General Physiology
Second Semester 2024
Lecture 15 and lecture 16
General organization of the nervous system
Basic structure and Functions of Synapses
Synaptic Potential (EPSP and IPSP)
Neurotransmitters
Neuronal Graded Potentials

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NERVOUS SYSTEM

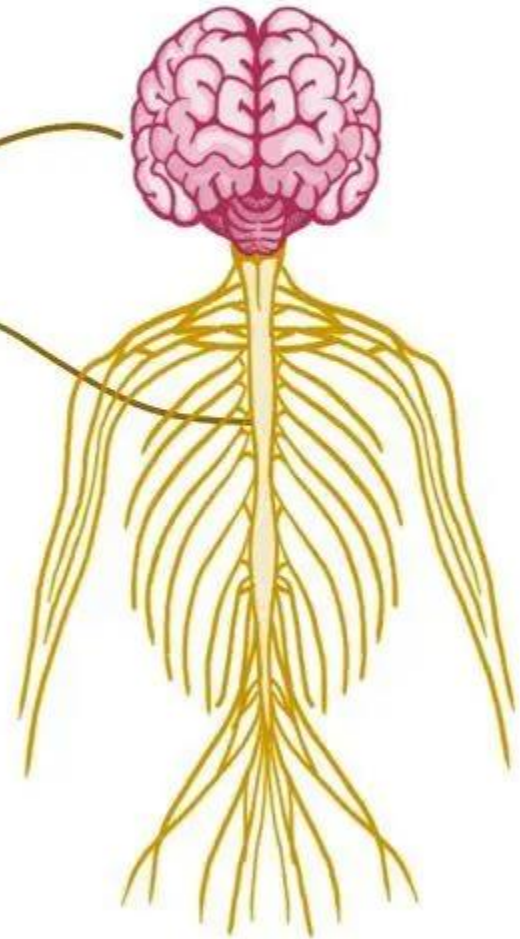
SEE, WALK, TALK

CENTRAL NERVOUS SYSTEM

- BRAIN
- SPINAL CORD

PERIPHERAL NERVOUS SYSTEM

- SOMATIC
- AUTONOMIC



AFFERENT

- SENSORY INFO
- OUTSIDE → CNS
- VISUAL, AUDITORY, CHEMORECEPTORS, & SOMATOSENSORY (TOUCH)

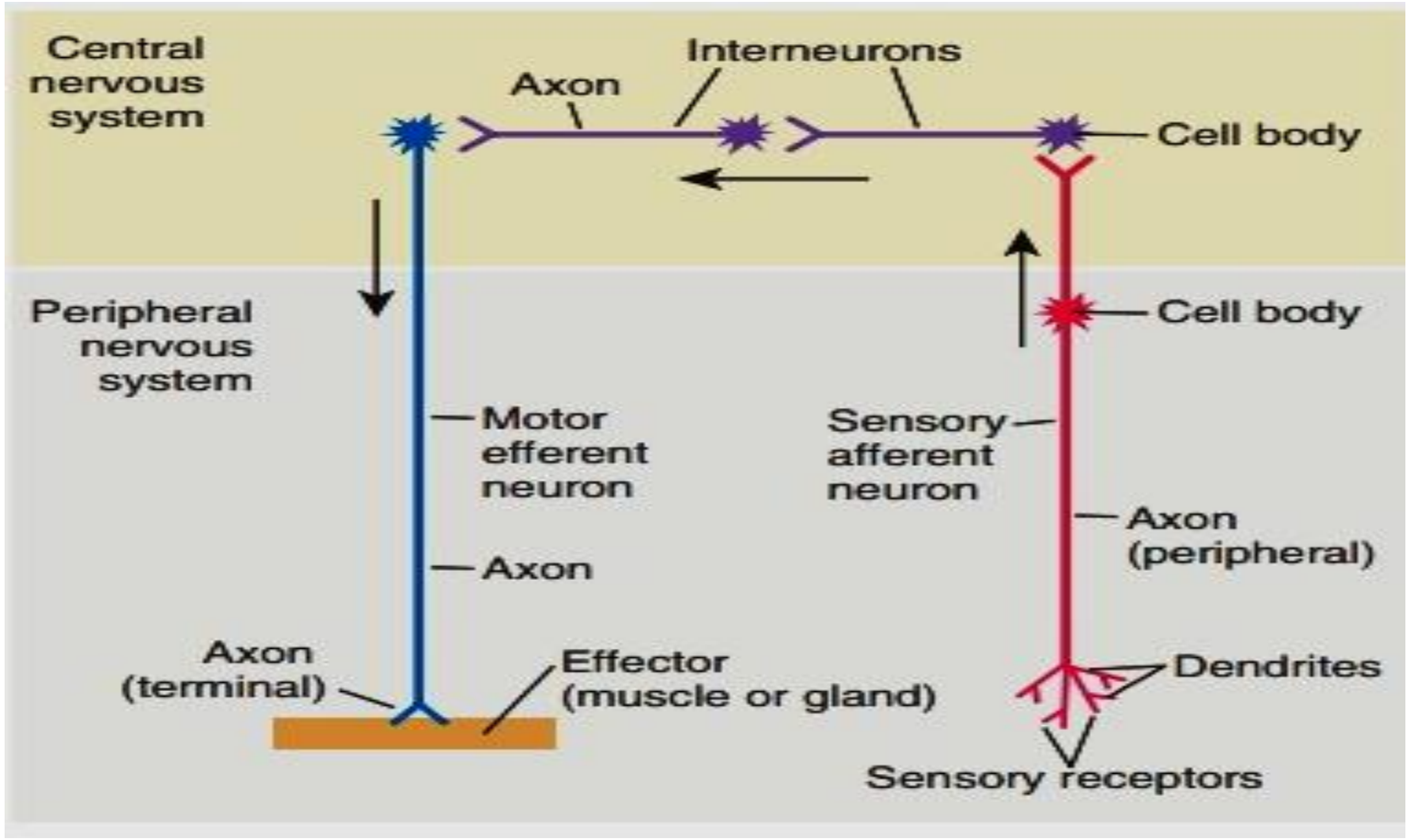
EFFERENT

- MOTOR INFO → PERIPHERY
- CONTRACTION OF SKELETAL MUSCLES
  - MOVEMENT THROUGH SOMATIC NS

Functional classification of neurons

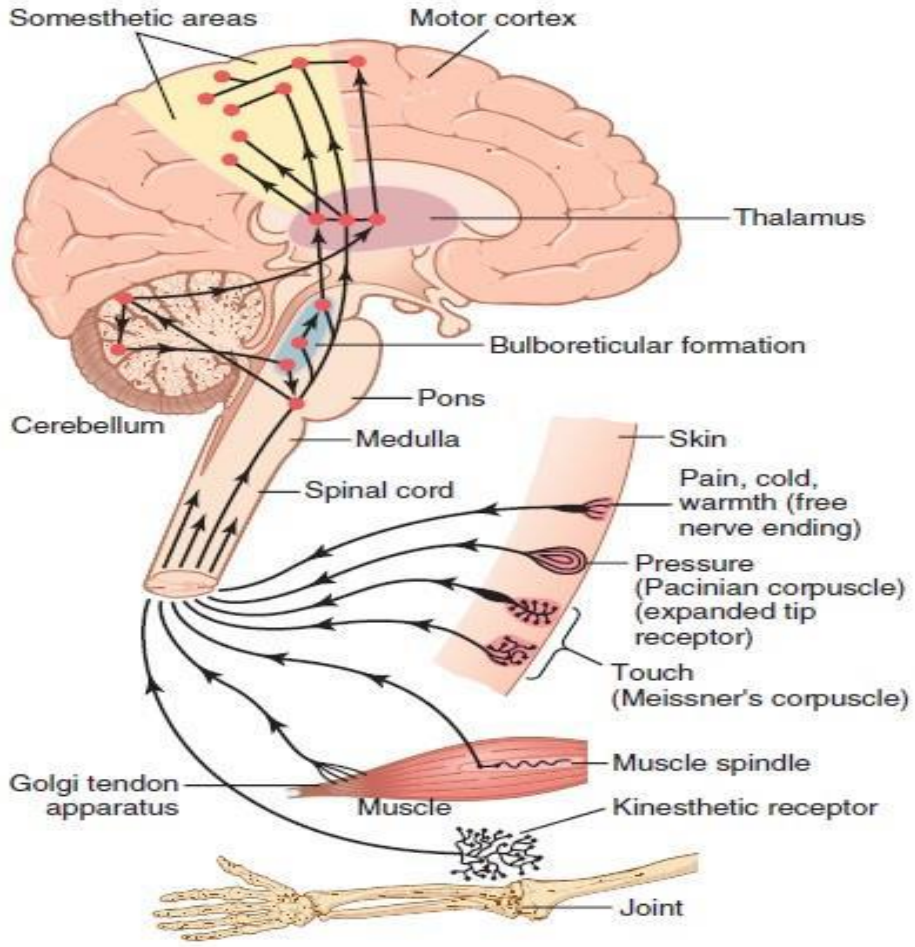
classification of nuerons

- Sensory /affèrent nuerons
- Motor /efférent nuerons
- Inter/association nuerons



Sensory function of the nervous system

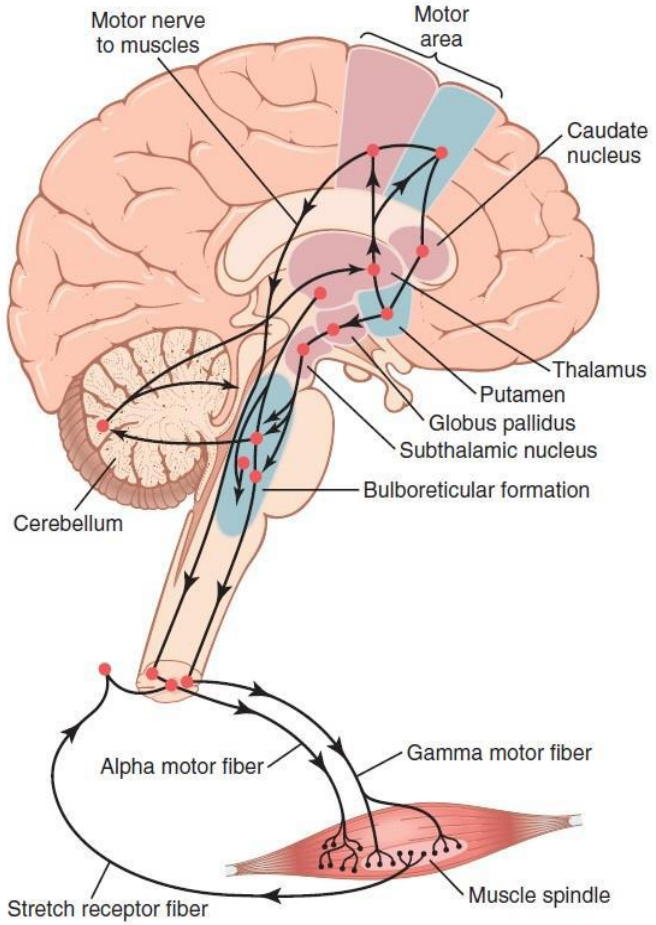
The figure shows an outline of sensory system, which transmits sensory information from
the receptors of the entire body surface and from some deep structures. This information enters the central nervous system through peripheral nerves and is conducted immediately to multiple sensory area he CNS areas via special sensory pathways



Somatosensory axis of the nervous system.

MOTOR PART OF THE NERVOUS SYSTEM—EFFECTORS

Motor functions of the nervous system,
(1) contraction of appropriate skeletal muscles throughout the body
(2) contraction of smooth muscle in the internal organs
(3) Secretion of active chemical substances by both exocrine and endocrine glands in many parts of the body. and the muscles and glands are called *effectors* because
they are the actual anatomical structures that perform the functions dictated by the nerve signals
The motor system consists of voluntary and involuntary part.
▪The control of skeletal muscle contraction is mediated by voluntary motor nerves, whereas the **autonomic nervous system** is responsible for the involuntary control of smooth muscle contraction and glandular secretion.



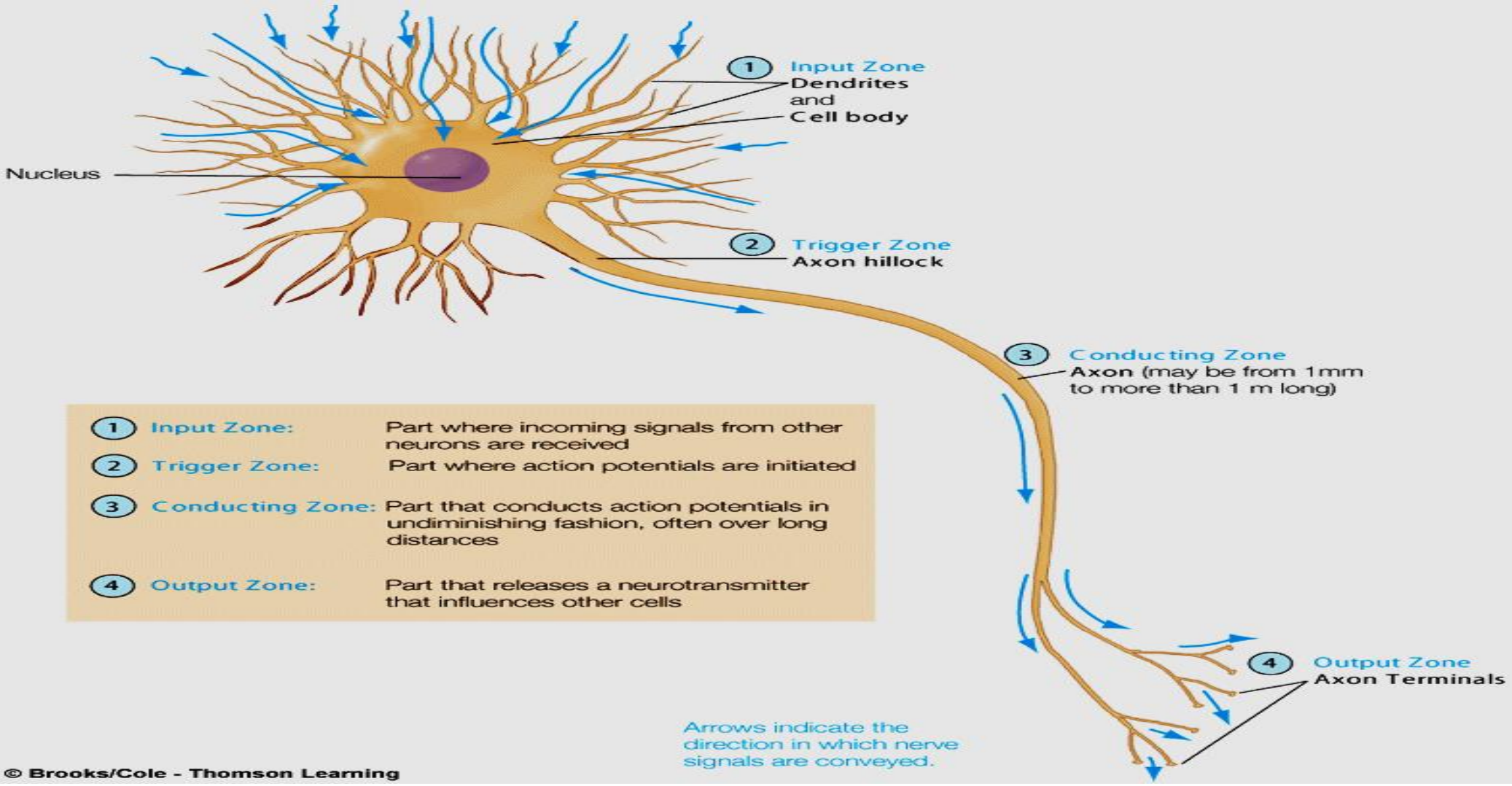
Skeletal motor nerve axis of the nervous system.

Neurons and glial cells

- Nervous tissue is composed of tow types of cells
- Neurons which are excitable and conduct information via nerve impulses and communicate with each through specialized junctions know as synapses
  - There are about 10 billion cells in the CNS
  - The basic functional unit of the nervous system is the NEURON. The CNS contains more than 100 billion neurons. Neurons mainly function to *store*, *communicate*, and *integrate information*

- Glial cells :which perform a variety of nonsignaling functions such as forming myelin to provide support and insulation between neurons, phagocytosing and removing cellular debris, removing excess neurotransmitters, and forming the blood-brain barrier

Functional component of a neuron



Synapses and Signal Transmission

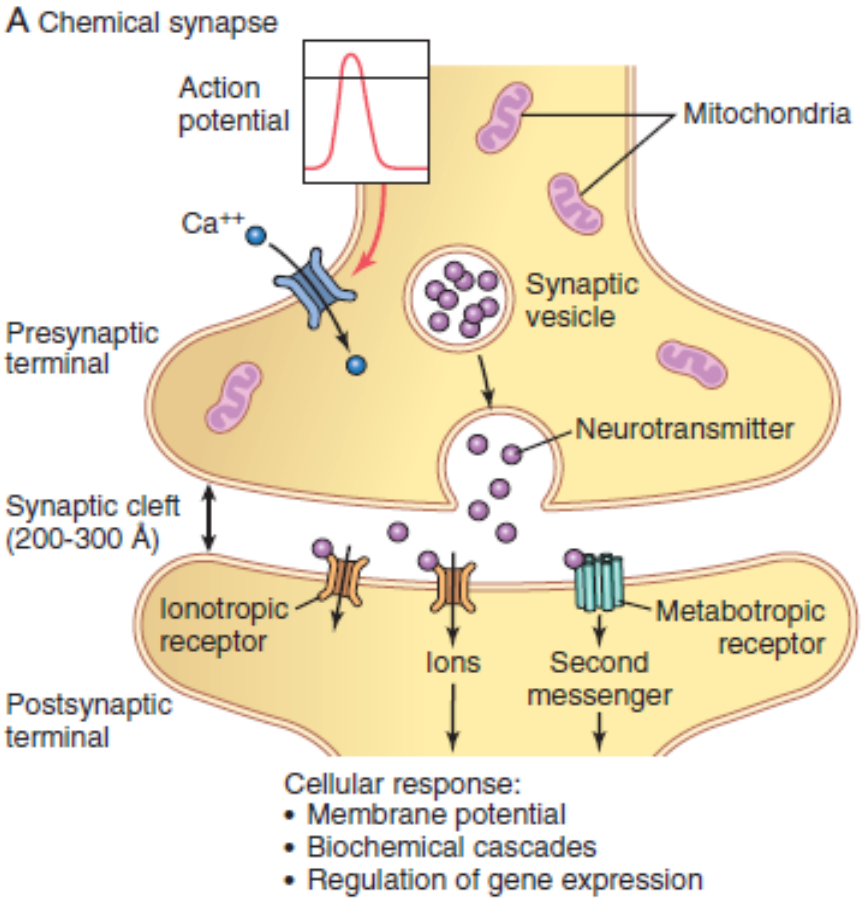
- A synapse is the junction between neurons or between a neuron and an effector like skeletal muscles

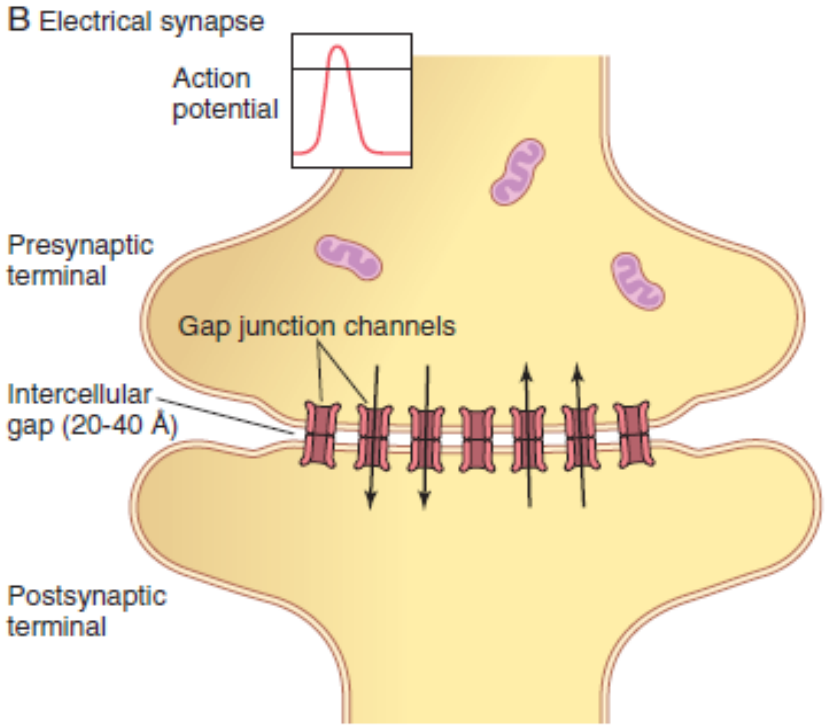
- Types of synapse
  - Electrical Synapse
  - Gap junctions connect cells and allow the transfer of electrical activity and to synchronize the activity of a group of cells
  - Chemical Synapse
  - One-way transfer of information from a presynaptic neuron to a postsynaptic neuron
  - The primary type of synapses in the nervous system

Types of Synapses
Electrical synapses and chemical synapses
Functional anatomy

Synaptic cleft

synaptic delay





Electrical synapses

- Electrical synapses are a physical connection between two neurons. cell membrane proteins called connexons form gap junctions between the neurons.
- The gap junctions form pores that allow ions to flow between neurons, so as an action potential propagates in the presynaptic neuron, the influx of sodium can move directly into the postsynaptic neuron and depolarize the cell.
- The response in the postsynaptic cell is almost immediate, with little to no delay between signaling in the pre- and postsynaptic neurons.
- Electrical synapses play an important role in the development of the nervous system but are also present throughout the developed nervous system, although in much smaller numbers compared chemical synapses.
- Compared to chemical synapses, electrical synapses conduct nerve impulses faster (almost no delay).

Electrical synapses

- The response is always the same sign as the source. For example, depolarization of the pre-synaptic membrane will always induce a depolarization in the post-synaptic membrane, and vice versa for hyperpolarization.
- Also, the response in the postsynaptic neuron is in general smaller in amplitude than the source.
- The relative speed of electrical synapses allows for many neurons to fire synchronously (at the same time). For example, certain hormone-secreting neurons within the hypothalamus are connected by electrical synapses, thus facilitating a burst of hormone secretion into the circulation
- Gap junctions are present in cardiac muscles and visceral (single unit smooth muscles)

Chemical synapses

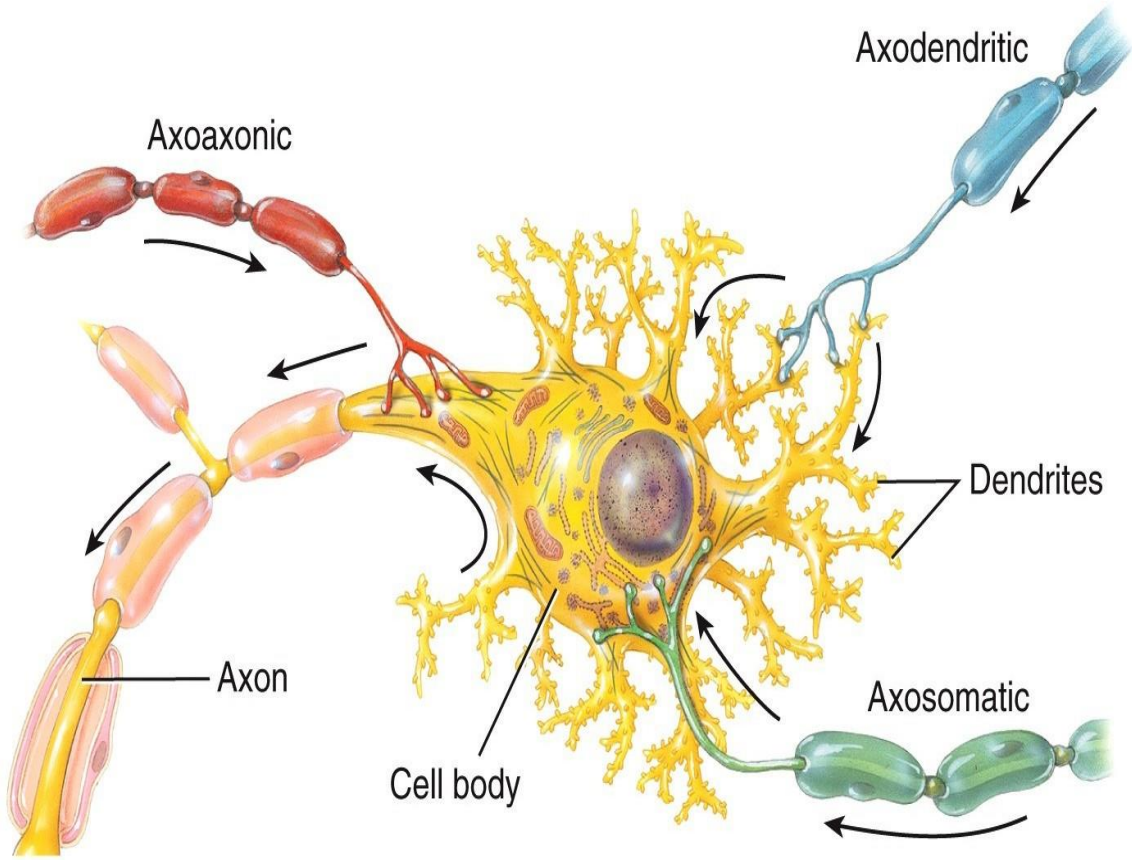
- Most synapses in Nervous system are chemicals synapses and the transmission of signal from presynaptic to postsynaptic cell occurs via the release of chemicals know as neurotransmitters
- Transmission is one direction (from presynaptic to postsynaptic neuron)
- Synaptic cleft : space between presynaptic and postsynaptic neurons
- Synaptic delay Time is needed for signal transmission from presynaptic to postsynaptic neuros

Function of chemical nervous system synapses

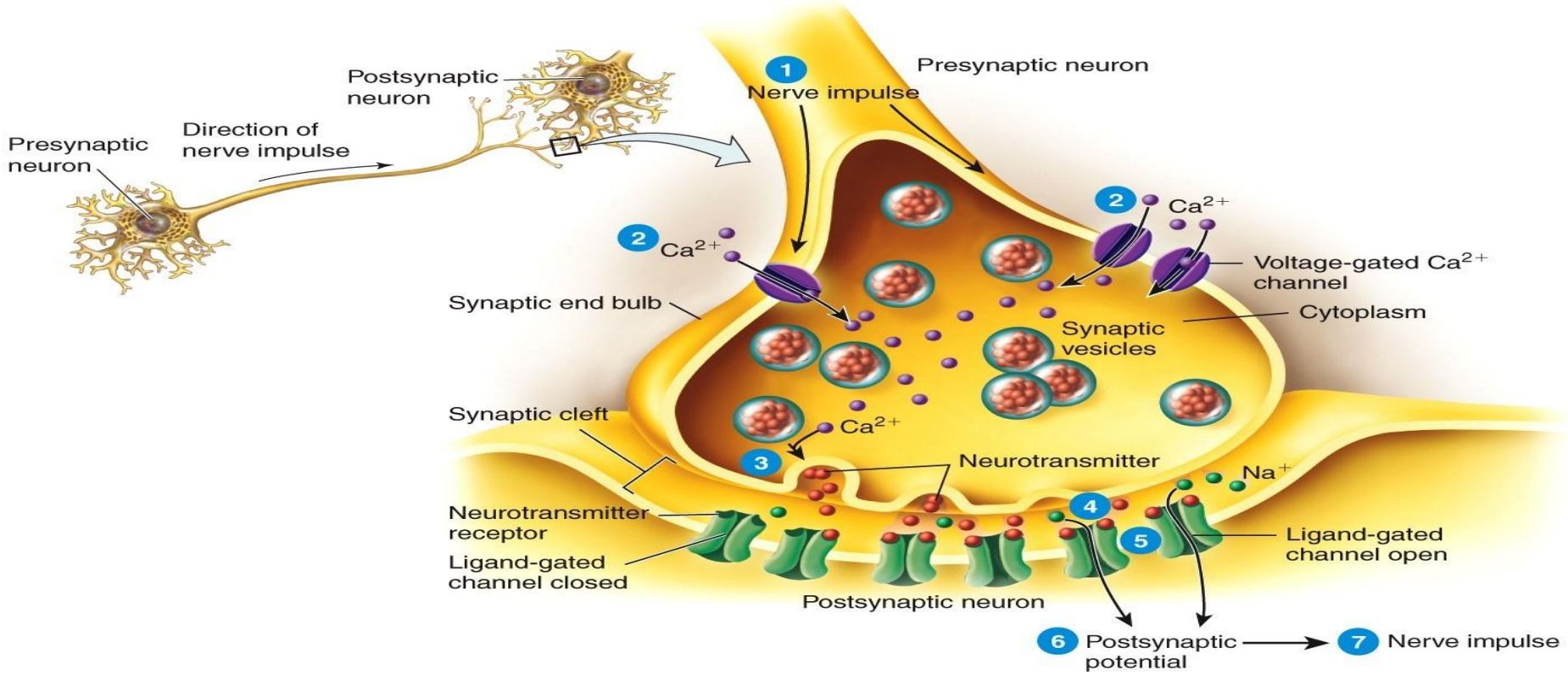
- Synapses determine the directions that the nervous signals will spread through the nervous system.
- Changing the impulse from a single into repetitive impulses (Signal amplification)
- *Facilitatory* and *inhibitory* signals from other areas in the nervous system can control synaptic transmission, sometimes opening the synapses for transmission and, at other times, closing them
- Some postsynaptic neurons respond with large numbers of output impulses ,and others respond with only a few. Thus, the synapses perform a selective action, often blocking weak signals while allowing strong signals to pass but, at other times, selecting and amplifying certain weak signals and often channeling these signals in many directions rather than in only one direction.
- Synapses also are important for storage of information is the process we call *memory*

Structure of a chemical synapse and types of different pattern of synaptic connection in nervous system

- A synapse involves a junction between an axon terminal of one neuron, known as the **presynaptic neuron**, and the dendrites or cell body of a second neuron, known as the **postsynaptic neuron**.
- This junction allows the transmission of nerve action potential (or nerve impulse) from one neuron to the next.
- There are different types of chemical synapses depending on the site of contact between presynaptic terminal and post synaptic cell
  - Axodendritic
  - Axosomatic
  - Axoaxonic



Steps of synaptic transmission and signal transmission at a Chemical synapses



The neurotransmitters (Small molecules) are synthesized and stored in vesicles in presynaptic terminal
Can be Excitatory neurotransmitters or Inhibitory neurotransmitters depending on the receptor and its interaction with neurotransmitter

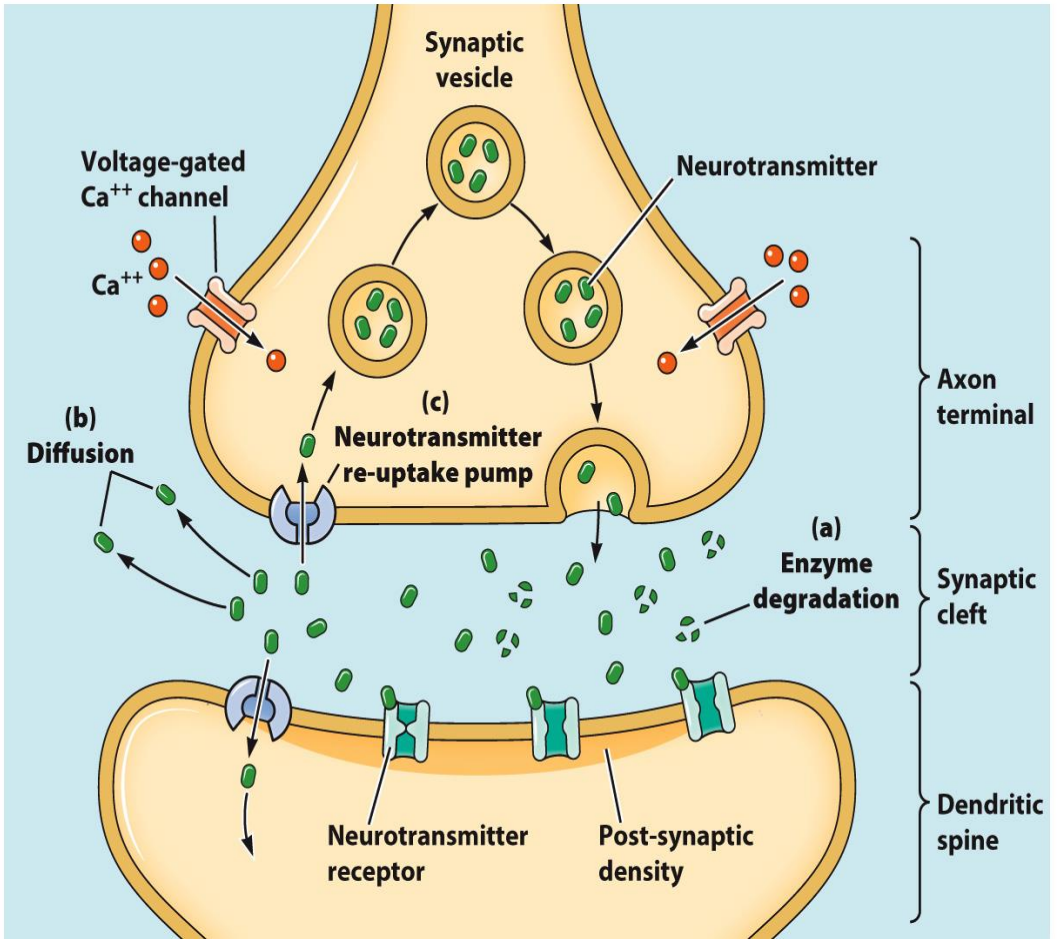
Basic Steps in chemical synaptic transmission

- Basic Steps
  - Neurotransmitter synthesis
  - Load neurotransmitter into synaptic vesicles
  - Depolarization opens voltage-sensitive Ca2 + channels in the presynaptic nerve terminal
  - Vesicles fuse to presynaptic terminal and release of NT by exocytosis
  - Neurotransmitter spills into synaptic cleft
  - Binds to postsynaptic receptors
  - Biochemical/Electrical response elicited in postsynaptic cell
  - Removal of neurotransmitter from synaptic cleft
  - Recycling of synaptic vesicles back into presynaptic terminals also occurs via clathrin mediated endocytosis .

Termination of action of neurotransmitters (Removal of Neurotransmitter)

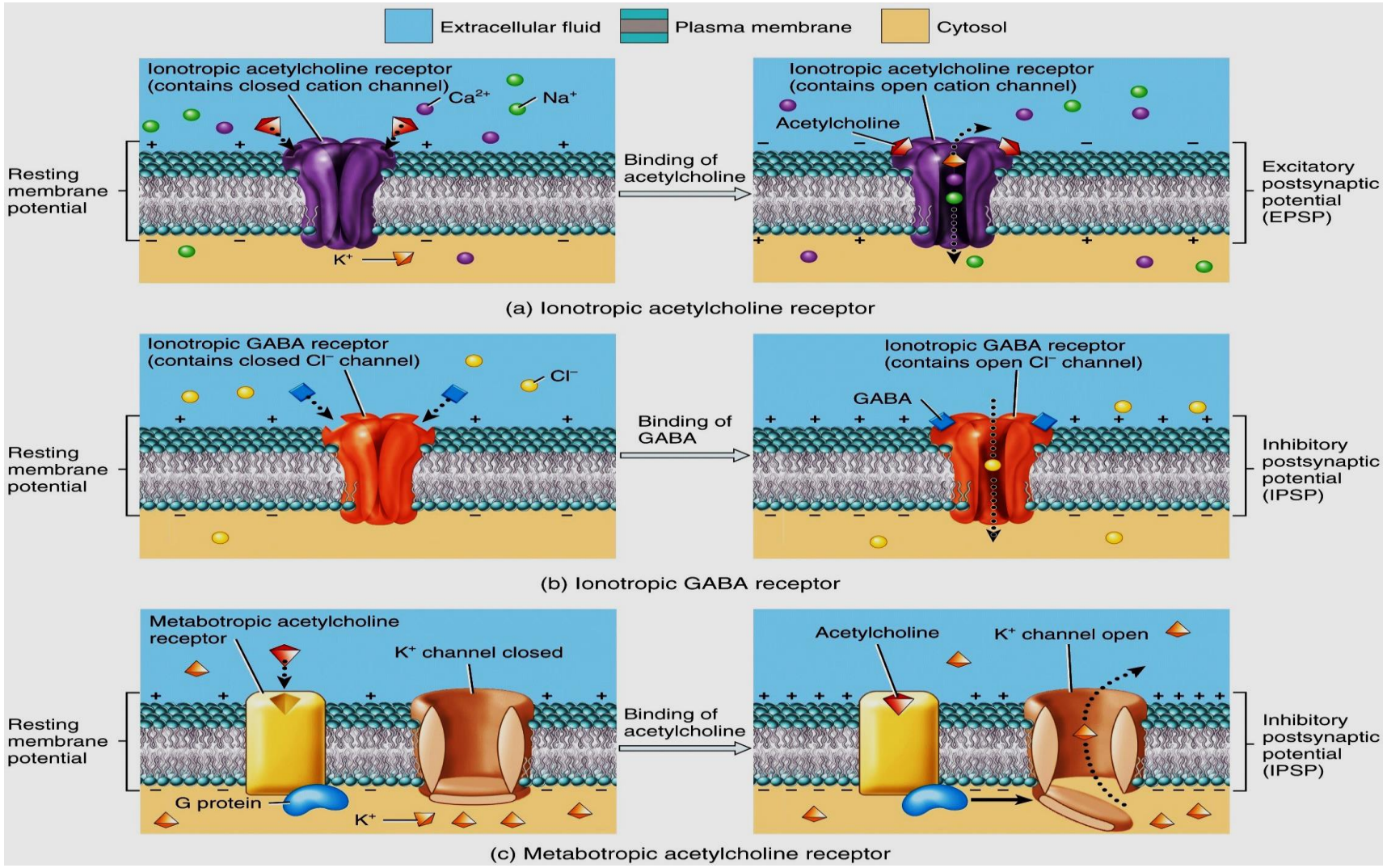
There are four ways three ways by which neurotransmitters are cleared from the cleft:

1. Diffusion
2. Enzymatic degradation Example Acetylcholine esterase at cholinergic synapses and MAO (Mono amino oxidase) in adrenergic synapses)
3. Reuptake into the nerve terminal by a transport protein coupled to the Na^+ gradient, for example, dopamine, norepinephrine, glutamate and GABA;
4. Uptake and metabolism by glial cells (glutamate)



Ionotropic & Metabotropic Receptors

-Ionotropic: Transmitter-gated ion channels
-Neurotransmitter receptors that directly gate ion channels are often called ionotropic receptors,
Metabotropic receptors : activating a second messenger through G proteins coupled receptors that gates the channel and alters permeability



Metabotropic Receptors
The second messenger system by which a neurotransmitter can affect the activity of postsynaptic cell
NTR complex are coupled to G protein coupled receptor

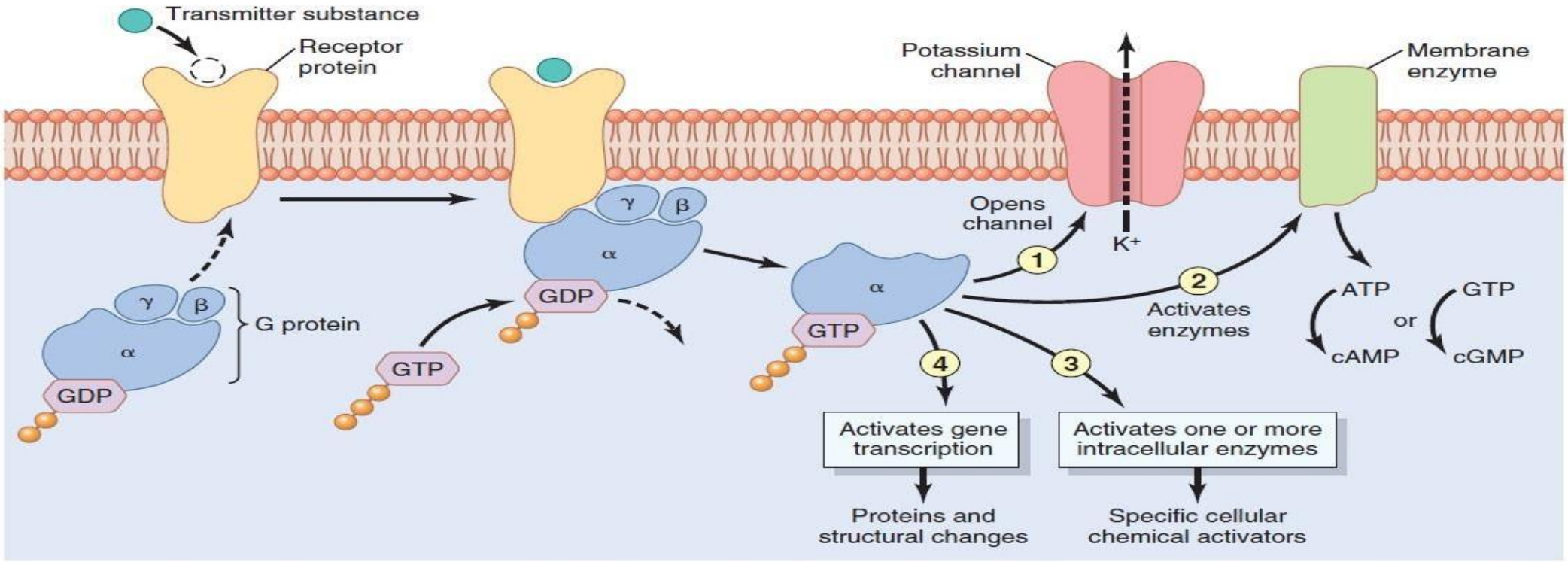


Figure The "second messenger" system by which a transmitter substance from an initial neuron can activate a second neuron by first causing a transformational change in the receptor that releases the activated alpha (α) subunit of the G protein into the second neuron's cytoplasm. Four subsequent possible effects of the G protein are shown, including *1,* opening an ion channel in the membrane of the second neuron; *2,* activating an enzyme system in the neuron's membrane; *3,* activating an intracellular enzyme system; and/or *4,* causing gene transcription in the second neuron. Return of the G protein to the inactive state occurs when guanosine triphosphate *(GTP)* bound to the α subunit is hydrolyzed to guanosine diphosphate *(GDP)* and the β and γ subunits are reattached to the α subunit.

Chemically gated channels

- The chemical-gated ion channels in the postsynaptic membrane are usually of two types:
  - 1) Cation channels (for Na+ but sometimes allow K+ and/or Ca2+ to pass)
  - 2) Anion channels that mainly allow Chloride to pass but allow minute quantities of other anions to pass as well.
- The neurotransmitter that opens cation channels are excitatory transmitter, whereas those that open anion channels are called inhibitory transmitters.
- Therefore, there are two types of synapses, depending on the permeability changes induced in the postsynaptic neuron by the neurotransmitter: excitatory synapses and inhibitory synapses

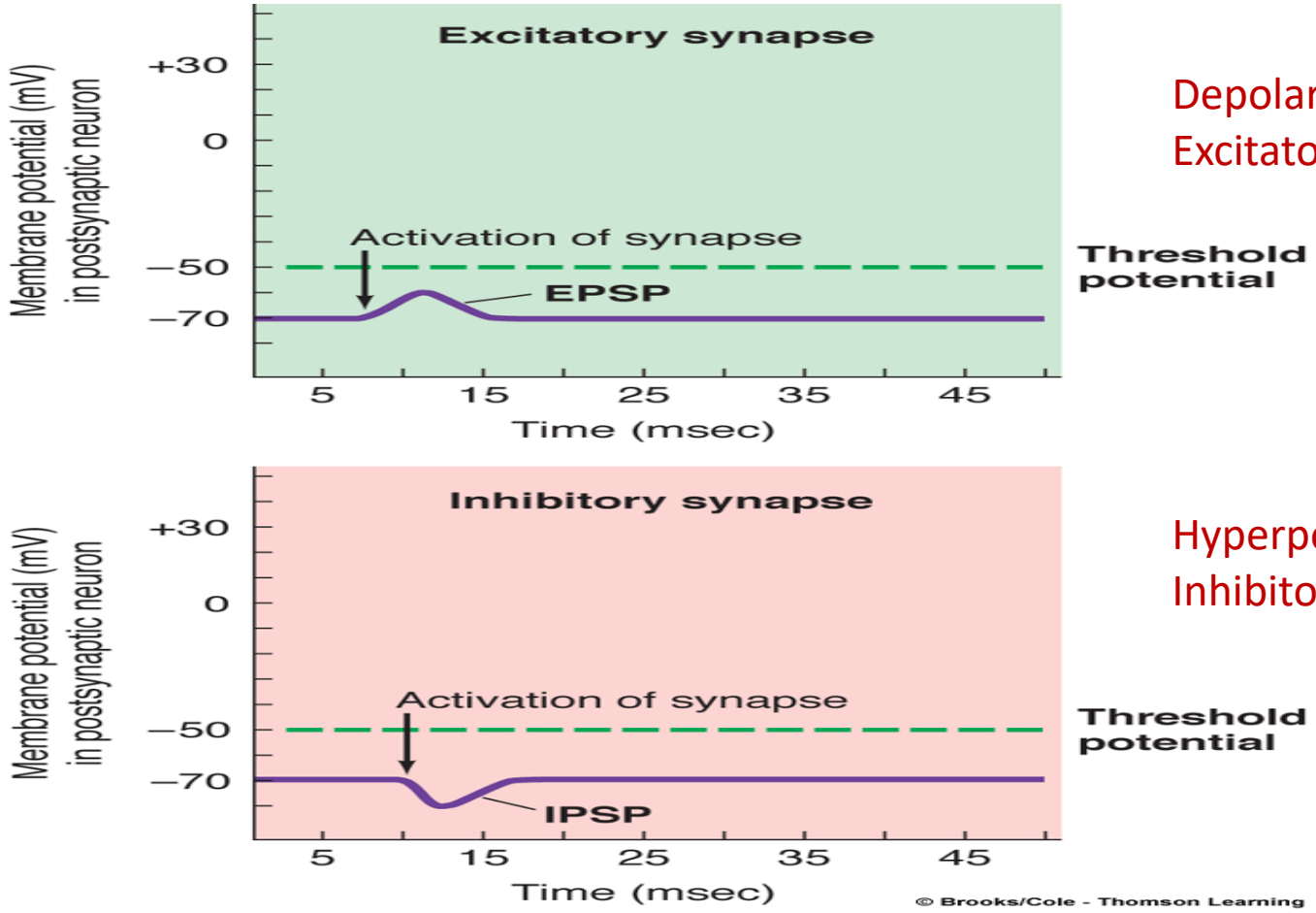
Membrane potential changes in excitatory and inhibitory synapses

- Activation of one excitatory synapse produces a small depolarization of the postsynaptic neuron. However, it can rarely depolarize the postsynaptic neuron sufficiently to bring it to threshold.
- Activation of one inhibitory synapse produces a small hyperpolarization of the postsynaptic neuron - having greater internal negativity. This small hyperpolarization moves the membrane potential even farther away from threshold

Electrical Events at Excitatory or Inhibitory synapses

Depolarization
EPSP

Hyperpolarization
IPSP

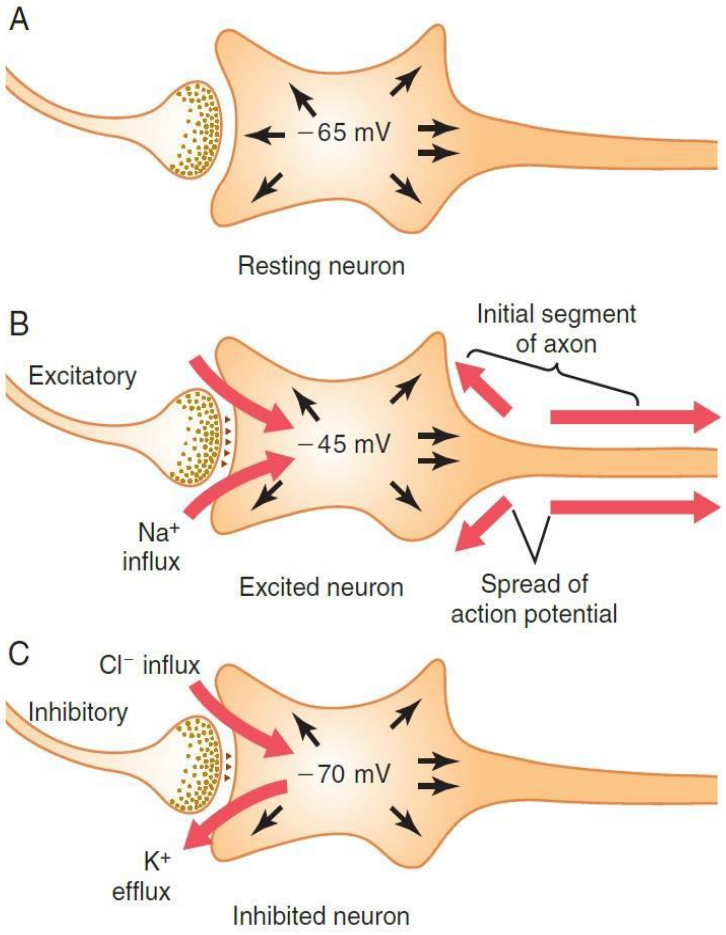


Depolarization
Excitatory synapse

Hyperpolarization
Inhibitory synapse

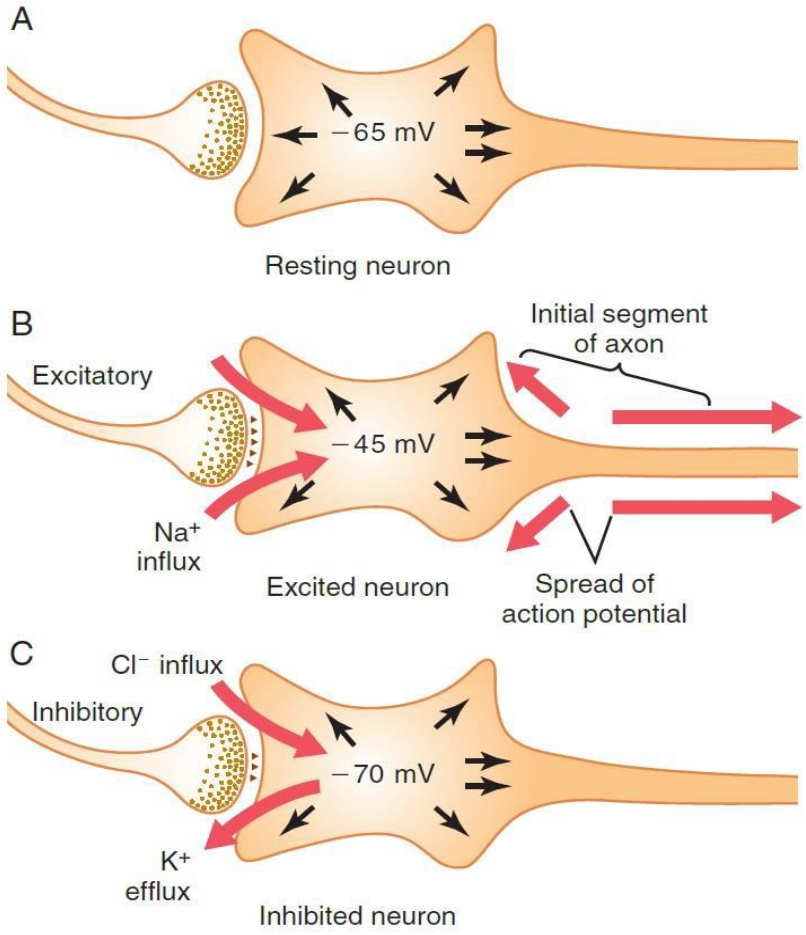
Excitatory Postsynaptic Potential –EPSP:

- Excitatory Postsynaptic Potential –EPSP
- This potential is generated when transmitter acts on the membrane excitatory receptor to increase the membrane's permeability to Na+.
- The rapid influx of positively charged Na+to the interior neutralizes part of the negativity of the resting membrane potential.
- In the figure the resting membrane potential has increased in the positive direction from -65 to -45 mV, to a less negative value. This less negative value (closure to the threshold) is called the excitatory postsynaptic potential (or EPSP).
- The mathematical value is EPSP= New membrane potential-RMP (resting membrane potential). The value is always positive (i.e. millivolts more positive than the resting value). It is +20 mV in this example.



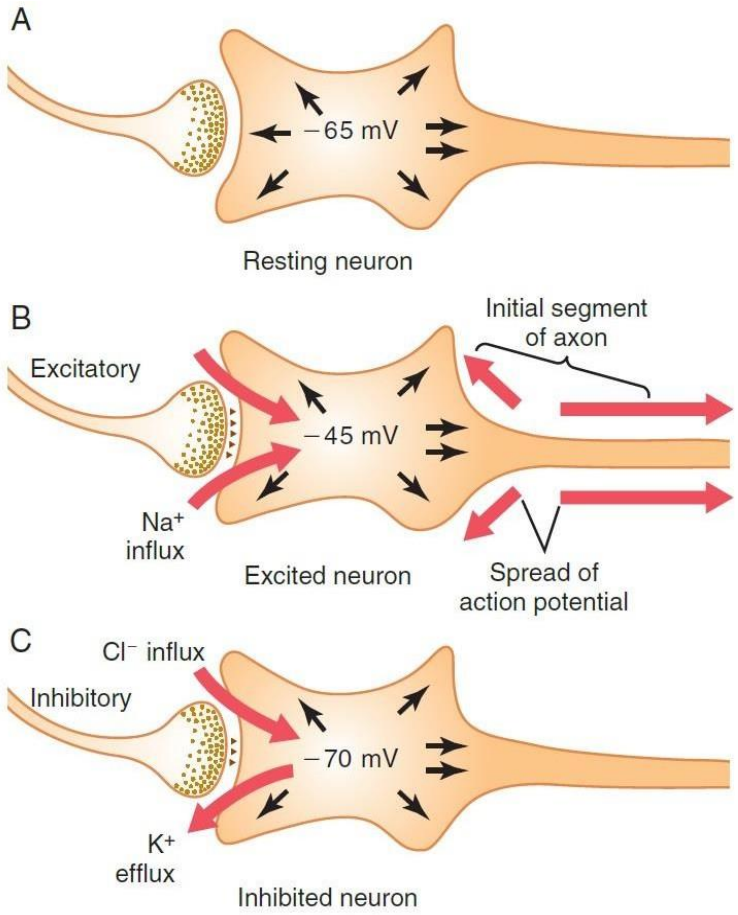
Excitatory Postsynaptic Potential –EPSP:

- Discharge of a single presynaptic terminal can only generate a small EPSP. In the spinal cord, discharge of as many as 40 to 80 terminals may be needed to bring large EPSP all the way up to -45 millivolts. This simultaneous discharge occurs by a process called **summation**.
- When the EPSP rises high enough in the positive direction, an action potential initiates in the initial segment of the axon where the axon leaves the neuronal soma (i.e. **axon hillock or** the trigger zone).
- The membrane of the hillock segment has seven times as great a concentration of voltage-gated sodium channels as does the soma and the dendrites and, therefore, can generate an action potential with much greater ease than can the soma.
- An EPSP between +10 and +20 mV will elicit an action potential in the axon initial segment

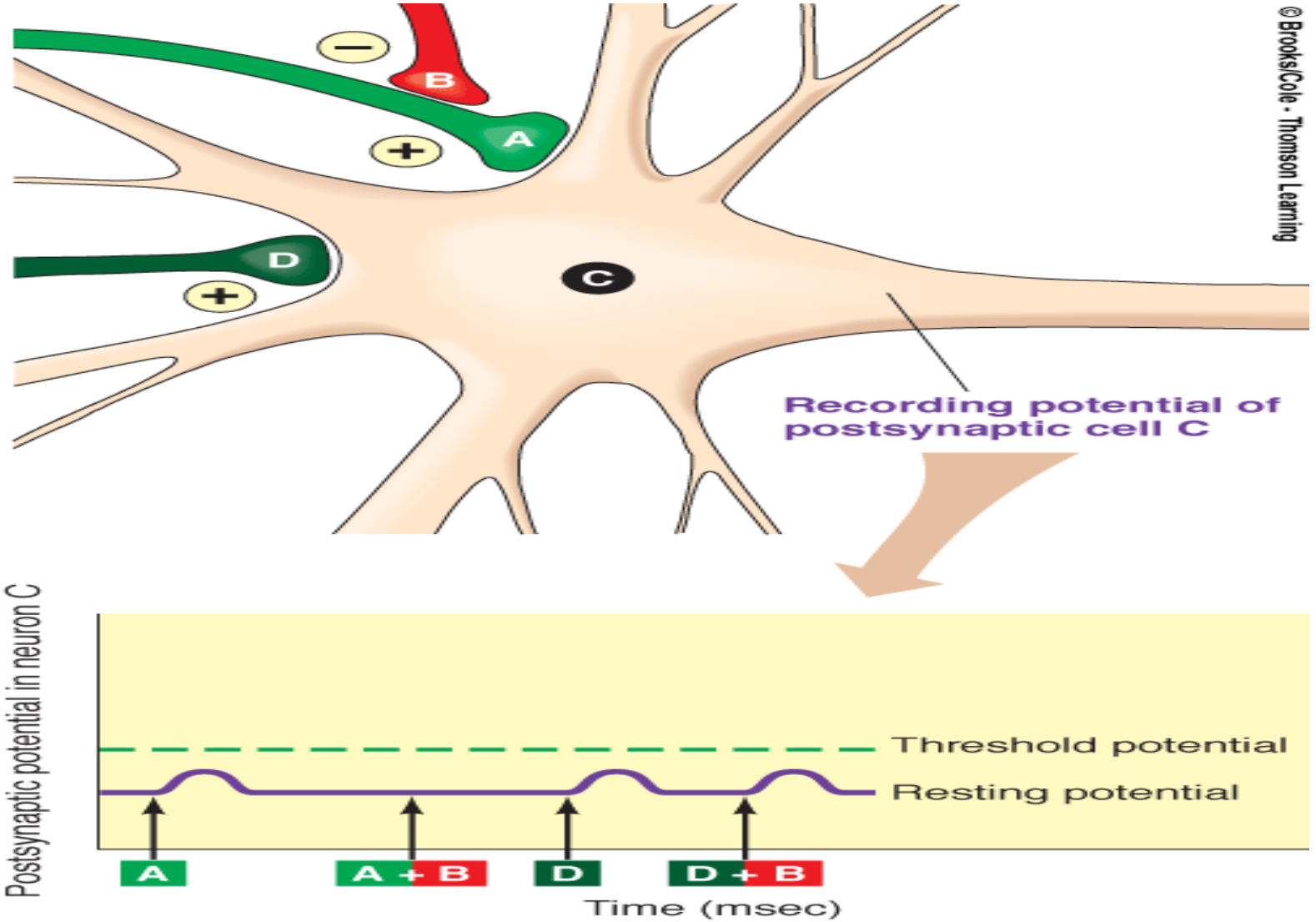


Inhibitory Postsynaptic Potential – IPSP:

- The inhibitory synapses open mainly chloride channels, allowing easy influx of chloride ions.
- Also opening potassium channels will allow positively charged K^+ to move to the exterior and will also make the interior membrane potential more negative.
- Thus, both Cl^- influx and K^+ efflux increase the degree of intracellular negativity (i.e.
  - hyperpolarization) → inhibitory postsynaptic potential (IPSP).
- In the diagram the value of the IPSP is -5mV. This means 5 millivolts more negative than normal, which inhibits transmission of the nerve signal through the synapse.



Presynaptic inhibition



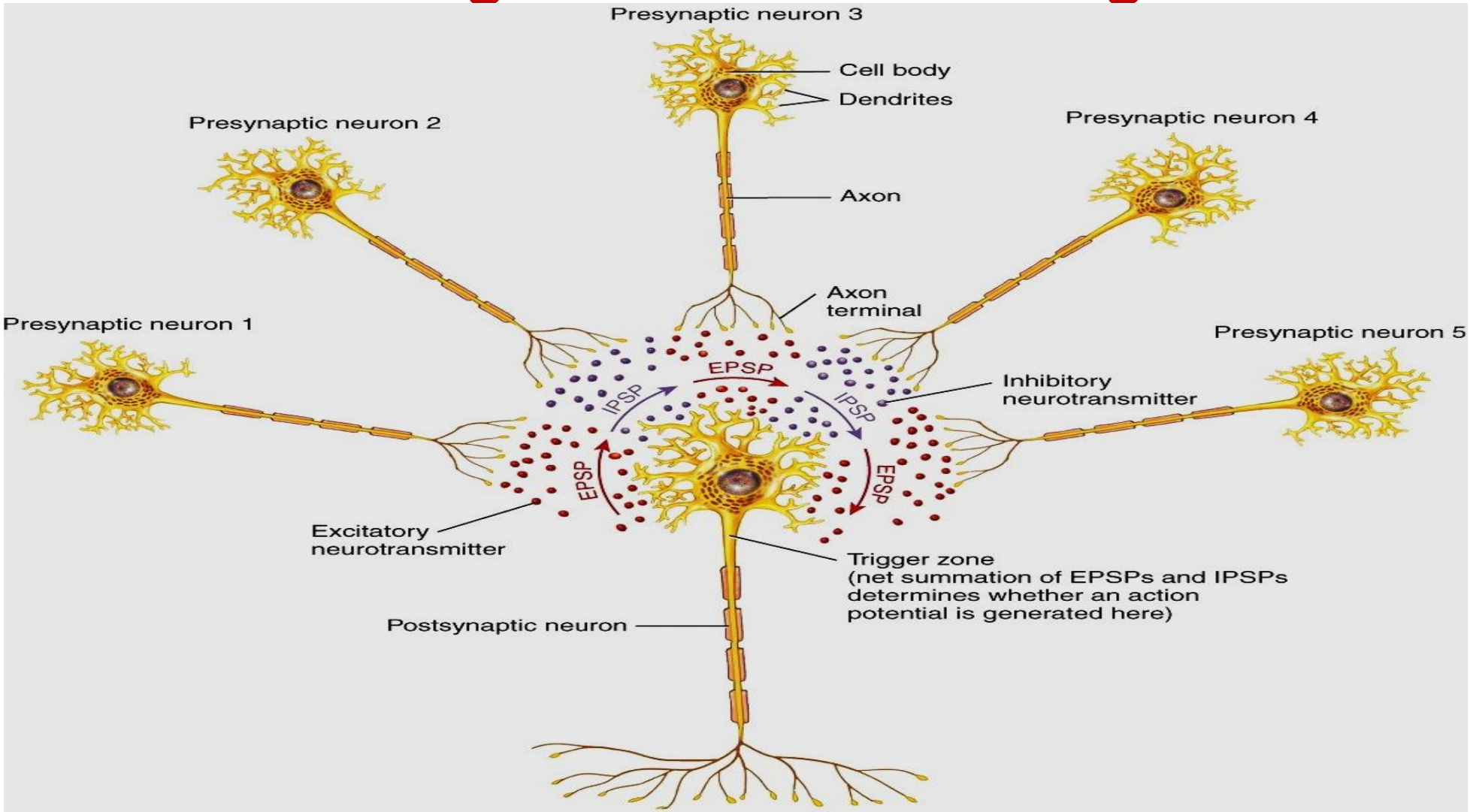
Presynaptic Inhibition

- It is an inhibitory input act on the presynaptic terminal before the signal ever reaches the synapse to make it less likely to communicate with postsynaptic neurons.
- Presynaptic inhibition is caused by release of an inhibitory substance, like GABA, acts on GABA receptors onto the outsides of the presynaptic nerve fibrils before their own endings terminate on the postsynaptic neuron.
- GABA receptors activation causes a chloride influx, which hyperpolarizes the cell that will cancel much of the excitatory effect of Na^+ that also enter the terminal fibrils when an action potential arrives.
- Presynaptic inhibition occurs in many of the sensory pathways in the nervous system.
- Mediated by axoaxonic synapse

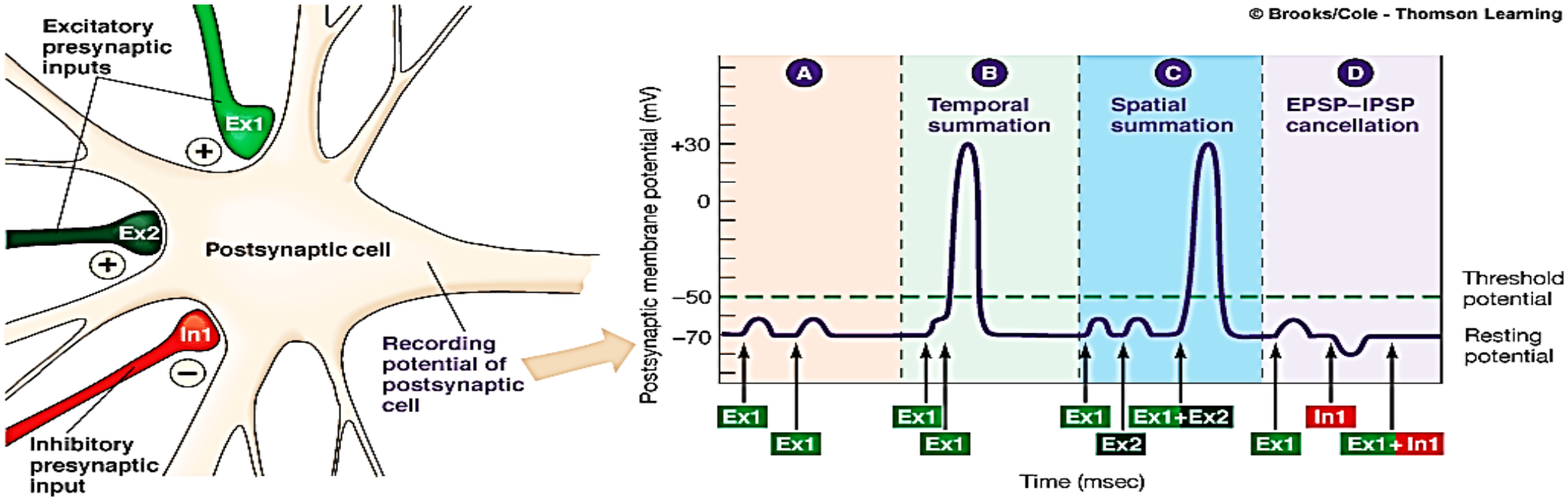
Properties of synaptic potential

- Graded potential : amplitude of EPSP or IPSP depends on neurotransmitter released
- Exhibit summation: Temporal and spatial summation
- Decremental ie decrease amplitude as signals moves a away from site of stimulation
- none propagated localized potential

Summation of Postsynaptic Potentials and integration of neuronal signals



Summation of Postsynaptic Potentials



Panel A If an excitatory presynaptic input (Ex1) is stimulated a second time after the first EPSP in the postsynaptic cell has died off, a second EPSP of the same magnitude will occur.

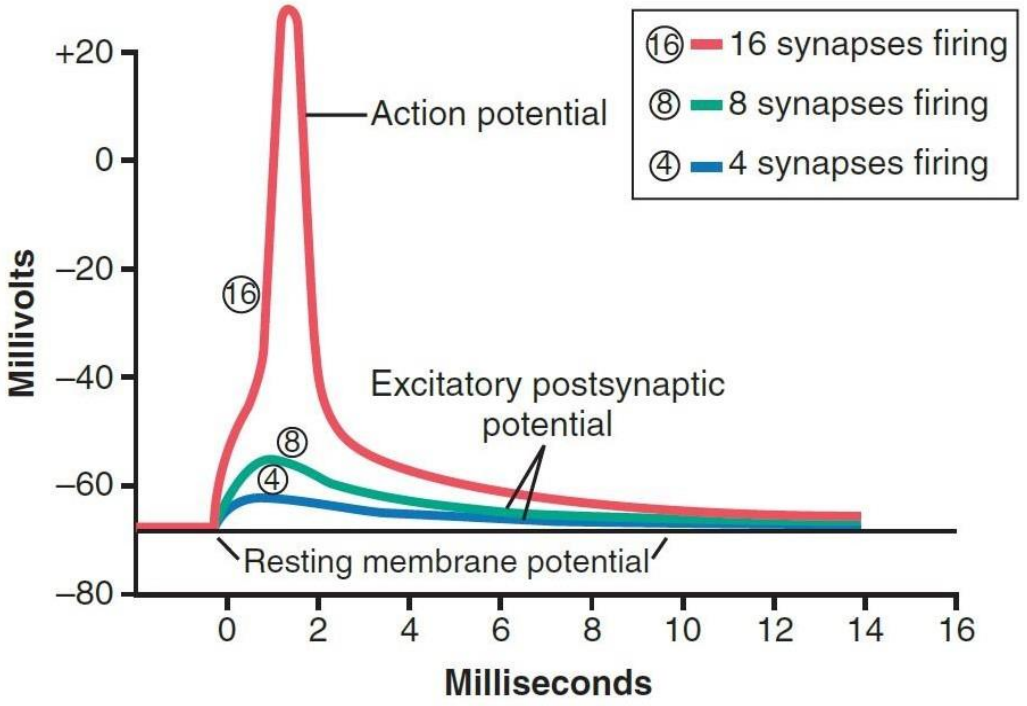
Panel B If, however, Ex1 is stimulated a second time before the first EPSP has died off, the second EPSP will add onto, or sum with, the first EPSP, resulting in *temporal summation*, which may bring the postsynaptic cell to threshold.

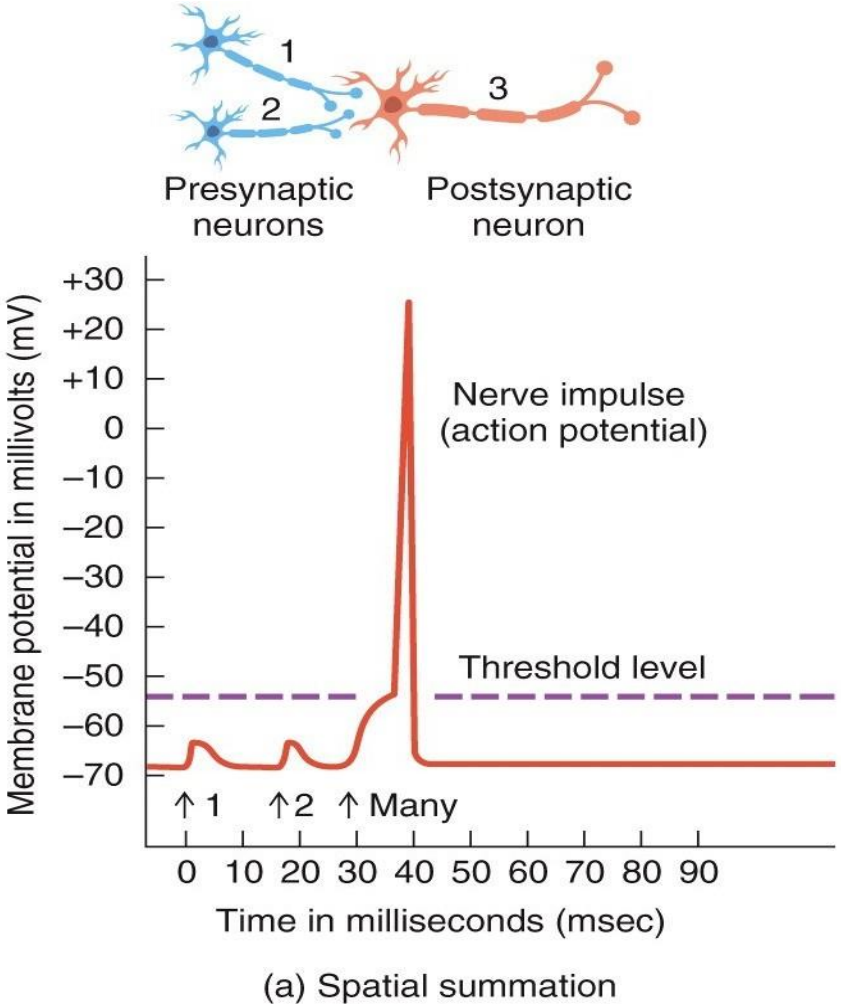
Panel C The postsynaptic cell may also be brought to threshold by *spatial summation* of EPSPs that are initiated by simultaneous activation of two (Ex1 and Ex2) or more excitatory presynaptic inputs.

Panel D Simultaneous activation of an excitatory (Ex1) and inhibitory (In1) presynaptic input does not change the postsynaptic potential, because the resultant EPSP and IPSP cancel each other out.

Spatial Summation

is the summation of EPSPs originating simultaneously from several different presynaptic inputs (that is, from different points in "space").

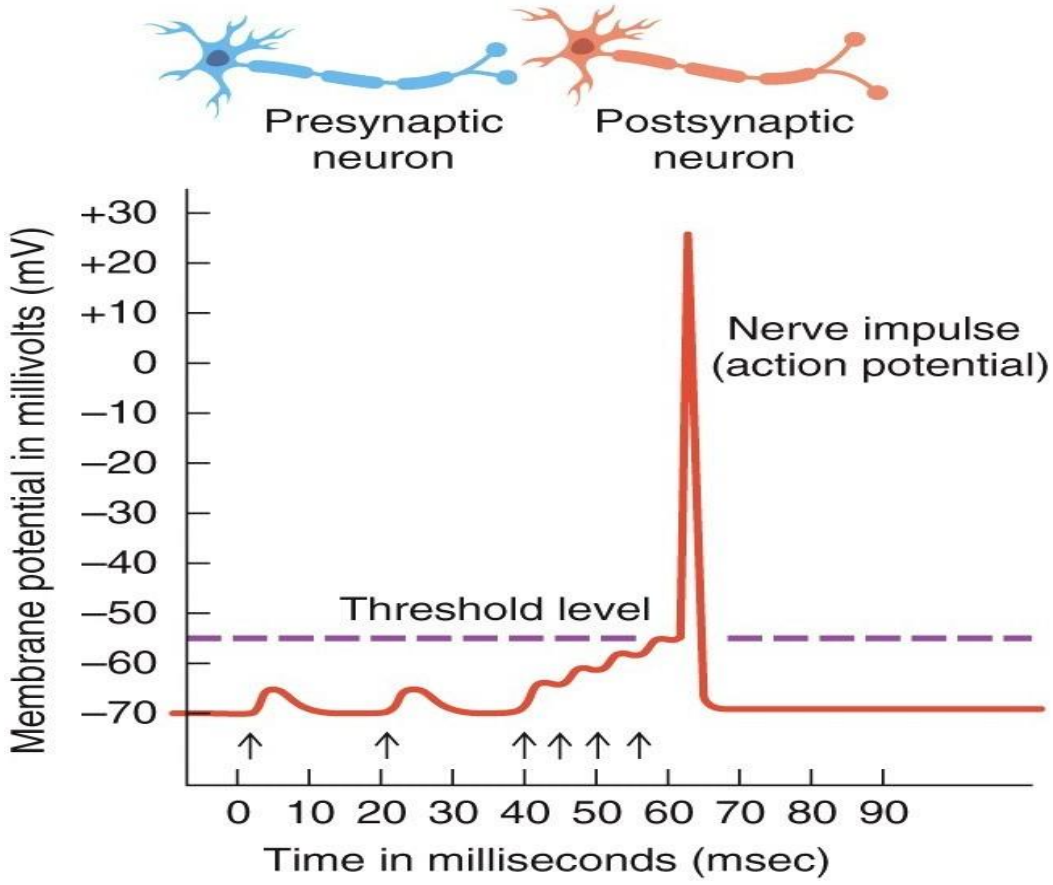




(a) Spatial summation

Temporal Summation

- The released transmitter substance opens the membrane channels for at most a millisecond or so. However, the changed postsynaptic potential lasts up to 15 milliseconds after the synaptic membrane channels have already closed.
- Therefore, if a presynaptic neuron fires quickly twice in row, causing two EPSPs, the second EPSP may arrive before the first one has dissipated, bumping the membrane potential toward threshold.
- The summing of several EPSPs occurring very close together in time because of successive firing of a single presynaptic neuron is known as temporal summation (tempus means "time").



(b) Temporal summation

Properties of chemical synaptic transmission

1. One way transmission
2. If an IPSP and an EPSP act on a neuron at the same time, these two effects can either completely or partially nullify each other. The summation of the membrane's EPSPs and IPSPs will determine the final membrane potential.
3. Synaptic potentials are localized graded and decremental neuronal potentials
4. EPSP and IPSP exhibit spatial and temporal summation
5. Repetitive neuronal stimulation at a rapid rate can develop **fatigue** of synaptic transmission. The mechanism of fatigue is mainly exhaustion or partial exhaustion of the stores of transmitter substance in the presynaptic terminals. The development of fatigue is a protective mechanism against excess neuronal activity.
6. **Alkalosis** greatly increases neuronal excitability (hyperventilation, which blows off CO_2 and elevates the pH, may precipitate an epileptic attack).
7. **Acidosis** greatly depresses neuronal activity. In very severe diabetic or uremic acidosis coma develops.
5. **Caffeine**, **theophylline** (found in coffee, tea, and cocoa) increase neuronal excitability, presumably by reducing the threshold for excitation of neurons.
5. Most **anesthetics** increase the neuronal membrane threshold for excitation and thereby decrease synaptic transmission at many points in the nervous system.

Neurotransmitters and chemical synapses

- N**eurotransmitters**
  - Chemicals synthesized, packed and released by presynaptic neurons
  - Diffuse across the synaptic cleft
  - and interact with postsynaptic neurons membrane receptors
  - Neurotransmitters either excite the neuron or inhibit or or modify its sensitivity of the postsynaptic neuron
  - Inhibition or excitations is determined by the neurotransmitter , its receptors and permeability changes in postsynaptic cell induced by neurotransmitter receptor interaction

The Neurotransmitters

- More than 50 chemical substances function as synaptic transmitters.
- These chemical substances can be grouped into; Small- molecule (rapidly acting transmitters) and Neuropeptide (slowly acting transmitters or growth factors).
- The small-molecule, rapidly acting transmitters cause most acute responses of the nervous system, such as **transmission** of sensory signals to the brain and of motor signals back to the muscles.
- The neuropeptides usually cause more prolonged actions, such as long-term changes in numbers of neuronal receptors, long-term opening or closure of certain ion channels, and possibly even long-term changes in numbers of synapses or sizes of synapses (Synaptic plasticity).

Small-Molecule, Rapidly Acting Transmitters:

- These types of transmitters are **synthesized in the cytosol** of the presynaptic terminal and are absorbed by means of active transport into the many transmitter vesicles in the terminal.
- Most often the effect of these transmitters is to increase or decrease conductance through ion channels.
- Small molecule transmitters are **continually recycled** and used over and over again. Acetylcholine, Norepinephrine, and Nitric oxide are examples of such transmitters.
- **Acetylcholine (Ach)**, in most instances, has an excitatory effect; however, it is known to have inhibitory effects at some peripheral parasympathetic nerve endings (as in the heart).
- **Norepinephrine (NE)** is synthesized within the vesicle from dopamine ithe enzyme dopamine β hydroxylase is present in the vesicle. NE in many areas within the CNS, activates excitatory receptors, but in a few areas, it activates inhibitory receptors instead.

Small-Molecule, Rapidly Acting Transmitters

- **Dopamine**, **Glycine**, and **GABA** (gamma-aminobutyric acid) are inhibitory transmitters. GABA is the primary inhibitory neurotransmitter of the CNS. It functions as a CNS depressant.
- **Glutamate** is secreted by the presynaptic terminals in many of the sensory pathways. Glutamate is the principle excitatory neurotransmitter of the CNS.
- **Serotonin** (or 5-hydroxytryptamine) acts as an inhibitor of pain pathways in the spinal cord, and an inhibitor action in the higher regions of the nervous system. Serotonin is involved in mood control, appetite control, and nausea. Perhaps it even causes sleep.
- **Nitric oxide** is a gas and is not preformed and stored in vesicles in the presynaptic terminal as are other transmitters. Instead, it is synthesized almost instantly as needed and then diffuses out of the presynaptic terminals over a period of seconds rather than being released in vesicular packets. It diffuses into the nearby postsynaptic neurons and changes intracellular metabolic functions that modify postsynaptic neuronal excitability.

The Neuropeptides:

- They are synthesized as integral parts of large-protein molecules by ribosomes **in the neuronal cell body**.
- The Golgi apparatus packages the neuropeptide into minute transmitter vesicles that are released into the cytoplasm. Then the transmitter vesicles are transported all the way to the tips of the nerve fibers by axonal streaming of the axon cytoplasm (**axoplasmic flow**), traveling at the slow rate of only a few centimeters per day.
- Much smaller quantities of neuropeptides than of the small-molecule transmitters are usually released at the neuronal terminals in response to action potentials.
- Neuropeptides are generally a thousand or more times as potent as the small-molecule transmitters and they often cause much more prolonged actions.

Small molecules rapidly acting neurotransmitters

Table 46-1 Small-Molecule, Rapidly Acting Transmitters

Class I
Acetylcholine
Class II: The Amines
Norepinephrine
Epinephrine
Dopamine
Serotonin
Melatonin
Histamine
Class III: Amino Acids
Gamma-aminobutyric acid
Glycine
Glutamate
Aspartate
Class IV
ATP
Arachidonic acid
Nitric oxide
Carbon monoxide

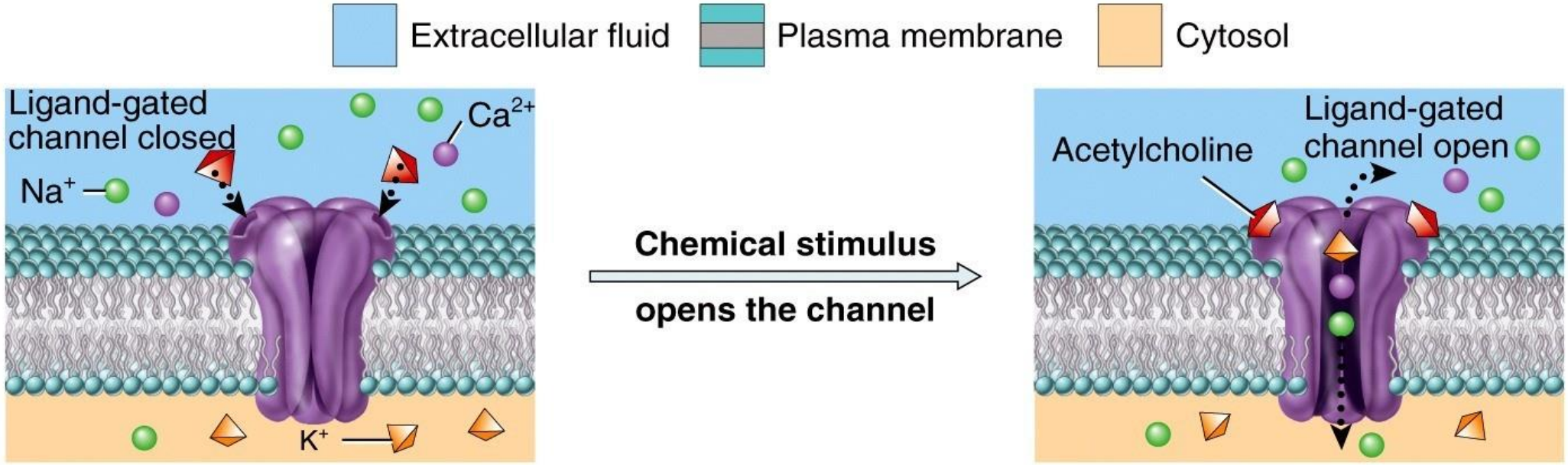
Neuropeptides, Slowly Acting Transmitters, or Growth Factors

Hypothalamic-Releasing Hormones
Thyrotropin-releasing hormone
Luteinizing hormone–releasing hormone
Somatostatin (growth hormone inhibitory factor)
Pituitary Peptides
Adrenocorticotropic hormone
β-Endorphin
α–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
Nerve growth factor
Brain-derived neurotropic factor
Neurotensin
Insulin
Glucagon
Peptides from Other Tissues
Angiotensin II
Bradykinin
Carnosine
Sleep peptides
Calcitonin

Neuronal Graded Potentials

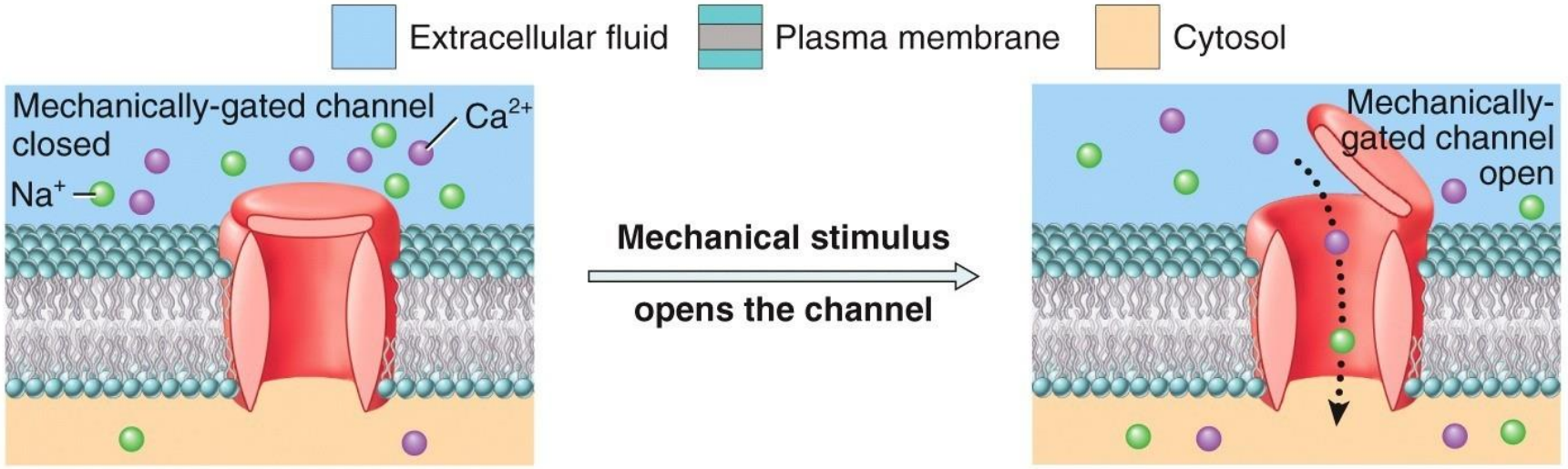
Ligand-gated channels respond to chemical stimuli (ligand binds to receptor)



(b) Ligand-gated channel

A graded potential occurs in response to the opening of ligand- gated ion channel

Mechanically-gated channels respond to mechanical vibration or pressure stimuli

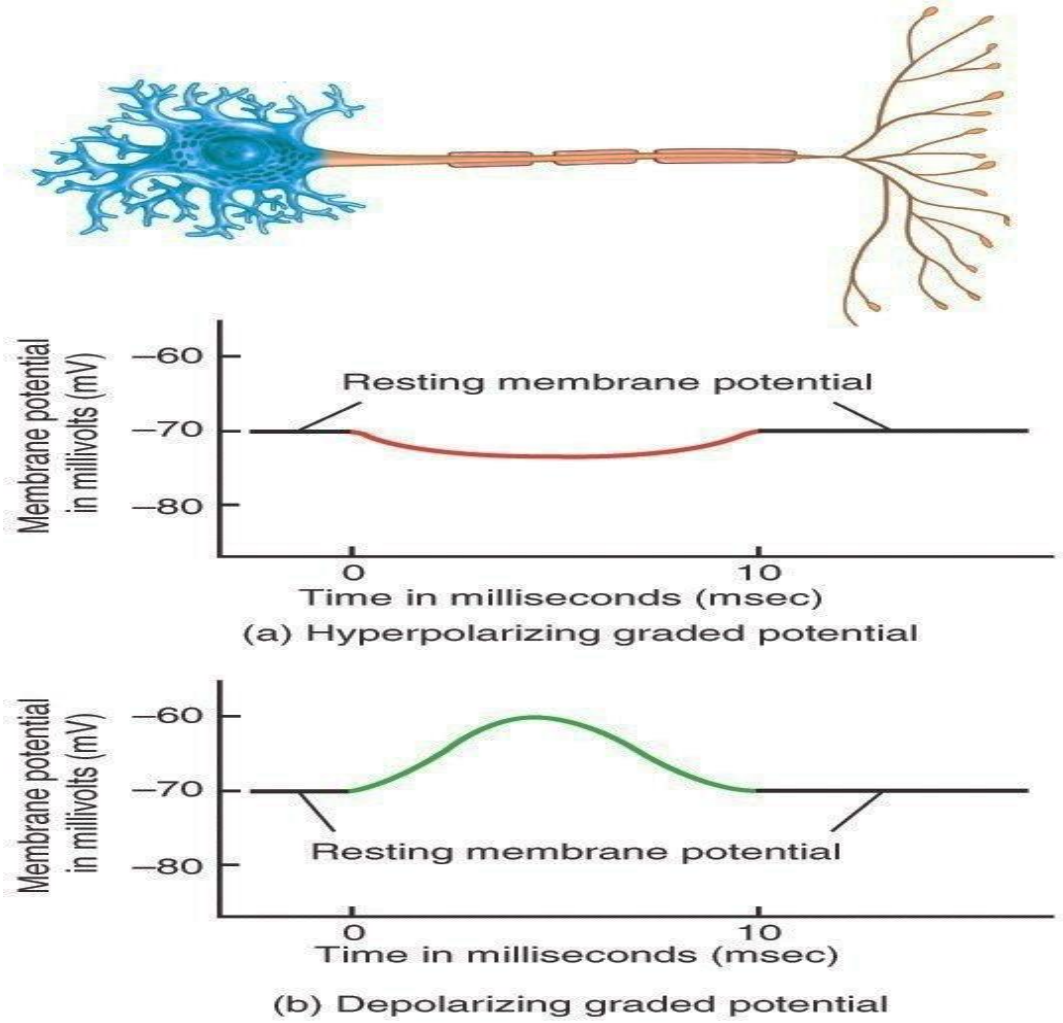


(c) Mechanically-gated channel

A graded potential occurs in response to the opening of a mechanically-gated

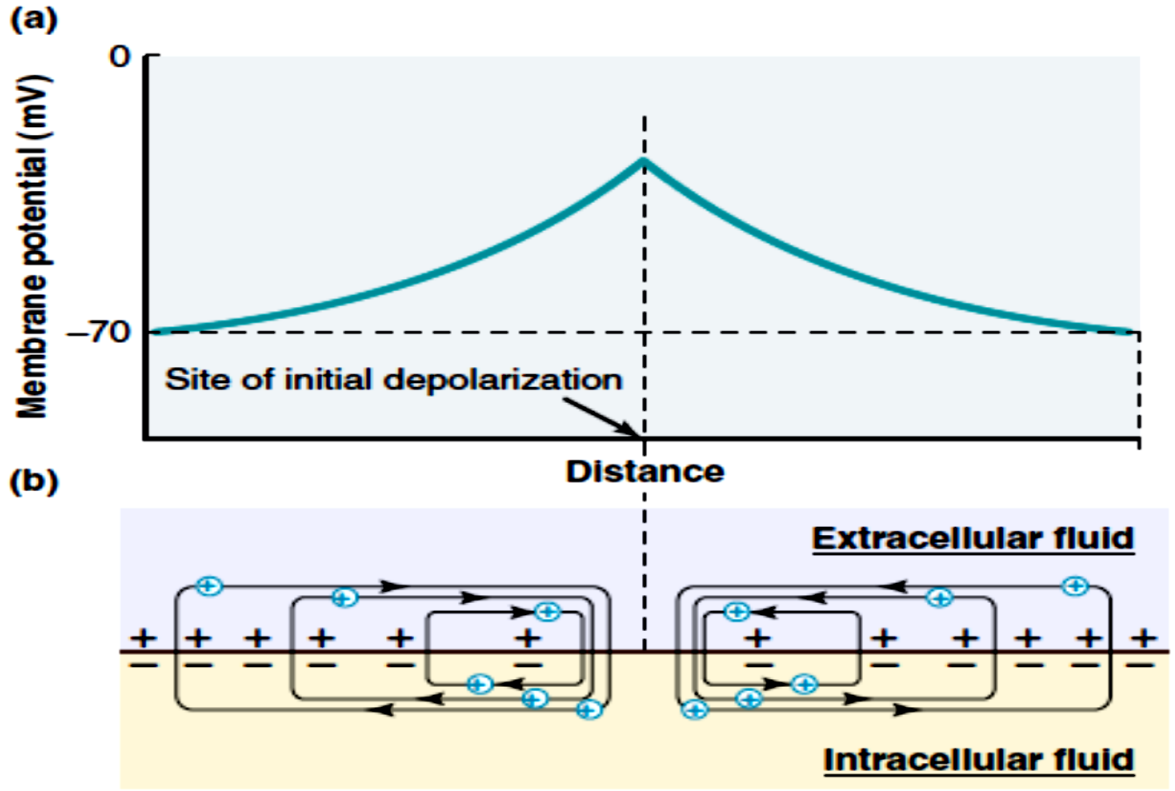
Graded Neuronal Potentials

- Small localized Changes (deviations)) in resting membrane potential initiated by an appropriate stimulus
- Graded potentials are brought about by external stimuli in sensory neurons, (receptor potentials) or by neurotransmitters released in synapses, where they cause graded potentials in the post-synaptic cells
- Graded potentials are the only means of communication used by some neurons play very important roles in the initiation and integration of the long-distance signals by neurons



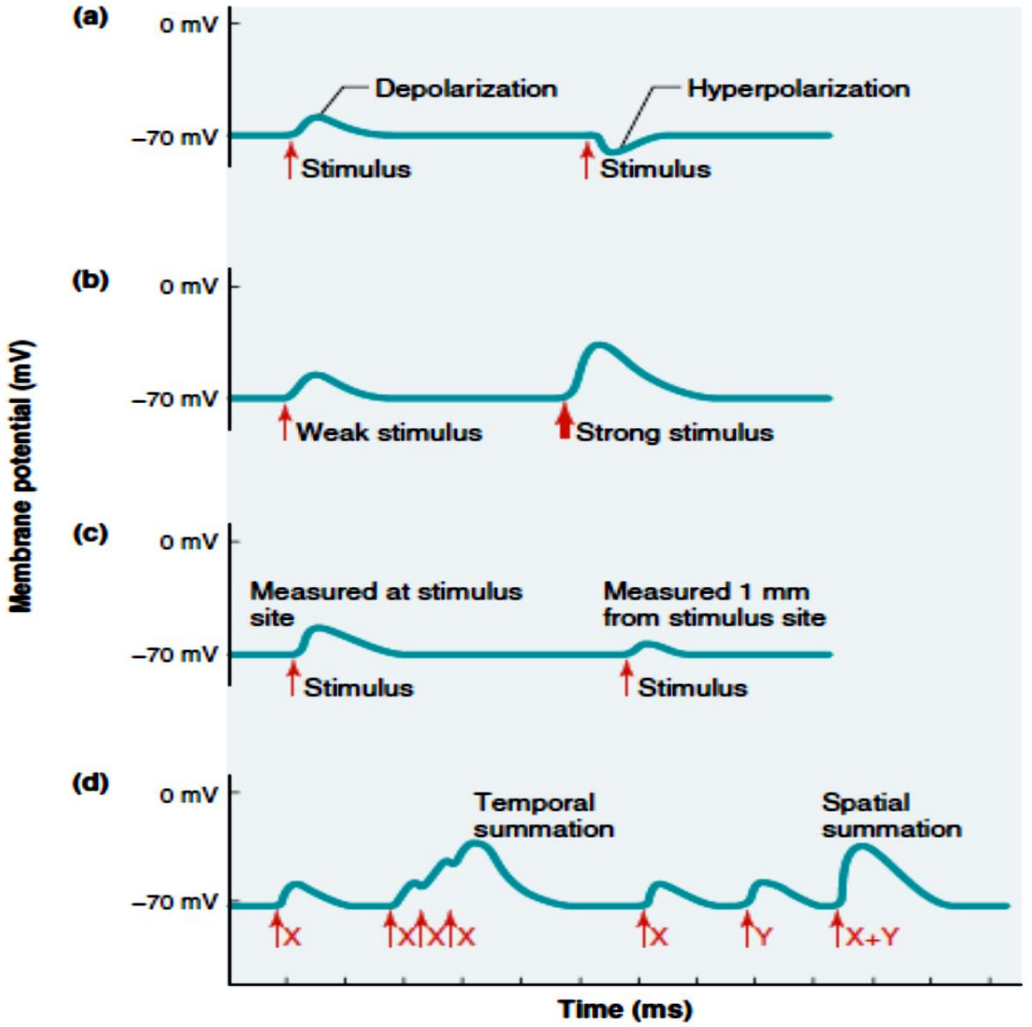
Graded potentials are localized and travel only a short distance form site of stimulation

The membrane potential of a cell can be depolarized by using a stimulating current generator, and the potential can be recorded by a pair of electrodes, one inside the cell and the other in the extracellular fluid,.
(a) Membrane potential is closer to the resting potential with increasing distance from the depolarization site.
(b) Local current surrounding the depolarized region produces depolarization of adjacent regions. Ie grades potentials are **decremental**



Graded potentials and their properties

- Graded potentials are neuronal potentials which can be recorded for examples at synaptic site or in various types of sensory receptor
- Example of graded potentials are synaptic potentials and receptor potentials
- Graded potentials properties :
  - can be depolarizing or hyperpolarizing
  - can vary in size and amplitude depending on stimulus strength
  - are conducted detrimentally, localized and do not propagate long distances
  - can be summed. Temporal and spatial summation



Comparison of graded potentials and action potential

Characteristic	Graded Potentials	Action Potentials
Origin	Arise mainly in dendrites and cell body (some arise in axons)	Arise at trigger zones and propagate along the axon.
Types of channels	Ligand-gated or mechanically gated ion channels.	Voltage-gated channels for Na^+ and K^+.
Conduction	Not propagated; localized and thus permit communication over a few micrometers.	Propagate and thus permit communication over long distance.
Amplitude	Depending on strength of stimulus, varies from less than 1 mV to more than 50 mV.	All-or-none; typically about 100 mV.
Duration	Typical longer, ranging from several msec to several min.	Shorter, ranging from 0.5 to 2 msec.
Polarity	May be hyperpolarizing (inhibitory to generation of an action potential) or depolarizing (excitatory to generation of an action potential).	Always consist of depolarizing phase followed by repolarizing phase and return to resting membrane potential.
Refractory period	Not present, thus spatial and temporal summation can occur.	Present, thus summation cannot occur.

Thank you for your attention