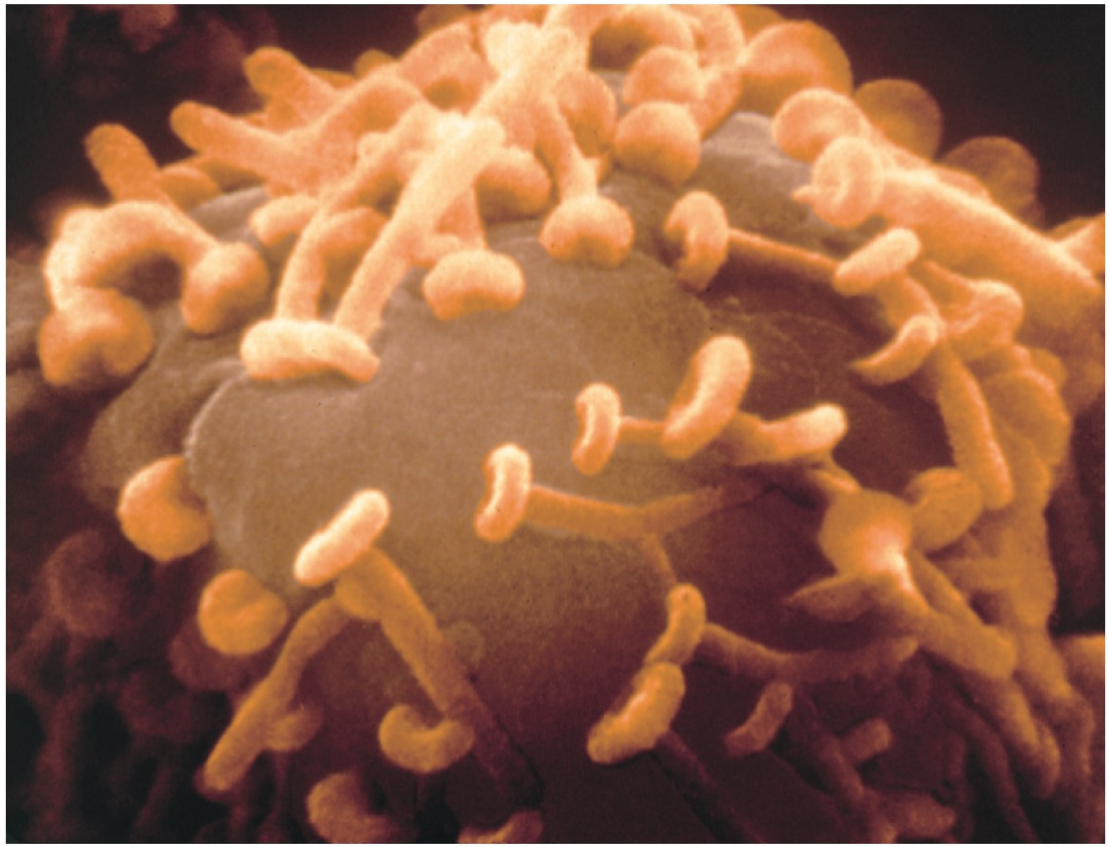
Chapter 12.3

The Synapse and Neurotransmitters



The Discovery of the Synaptic Cleft

- Early physiologist thought neurons were “continuous thread like fibers” that transmitted electrical impulses (i.e. the reticular theory) to their target tissue.

  - Camillo Golgi – Italian physician developed a “silver staining technique” to visualize nervous tissue (1873) for the first time.

  - Ramón y Cajal used the “Golgi method” to show gaps (i.e. synapse) between neurons (early 1989's) which led to the “neuron doctrine”

  - Cajal's work challenged the notion of the day about a “pure” electrical nervous system and his work led to the “neuron doctrine” and discredited the reticular theory

  - Cajal showed that the brain's function was dependent on the “chemical synapse” which is now recognized as a type of ***electrochemical junction*** /// 50 nanometers wide (1 x 10 to the negative 9 meters)

  - In the 1970s Dr. Eric Kandel demonstrated the difference between short term and long term learning that occurs across the synapse.

The Discovery of Neurotransmitters

- Otto Loewi, in 1921, demonstrated that neurons communicate with each other and their target tissue by releasing chemicals – establishing the chemical synapse
  - he flooded exposed two frog hearts with saline
  - stimulated vagus nerve of the first frog and the heart slowed
  - removed saline fluid from frog #1, added it to frog #2, and found the fluid from frog #1 slowed heart of frog #2
  - named it Vagusstoffe ("vagus substance") // later re-named acetylcholine. This was the discovery of the first neurotransmitter.
  - takes 0.50 milliseconds for a neurotransmitter to cross this distance

The Synapse

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

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

- A chemical synapse consist of three components
  - Pre-synaptic membrane
  - Synaptic cleft
  - Post-synaptic membrane

- *One type of neurotransmitter may stimulate a new local potential on the post-synaptic membrane, making it more likely to create a new local potential on the post synaptic membrane.*

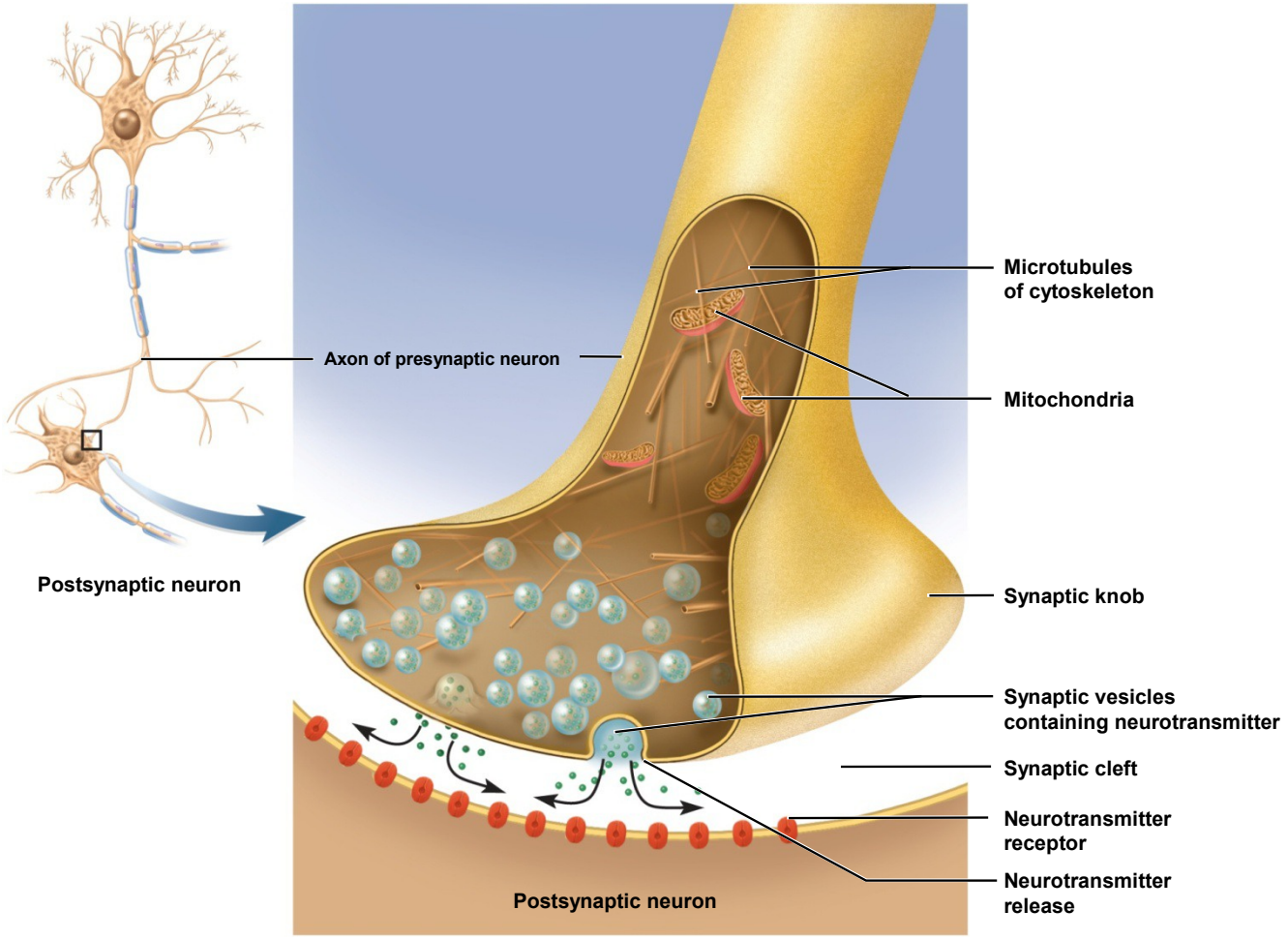
- *Another type of neurotransmitter may inhibit forming a local potential, making it less likely to stimulate a new local potential on the post synaptic membrane.*

- *What is now possible? Significance?*

Synapses

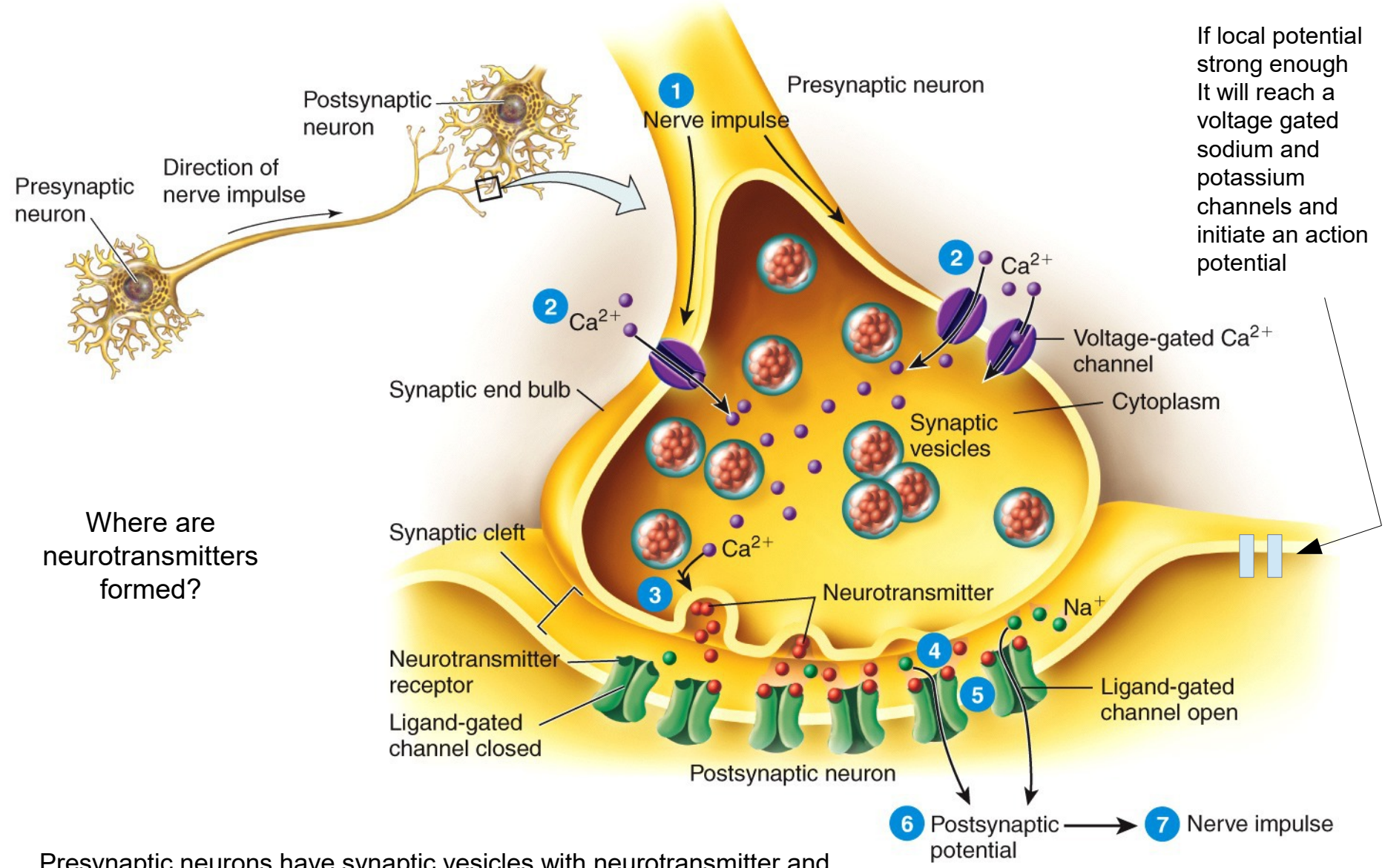
- When a synapse is between two neurons we use the following syntax.
  - 1st neuron in the signal pathway is called the **presynaptic neuron** / it releases neurotransmitter
  - 2nd neuron is the **postsynaptic neuron** / it has receptors for the neurotransmitter

Structure of a Chemical Synapse



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

Structure of a Chemical Synapse



If local potential strong enough It will reach a voltage gated sodium and potassium channels and initiate an action potential

Where are neurotransmitters formed?

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

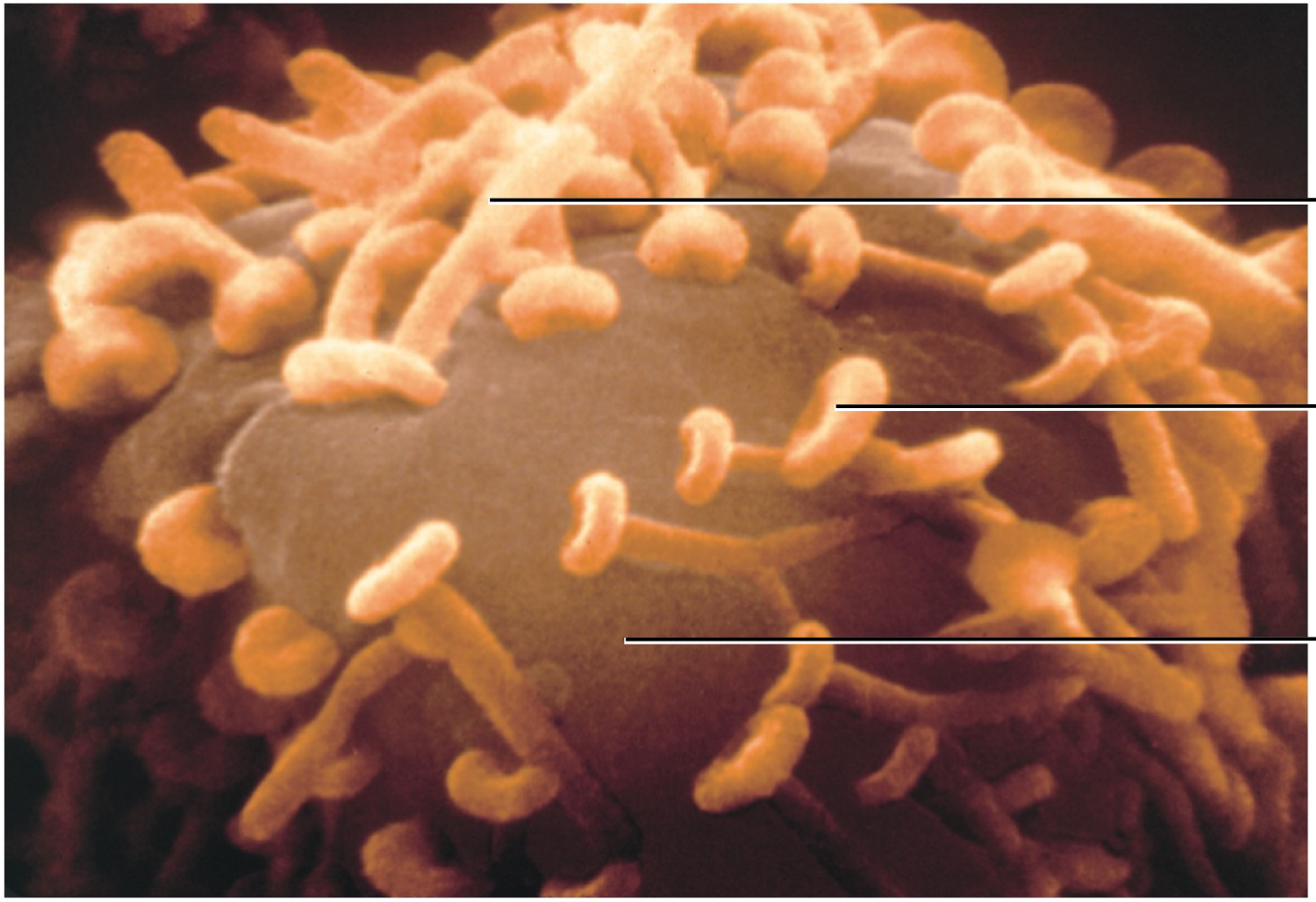
Synapses

- A neuron may have an enormous number of other neurons forming synapses on their dendrites and/or soma
  - spinal cord motor neuron soma have about 10,000 unique synaptic knobs from other neurons
    - 8,000 ending on its dendrites
    - 2,000 ending on its soma
  - Cerebellum's soma may have as many as 100,000 synapses!!!!!
- *Note: all these incoming signals must be "integrated" (measure the stimulate VS inhibit neurotransmitters) to determine if a new action potential will be created at the axon hillock of the post synaptic neuron. In the cerebellum, 100,000 incoming signals will only result in one of two possible outcomes: no action potential or an action potential.*

Structure of a Chemical Synapse

- synaptic knob stores synaptic vesicles containing neurotransmitters
  - many docked on interior face of the plasma membrane / ready to release neurotransmitter on demand into synaptic cleft
  - a reserve pool of synaptic vesicles are located further away from inner face of synaptic knob's membrane
- postsynaptic neuron membrane contains receptors (docking stations made up of proteins) embedded into membrane / transmembrane protein
  - receptors represent ligand-regulated ion gates
  - Note: other gates may be regulated by voltage or mechanical stimuli

The Synaptic Knob



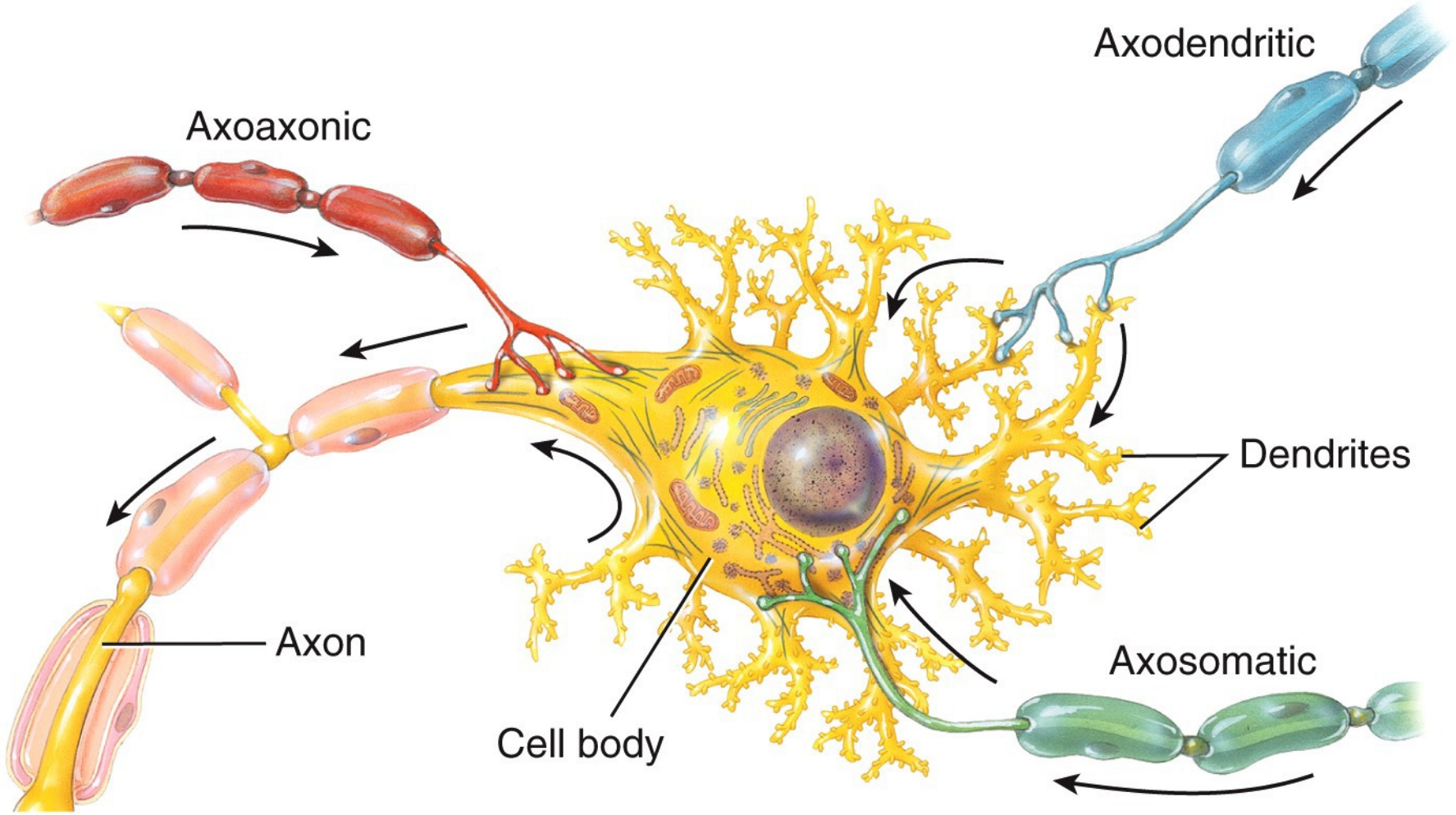
Where May Synapses Occur?

- **The presynaptic neuron** may synapse with
  - Dendrite
  - Soma
  - Axon of postsynaptic neuron

– form different types of synapses

- **Axodendritic synapses**
- **Axosomatic synapses**
- **Axoaxonic synapses**

Synaptic Relationships Between Neurons



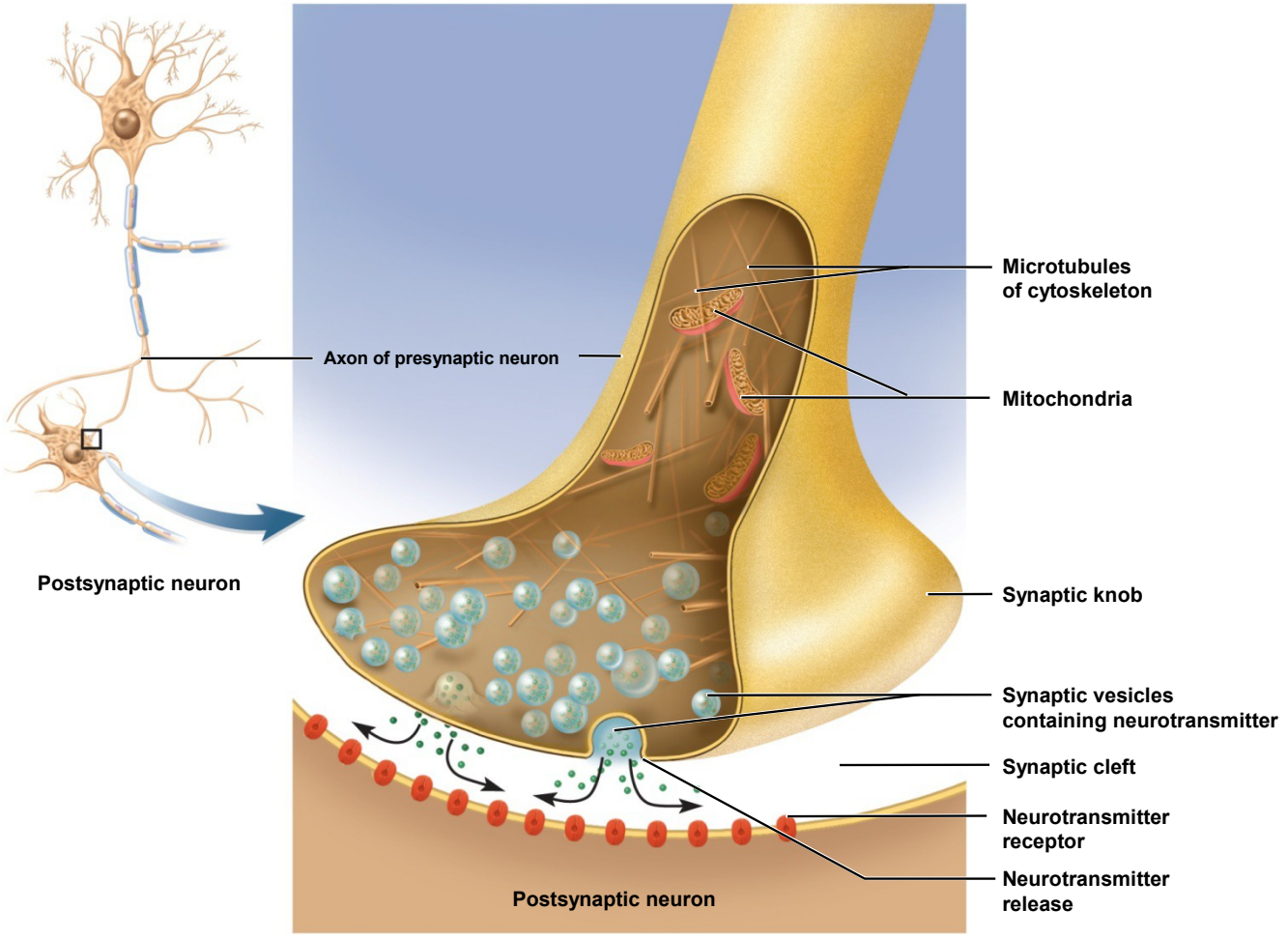
Are there "purely" electrical synapse?

- Gap junctions are a type of synapse which allows action potentials to move rapidly between adjacent cells!
  - Occur between some neurons, neuroglia, cardiac cells and single-unit smooth muscle
  - G**ap junctions** join adjacent cells /// ions or electrical current diffuse through the gap junctions from one cell to the next
  - **Advantage** = quick transmission // no delay for release and binding of neurotransmitter // pure electrical synapes are used in cardiac and smooth muscle, embryonic cells, and some neurons
  - **Disadvantage** = they can not integrate information and can not be used in making decisions

Two Types of Neurotransmitter 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 have different types of integral proteins
  - metabotropic receptors are “ligand receptors” on external face of membrane that releases “G protein” on their internal face of membrane
  - G protein travels to a second integral protein and this intergral protein then functions as the ion channel
  - this is Second messenger sytem

Structure of a Chemical Synapse



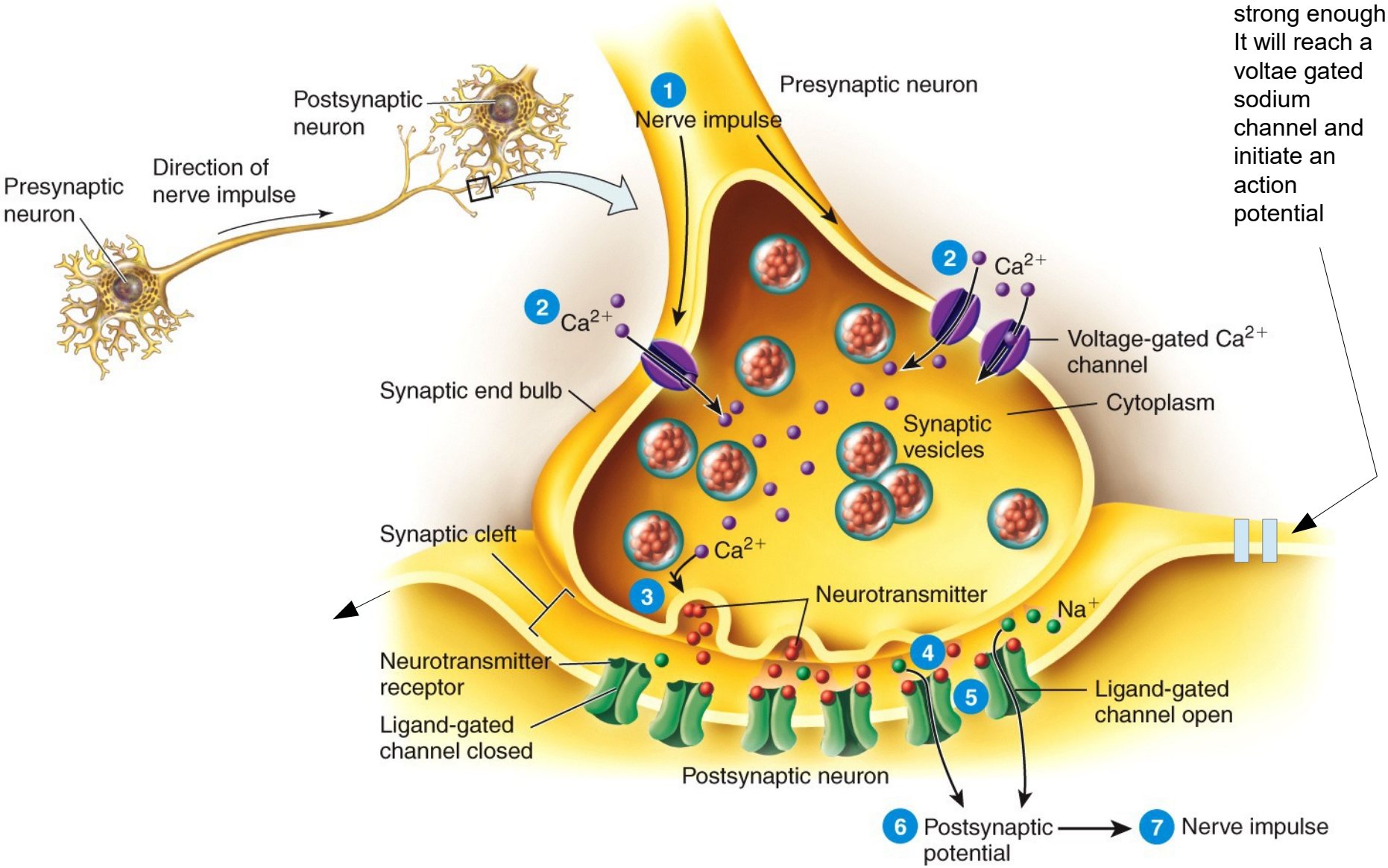
- presynaptic neurons have synaptic vesicles with neurotransmitter and postsynaptic have receptors and ligand-regulated ion channels

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
  - What is the difference between a mono-synaptic reflex VS poly-synaptic reflex? Significance?

Structure of a Chemical Synapse

If local potential strong enough It will reach a voltae gated sodium channel and initiate an action potential



Function of Neurotransmitters at the Synapse

- Neurotransmitters are synthesized in the presynaptic neuron's soma / transported down axon by nanomotor molecules to synaptic knob
- NT are released in response to an action potential (or a post-synaptic neuron's secretion)
- released neurotransmiter binds to specific receptors on the postsynaptic cell
- they alter the the post-synaptic membrane // moves resting membrane potential towards threshold or away from threshold
- The receptor and not the neurotransmitter will dictate the outcome!!!
- Dopamine's DA1R stimulates neuron (increases cAMP) and DA2R inhibits (decrease cAMP) to stop signal.

Effects of Neurotransmitters

- The same neurotransmitter may may have different effects on different target tissue in the body

- There are multiple receptors that exist for each neurotransmitter /// E.g. 14 different receptor types for serotonin

- It is the receptor that determines the effect of the neurotransmitter on the target cell /// E.g. – In different tissues, Acetylcholine may use either ionotropic and metabotropic receptors.

  - Ionotropic receptors are always stimulatory.

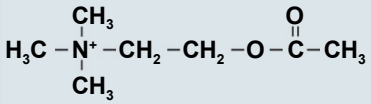
  - Metabotropic acetylcholine receptors can be either stimulatory or inhibitory // depends on downstream effect of the second integral protein which is activated by the G protein

- *Note: another key idea --- the same molecule in different mechanisms may function as a hormone, a neurotransmitter, or a neuromodulator!*

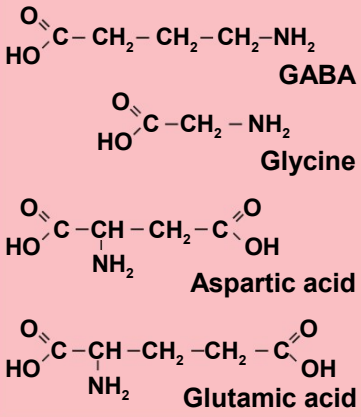
Categories of Neurotransmitters

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

Acetylcholine

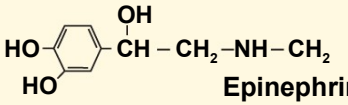


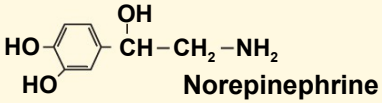
Amino acids

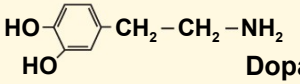


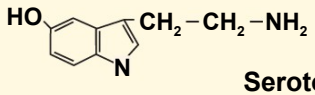
Monoamines

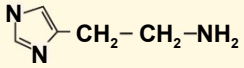
Catecholamines



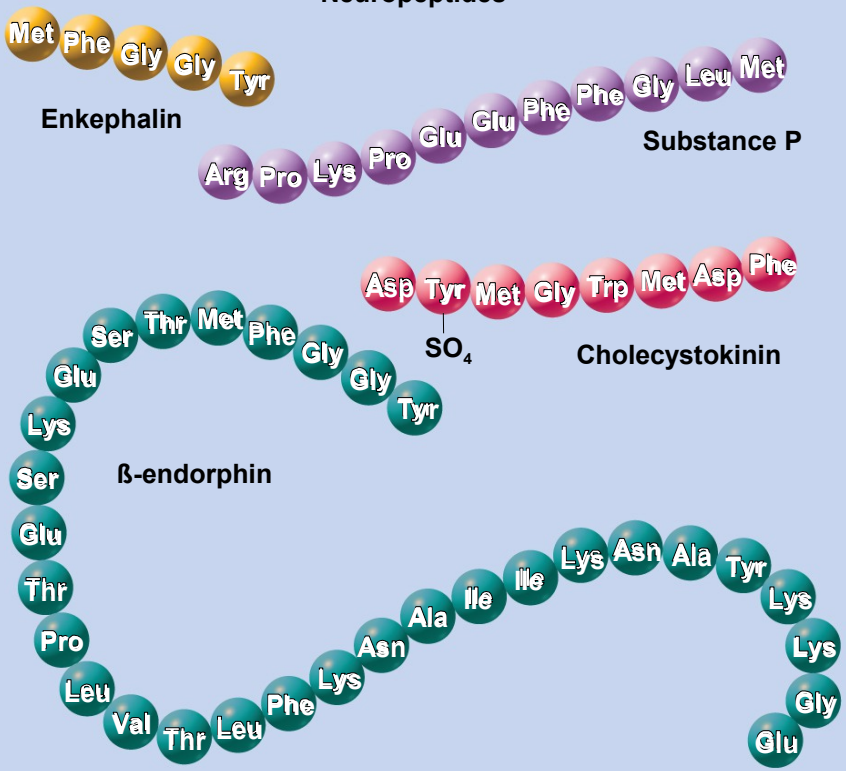








Neuropeptides



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 monamine receptors

Other Neurotransmitters

- Neuropeptides // substance P, endorphins, enkephalins (i.e. endogenous opioids) /// this class also include gut-brain peptides (produced my non-neural tissue but have receptors in the brain)

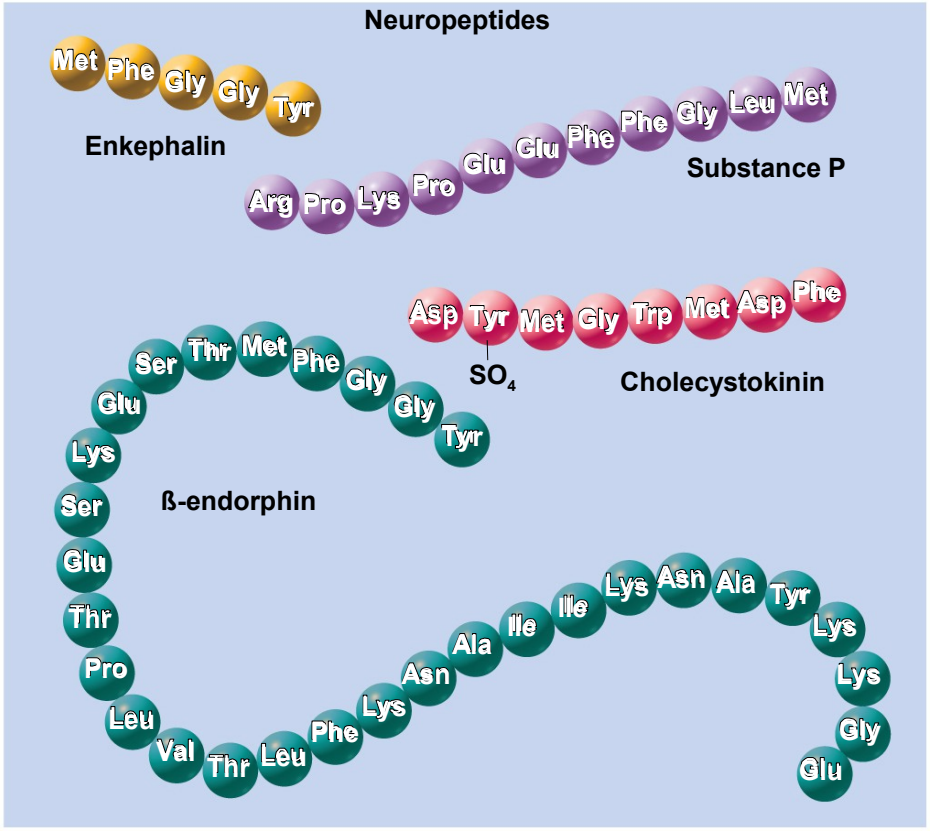
- Pruines // adenosine triphosphate (ATP) / now recognized as major neurotransmitter in CNS and PNS

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

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

Neuropeptides

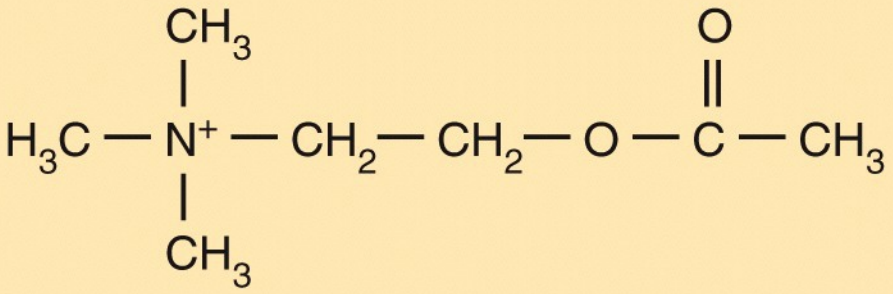
- chains of 2 to 40 amino acids
- act at lower concentrations than other neurotransmitters
- e.g beta-endorphin and substance P
- longer lasting effects
- stored in axon terminal as larger **secretory granules** (called dense-core vesicles)
- some function as hormones or neuromodulators
- some also released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



Many other neuropeptide neurotransmitters not shown here!

SMALL-MOLECULE NEUROTRANSMITTERS

Acetylcholine



Nitric oxide

N═O

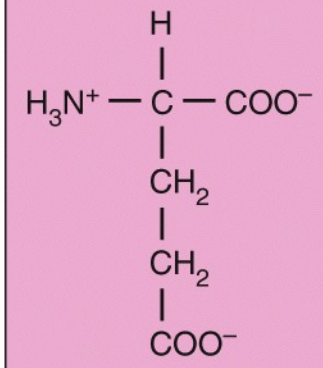
Carbon monoxide

C≡O

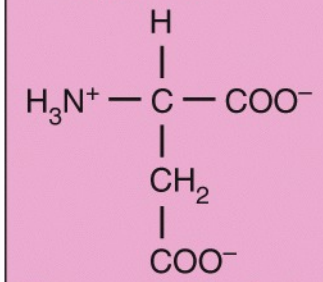
SMALL-MOLECULE NEUROTRANSMITTERS

Amino Acids

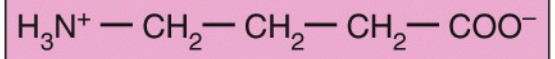
Glutamate



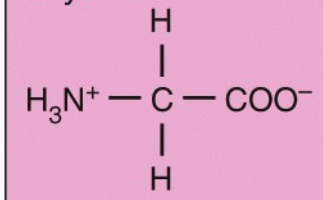
Aspartate



Gamma aminobutyric acid (GABA)



Glycine



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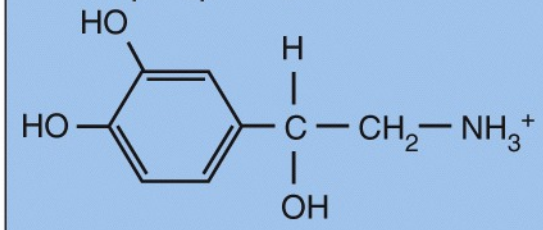
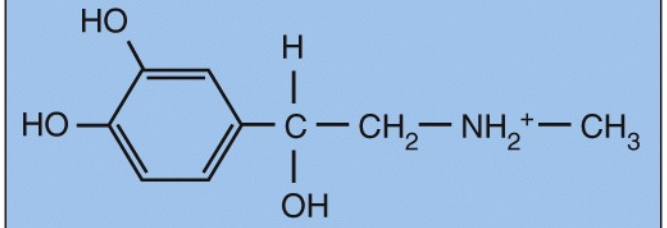
Biogenic Amines

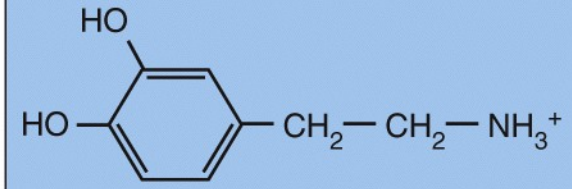
Norepinephrine



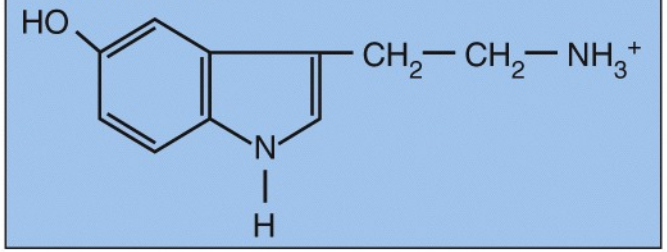
Epinephrine



Dopamine



Serotonin



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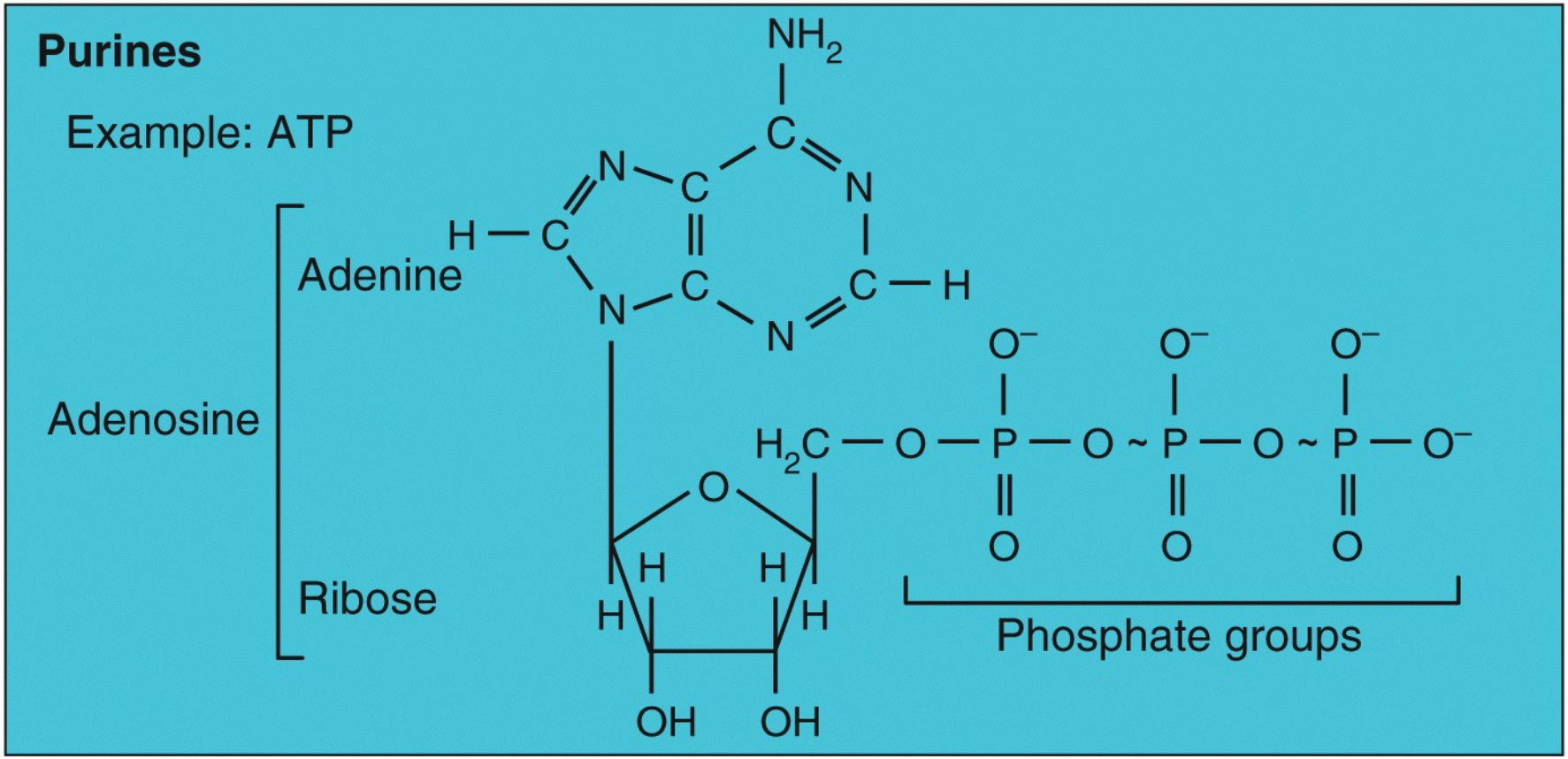

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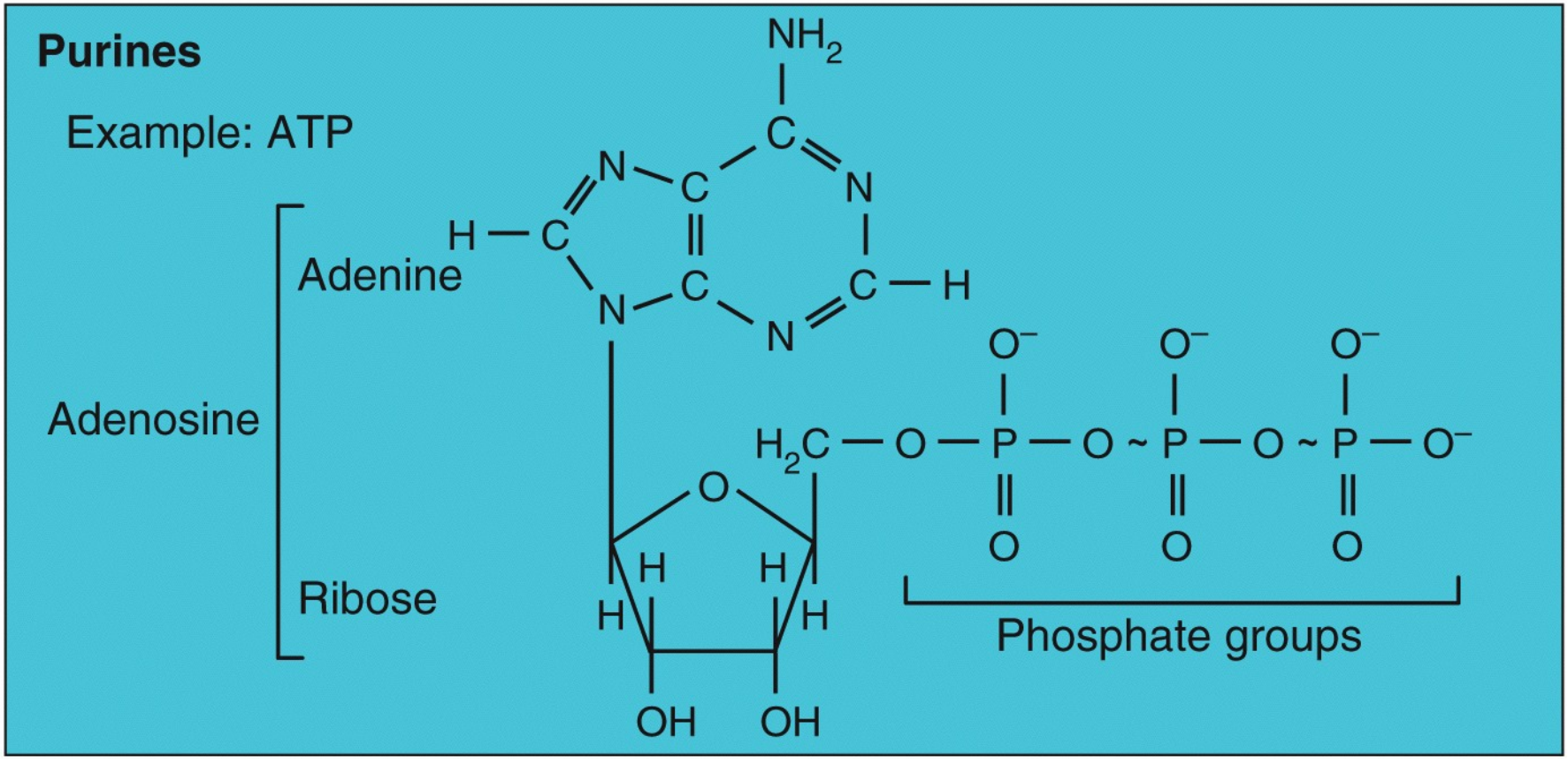
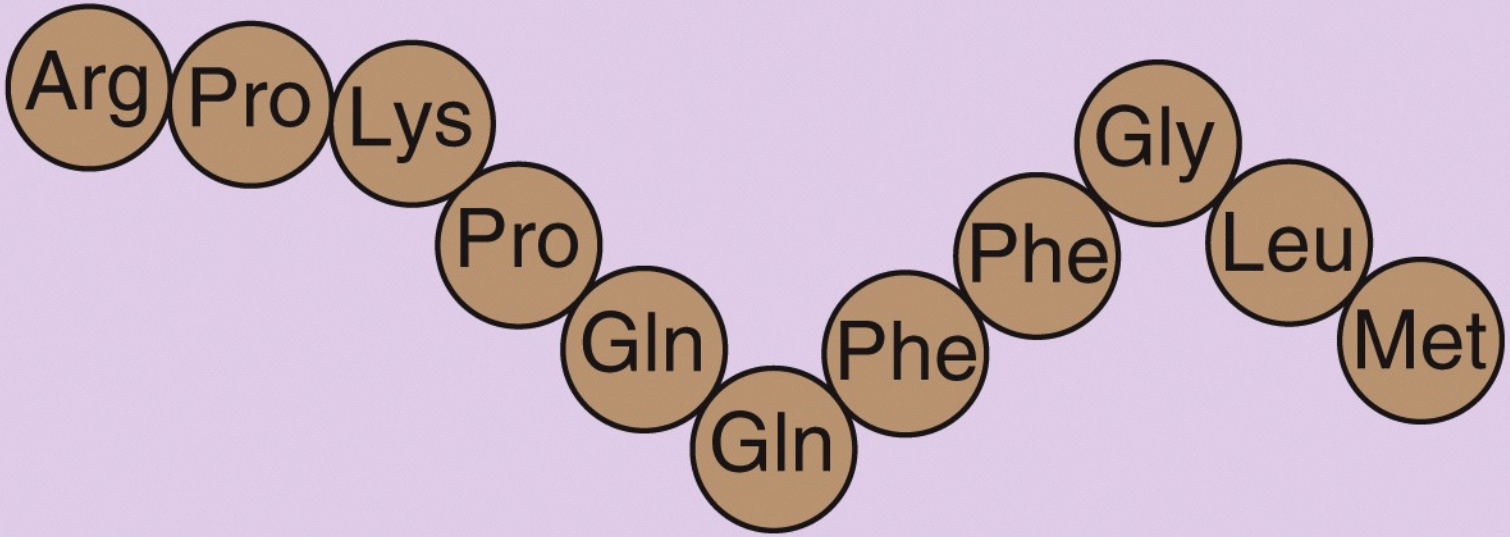


NEUROPEPTIDES

Example: Substance P



Function of Key Neurotransmitters

- Acetylcholine
  - Located at neuromuscular junctions, ANS, brain and spinal cord
  - Largely excitatory / however some acetylcholine receptors in PNS inhibitory
- Monoamine
  - Norepinephrine – largely in ANS / in CNS area of brain stem called locus coeruleus – sleep & wake cycles, attention, feeding behavior
  - Epinephrine – largely ANS similar effects as norepinephrine / more widely used as hormone
  - Dopamine – CNS / many CNS functions – coordinates movements, motivation, reward
  - (see next slide)

Key Neurotransmitters' Functions

- Monoamines (Biogenic Amines)
  - Serotonin – mainly CNS brain stem with projections throughout brain / mood regulation, affects emotions, attention, cognitive functions, motor behaviors, feeding behaviors, daily rhythms
  - Histamine – CNS for attention and arousal // outside CNS mediator of allergic responses // note – antihistamines make you drowsy!
- Amino Acid Neurotransmitters
  - Glutamate – most import excitatory CNS – half of all CNS synapses release glutamate!
  - Glycine & GABA – two of the major inhibitory neurotransmitters / GABA – GABA very important in CNS / Glycine – ½ synapses in spinal cord release glycine other ½ in CNS

Key Neurotransmitters' Functions

- Neuropeptides
  - Substance P – released from type C sensory neurons that carry pain and temperature signals / also released in CNS, spinal cord, and gut
  - Opiods – endorphins, dynorphins, and enkephalins / eliciting pain relief (analgesia) / general CNS depressant / also involved in sexual attraction, aggressive or submissive behaviors
  - Neuropeptide Y – feeding behaviors, mediate hunger or feeling full

Synaptic Transmission

- **Neurotransmitters** are diverse in their action
  - some are excitatory and others are inhibitory
  - sometimes the same neurotransmitter may be excitatory or inhibitory depending on the “receptor”
  - effect depends on what kind of receptor the postsynaptic cell has // same neurotransmitter can cause either excitation or inhibition depending on the receptor // this is the case with metabotrophic receptors
  - some open ligand-regulated ion gates /// ionotropic receptors are simply ion channels
  - other neurotransmitters operate through metabotropic receptors /// second messenger systems // provide variable downstream outcomes

Three Different Mechanisms of Synaptic Transmission

- Explore the function of three different types of synapses // each synapse will use a different type of neurotransmitter and post synaptic receptor

- Results in different modes of action

  - excitatory cholinergic synapse (ionotropic)

  - inhibitory GABA-ergic synapse (ionotropic)

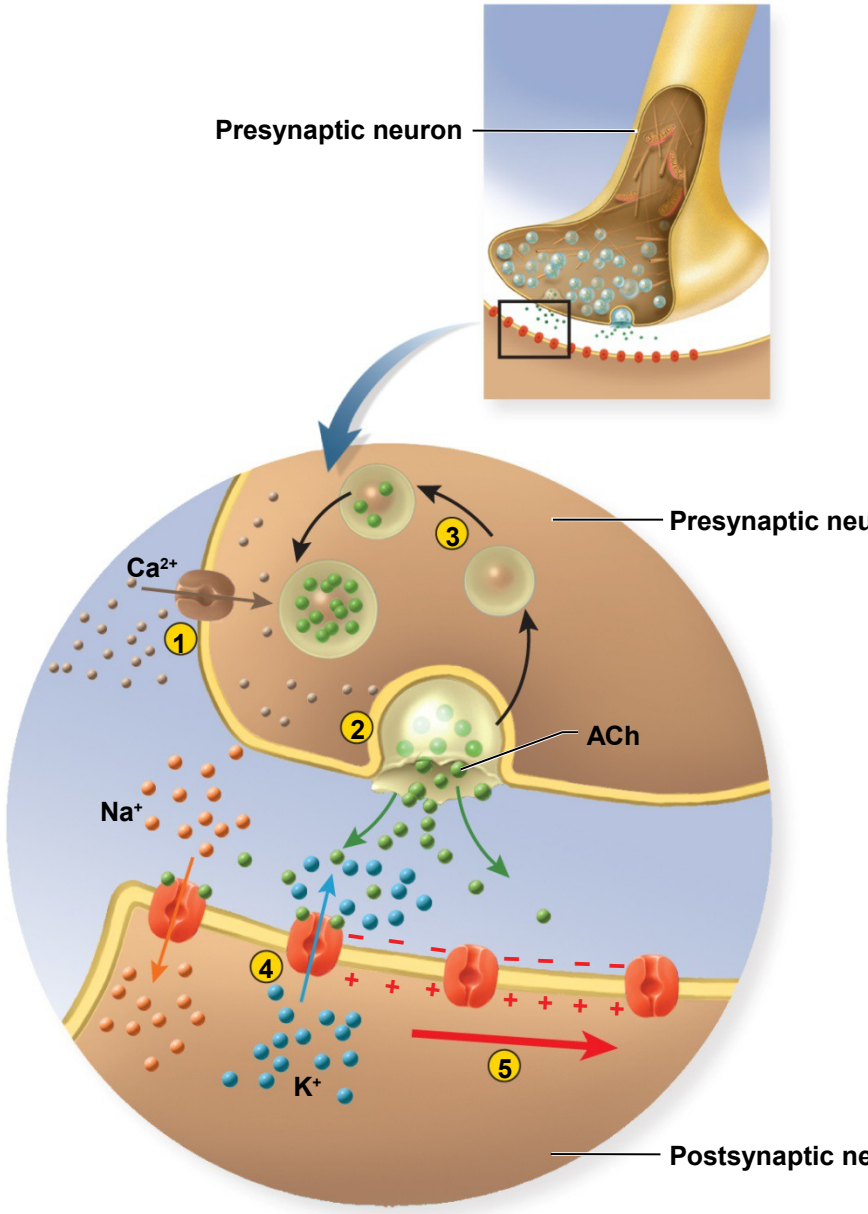
  - excitatory adrenergic synapse (metabotropic)

  - Note: metabotropic = second messenger system receptor) /// this maybe either inhibitory or excitatory

Excitatory Cholinergic Synapse

- Cholinergic synapse – employs acetylcholine (ACh) as its neurotransmitter
  - ACh excites most postsynaptic cells (e.g. at skeletal muscle and at sympathetic ganglia)
  - However, may inhibits others (e.g. cardiocytes at AV node)

How this is possible?



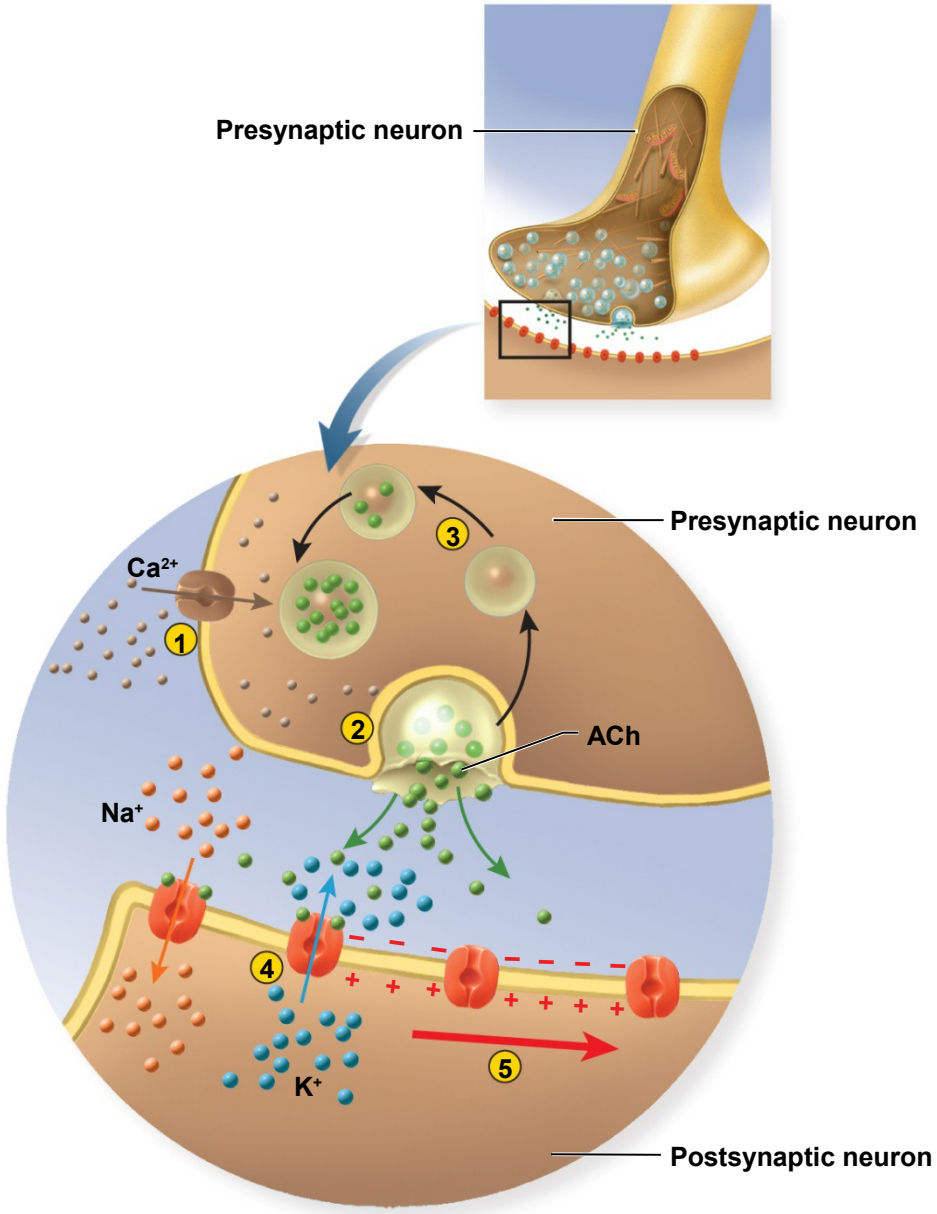
Excitatory Cholinergic Synapse

- 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

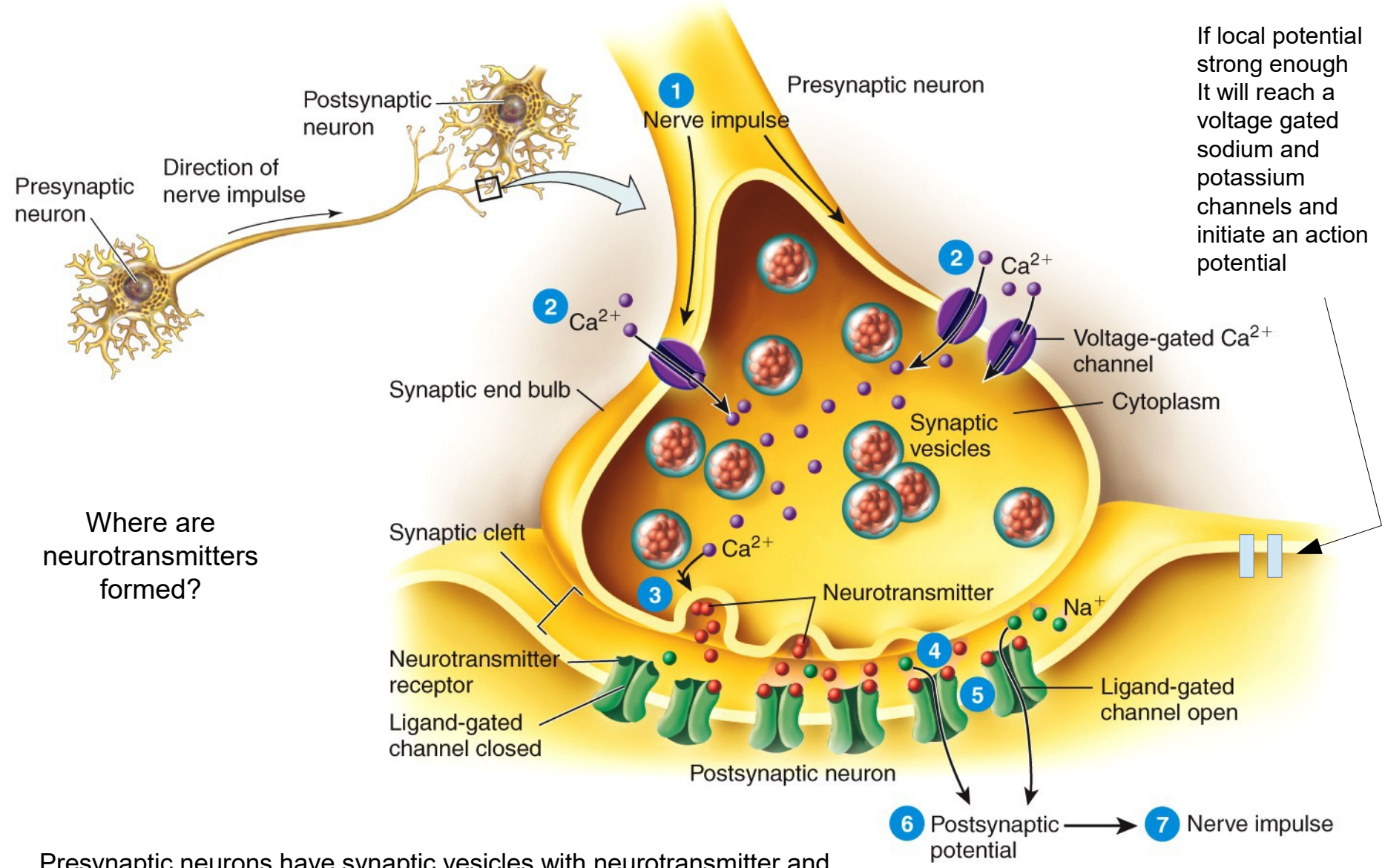
Excitatory Cholinergic Synapse

- 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



Structure of a Chemical Synapse



If local potential strong enough It will reach a voltage gated sodium and potassium channels and initiate an action potential

Where are neurotransmitters formed?

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

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 /// ionotropic receptor type**
- **Cl^-** enters cell and makes the inside more negative than the resting membrane potential /// move away from threshold!
- postsynaptic neuron is inhibited
- less likely to fire

Adrenergic Excitatory Synapse

- Adrenergic synapse /// employs the neurotransmitter norepinephrine (NE) also called noradrenaline

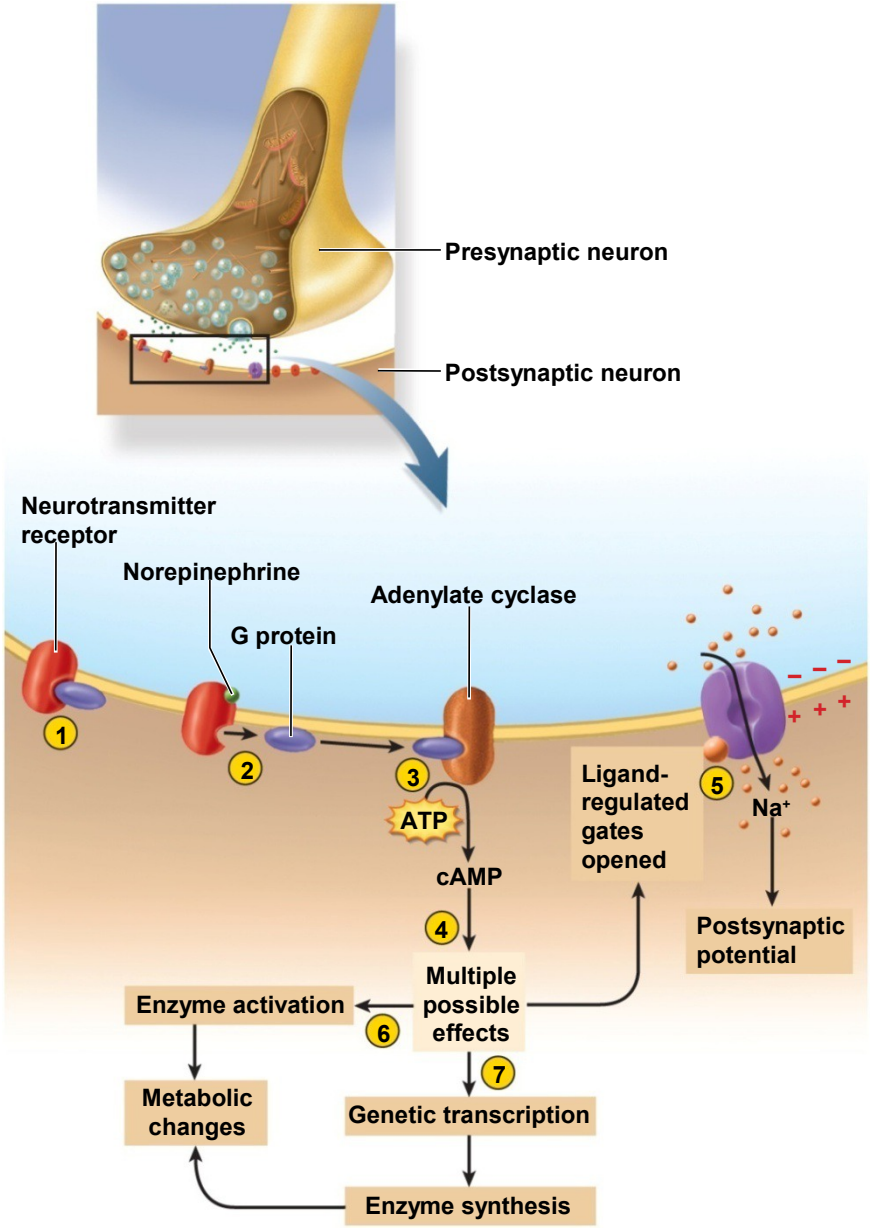
- The receptor on post synaptic membrane for the adrenergic synapses is a metabotropic type receptor

  - not an ion gate but a second messenger system

  - a transmembrane protein associated with a G protein (i.e. metabotropic receptor)

- NE , monoamines and neuropeptides acts through second messenger systems (e.g. such as cyclic AMP (cAMP)

Adrenergic Excitatory Synapse



Note: Step 4

The Action of Adrenergic Receptors and Their G Protein (The Second Messenger Transmission Mechanism)

- 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**

The Action of Adrenergic Receptors and Their G Protein (The Second Messenger Transmission Mechanism)

- The second messenger cyclic AMP may cause many different alternative outcomes 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

The Action of Adrenergic Receptors and Their G Protein (The Second Messenger Transmission Mechanism)

- slower to respond than cholinergic and GABA-ergic type synapses
- However, second messenger systems have advantage of **enzyme amplification**
  - single molecule of NE can produce vast numbers of second messengers (e.g. cAMP) in the cell

Cessation of the Signal

- To stop transmission there must be a mechanisms to stop the release of neurotransmitter from presynaptic neuron **so** postsynaptic neuron will not start a local potential

  - 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 stays stimulated

Cessation of the Signal

- When synaptic knob stops adding neurotransmitter into synaptic cleft and existing neurotransmitter is degraded then local potential stops at postsynaptic nerve fiber

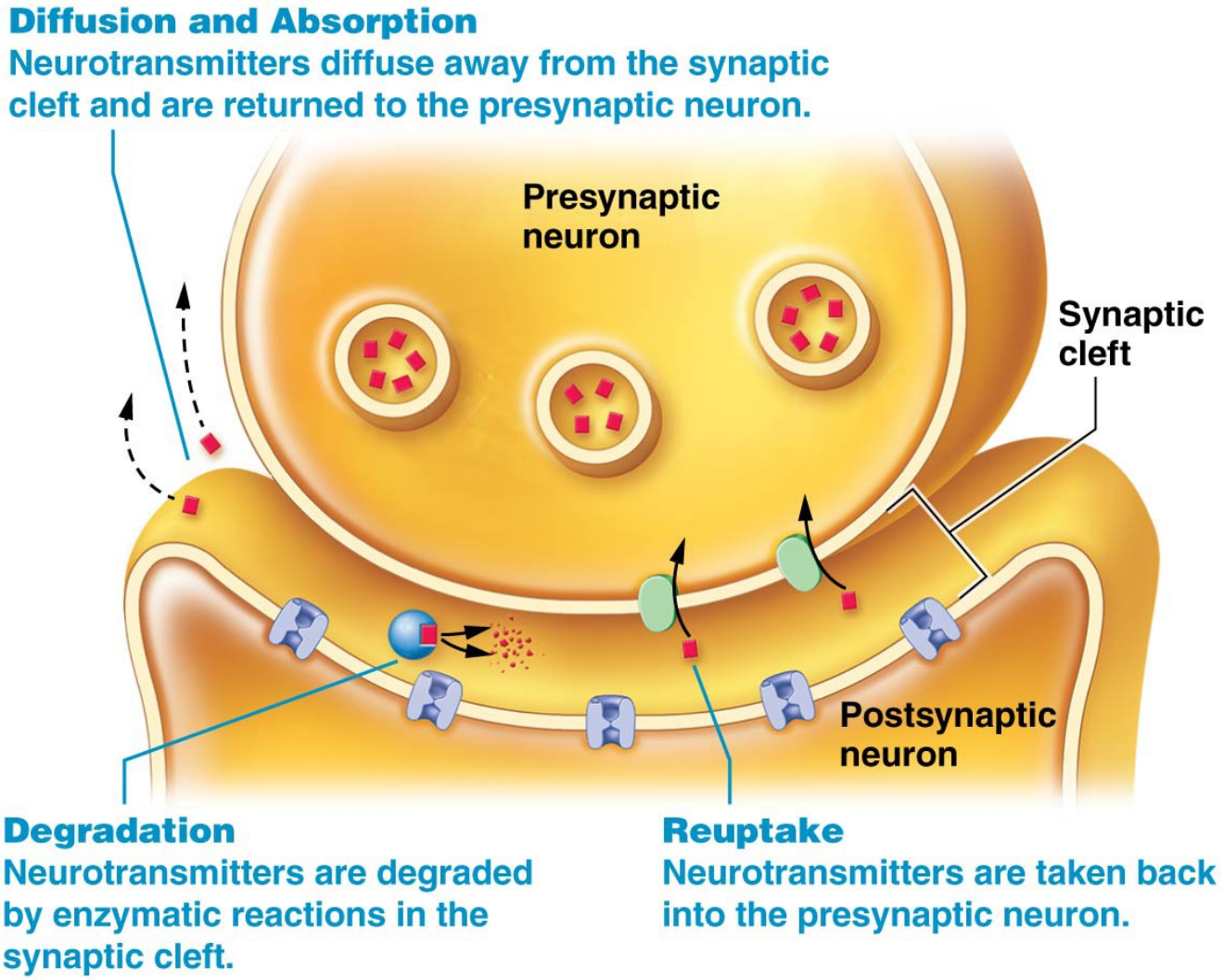
  - remove neurotransmitter by:

    - diffusion // neurotransmitter escapes the synapse into the nearby ECF // astrocytes in CNS absorb it and return it to neurons

    - re-uptake // synaptic knob reabsorbs amino acids and monoamines by endocytosis //

    - degradation by enzymes // see next slide

Methods of termination of synaptic transmission.



Cessation of the Signal

- Degradation of neurotransmitters by enzymes
  - *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: neither MAO & COMT are not found in blood
    - » Why is this important? Significance? Hint: adrenal gland!

Neuromodulators

- Hormones, neuropeptides, and other messenger molecules that modify synaptic transmission of the 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

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
  - released by post-synaptic neuron and diffuses into the presynaptic neuron
  - stimulates pre-synaptic neuron to release more neurotransmitter
  - how the one neuron's tells the other neuron to 'give me more' - this occurs during learning – positive feedback
  - This is an example of a chemical communication that goes backward across the synapse

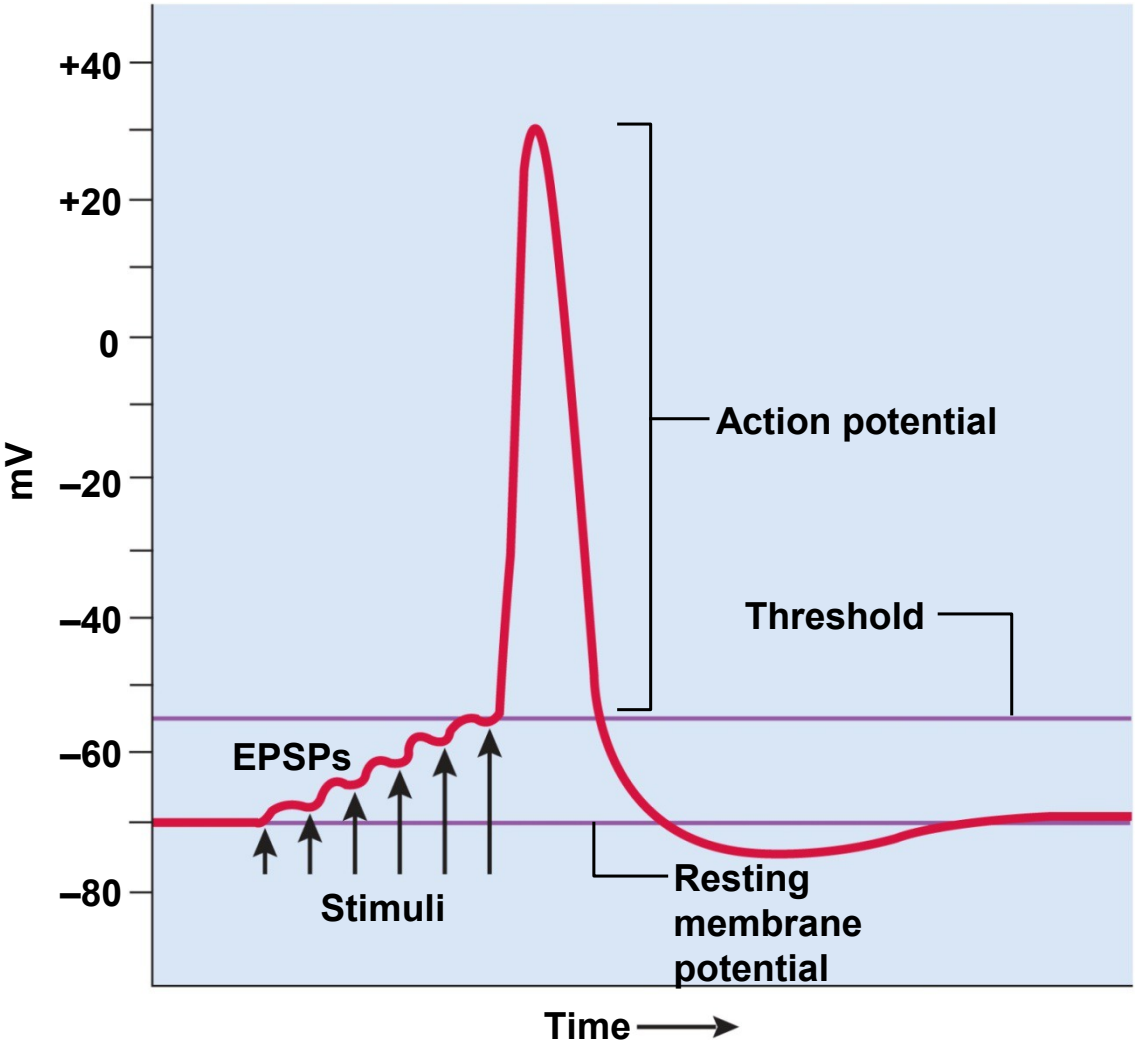
Summation, Facilitation, and Inhibition

- 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

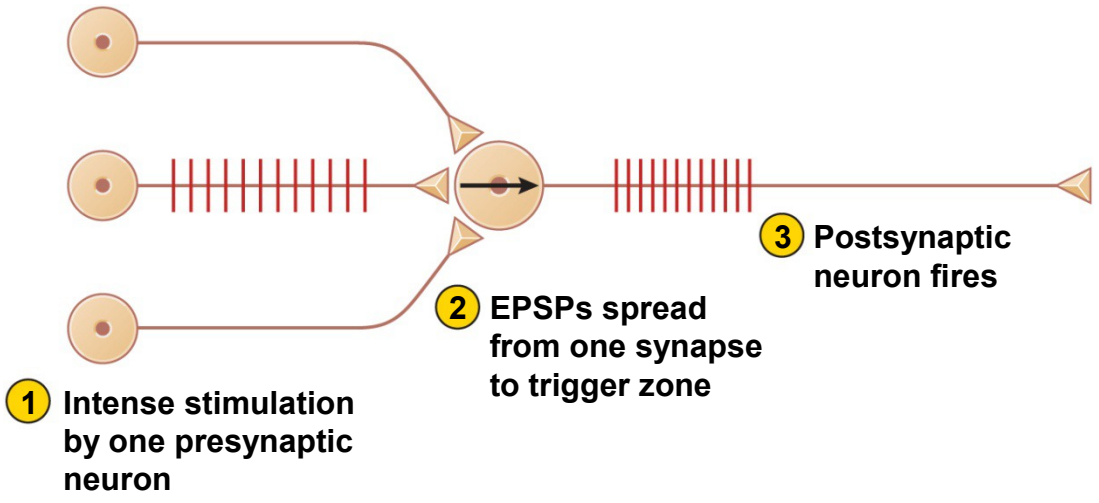
Summation, Facilitation, and Inhibition

- **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

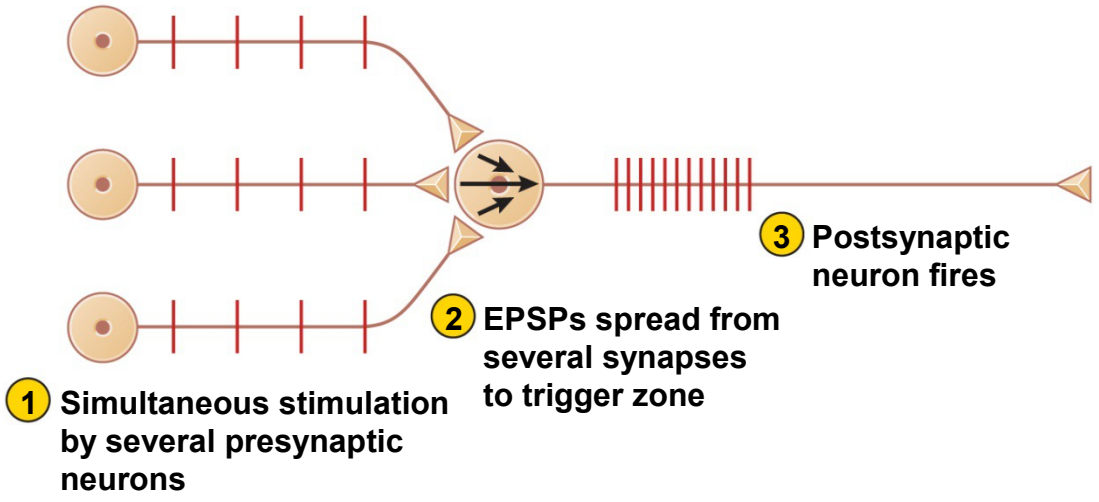
Summation of EPSPs



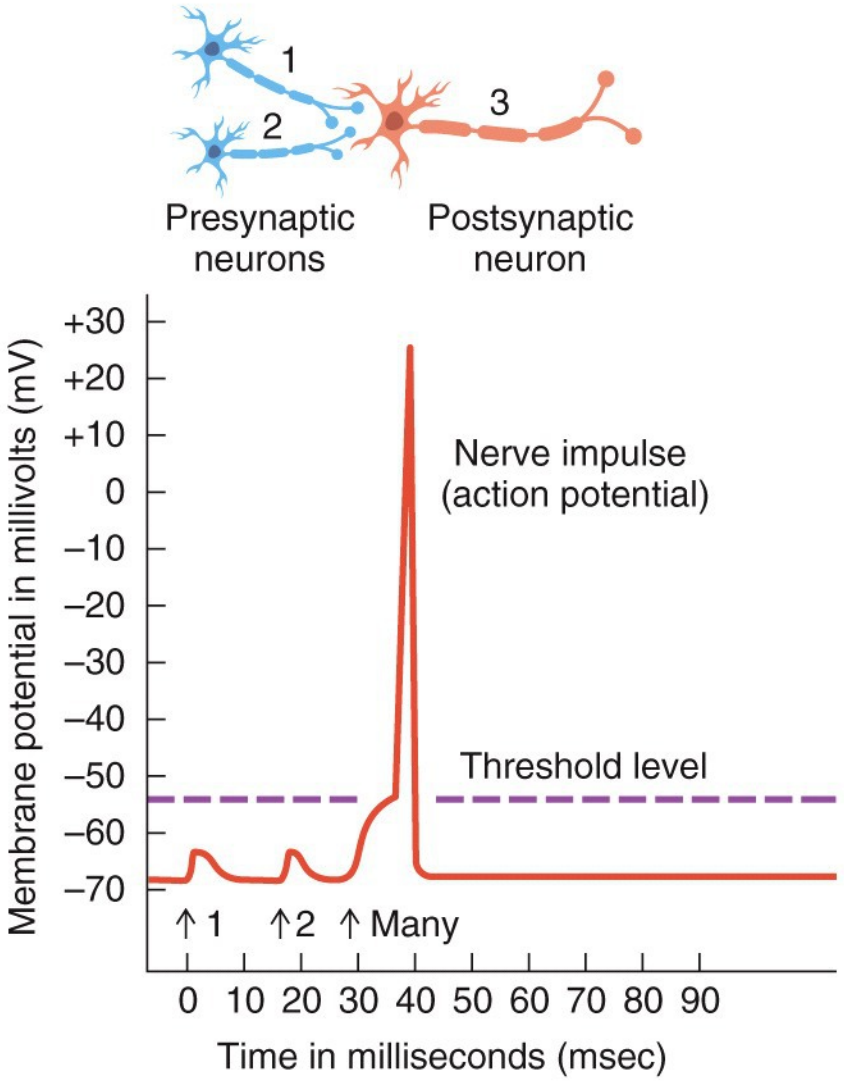
Temporal and Spatial Summation



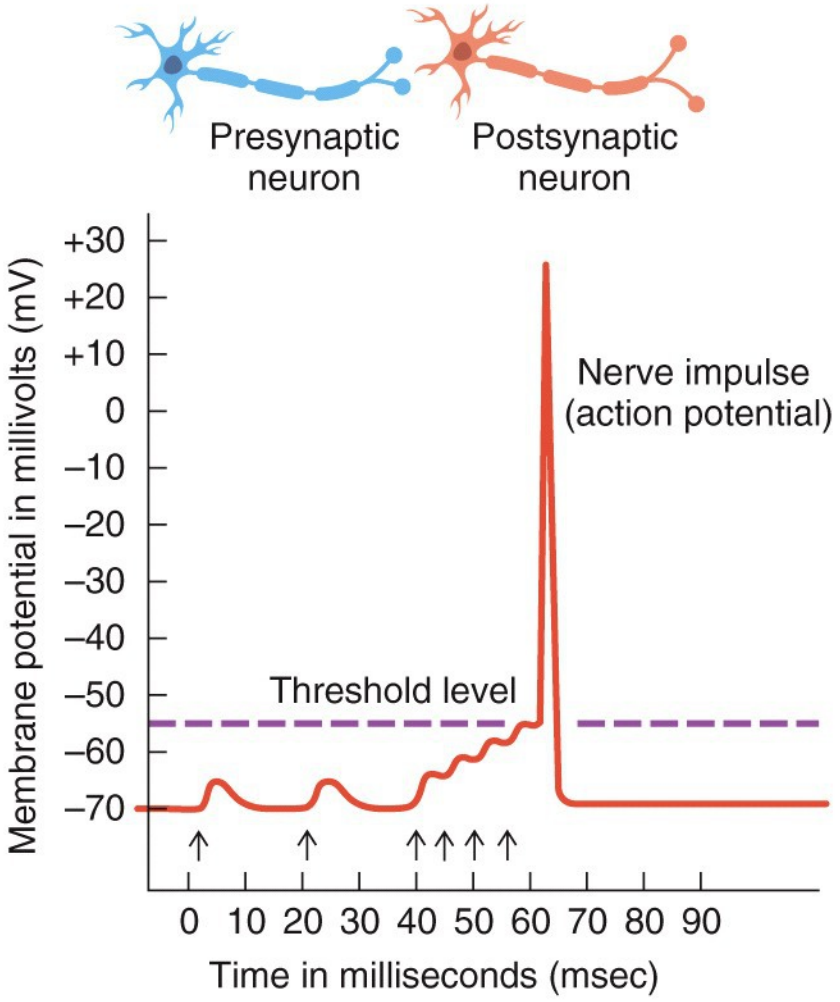
(a) Temporal summation



(b) Spatial summation



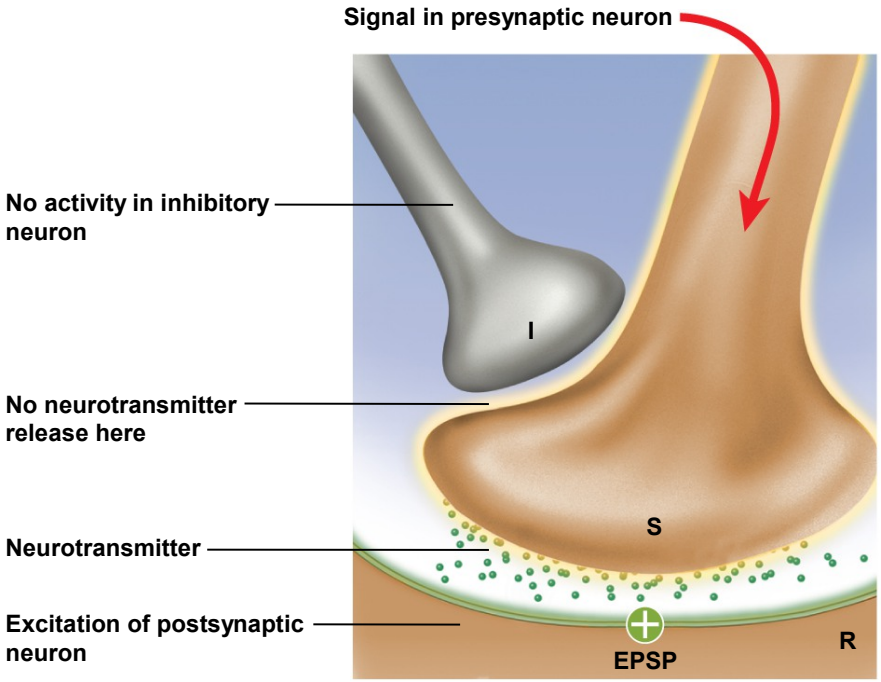
(a) Spatial summation

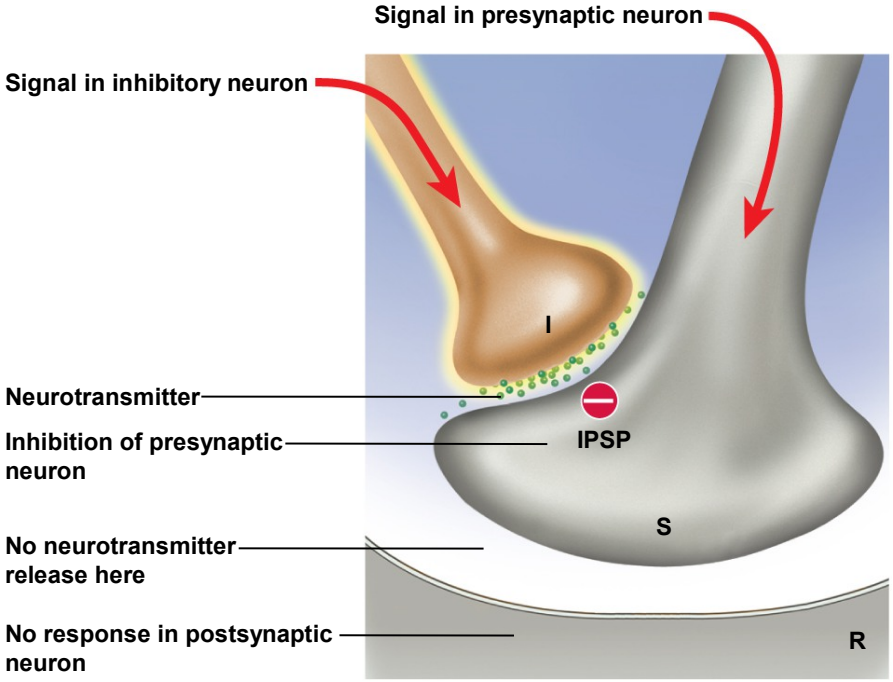


(b) Temporal summation

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

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 CNS (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

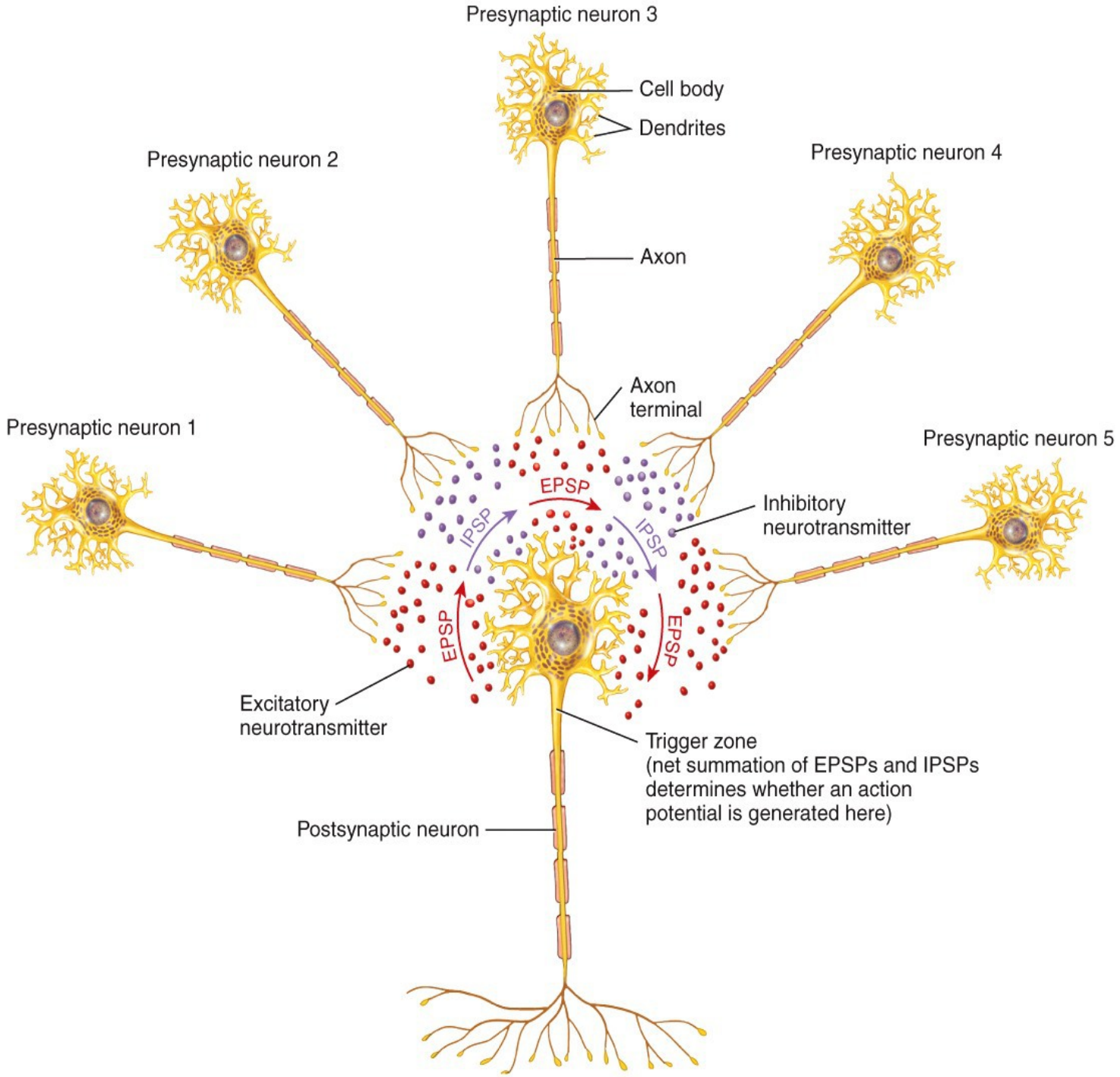
- Glycine and GABA produce IPSPs /// move potential away from threshold /// inhibitory

- Acetylcholine (ACh) and norepinephrine are excitatory however for some cells (with different receptors) maybe inhibitory

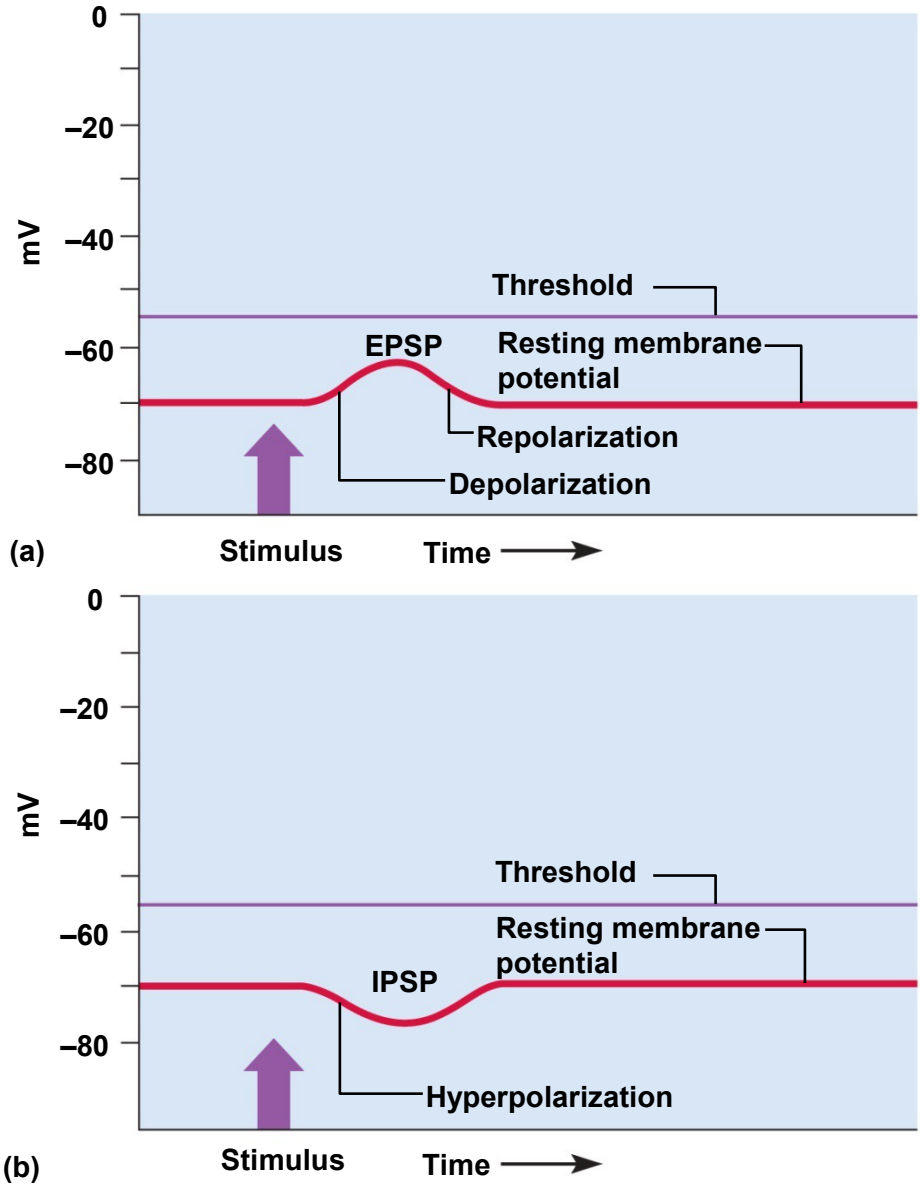
  - depending on the *type of receptors* on the target cell

  - *It is the receptor that has final say on the outcome!*

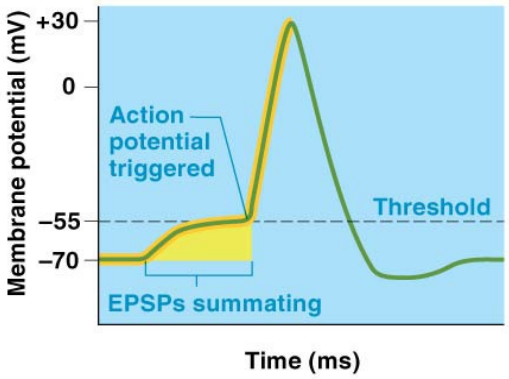
  - ACh excites skeletal muscle, but inhibits cardiac muscle due to the different type of receptors

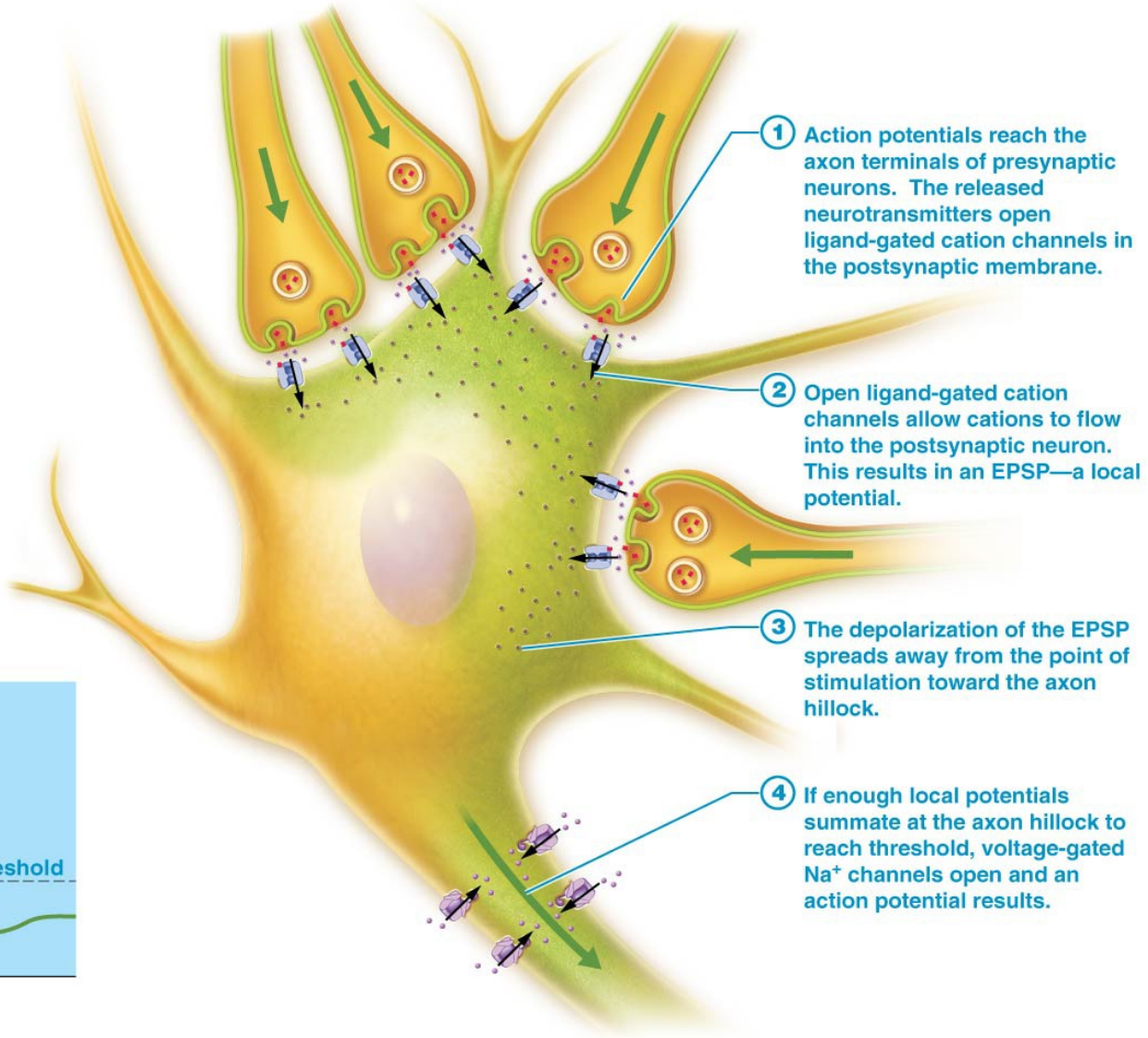

Presynaptic neuron 3
Cell body
Dendrites
Presynaptic neuron 2
Presynaptic neuron 4
Axon
Axon terminal
Presynaptic neuron 1
Presynaptic neuron 5
EPSP
IPSP
IPSP
Inhibitory neurotransmitter
EPSP
EPSP
Excitatory neurotransmitter
Trigger zone (net summation of EPSPs and IPSPs determines whether an action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

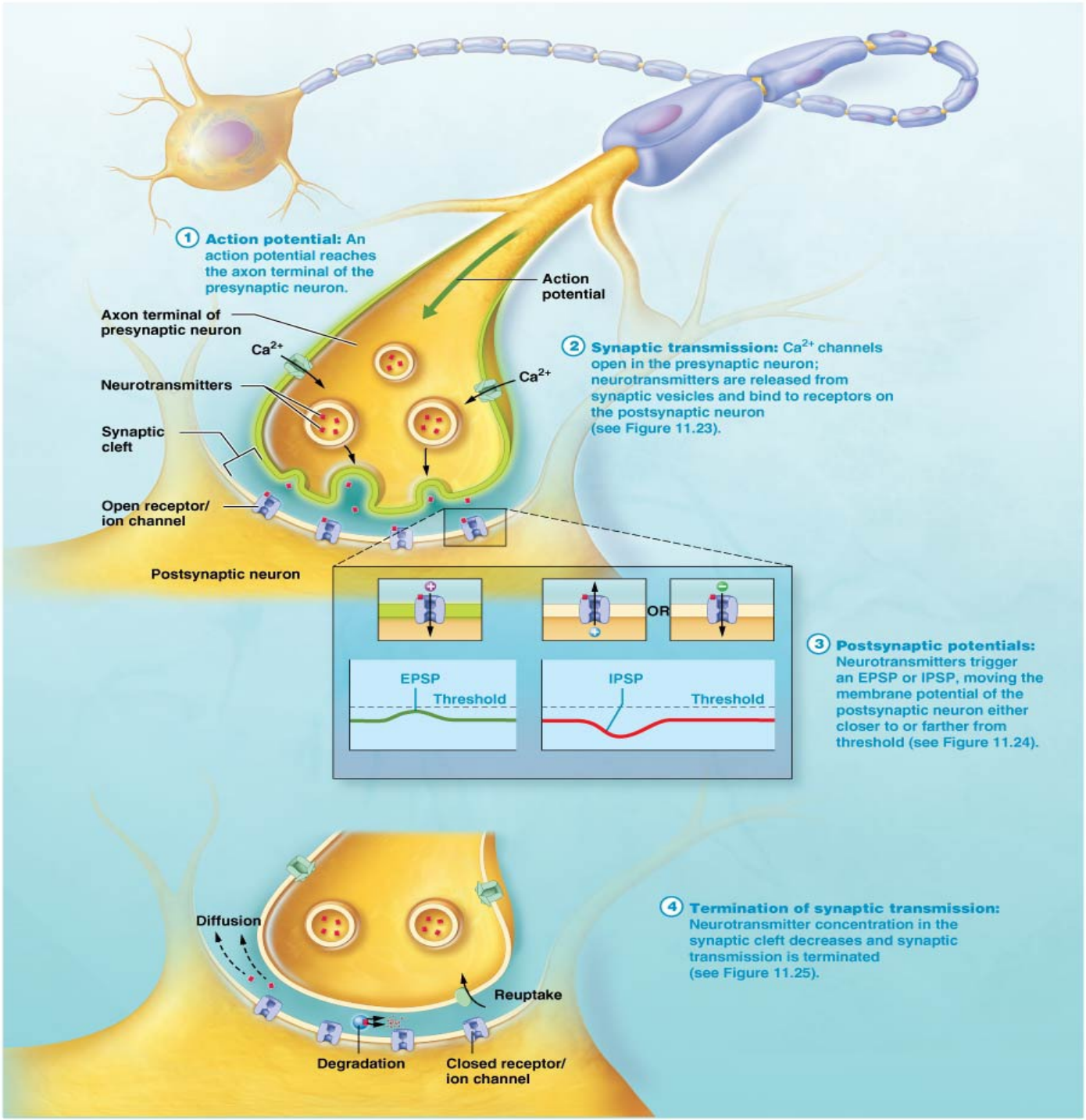
Postsynaptic Potentials



Local potentials summating and leading to an action potential.



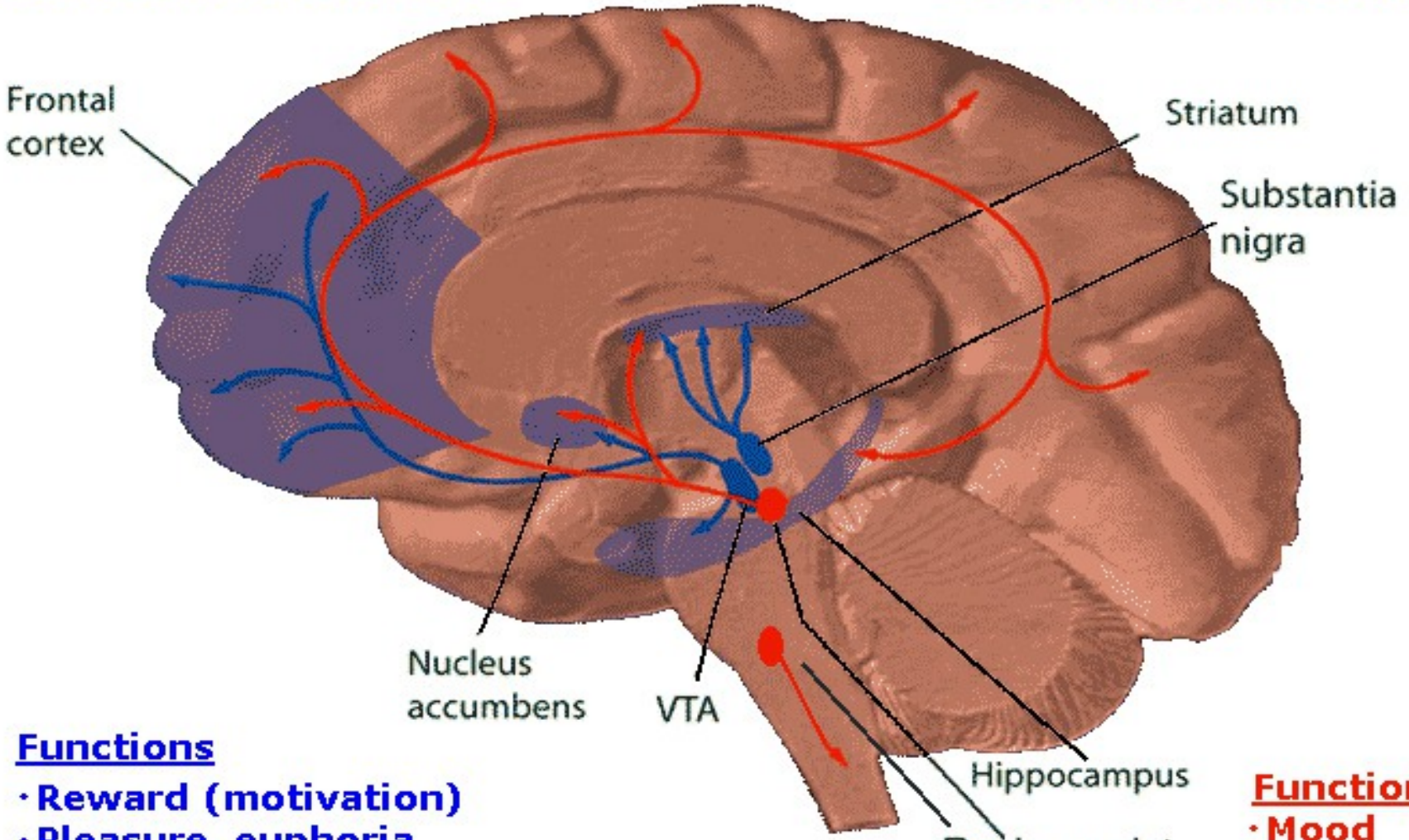




The Big Picture of Chemical Synaptic Transmission.

Dopamine Pathways

Serotonin Pathways

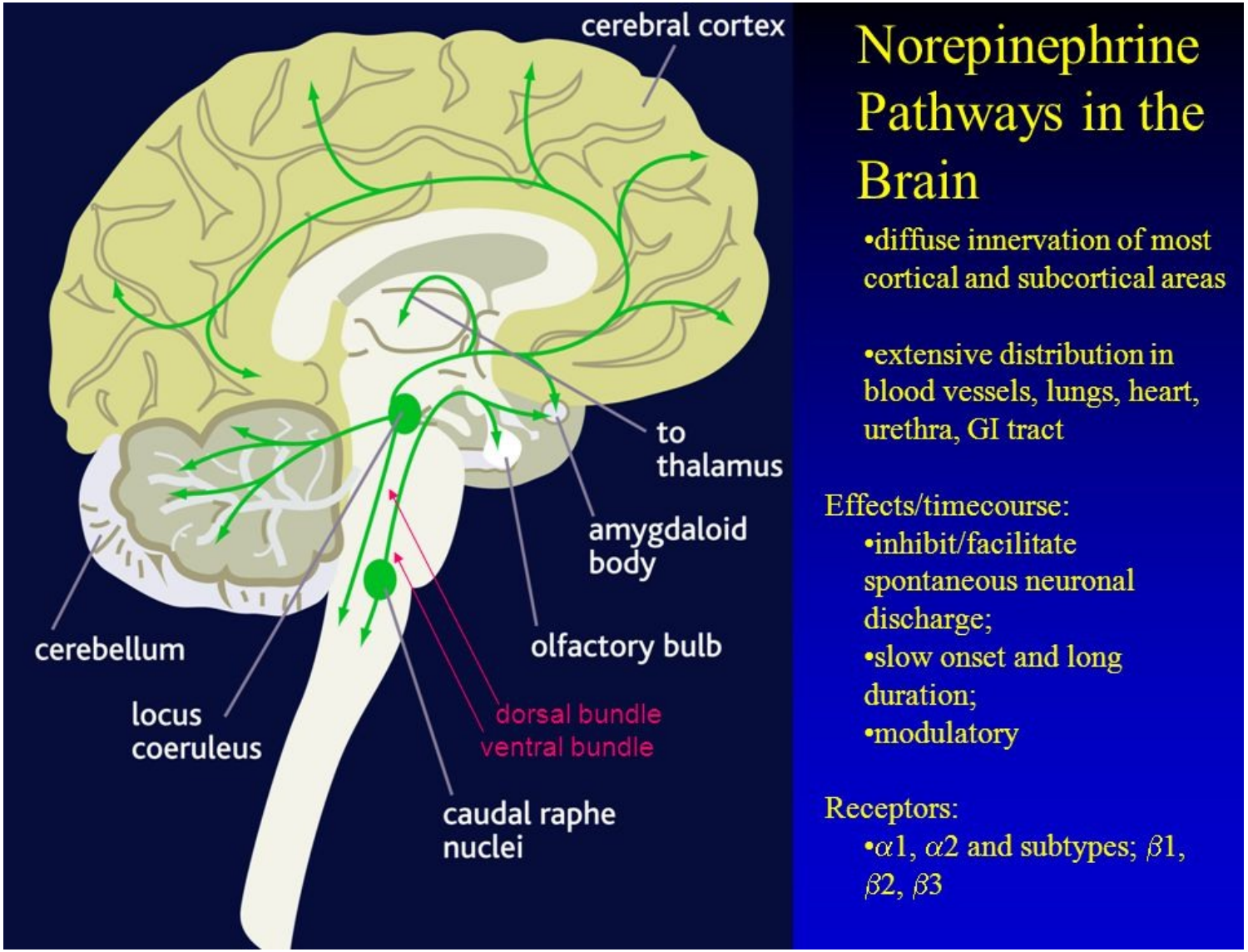


Functions

- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine tuning)
- Compulsion
- Perseveration

Functions

- Mood
- Memory processing
- Sleep
- Cognition



Norepinephrinergic Neurons (secrete norepinephrine) project bilaterally (send signals to both sides of the brain) from the locus ceruleus along distinct pathways to many locations, including the cerebral cortex, limbic system, and the spinal cord, forming a neurotransmitter system.

Main Roles of the Locus Ceruleus

Alertness/Wakefulness

Sympathetic Activation

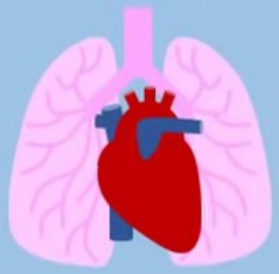
Psychological Stress

Main Roles of the Locus Ceruleus

Alertness/Wakefulness

"Fight or Flight"
Sympathetic Activation

Psychological Stress



Sweating

Pupil dilation

Increased heart and breathing rate

Main Roles of the Locus Ceruleus

When opioids bind…

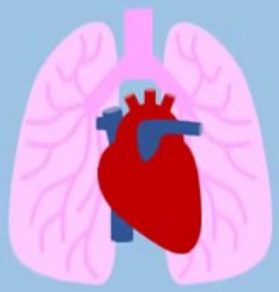
Opioid use symptoms are
OPPOSITE OF
normal Locus Ceruleus function

"Rest and Digest"

Drowsiness — **Parasympathetic Activation** — **Sedation**

Reduced sweating

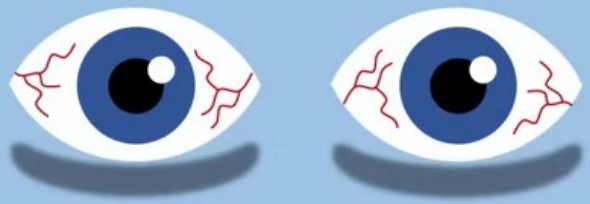
Pupil constriction
"Pinpoint pupils"



Decreased heart and breathing rate

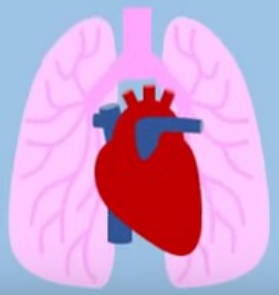
Main Roles of the Locus Ceruleus

During Withdrawal...



"Fight or Flight"

Jitteriness/Insomnia — **Sympathetic Overactivation** — **Anxiety/Panic/Stress**



Excessive sweating | Pupil dilation | Increased heart and breathing rate

Opiod Mu receptors (DA 2R) are on locus ceruleus neurons. When opiod binds to the G protein linked receptor (second messenger/ metabotropic) it lowers the cytoplasmic cAMP to reduce locus ceruleus secretion of norepinephrine.