Chapter 12

Synapses and Neurotransmitters

The Synapse

- a nerve's action potential can go no further than the synaptic knob / distal end of the axon

  - *action potential must trigger the release of a neurotransmitter // stored in vesicles inside terminal end (synaptic knob)*

  - *stimulates a new local potential on the post-synaptic membrane // the cell across from the synaptic knob*

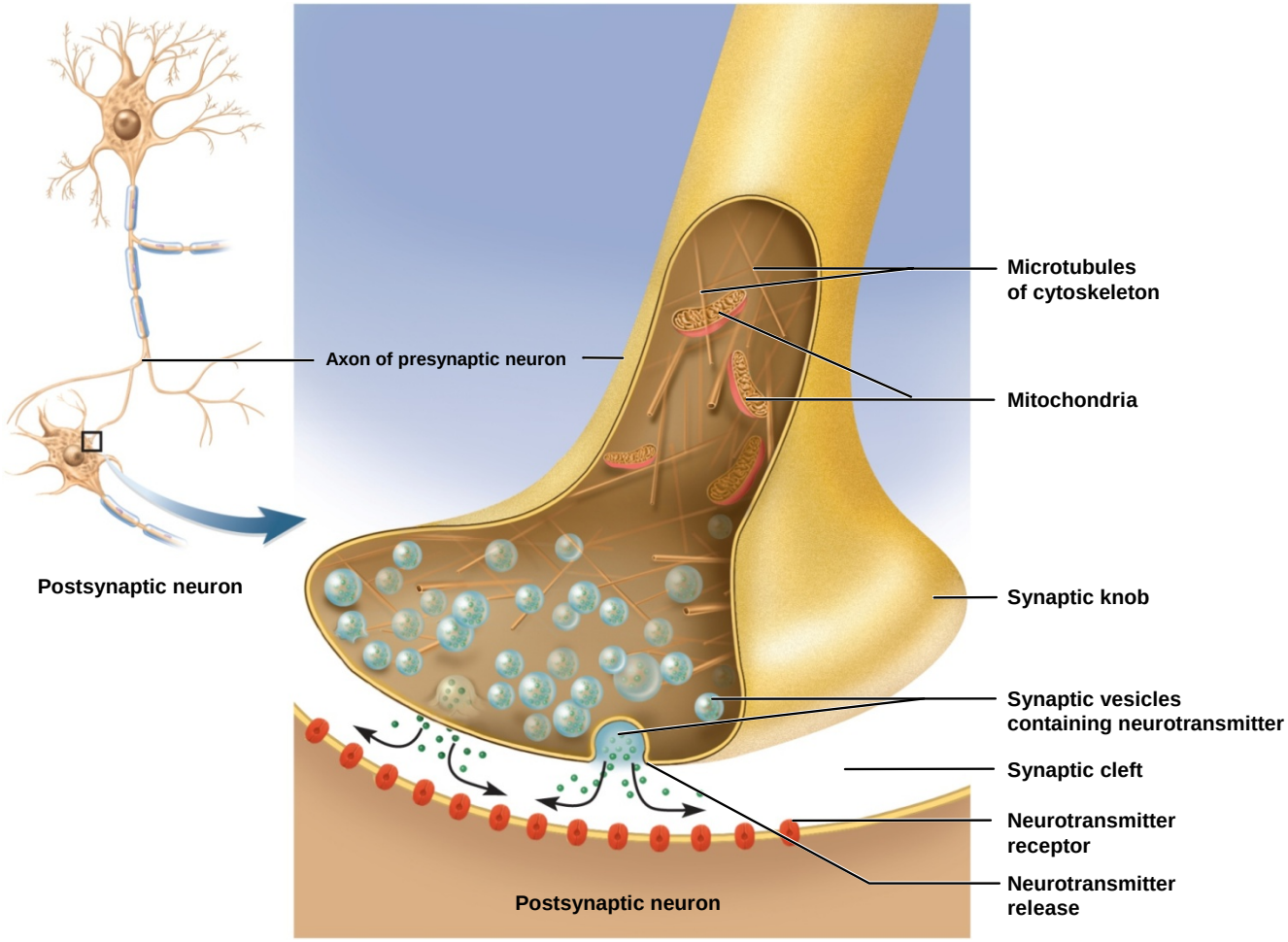
- A chemical synapse consist of three components

  - Pre-synaptic membrane
  - Synaptic cleft
  - Post-synaptic membrane

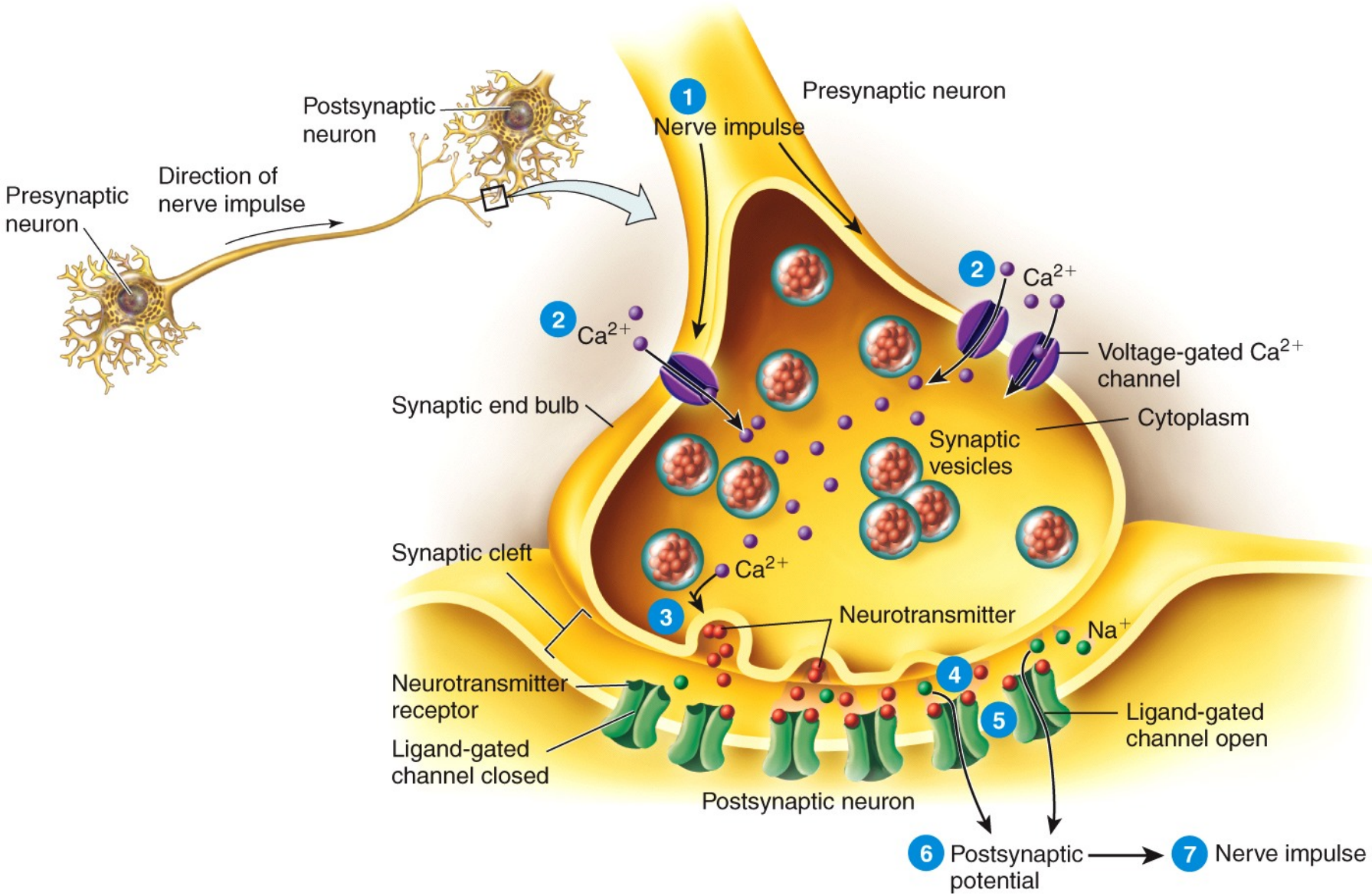
Synapses

- When synapse exist between two neurons
  - 1st neuron in the signal path is the **presynaptic neuron /** releases neurotransmitter
  - 2nd neuron is **postsynaptic neuron /** has reseptors for the neurotransmitter

Structure of a Chemical Synapse



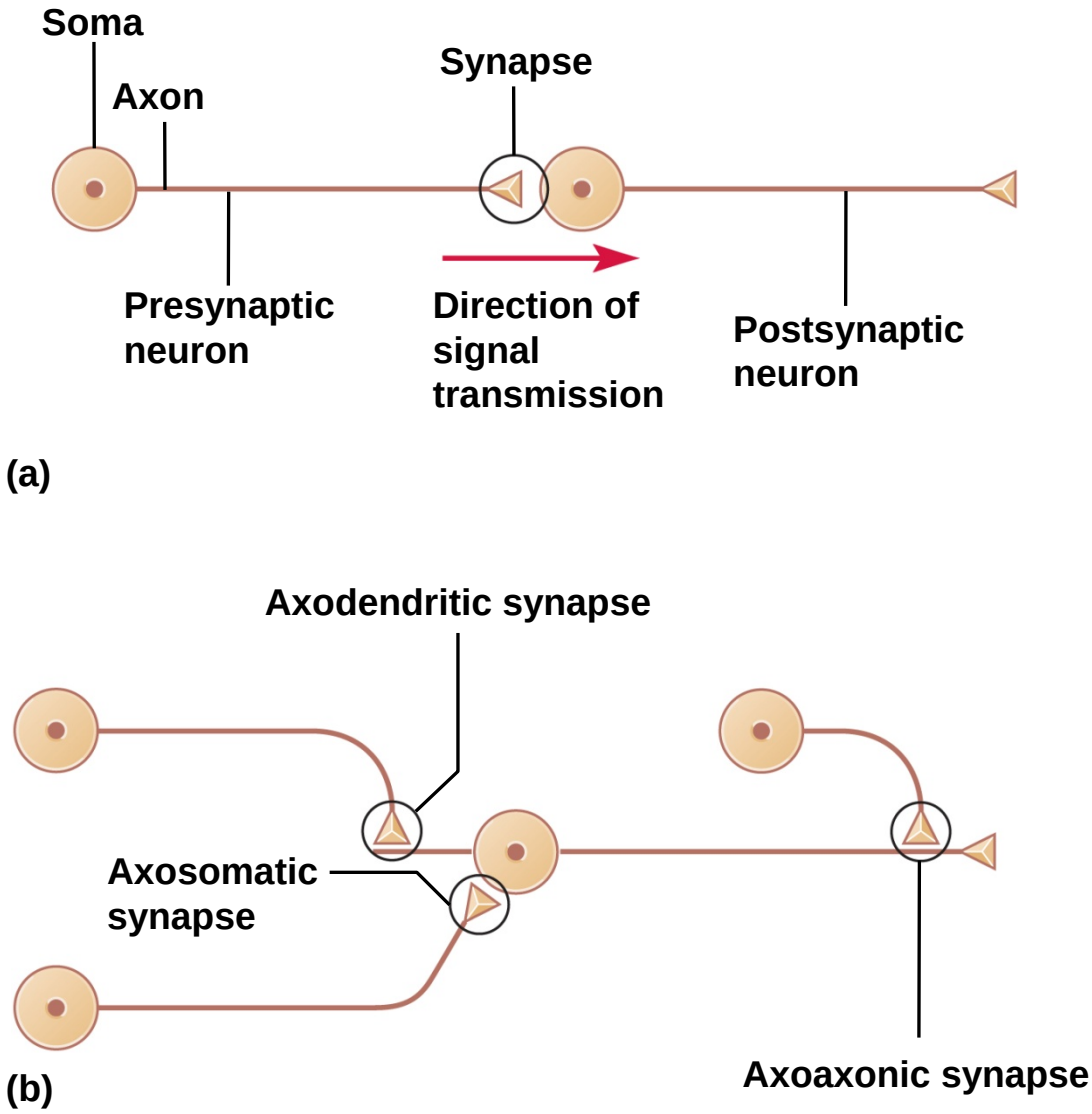
- presynaptic neurons have synaptic vesicles with neurotransmitter and postsynaptic have receptors with ligand-regulated ion channels

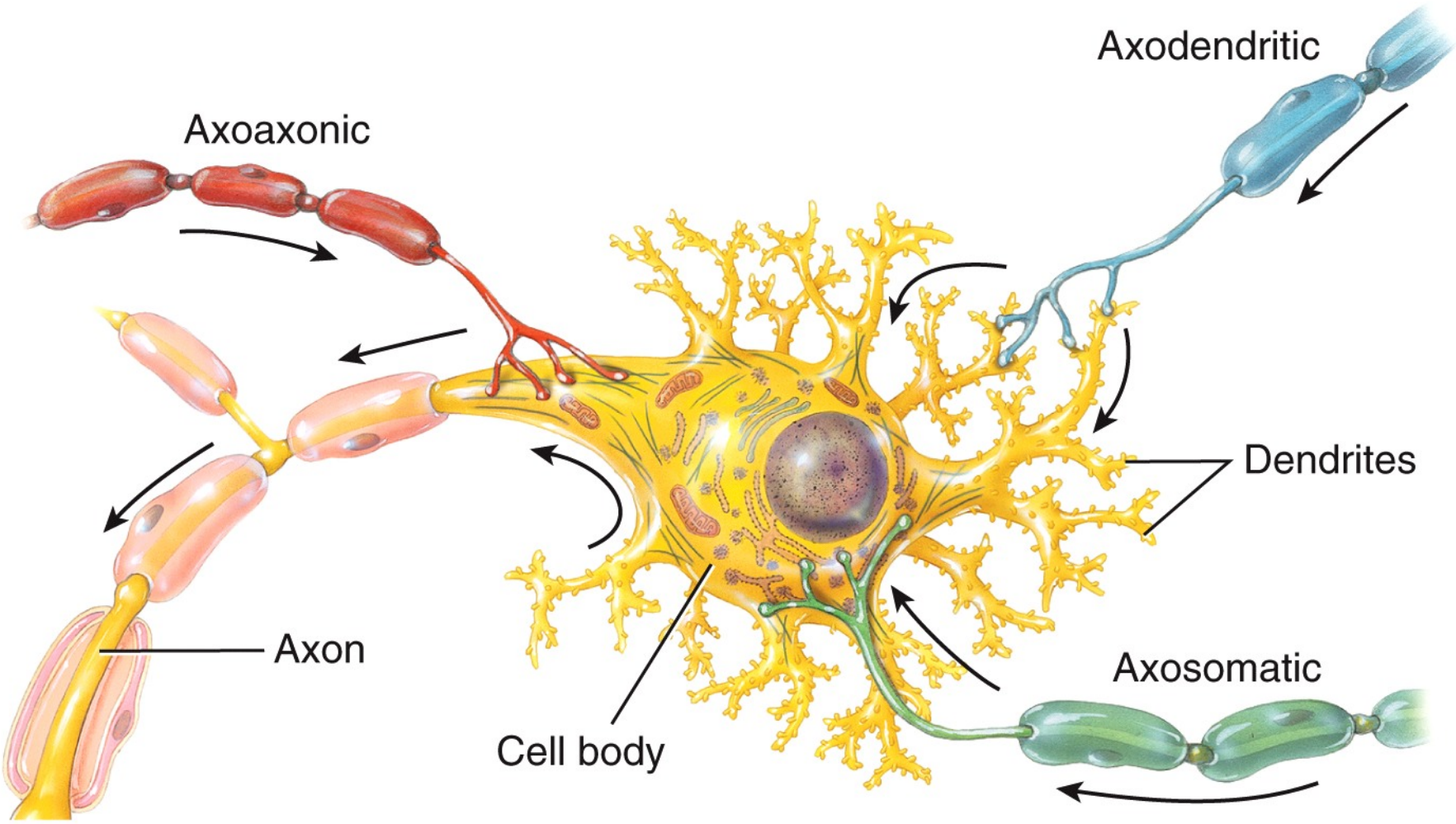

Postsynaptic neuron
Direction of nerve impulse
Presynaptic neuron
1
Nerve impulse
Presynaptic neuron
2
Ca^{2+}
2
Ca^{2+}
Voltage-gated Ca^{2+} channel
Synaptic end bulb
Cytoplasm
Synaptic vesicles
Synaptic cleft
Ca^{2+}
3
Neurotransmitter
Na^{+}
4
5
Neurotransmitter receptor
Ligand-gated channel closed
Ligand-gated channel open
Postsynaptic neuron
6
Postsynaptic potential
7
Nerve impulse

Synapses

- **presynaptic neuron (between two neurons)**
  - may synapse with
    - Dendrite
    - Soma
    - Axon of postsynaptic neuron
  - form different types of synapses
    - **Axodendritic synapses**
    - **Axosomatic synapses**
    - **Axoaxonic synapses**

Synaptic Relationships Between Neurons




Axodendritic
Axoaxonic
Dendrites
Axon
Axosomatic
Cell body

Synapses

- neuron can have an enormous number of synapses
  - spinal motor neuron's soma covered by about 10,000 synaptic knobs from other neurons
    - 8000 ending on its dendrites
    - 2000 ending on its soma
  - Cerebellum's soma can have as many as 100,000 synapses!!!!!
- **Note: all these incoming signals must be "integrated" to determine if there is going to be a new action potential created at the axon hillock.**

The Discovery of Neurotransmitters (1 of 3)

- The synaptic cleft
  - gap between neurons was discovered by Ramón y Cajal through histological observations
  - Challenged the notion of a “pure” electrical nervous system
  - Now recognized as an ***electrochemical junction***
  - 50 nanometers wide (1 x 10 to the negative 9 meters)
  - Takes 0.50 milliseconds for a neurotransmitter to cross this distance

The Discovery of Neurotransmitters (2 of 3)

- Otto Loewi, in 1921, demonstrated that neurons communicate by releasing chemicals – advent of the chemical synapses
  - he flooded exposed hearts of two frogs with saline
  - stimulated vagus nerve of the first frog and the heart slowed
  - removed saline from that frog and found it slowed heart of second frog
  - named it Vagusstoffe (“vagus substance”) // later renamed acetylcholine, the first discovered neurotransmitter

Discovery of Neurotransmitters (3 of 3)

- **What is an electrical synapse?** they exist in our physiology as gap junctions
  - some neurons, neuroglia, cardiac cells and single-unit smooth muscle
  - **gap junctions** join adjacent cells
    - ions diffuse through the gap junctions from one cell to the next
  - **advantage** of quick transmission // no delay for release and binding of neurotransmitter // cardiac and smooth muscle, embryonic cells, and some neurons
  - **disadvantage** = they cannot integrate information and make decisions

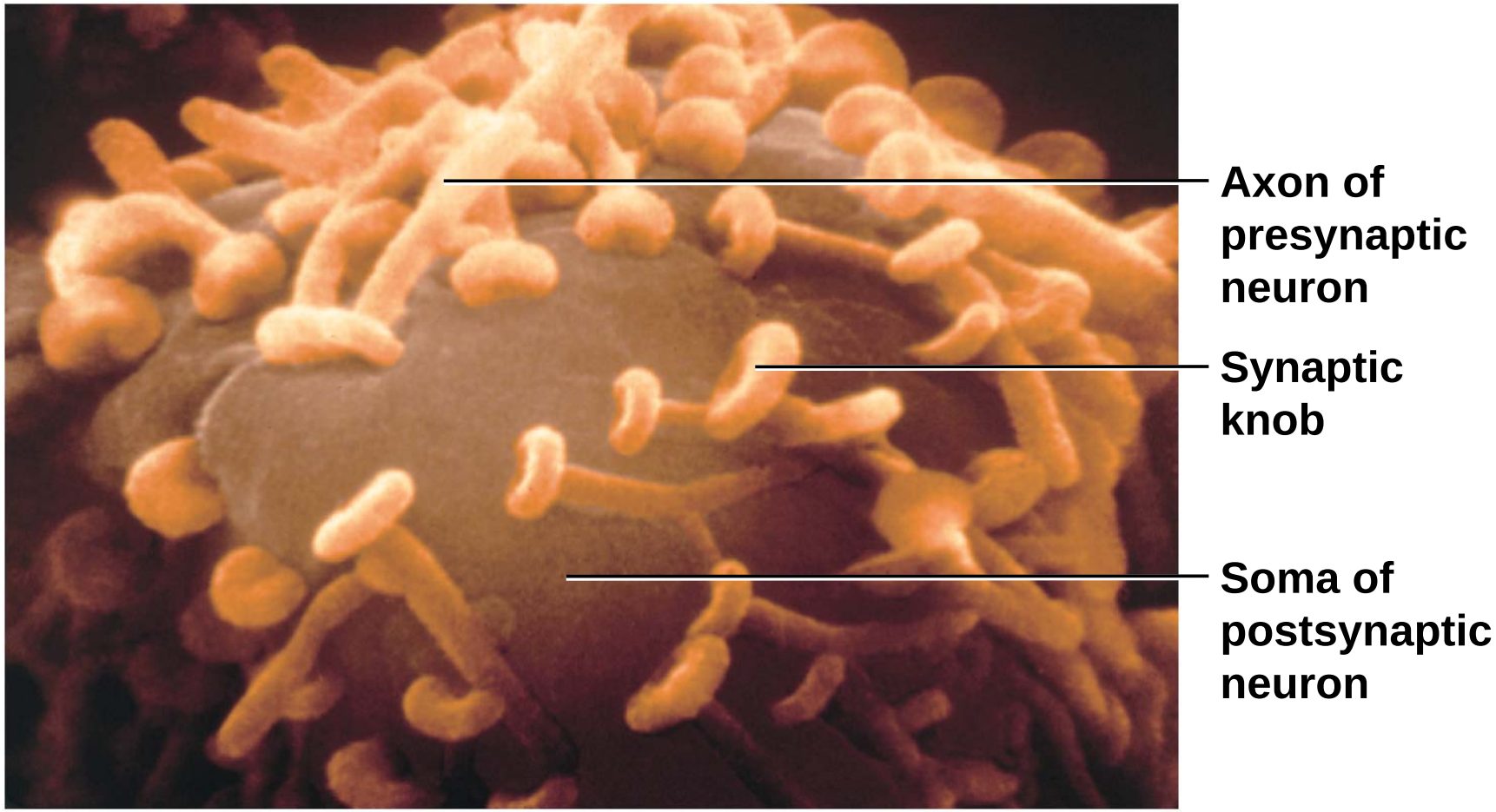
Structure of Neurotransmitter Receptors
(Ionotropic VS Metabotropic Receptors)

- **Ionotropic receptors**
  - Ligand binds to integral protein channels which allows either cation or anion to cross plasma membrane
  - Ligand receptor and ion channel are part of same protein
  - If cations enter cell then it depolarizes / if anions enter cell then it hyperpolarizes
- **Metabotropic receptors**
  - Ligand receptor and ion channel are different integral proteins
  - Ligand receptor on external face of membrane releases “G protein” on internal face of membrane
  - G protein travels to second integral protein which functions as the ion channel

How Neurotransmitter Removed from Synaptic Cleft

- Need to remove neurotransmitter form synaptic cleft to stop “signal”
  - Diffusion
  - Enzymatic degradation
  - Uptake by synaptic knob or by neighboring neuroglia cells (astrocytes)
  - Note: we will look at this in greater detail when we discuss the cessation of the neurotransmitter signal

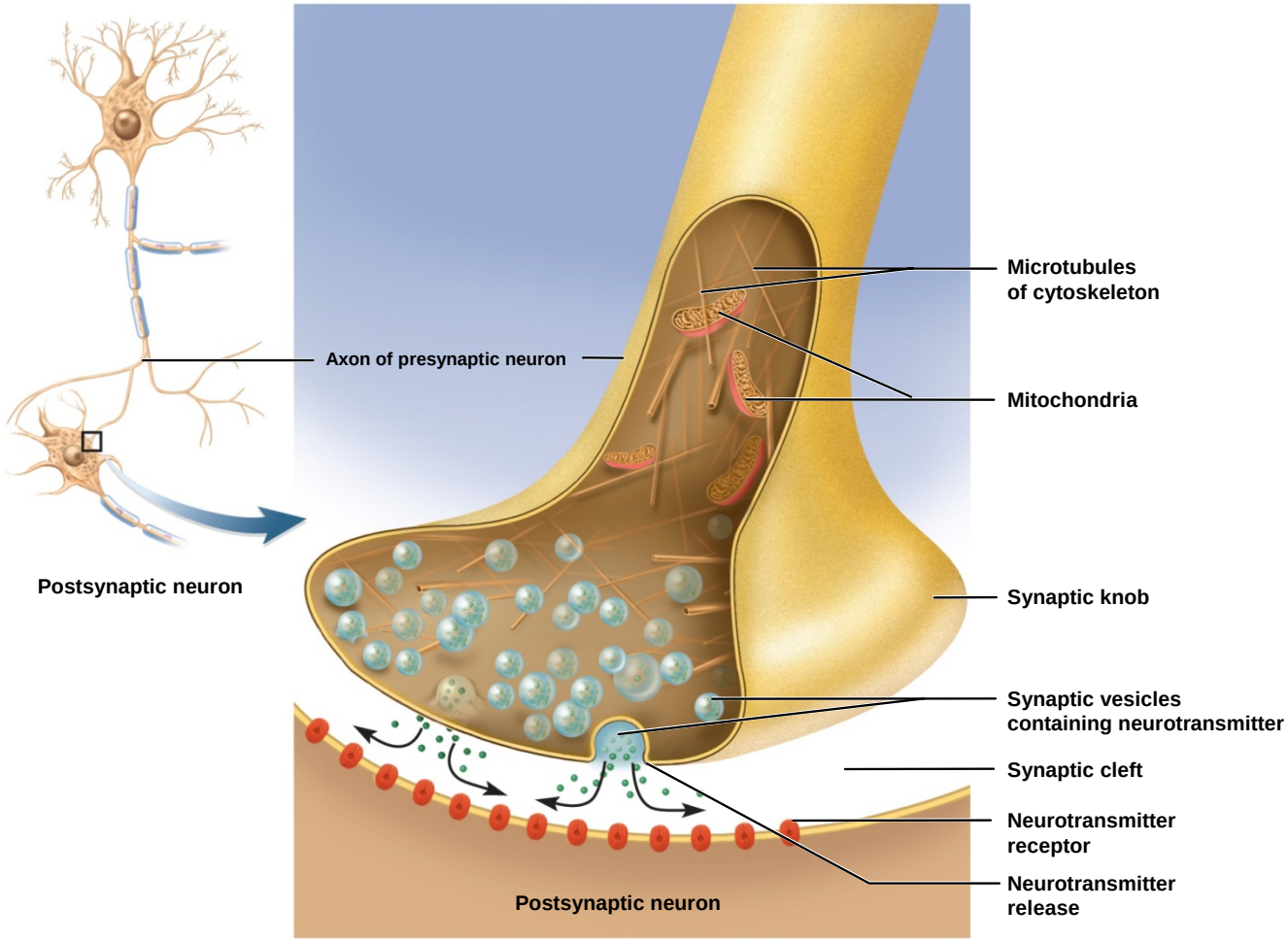
The Synaptic Knob



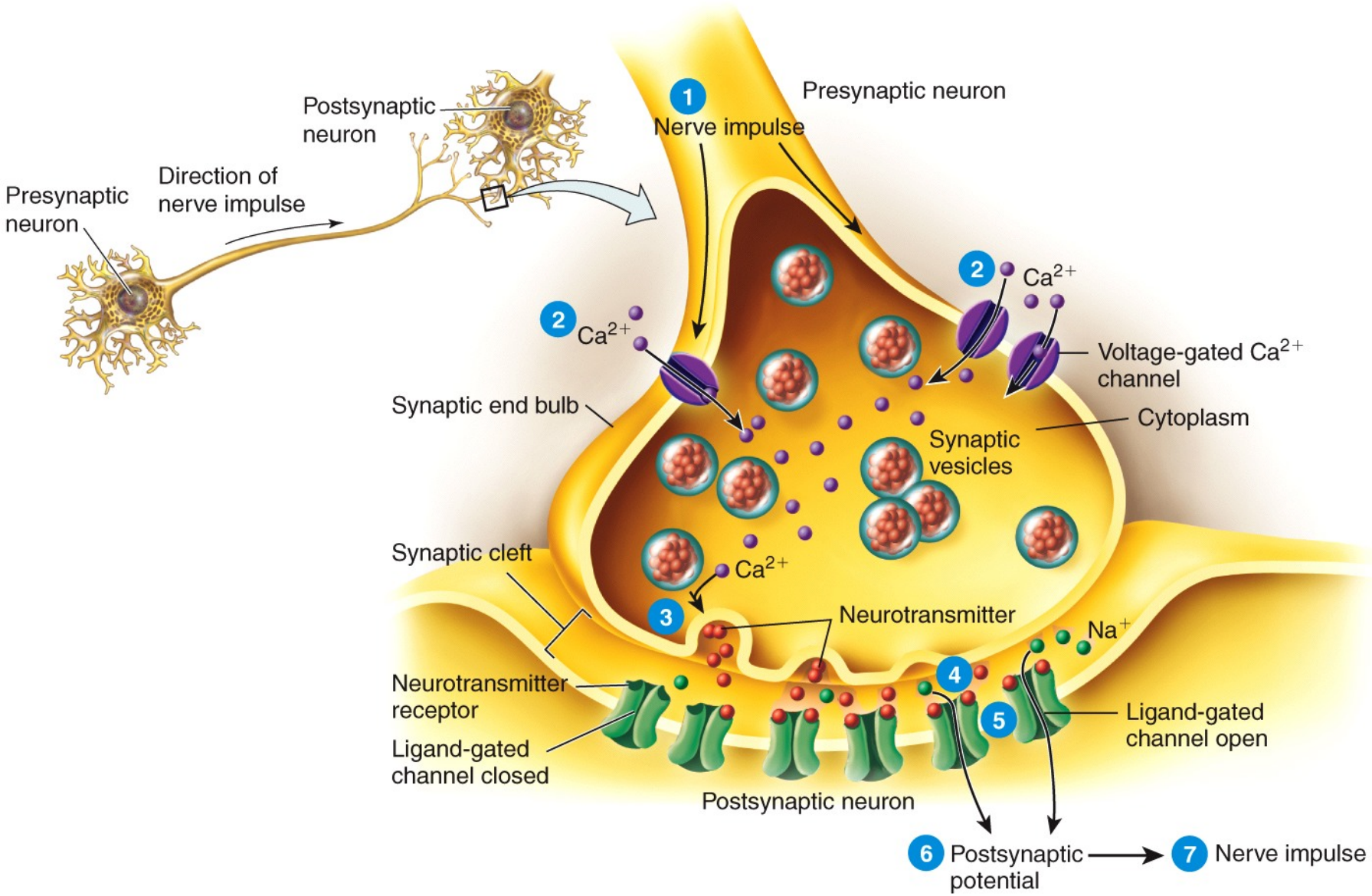
Structure of a Chemical Synapse

- synaptic knob of presynaptic neuron contains synaptic vesicles containing neurotransmitter
  - many docked on release sites of the plasma membrane / ready to release neurotransmitter on demand
  - a reserve pool of synaptic vesicles located further away from membrane
- postsynaptic neuron membrane contains proteins embedded into membrane / transmembrane protein
  - function as receptors // here they function as ligand-regulated ion gates
  - Note: gates can also be regulated by voltage and mechanical stimuli

Structure of a Chemical Synapse



- presynaptic neurons have synaptic vesicles with neurotransmitter and postsynaptic have receptors and ligand-regulated ion channels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Ligand-gated channel open
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Function of Neurotransmitters at Synapse

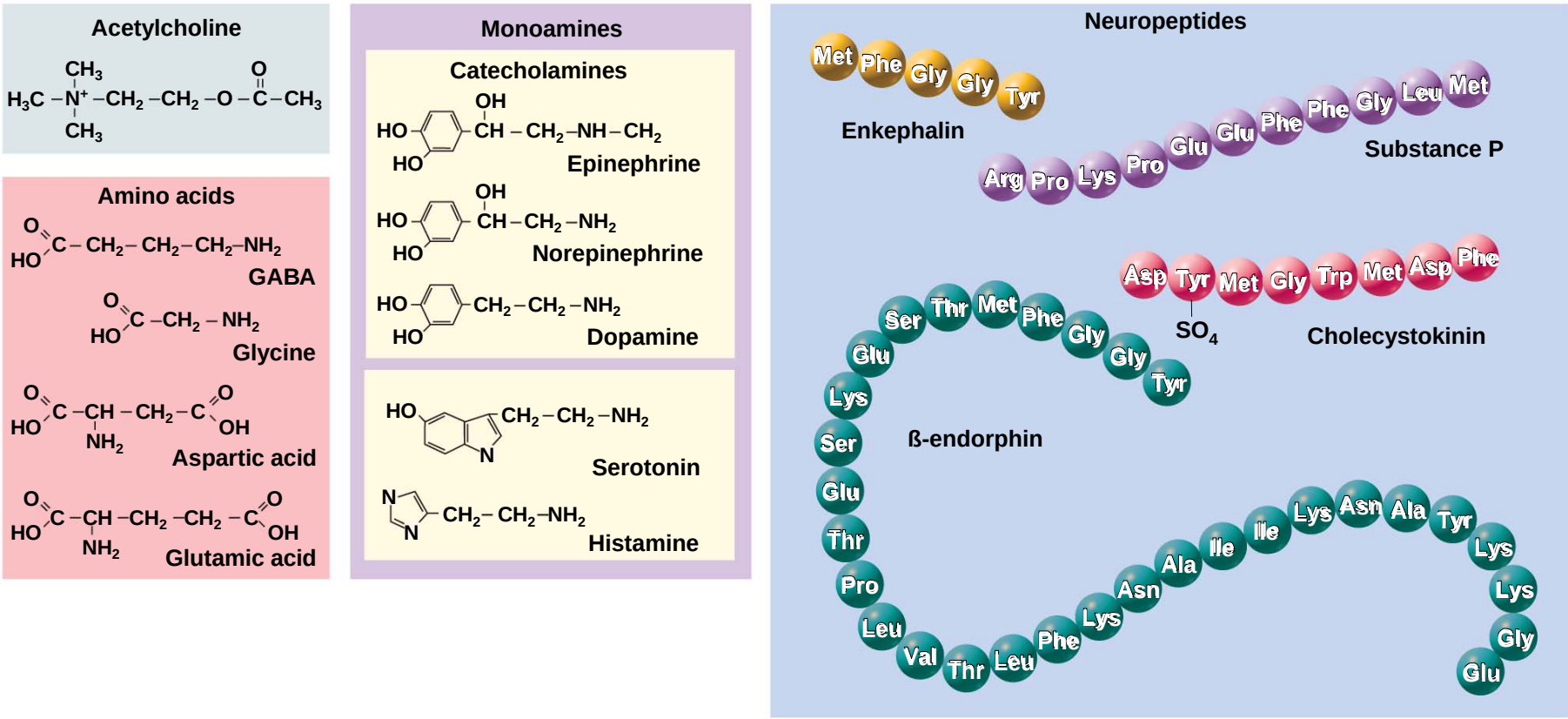
- they are synthesized by the presynaptic neuron
- they are released in response to stimulation
- they bind to specific receptors on the postsynaptic cell
- they alter the physiology of the cell // alter resting membrane potential

Effects of Neurotransmitters

- The same neurotransmitter does not have the same effect on all target tissues in the body
- multiple receptors exist for each neurotransmitter
  - E.g. 14 receptor types for serotonin
- It is the receptor that determines the effect of the neurotransmitter on the target cell
- Acetylcholine uses both ionotropic and metabotropic receptors in different tissues. Ionotropic receptors are always stimulatory however. Metabotropic acetylcholine receptors can be either stimulatory or inhibitory due to what type of second integral protein activated by the G protein
- *Note: the same molecule in different mechanisms may function as a hormone, a neurotransmitter, or a neuromodulator!*

Categories of Neurotransmitters

- more than 100 neurotransmitters have been identified
- major neurotransmitter categories according to chemical composition



Neurotransmitters and Related Messengers

- **Acetylcholine** ***//*** in a class by itself // formed from acetic acid and choline

- **Amino acid neurotransmitters** ***//*** include glycine, glutamate, aspartate, and γ-aminobutyric acid (GABA)

Neurotransmitters and Related Messengers

- **Monoamines or Biogenic Amines** // synthesized from amino acids by removal of the –COOH group // retaining the $–NH_2$ (amino) group

  - major monoamines are:

    - the catecholamines = epinephrine, norepinephrine, dopamine

    - the indoamines = histamine and serotonin

    - Note: LSD and mescaline bind to biogenic amine receptors

Neurotransmitters and Related Messengers

- Neuropeptides // substance P, endorphins, enkephalins, gut-brain peptides (produced my non-neural tissue but have receptors in the brain)

- Pruines // adenosine triphosphate (ATP) / now recognized as major neurotransmitter in CNS and PNS

- Gases & Lipids // nitric oxide (NO) & carbon monoxide // activate guanylyl cyclase / function in brain / hydrogen sulfide // (note: NO causes smooth muscle to dialate)

- Endocannabinoids (or simply cannabinoids) // brain neurotransmitter / tetrahydrocannabiol (THC) interacts with the endocannabinoid receptors

Neuropeptides

- chains of 2 to 40 amino acids
  - beta-endorphin and substance P
- act at lower concentrations than other neurotransmitters
- longer lasting effects
- stored in axon terminal as larger **secretory granules** (called dense-core vesicles)
- some function as hormones or neuromodulators
- some also released from digestive tract
  - Note: gut-brain peptides cause food cravings

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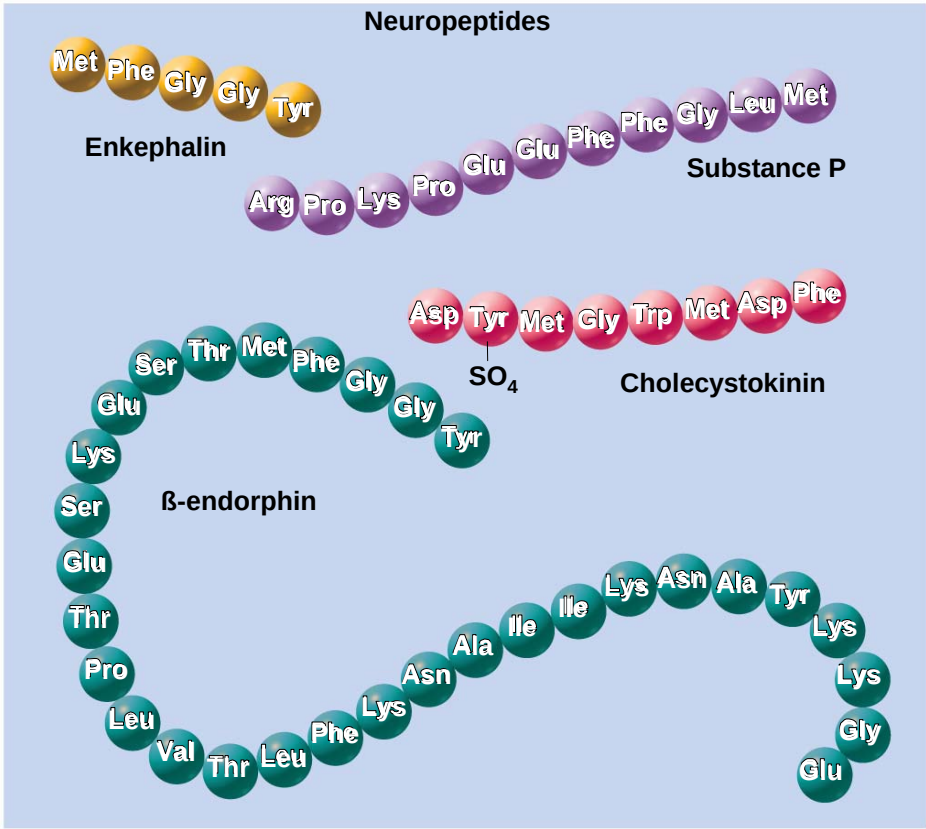
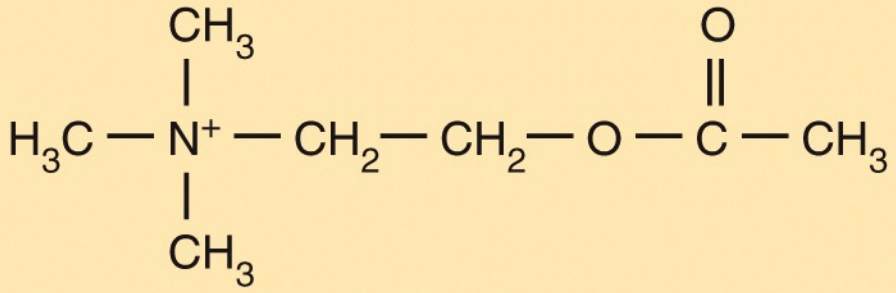


SMALL-MOLECULE NEUROTRANSMITTERS

Acetylcholine



Nitric oxide

$N{=}O$

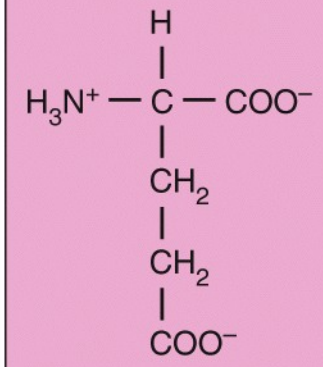
Carbon monoxide

$C{\equiv}O$

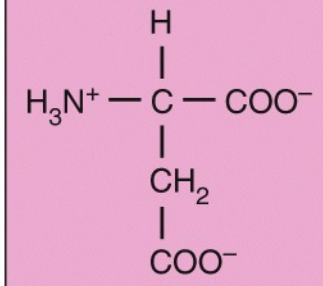
SMALL-MOLECULE NEUROTRANSMITTERS

Amino Acids

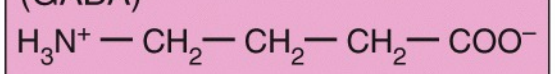
Glutamate



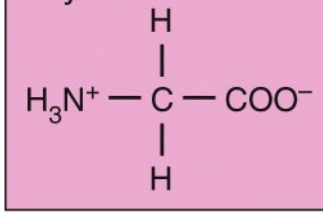
Aspartate



Gamma aminobutyric acid (GABA)



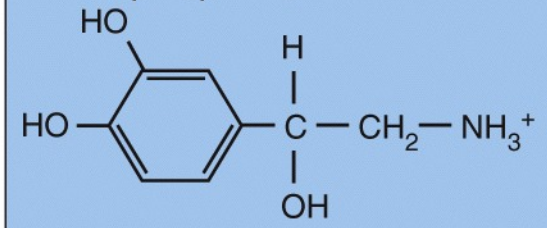
Glycine



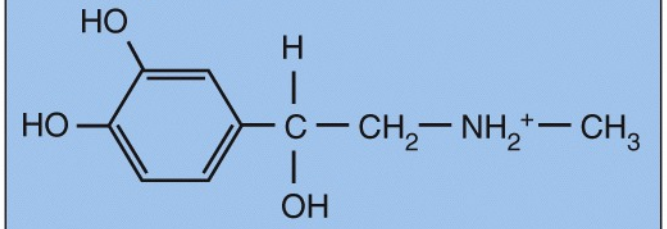
SMALL-MOLECULE NEUROTRANSMITTERS

Biogenic Amines

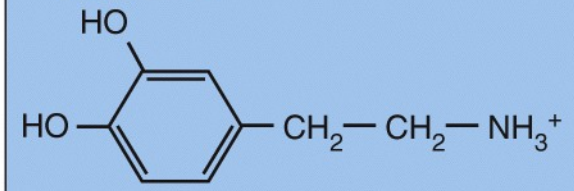
Norepinephrine



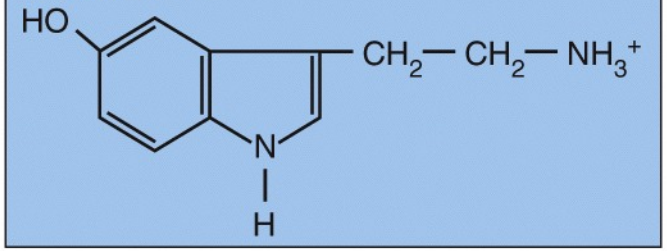
Epinephrine



Dopamine



Serotonin



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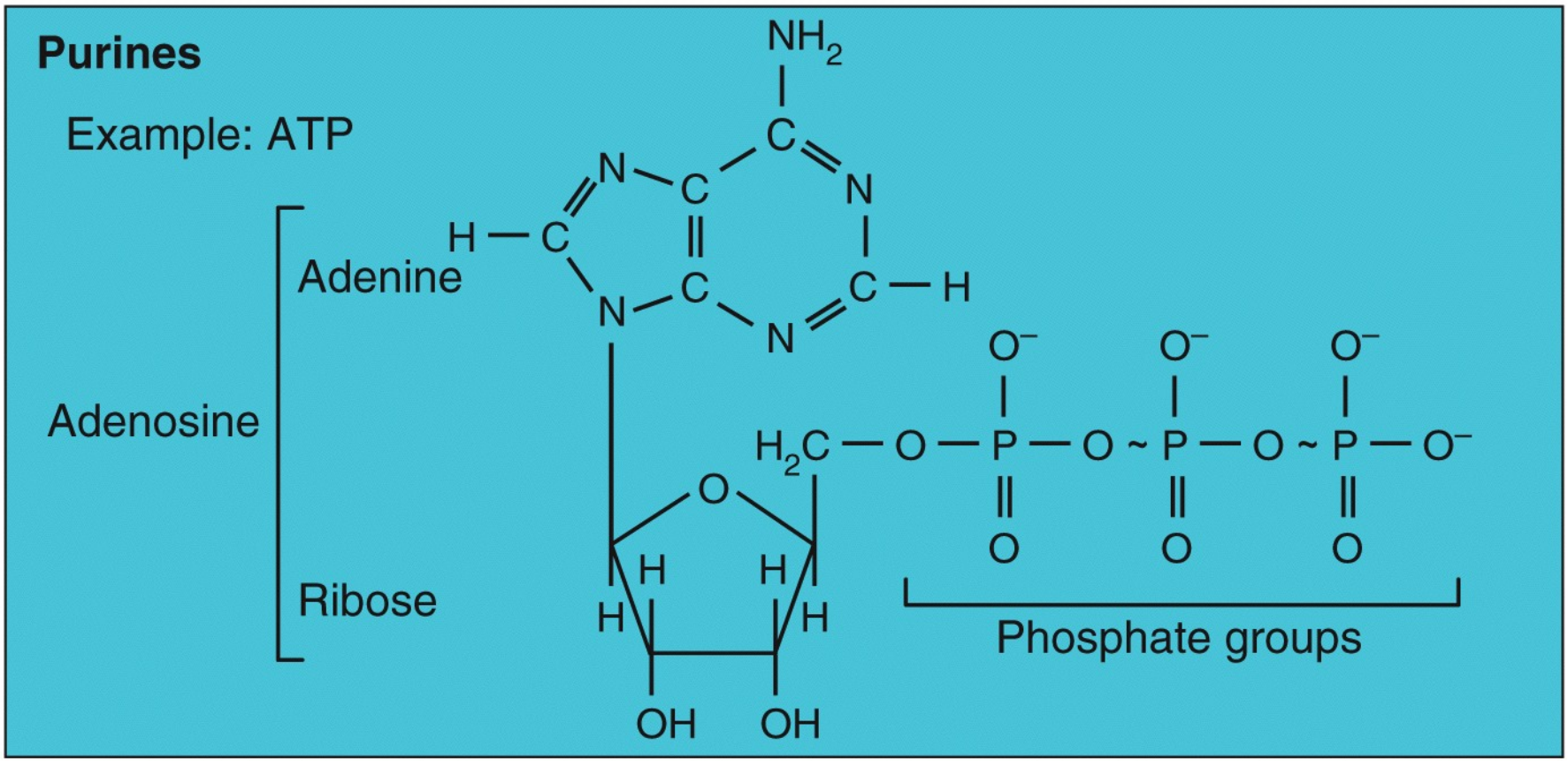
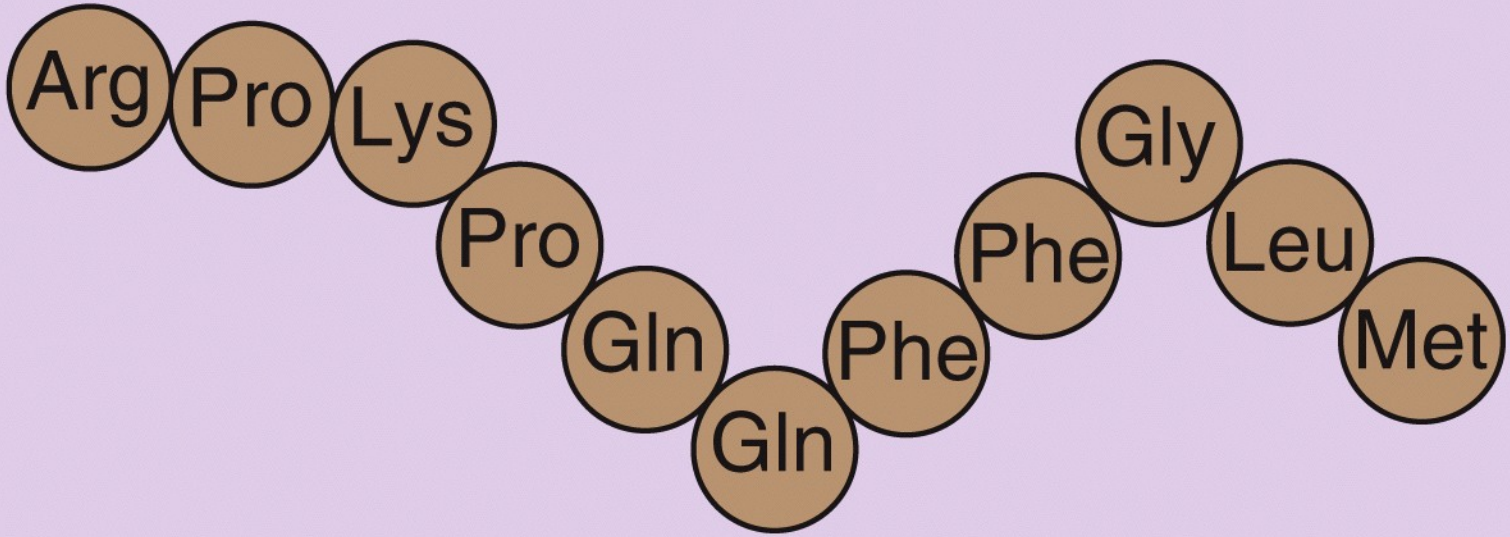


NEUROPEPTIDES

Example: Substance P



Synaptic Transmission

- **neurotransmitters** are diverse in their action
  - some excitatory
  - some inhibitory
  - some the effect depends on what kind of receptor the postsynaptic cell has // same neurotransmitter can cause either excitation or inhibition depending on the receptor
  - some open ligand-regulated ion gates
  - some act through second-messenger systems

Synaptic Transmission

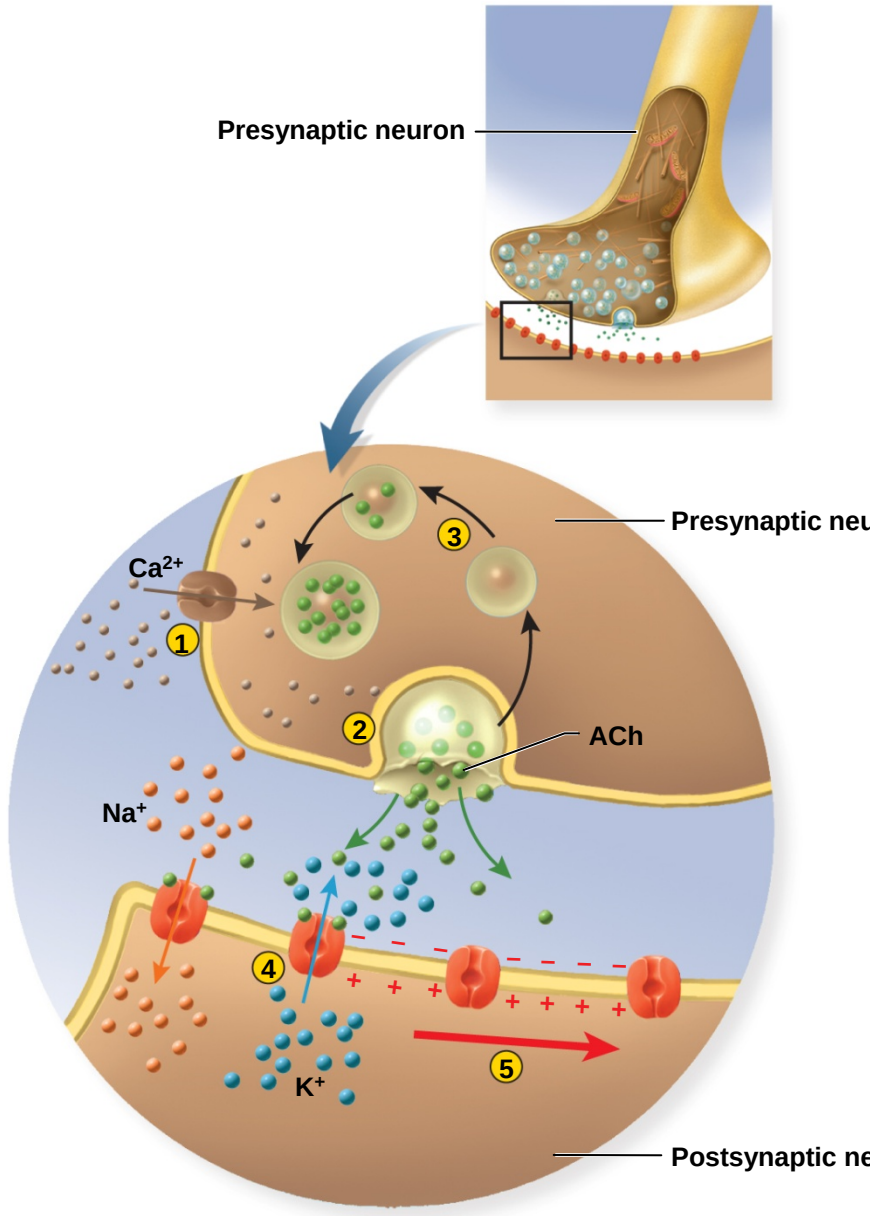
- synaptic delay – time from the arrival of a signal at the axon terminal of a presynaptic cell to the beginning of an action potential in the postsynaptic cell
  - 0.5 msec for all the complex sequence of events to occur
  - Mono-synaptic reflex VS polysynaptic reflex

Three Different Examples of Synaptic Transmission

- Three different types of synapses
- Each synapse used different type of neurotransmitter and post synaptic receptor
- Results in different modes of action
  - excitatory cholinergic synapse (ionotropic)
  - inhibitory GABA-ergic synapse (ionotropic)
  - excitatory adrenergic synapse (metabotropic or second messenger system)

Excitatory Cholinergic Synapse

- cholinergic synapse – employs acetylcholine (ACh) as its neurotransmitter
  - ACh excites some (most!) postsynaptic cells (e.g. skeletal muscle
  - may inhibits others (e.g. cardiocytes at AV node)



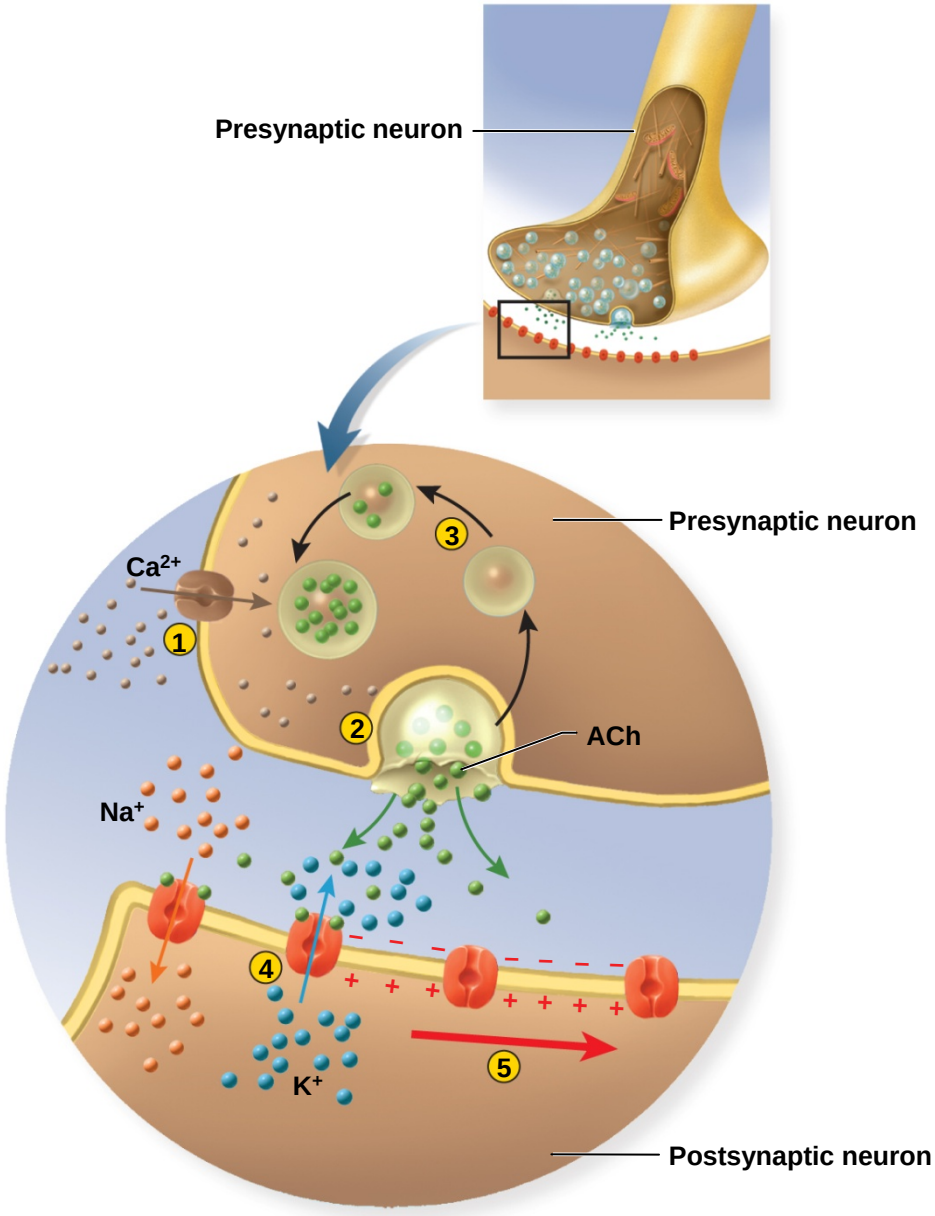
Excitatory Cholinergic Synapse

- Describing the **excitatory action**
  - nerve signal approaching the synapse // opens the voltage-regulated calcium gates at junction between axon and synaptic knob
  - Ca^{2+} enters the knob // triggers exocytosis of synaptic vesicles releasing Ach
  - empty vesicles drop back into the cytoplasm to be refilled with Ach
  - reserve pool of synaptic vesicles move to the active sites and release their Ach
  - ACh diffuses across the synaptic cleft

Excitatory Cholinergic Synapse

- Describing excitatory action (cont)
  - binds to ligand-regulated gates on the postsynaptic neuron
  - gates open // allowing Na^+ to enter cell and K^+ to leave // pass in opposite directions through same gate
  - as Na^+ enters the cell it spreads out along the inside of the plasma membrane and depolarizes it producing a local potential called the postsynaptic potential
  - if it is strong enough and persistent enough
  - it opens voltage-regulated ion gates in the trigger zone
  - causing the postsynaptic neuron to fire

Excitatory Cholinergic Synapse



Inhibitory GABA-ergic Synapse

- GABA-ergic synapse employs **γ-aminobutyric acid** as its neurotransmitter
- nerve signal triggers release of GABA into synaptic cleft
- GABA receptors are **chloride channels**
- **Cl^-** enters cell and makes the inside more negative than the resting membrane potential
- postsynaptic neuron is inhibited
- less likely to fire

Excitatory Adrenergic Synapse

- adrenergic synapse
  - employs the neurotransmitter norepinephrine (NE) also called noradrenaline
- Receptor for adrenergic synapses
  - not an ion gate // a transmembrane protein associated with a G protein
- NE , monoamines and neuropeptides acts through second messenger systems (e.g. such as cyclic AMP (cAMP)

Action of Adrenergic Transmembrane Receptors and G Protein / Second Messenger Transmission

- G protein is bound to the inside surface of the transmembrane NE receptor
  - binding of NE to the receptor causes the G protein to dissociate
  - G protein binds to adenylate cyclase // activates this enzyme
  - induces the conversion of **ATP** to **cyclic AMP**

Action of Adrenergic Transmembrane Receptors and G Protein / Second Messenger Transmission

- cyclic AMP can induce several alternative effects in the cell

  - causes the production of an internal chemical that binds to a ligand-regulated ion gate from inside of the membrane, opening the gate and **depolarizing the cell**

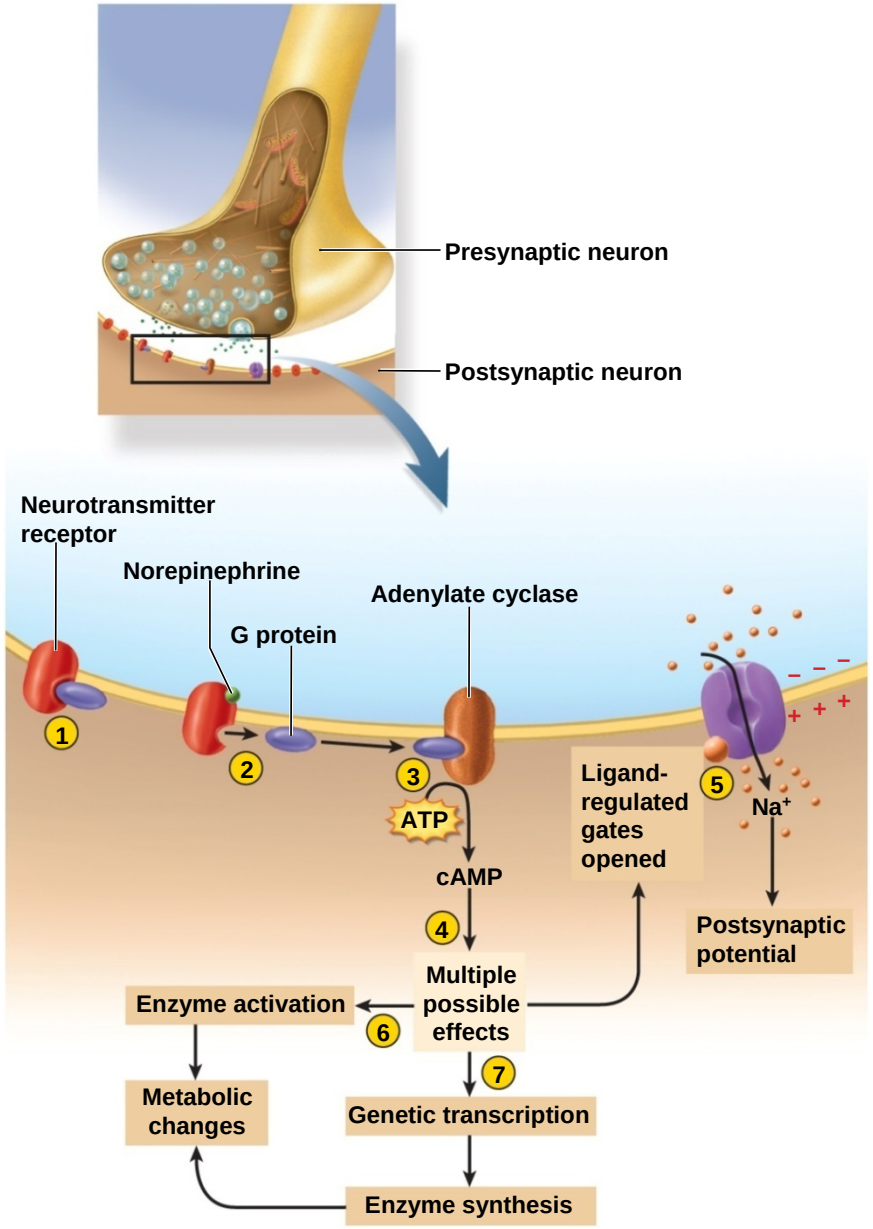
  - can activate preexisting **cytoplasmic enzymes** that lead do diverse metabolic changes

  - can induce **genetic transcription**, so that the cell produces new cytoplasmic enzymes that can lead to diverse metabolic effects

Action of Adrenergic Transmembrane Receptors and G Protein / Second Messenger Transmission

- slower to respond than cholinergic and GABA-ergic type synapses
- has advantage of **enzyme amplification**
  - single molecule of NE can produce vast numbers of product molecules in the cell

Excitatory Adrenergic Synapse



Cessation of the Signal

- mechanisms to **turn off stimulation** to keep postsynaptic neuron from firing indefinitely

  – neurotransmitter molecule binds to its receptor for only 1 msec or so // then dissociates from it

  – if presynaptic cell continues to release neurotransmitter // one molecule is quickly replaced by another and the neuron is re-stimulated

Cessation of the Signal

- When synaptic knob stops adding neurotransmitter into synaptic cleft and existing Acetylcholine is degraded // stop signals in the postsynaptic nerve fiber
  - getting rid of neurotransmitter by:
    - diffusion // neurotransmitter escapes the synapse into the nearby ECF // astrocytes in CNS absorb it and return it to neurons
    - reuptake // synaptic knob reabsorbs amino acids and monoamines by endocytosis //
    - degradation by enzymes // see next slide

Cessation of the Signal

- degradation by enzymes (cont.)
  - *acetylcholinesterase (AChE)* in synaptic cleft degrades ACh into acetate and choline // choline reabsorbed by synaptic knob
  - Catecholines also degradation by enzymes
    - » *monoamine oxidase (MAO) enzyme* // enzyme located in synaptic knob // after release from synaptic knob neurotransmitter reabsorbed by synaptic knob and degraded by enzyme // some antidepressant drugs work by inhibiting MAO
    - » catochol-O-methyltransferase (COMT) // enzyme located within interstitial spaces of tissue //
    - » Note: MAO & COMT are not found in blood // Why is this important!!!!

Neuromodulators

- hormones, neuropeptides, and other messenger molecules that modify synaptic transmission of neurotransmitters
  - may stimulate a neuron to install more receptors in the postsynaptic membrane adjusting its sensitivity to the neurotransmitter
  - may alter the rate of neurotransmitter synthesis, release, reuptake, or breakdown
- **enkephalins** & **endorphins //** important CNS neuromodulators
  - small peptides that inhibit spinal interneurons from transmitting pain signals to the brain
  - cont. next slide

Neuromodulators

- nitric oxide (NO) – a simple neuromodulator
  - a lightweight gas release by the postsynaptic neurons in some areas of the brain concerned with learning and memory
  - diffuses into the presynaptic neuron
  - stimulates it to release more neurotransmitter
  - one neuron's way of telling the other to 'give me more'
  - some chemical communication that goes backward across the synapse

Neural Integration

- This is the ability of your neurons to process information, store the information and recall the information, and make decisions
  - synaptic delay slows the transmission of nerve signals
  - more synapses in a neural pathway, the longer it takes for information to get from its origin to its destination
    - synaptic delay is due to limitation of nerve fiber length
    - gap junctions allow some cells to communicate more rapidly than chemical synapses

Neural Integration

- So why do we need synapses?
  - to process information, store it, and make decisions
  - chemical synapses are the decision making devises of the nervous system
  - the more synapses a neuron has /// the greater its information-processing capabilities.
  - **pyramidal cells** in cerebral cortex have about 40,000 synaptic contacts with other neurons
  - **cerebral cortex** (main information-processing tissue of your brain) has an estimated 100 trillion (10^{14}) synapses

Excitatory Postsynaptic Potentials - EPSP

- neural integration is based on the postsynaptic potentials produced by neurotransmitters
- typical neuron has a resting membrane potential of -70 mV and threshold of about -55 mV
- excitatory postsynaptic potentials (EPSP)
  - any voltage change in the direction of threshold that makes a neuron more likely to fire
  - usually results from Na^+ flowing into the cell cancelling some of the negative charge on the inside of the membrane
  - glutamate and aspartate are excitatory brain neurotransmitters that produce EPSPs

Inhibitory Postsynaptic Potentials - IPSP

- Inhibitory postsynaptic potentials (IPSP)
  - any voltage change away from threshold that makes a neuron less likely to fire
    - neurotransmitter hyperpolarizes the postsynaptic cell and makes it more negative than the RMP making it less likely to fire
    - produced by neurotransmitters that open ligand-regulated chloride gates // causing inflow of Cl- making the cytosol more negative

Inhibitory Postsynaptic Potentials - IPSP

- glycine and GABA produce IPSPs and are inhibitory
- acetylcholine (ACh) and norepinephrine are excitatory to some cells and inhibitory to others
  - depending on the *type of receptors* on the target cell
  - ACh excites skeletal muscle, but inhibits cardiac muscle due to the different type of receptors

Postsynaptic Potentials

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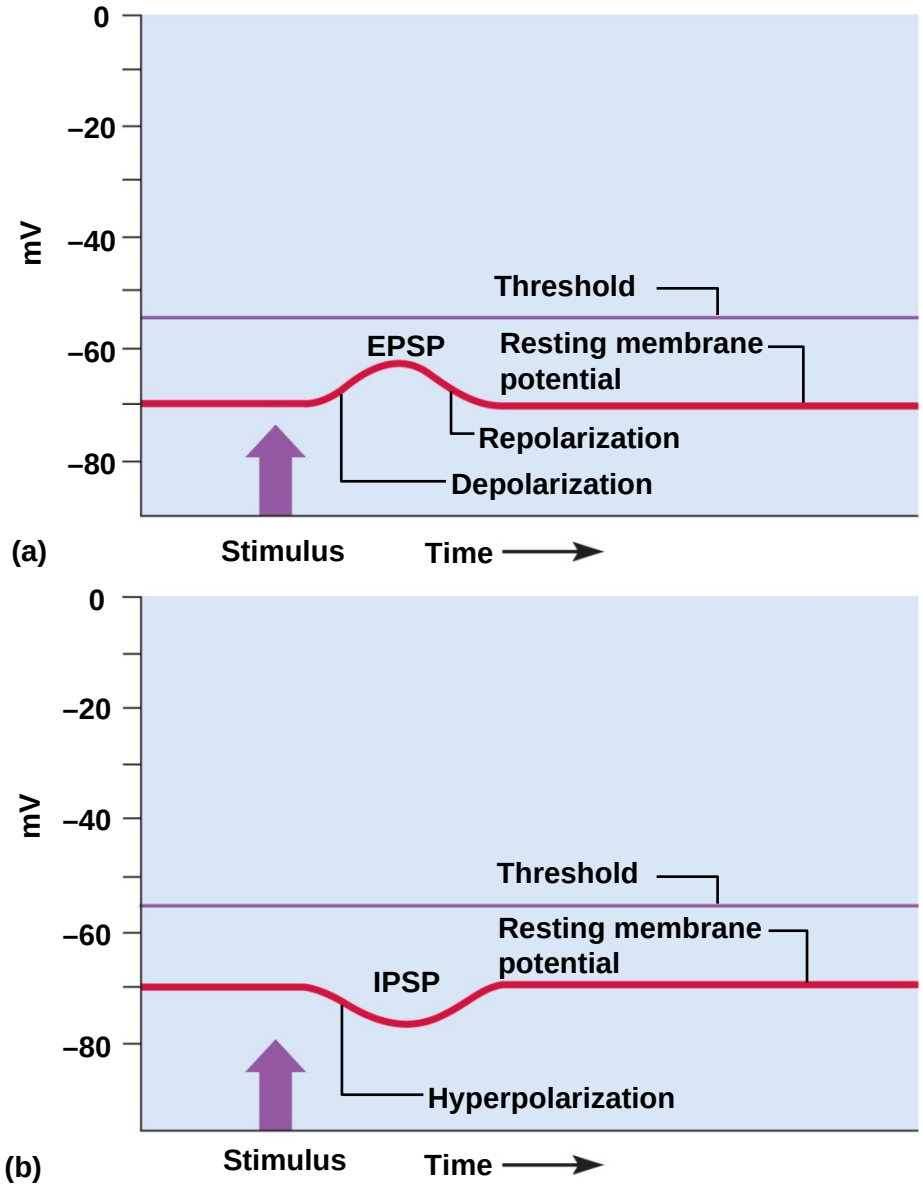
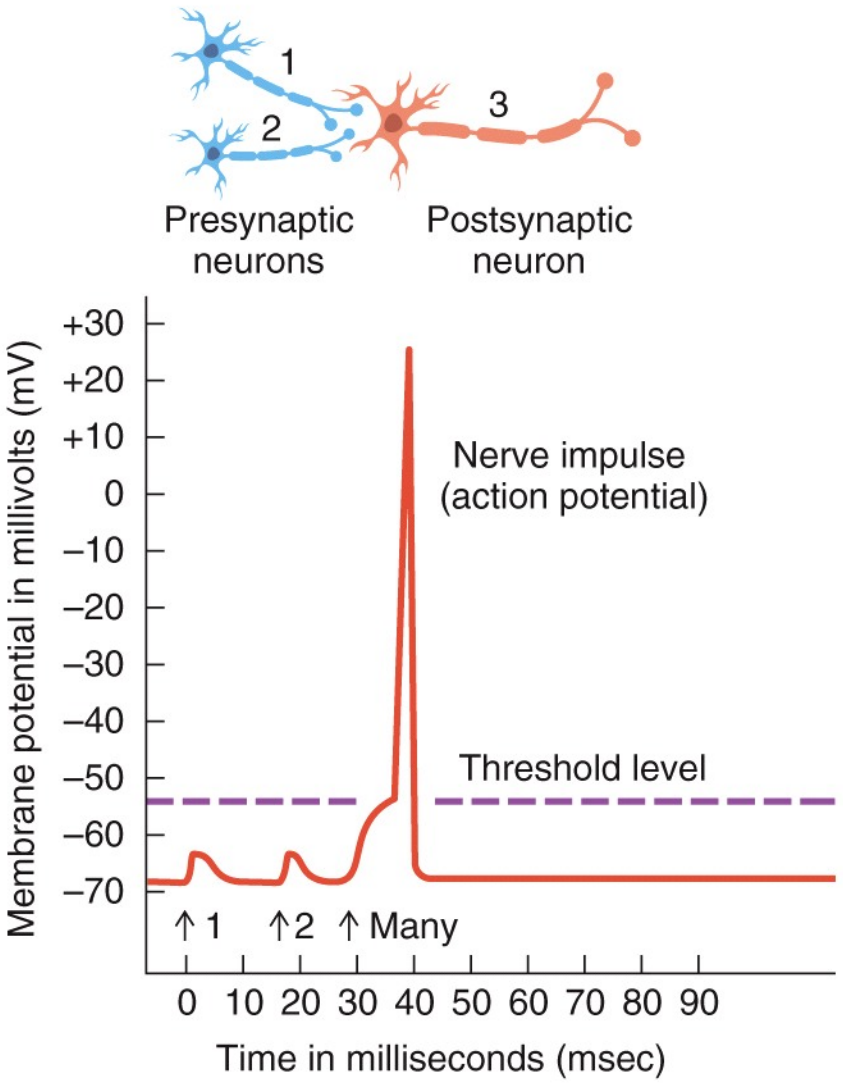


Summation, Facilitation, and Inhibition

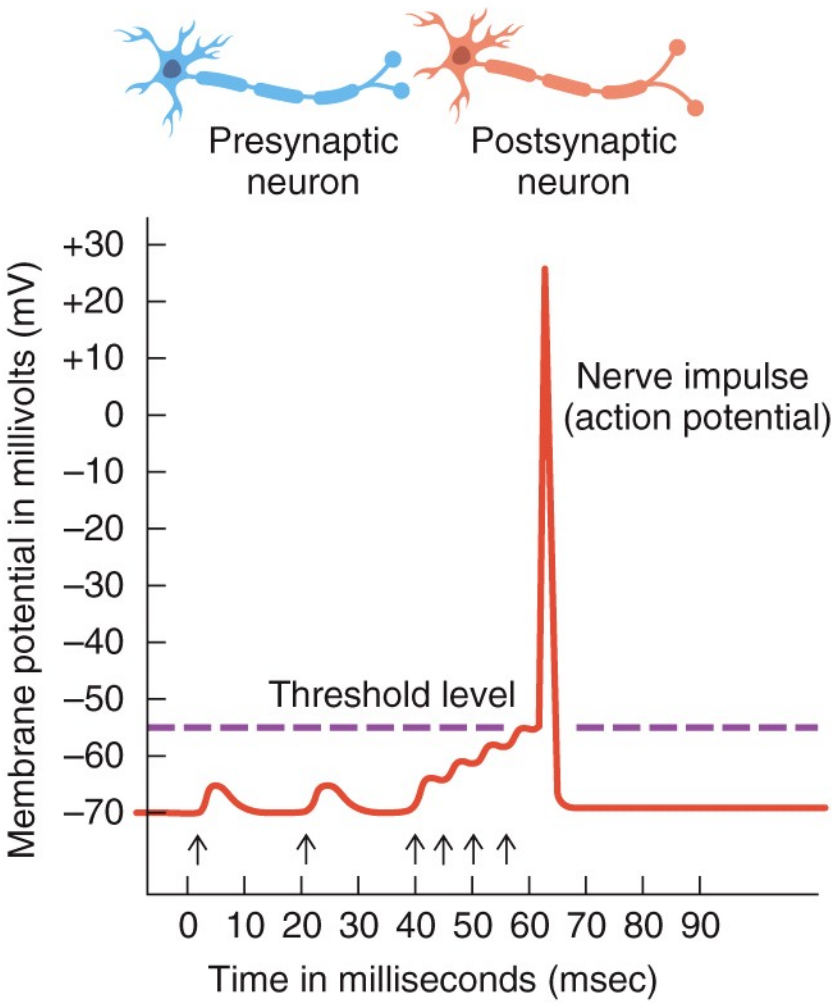
- one neuron can receive input from thousands of other neurons
- some incoming nerve fibers may produce EPSPs while others produce IPSPs
- neuron's response depends on whether the net input is excitatory or inhibitory
- **summation** – the process of adding up postsynaptic potentials and responding to their **net** effect // occurs in the trigger zone
- the balance between EPSPs and IPSPs enables the nervous system to make decisions

Summation, Facilitation, and Inhibition

- **temporal summation** – occurs when a single synapse generates EPSPs so quickly that each is generated before the previous one fades
  - allows EPSPs to add up over time to a threshold voltage that triggers an action potential
- **spatial summation** – occurs when EPSPs from several different synapses add up to threshold at an axon hillock.
  - several synapses admit enough Na^+ to reach threshold
  - presynaptic neurons cooperate to induce the postsynaptic neuron to fire

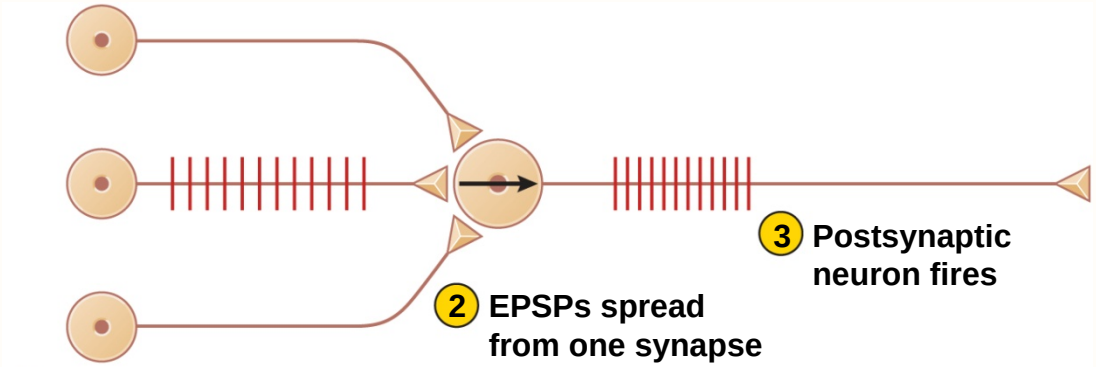


(a) Spatial summation

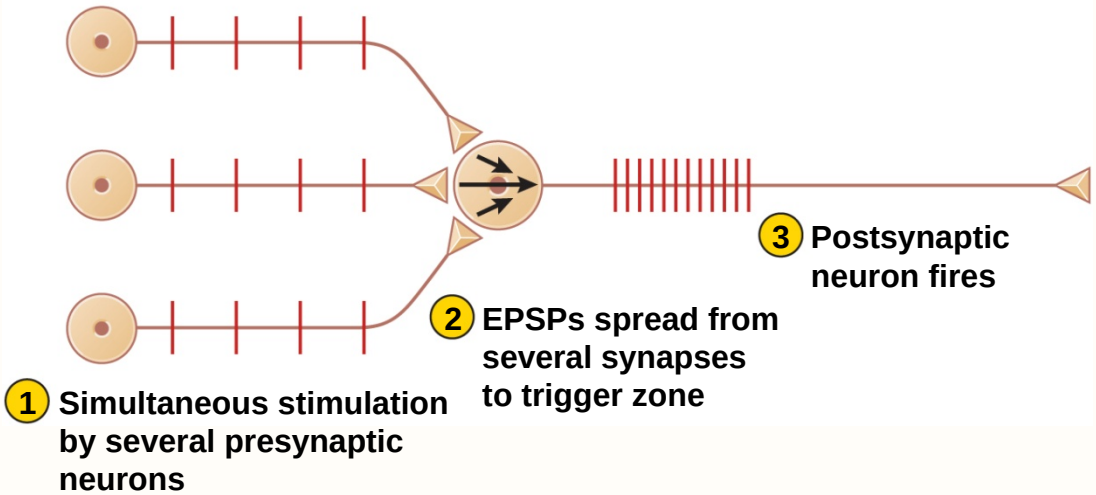


(b) Temporal summation

Temporal and Spatial Summation

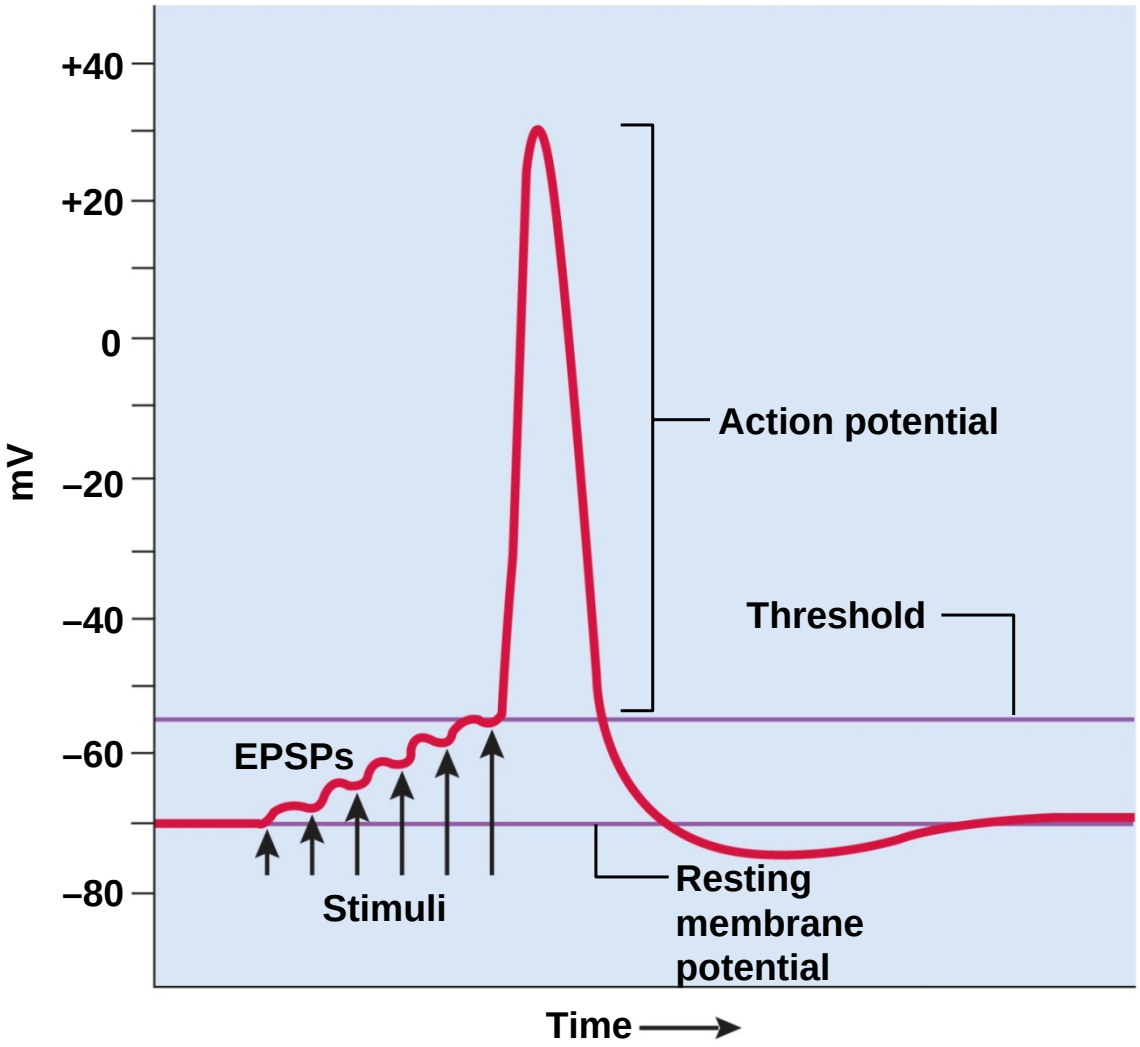


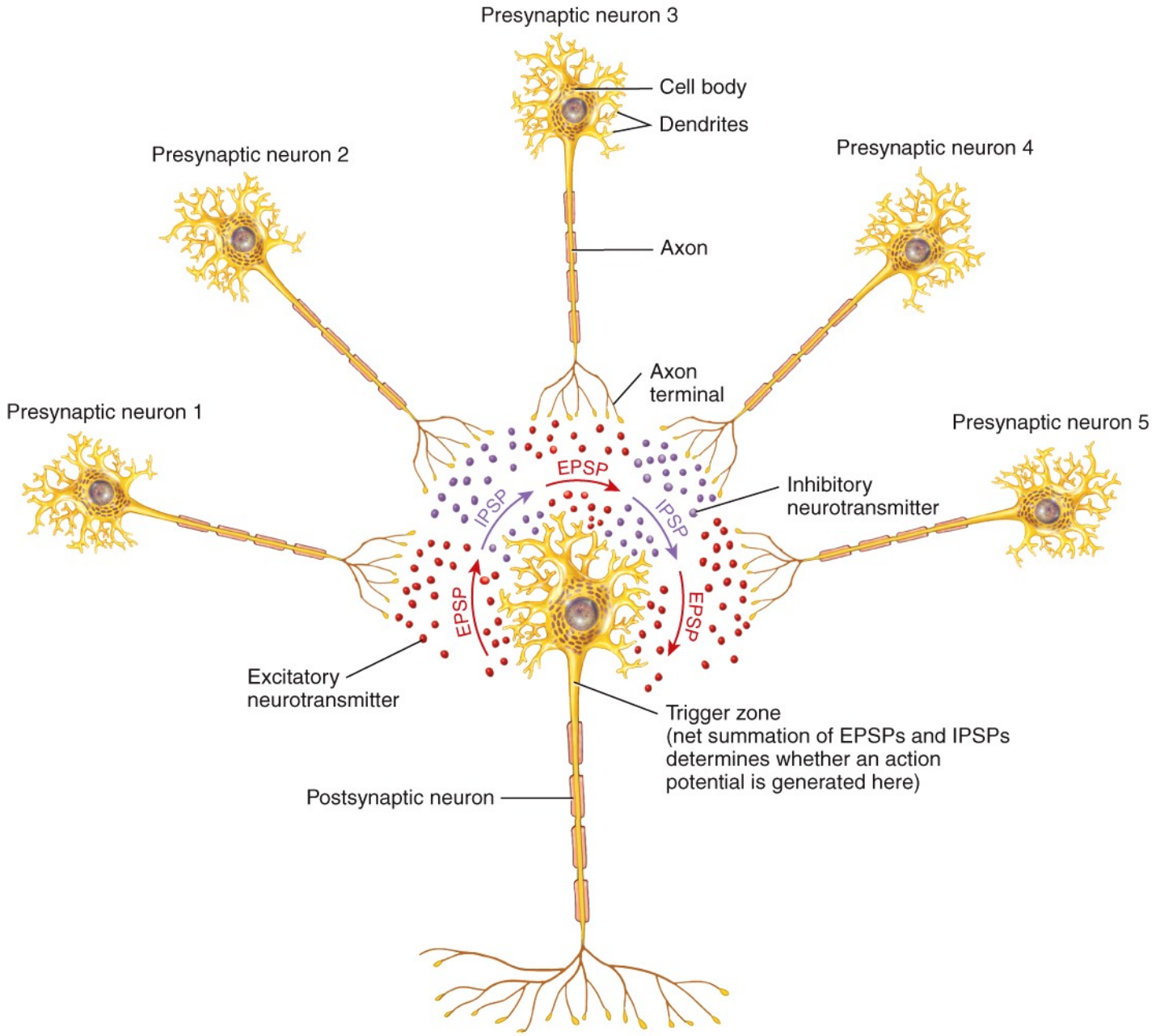
(a) Temporal summation



(b) Spatial summation

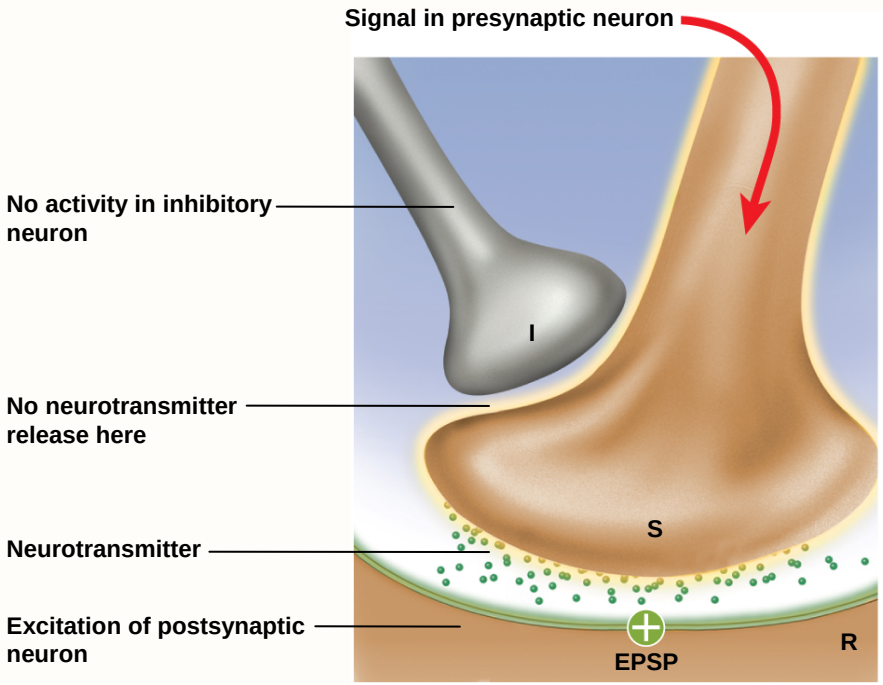
Summation of EPSPs

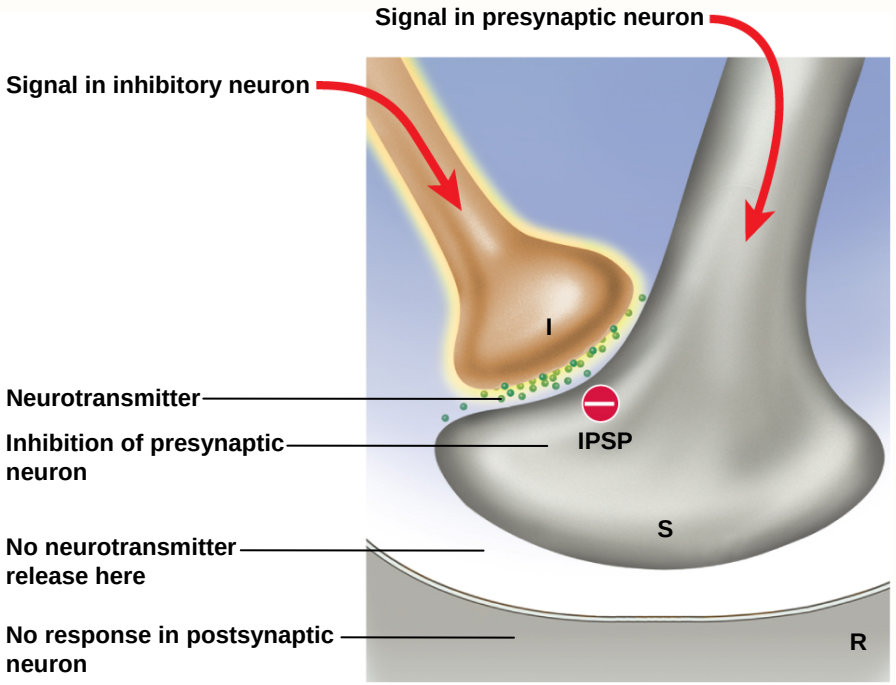



Presynaptic neuron 3
Cell body
Dendrites
Presynaptic neuron 2
Presynaptic neuron 4
Axon
Axon terminal
Presynaptic neuron 1
Presynaptic neuron 5
EPSP
IPSP
IPSP
Inhibitory neurotransmitter
EPSP
EPSP
Excitatory neurotransmitter
Trigger zone (net summation of EPSPs and IPSPs determines whether an action potential is generated here)
Postsynaptic neuron

Summation, Facilitation, and Inhibition

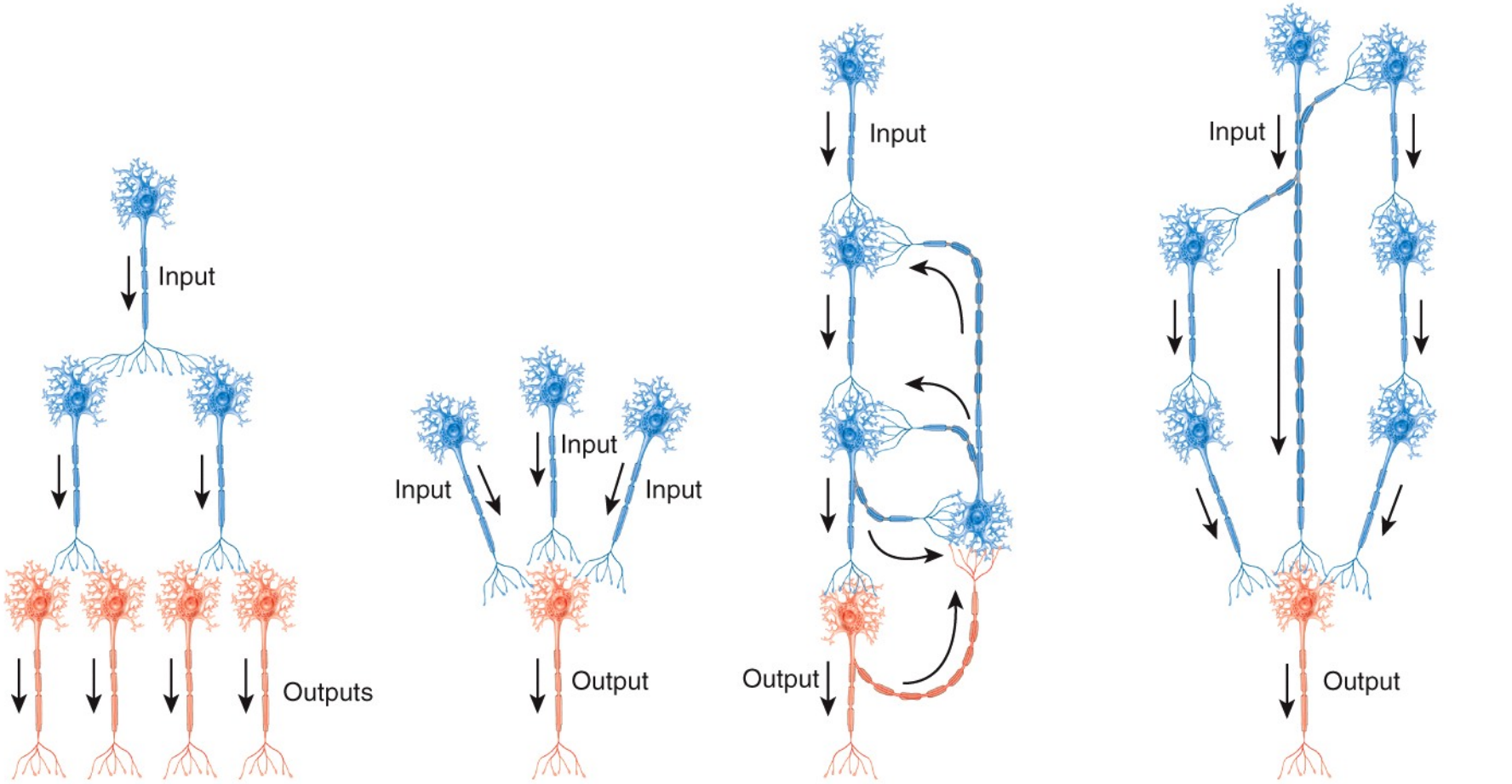
- neurons routinely work in groups to modify each other's action
- facilitation – a process in which one neuron enhances the effect of another one /// combined effort of several neurons facilitates firing of postsynaptic neuron





Summation, Facilitation, and Inhibition

- **presynaptic inhibition** – process in which one presynaptic neuron suppresses another one
  - the opposite of facilitation // reduces or halts unwanted synaptic transmission
  - neuron I releases inhibitory GABA // prevents voltage-gated calcium channels from opening in synaptic knob and presynaptic neuron releases less or no neurotransmitter



(a) Diverging circuit (b) Converging circuit (c) Reverberating circuit (d) Parallel after-discharge circuit