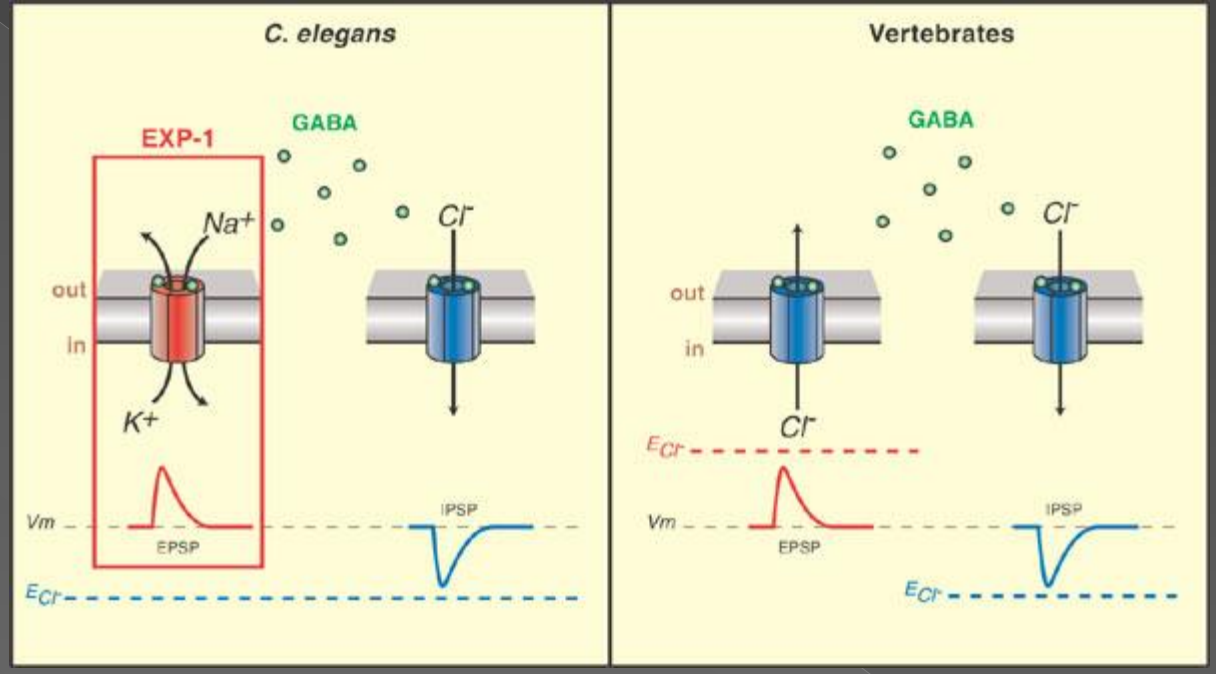
- **Inhibition**

1. *Opening of chloride ion channels through the postsynaptic neuronal membrane*. This allows rapid diffusion of negatively charged chloride ions from outside the postsynaptic neuron to the inside, thereby carrying negative charges inward and increasing the negativity inside, which is inhibitory.
2. *Increase in conductance of potassium ions out of the neuron*. This allows positive ions to diffuse to the exterior, which causes increased negativity inside the neuron; this is inhibitory.
3. *Activation of receptor enzymes* that inhibit cellular metabolic functions that increase the number of inhibitory synaptic receptors or decrease the number of excitatory receptors.

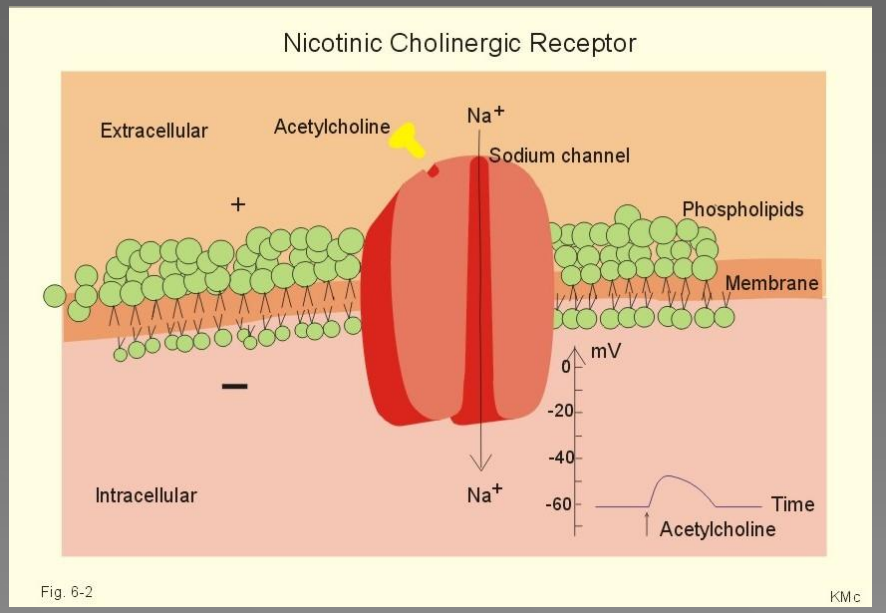
Time Course of Postsynaptic Potentials

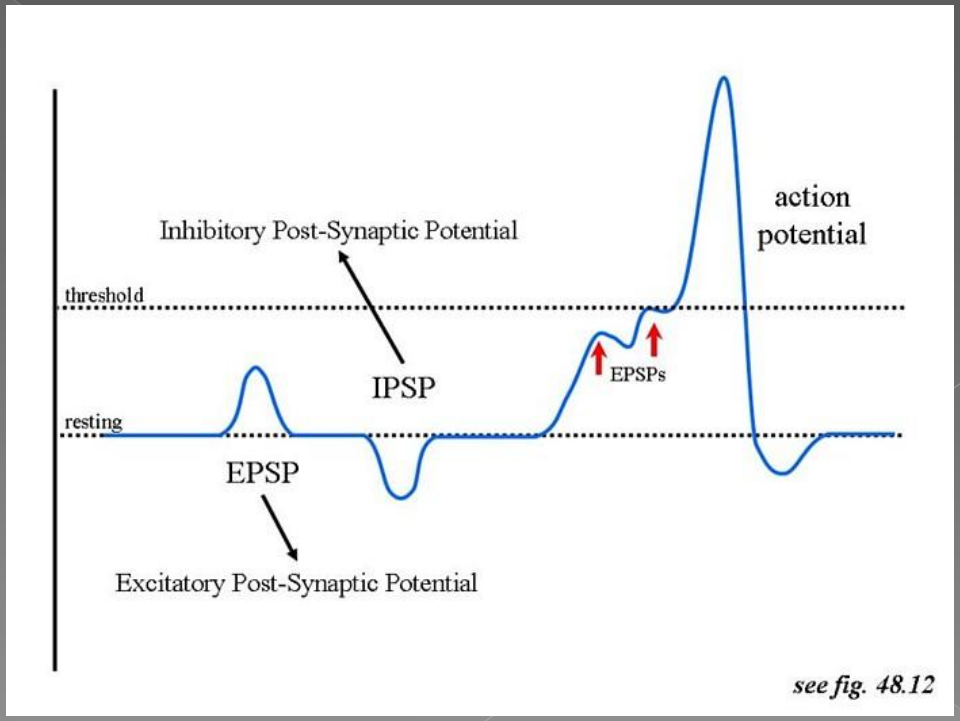
- When an excitatory synapse excites the anterior motor neuron, the neuronal membrane becomes highly permeable to sodium ions for 1 to 2 milliseconds. During this very short time, enough sodium ions diffuse rapidly to the interior of the postsynaptic motor neuron to increase its intraneuronal potential by a few millivolts, thus creating the excitatory postsynaptic potential (EPSP).
- This potential then slowly declines over the next 15 milliseconds because this is the time required for the excess positive charges to leak out of the excited neuron and to re-establish the normal resting membrane potential.

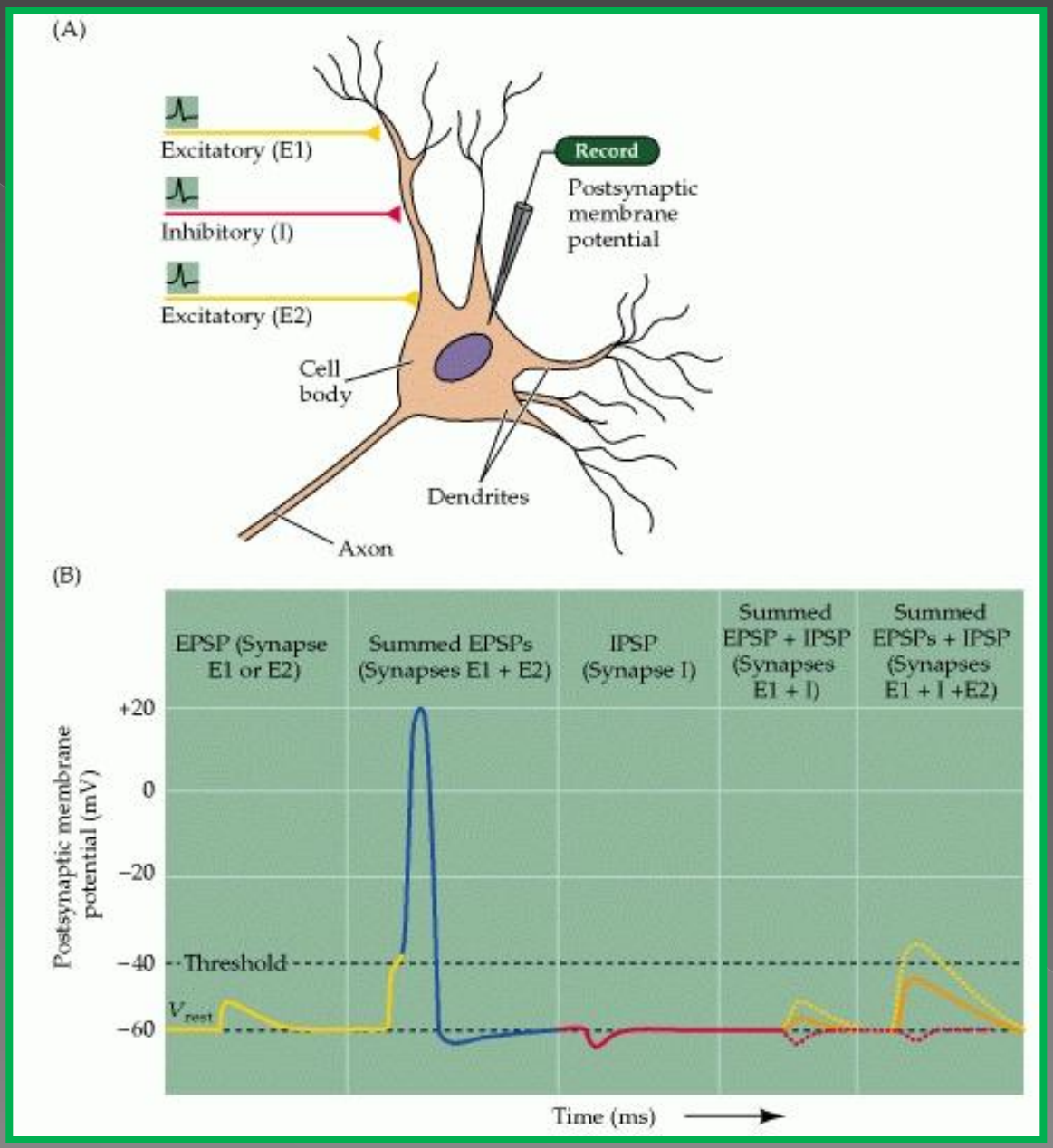
- Precisely the opposite effect occurs for an IPSP; that is, the inhibitory synapse increases the permeability of the membrane to potassium or chloride ions, or both, for 1 to 2 milliseconds, and this decreases the intraneuronal potential to a more negative value than normal, thereby creating the IPSP.
- This potential also dies away in about 15 milliseconds.
- Other types of transmitter substances can excite or inhibit the postsynaptic neuron for much longer periods - for hundreds of milliseconds or even for seconds, minutes, or hours. This is especially true for some of the neuropeptide types of transmitter substances.

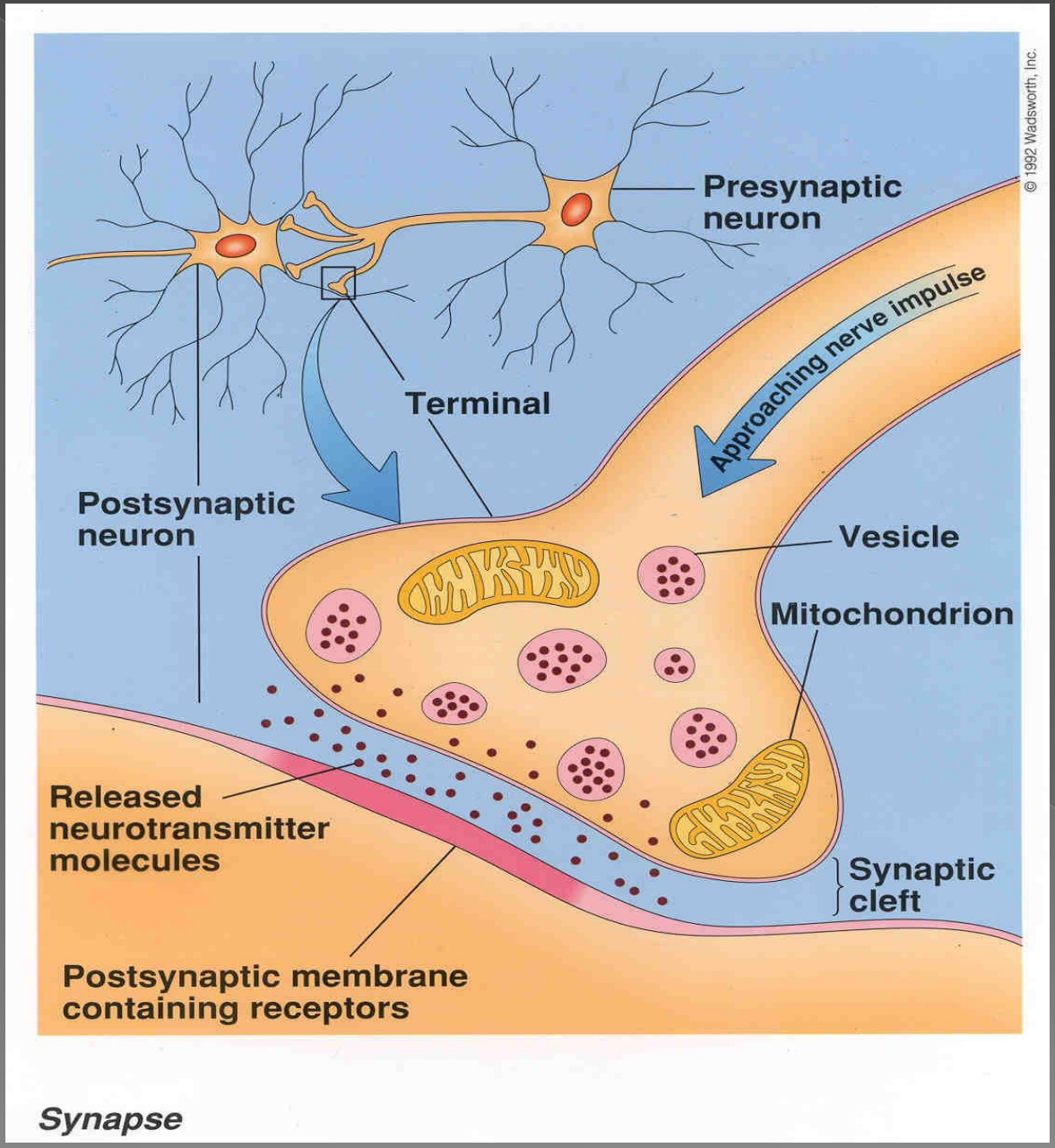


Postsynaptic potentials






(A)
Excitatory (E1)
Inhibitory (I)
Excitatory (E2)
Record
Postsynaptic membrane potential
Cell body
Dendrites
Axon
(B)
EPSP (Synapse E1 or E2)
Summed EPSPs (Synapses E1 + E2)
IPSP (Synapse I)
Summed EPSP + IPSP (Synapses E1 + I)
Summed EPSPs + IPSP (Synapses E1 + I +E2)
Postsynaptic membrane potential (mV)
+20
0
−20
−40
−60
Threshold
V_{rest}
Time (ms)



Synapse

Some Special Characteristics of Chemical Synapses Transmission:

- One way direction
- Delay
- Fatigue
- Partial or temporal summation of postsynaptic potentials

Small-Molecule, Rapidly Acting Transmitters

Class I

- Acetylcholine

Class II: The Amines

- Norepinephrine
- Epinephrine
- Dopamine
- Serotonin
- Histamine

Class III: Amino Acids

- Gamma-aminobutyric acid (GABA)
- Glycine
- Glutamate
- Aspartate

Class IV

- Nitric oxide (NO)

Neuropeptide, Slowly Acting Transmitters or Growth Factors

Hypothalamic-releasing hormones

- Thyrotropin-releasing hormone
- Luteinizing hormone–releasing hormone
- Somatostatin (growth hormone inhibitory factor)

Pituitary peptides

- Adrenocorticotropic hormone (ACTH)
- b-Endorphin
- a-Melanocyte-stimulating hormone
- Prolactin
- Luteinizing hormone
- Thyrotropin
- Growth hormone
- Vasopressin
- Oxytocin

Peptides that act on gut and brain

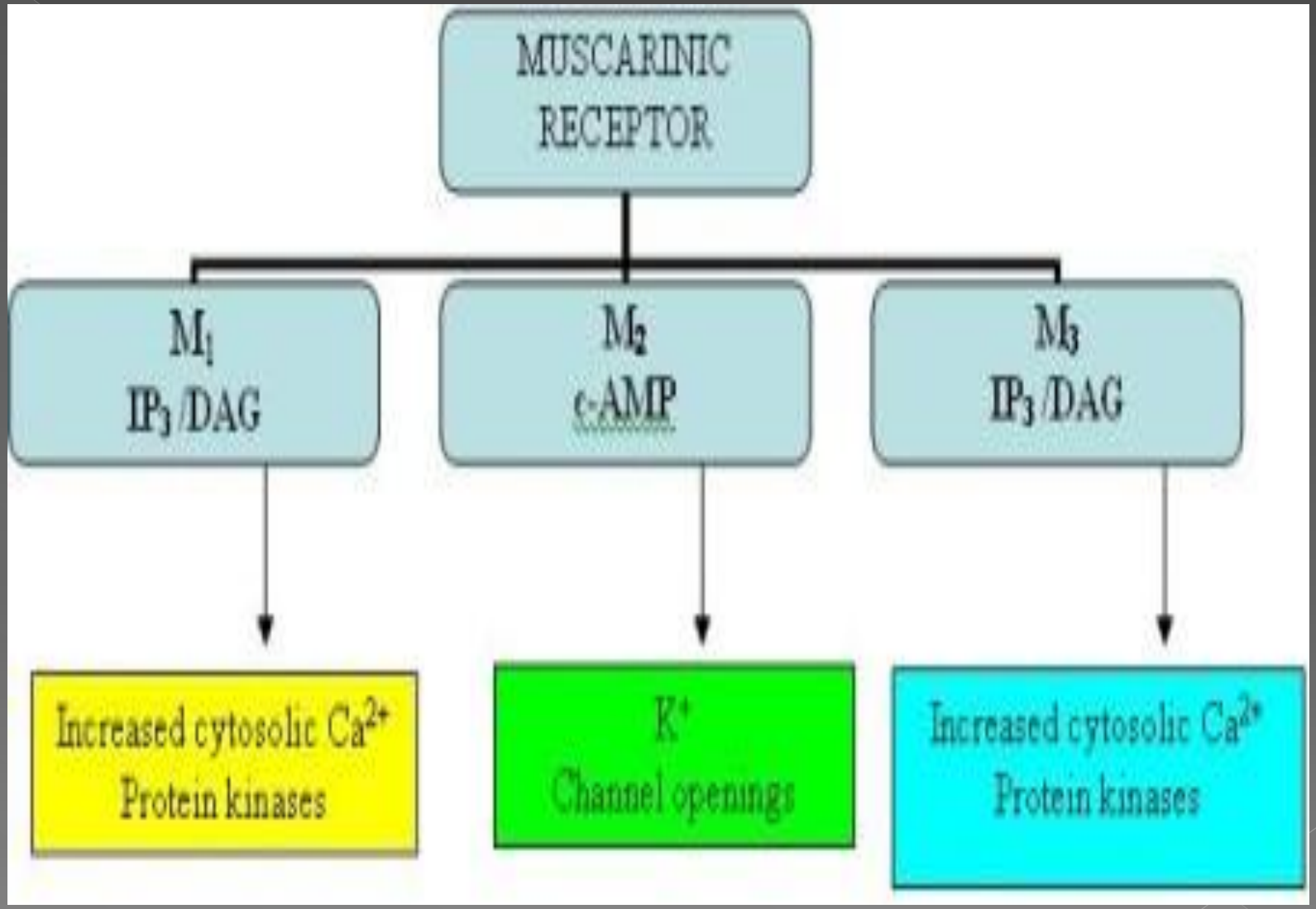
- Leucine enkephalin
- Methionine enkephalin
- Substance P
- Gastrin
- Cholecystokinin
- Vasoactive intestinal polypeptide (VIP)
- Nerve growth factor
- Brain-derived neurotropic factor
- Neurotensin
- Insulin
- Glucagon

From other tissues

- Angiotensin II
- Bradykinin
- Carnosine
- Sleep peptides
- Calcitonin

Cholinergic receptors

- **Characteristic of important subtypes of nicotinic receptor**
- *Nicotinic receptors are of two types' N_m and N_n.*
- N_m is located in neuromuscular junction causes contraction of skeletal muscles because it causes depolarization of muscle end plate.
- N_n causes depolarization in autonomic ganglia result in post ganglionic impulse.
- Also cause release of catecholamine from adrenal medulla and also site specific excitation or inhibition in brain.
- Both N_m and N_n are Na^+ and K^+ channel linked but N_n also linked with an extra Ca^{++} channel.


MUSCARINIC RECEPTOR
M1
IP3 /DAG
M2
c-AMP
M3
IP3 /DAG
Increased cytosolic Ca2+
Protein kinases
K+
Channel openings
Increased cytosolic Ca2+
Protein kinases

- **Characteristic of important subtypes of muscarinic receptor**

  M_1 , M_2 and M_3 are subtypes of muscarinic receptor.

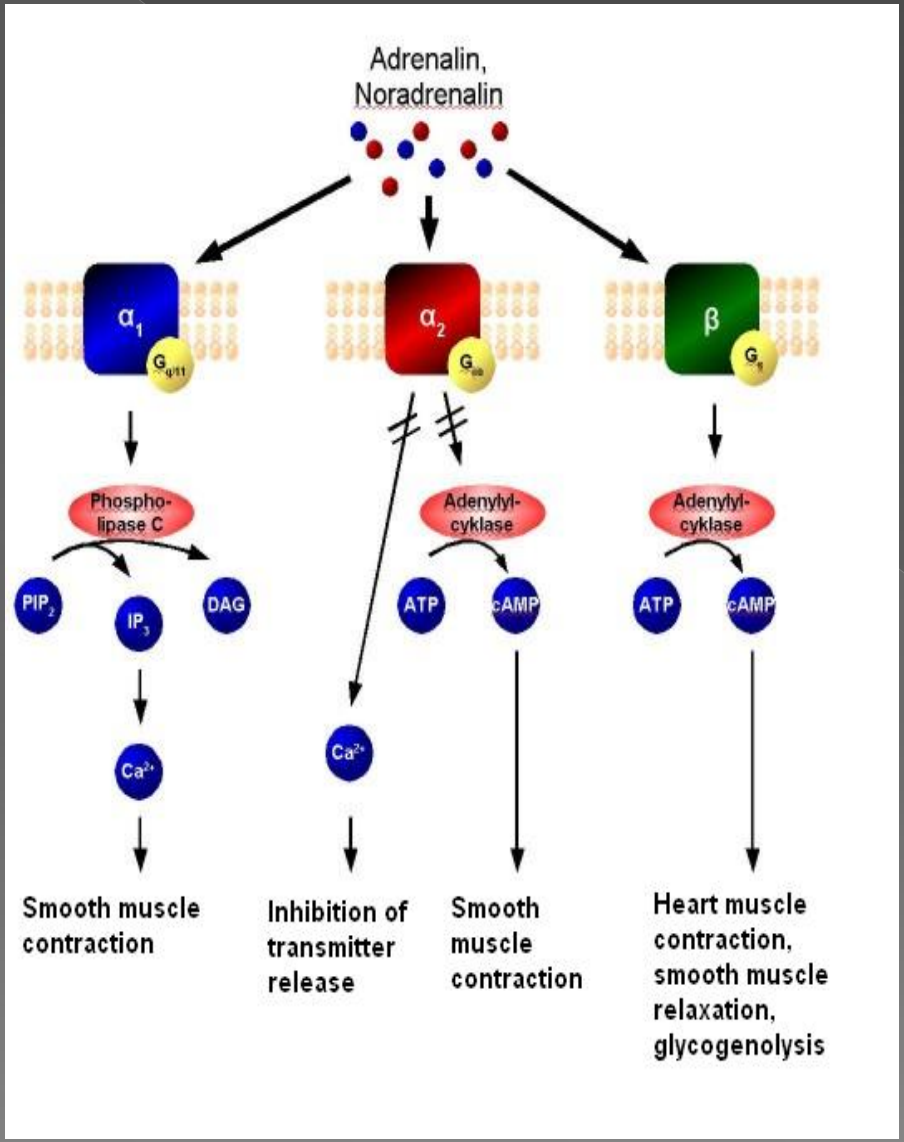
  M_1 receptor is G-protein coupled receptor which is linked with IP 3 / DAG. This activated system will result in increase concentration of cytosolic calcium. And as we know calcium is responsible for long phase depolarization in autonomic ganglia and also result in release of histamine and acid from gland located in GIT (gastrointestinal tract). Its action in CNS is unknown.

M_2 receptor is located in heart which is also G-protein coupled but its activation will down regulate the activity of c-AMP and also responsible for the opening of potassium channel as both are responsible for decreased activity because of hyper polarization activity. As these receptors are found in heart they will decrease the generation of impulse as a result of this decrease heart rate and slow conduction of impulses.

M_3 is also IP 3 /DAG linked but they are located on smooth muscle and exocrine glands will result in the contraction of muscles and secretion from gland because it will increase the cytosolic calcium.

There are two main groups of adrenergic receptors, α and β, with several subtypes.

Alpha Receptors 1. Vasoconstriction of a. Coronary arteries b. Veins 2. ↓motility of GIT smooth muscle cells		**Beta Receptors**	
α1 (postsynaptic)	**α2 (presynaptic)**	**β1 (postsynaptic)**	**β2 (postsynaptic)**
Gq protein coupled Activates **Phospholipase C** **PIP2 →IP3 + DAG**	**Gi protein** coupled Inhitbits **Adenyl Cyclase** **ATP →X→cAMP**	**Gs protein** coupled Activates **Adenyl Cyclase** **ATP → cAMP**	
1. Vasoconstriction of blood vessels of a. Skin b. GIT c. Kidney d. Brain 2. Contraction of smooth muscles of a. Ureter b. Vas deferens c. Urethral spinchter d. Uterus e. Cilliary body (mydiarisis) 3. Glucose metabolism a. Gluconeogenesis b. Glucolysis	1. Glucose metabolism a. Inhibits insulin release b. Stimulates glucagon release 2. Contraction of anal spinchter 3. Inhibits release of Norepinephrine	1. The heart a. ↑heart rate (+ chronotropic) b. ↑impulse conduction (+dromotropic) c. ↑contraction (+ inotropic) d. ↑ejection fraction 2. ↑renin release by Juxtaglomerular cells 3. ↑hunger a. ↑ghrelin release by stomach	1. Smooth muscle relaxation of a. Bronchus b. Bronchioles c. Detrusor muscle d. Uterine muscle 2. Contraction of urethral spinchter 3. ↑renin release by Juxtaglomerular cells 4. Glucose metabolism a. Inhibits insulin release b. Stimulate i. Gluconeogenesis ii. Glucolysis 5. Lipolysis 6. Thickened salivary secretion



The mechanism of adrenergic receptors:

Adrenaline or noradrenaline are receptor ligands to either α_1, α_2 or β-adrenergic receptors.

α_1 couples to Gq, which results in increased intracellular Ca^{2+} which results in smooth muscle contraction.

α_2, on the other hand, couples to Gi, which causes a decrease of cAMP activity, resulting in smooth muscle contraction. β receptors couple to Gs, and increases intracellular cAMP activity, resulting in e.g. heart muscle contraction, smooth muscle relaxation and glycogenolysis.

- ***a_1-adrenergic receptors*** are members of the Gq protein-coupled receptor superfamily. Upon activation, a heterotrimeric G protein, Gq, activates phospholipase C (PLC). The PLC cleaves phosphatidylinositol 4,5-bisphosphate (PIP2), which in turn causes an increase in inositol triphosphate (IP3) and diacylglycerol (DAG). The former interacts with calcium channels of endoplasmic and sarcoplasmic reticulum, thus changing the calcium content in a cell. This triggers all other effects.
- Specific actions of the a_1 receptor mainly involve smooth muscle contraction. It causes vasoconstriction in many blood vessels, including those of the skin, gastrointestinal system, kidney and brain.
- ***The a_2 receptor*** is a presynaptic receptor, causing negative feedback on, for example, norepinephrine. When NA is released into the synapse, it feeds back on the a_2 receptor, causing less NA release from the presynaptic neuron. This decreases the effect of NA.

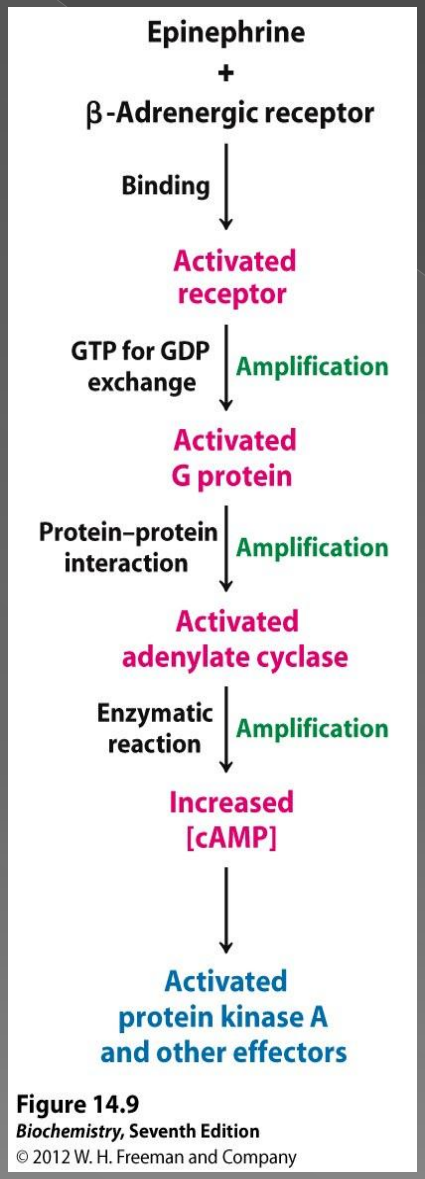


Figure 14.9
Biochemistry, Seventh Edition

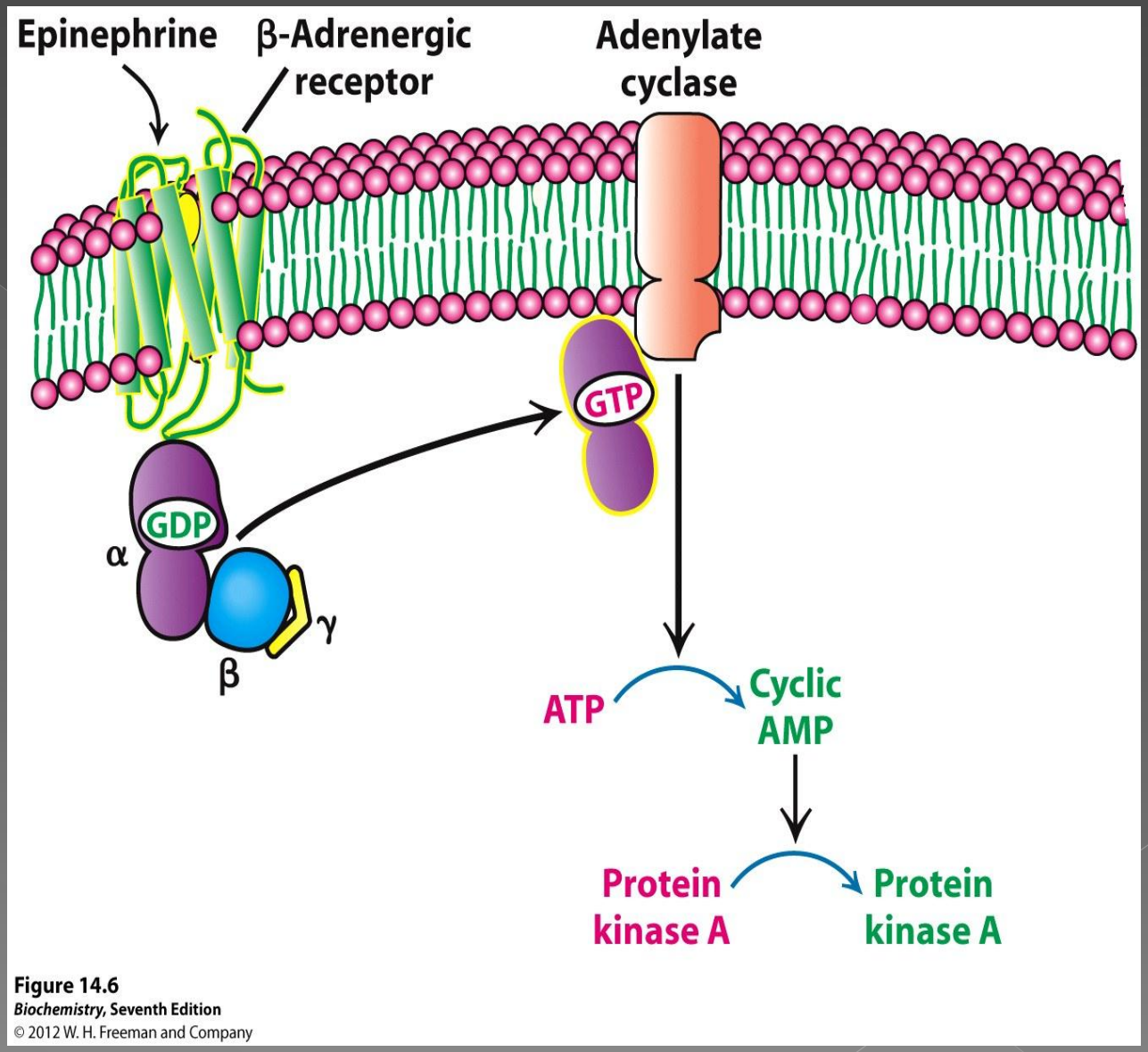
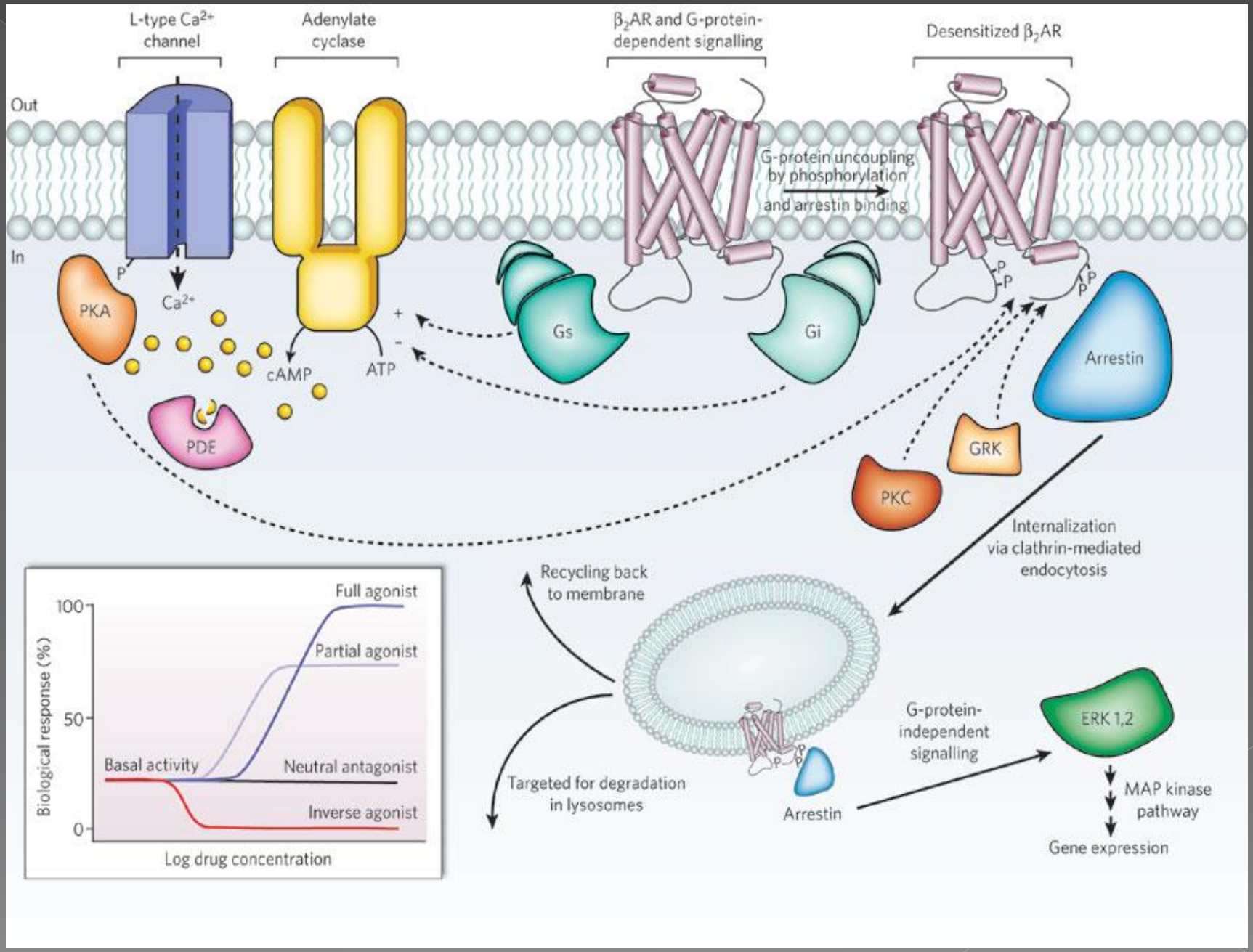


Figure 14.6
Biochemistry, Seventh Edition

- The type 2 beta adrenergic receptor (β_2AR) can activate two G proteins, Gs and Gi, which differentially regulate adenylate cyclase.
- Adenylate cyclase generates cyclic AMP (cAMP), which activates protein kinase A (PKA), a kinase that regulates the activity of several cellular proteins including the L-type Ca^{2+} channel and the β_2AR.
- cAMP second messenger levels are downregulated by specific phosphodiesterase proteins (PDEs). Activation of the β_2AR also leads to phosphorylation by a G-protein-coupled receptor kinase (GRK) and subsequent coupling to arrestin.
- Arrestin is a signalling and regulatory protein that promotes the activation of extracellular signal-regulated kinases (ERK), prevents the activation of G proteins and promotes the internalization of the receptor through clathrin-coated pits.


L-type Ca2+ channel
Adenylate cyclase
β2AR and G-protein-dependent signalling
Desensitized β2AR
Out
In
G-protein uncoupling by phosphorylation and arrestin binding
PKA
Ca2+
cAMP
ATP
PDE
Gs
Gi
Arrestin
GRK
PKC
Internalization via clathrin-mediated endocytosis
Recycling back to membrane
Targeted for degradation in lysosomes
Arrestin
G-protein-independent signalling
ERK 1,2
MAP kinase pathway
Gene expression
Full agonist
Partial agonist
Basal activity
Neutral antagonist
Inverse agonist
Biological response (%)
100
50
0
Log drug concentration

How neurotransmitters can inactivate?

1. Release of special enzyme in synaptic cleft that causes breakdown (acetylcholine esterase, KOMT, MAO etc.)
2. Diffusion back trough presynaptic membrane (acetylcholine)

Благодаря за вниманието!