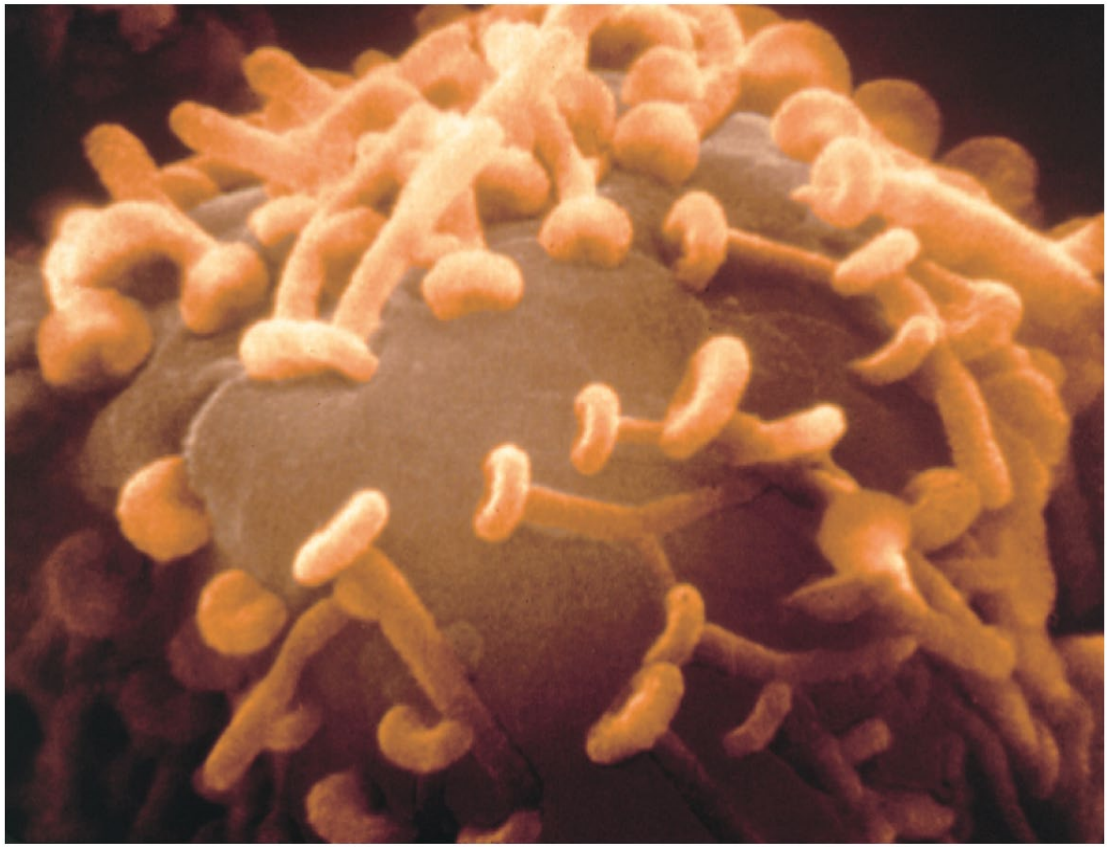
Chapter 12.3

# Synapses and Neurotransmitters



# The Discovery of the Synaptic Cleft

Early physiologist thought neurons were “continuous thread like fibers” that transmitted an electrical signal between the brain and the target tissue. (i.e. the reticular theory)

–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 ***electro-chemical junction*** /// 50 nanometers wide (1 x 10 to the negative 9 meters)

–In the 1970s Dr. Eric Kandel demonstrated how the synapse change during learning. He also showed differences in how synapses changed between short term and long-term learning. (see Dr. Kandel's videos)

# The Discovery of Neurotransmitters

Otto Loewi, in 1921, demonstrated how neurons communicate with each other or how neurons communicate their target tissue by releasing chemicals – establishing the chemical synapse

flooded two exposed 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

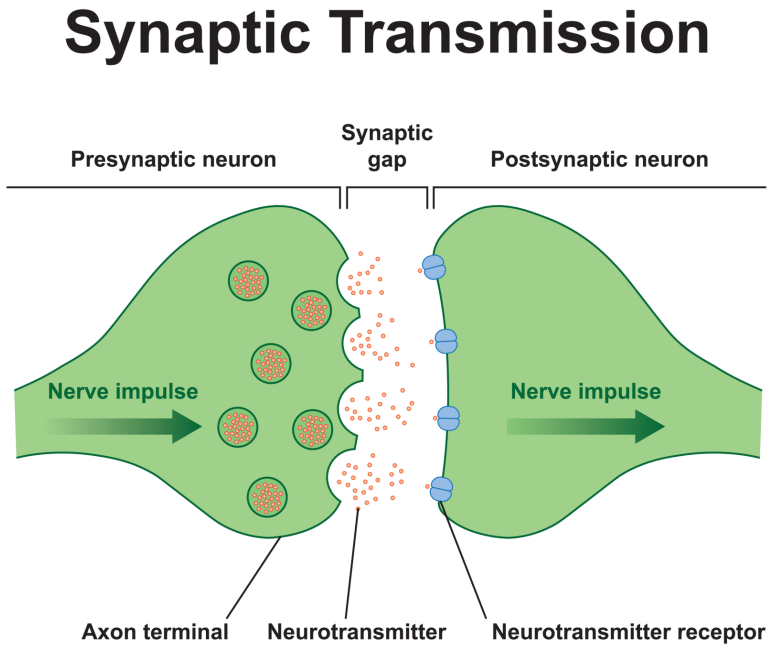
named it Vagusstoffe ("vagus substance") // later re-named acetylcholine. This was the discovery of the first neurotransmitter.

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?*

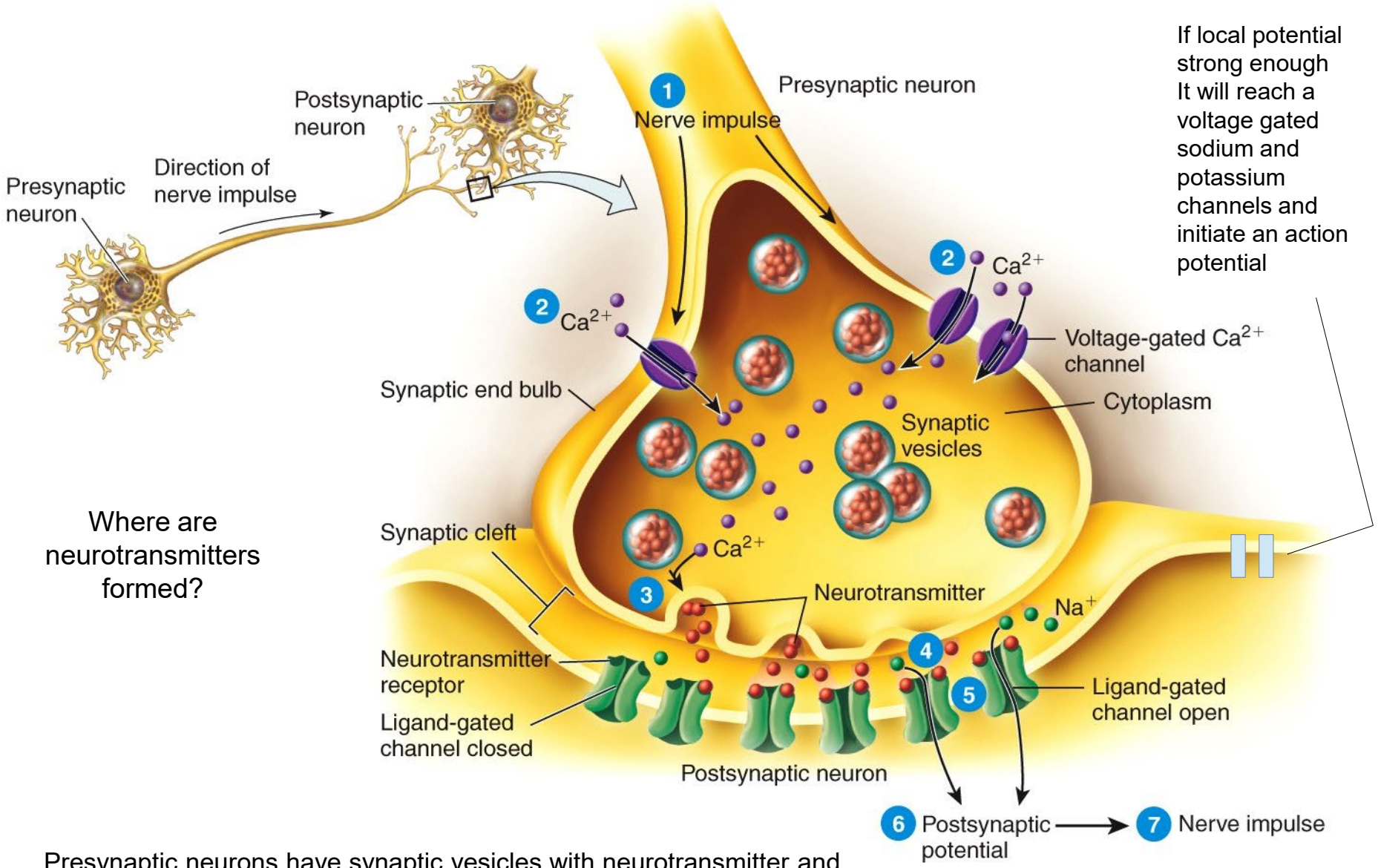
# The Synapse

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




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 synapses on their dendrites and/or soma

Spinal cord motor neuron soma have about 10,000 unique synaptic knobs from other neurons //  some excitatory others inhibitory

- 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 excitatory VS inhibitory signals) 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 onto a single neuron will only result in one of two possible outcomes: no action potential or an action potential on the post synaptic neuron.*

# 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

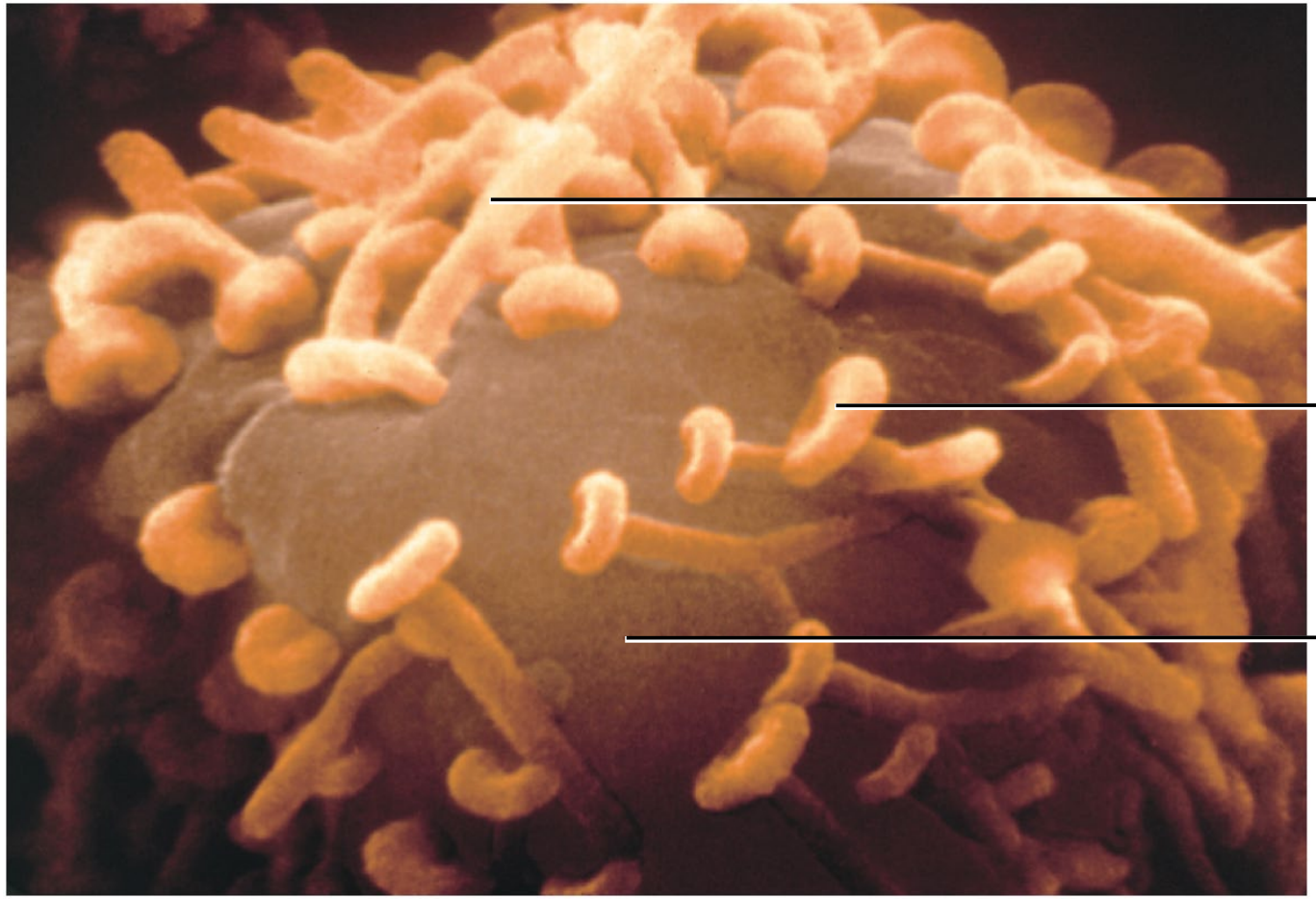
a reserve pool of synaptic vesicles are located further away from inner face of synaptic knob's membrane

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



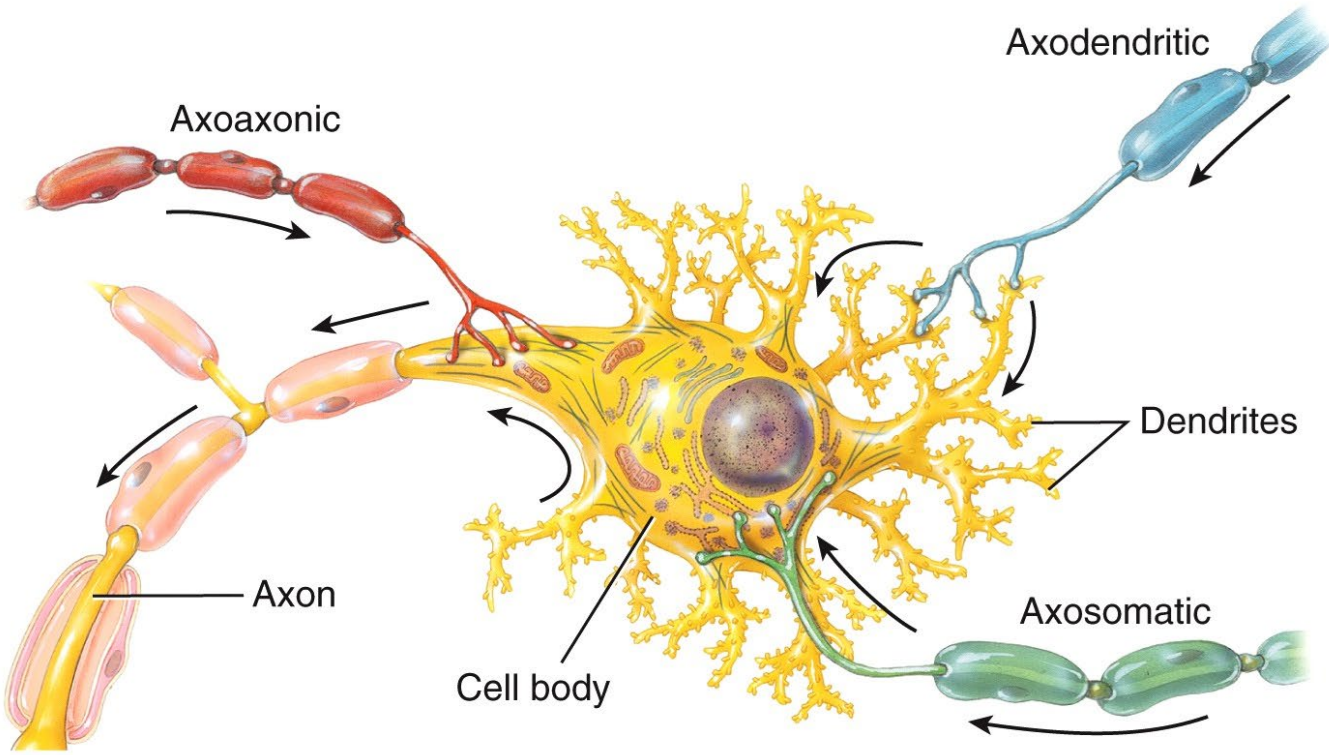
# Where May A Synapse Occur?

The presynaptic neuron may synapse with

- Dendrite
- Soma
- Axon of postsynaptic neuron

Form different types of synapses

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



# What is a “purely electrical synapse”?

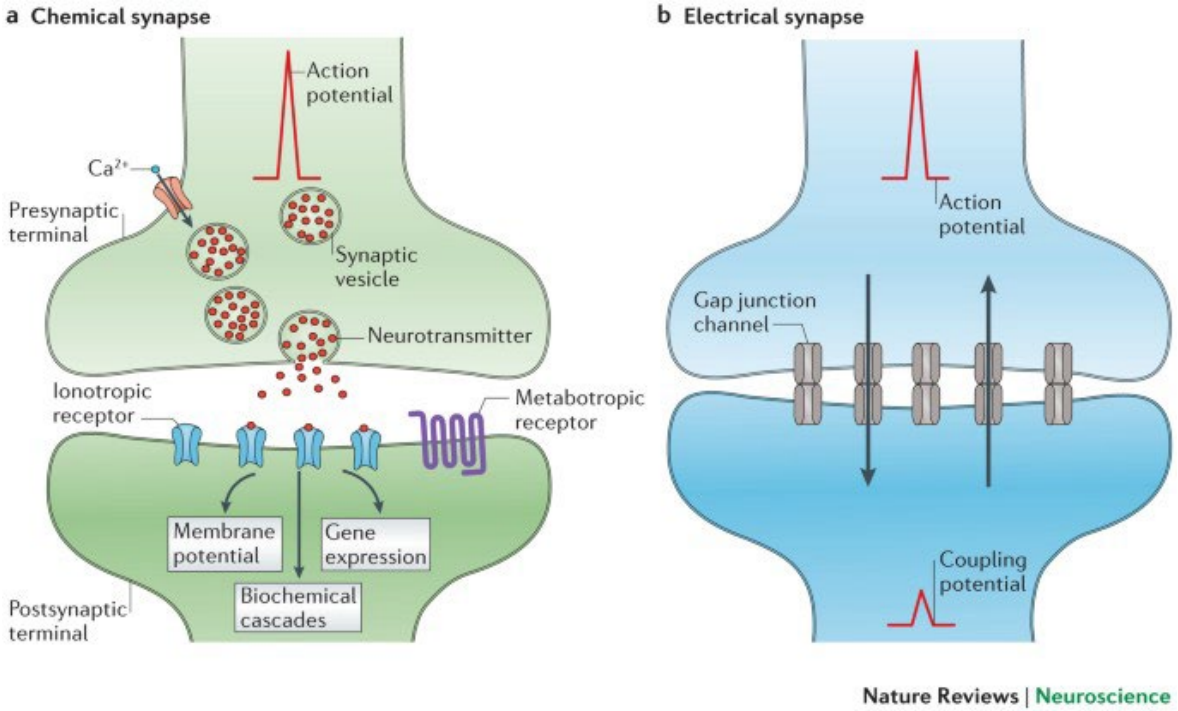
It is a gap junction! Gap junctions allow action potentials to move rapidly between adjacent cells! // no neurotransmitter

Occur between some neurons, neuroglia, cardiac cells and single-unit smooth muscle, embryonic cells

**Gap 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

**Disadvantage** = they <u>can not integrate information and can not be used in making decisions</u>



# Two Types of Neurotransmitter Receptors: Ionotropic VS Metabotropic

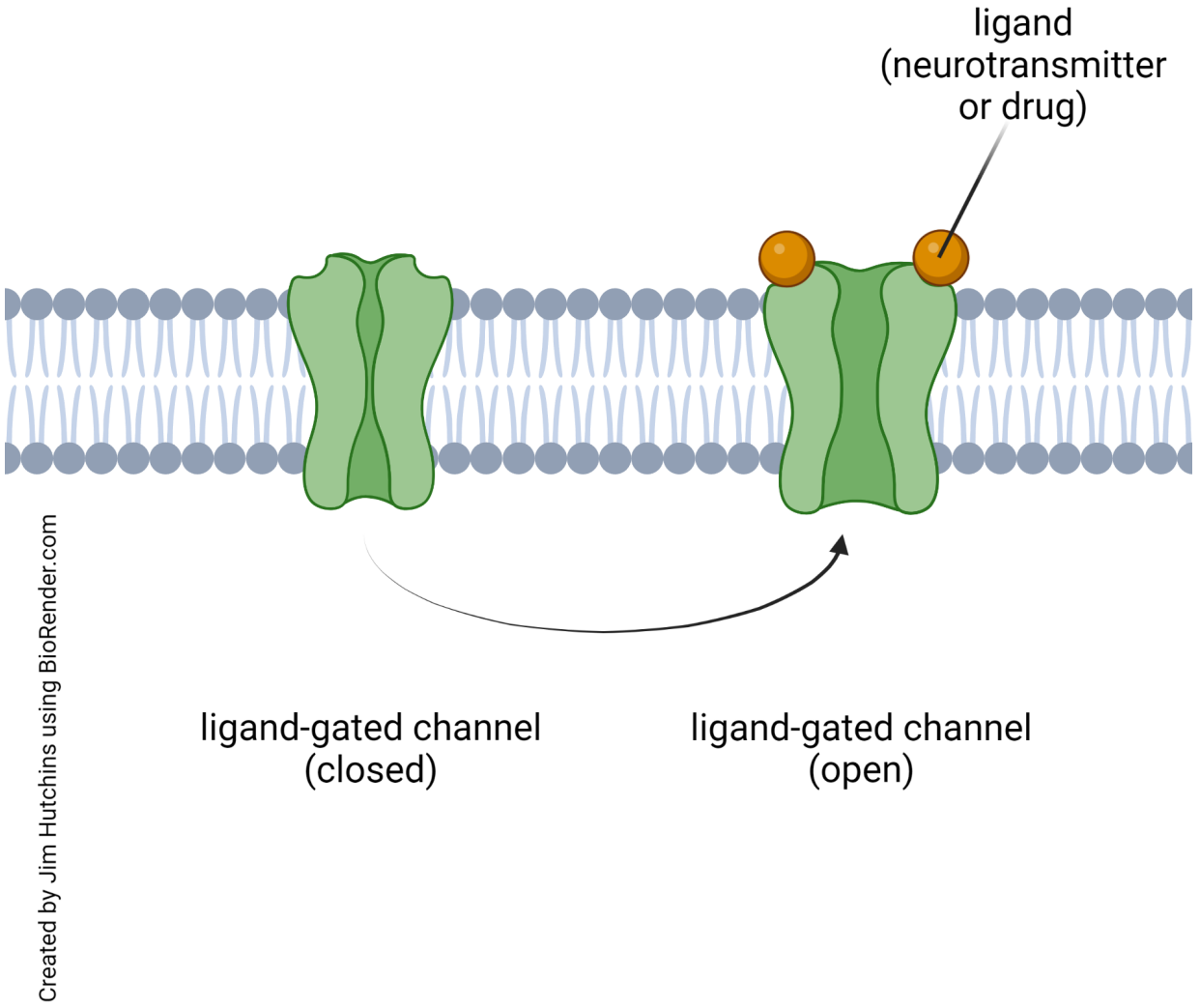
## Ionotropic receptors

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



# Two Types of Neurotransmitter Receptors: Ionotropic VS Metabotropic

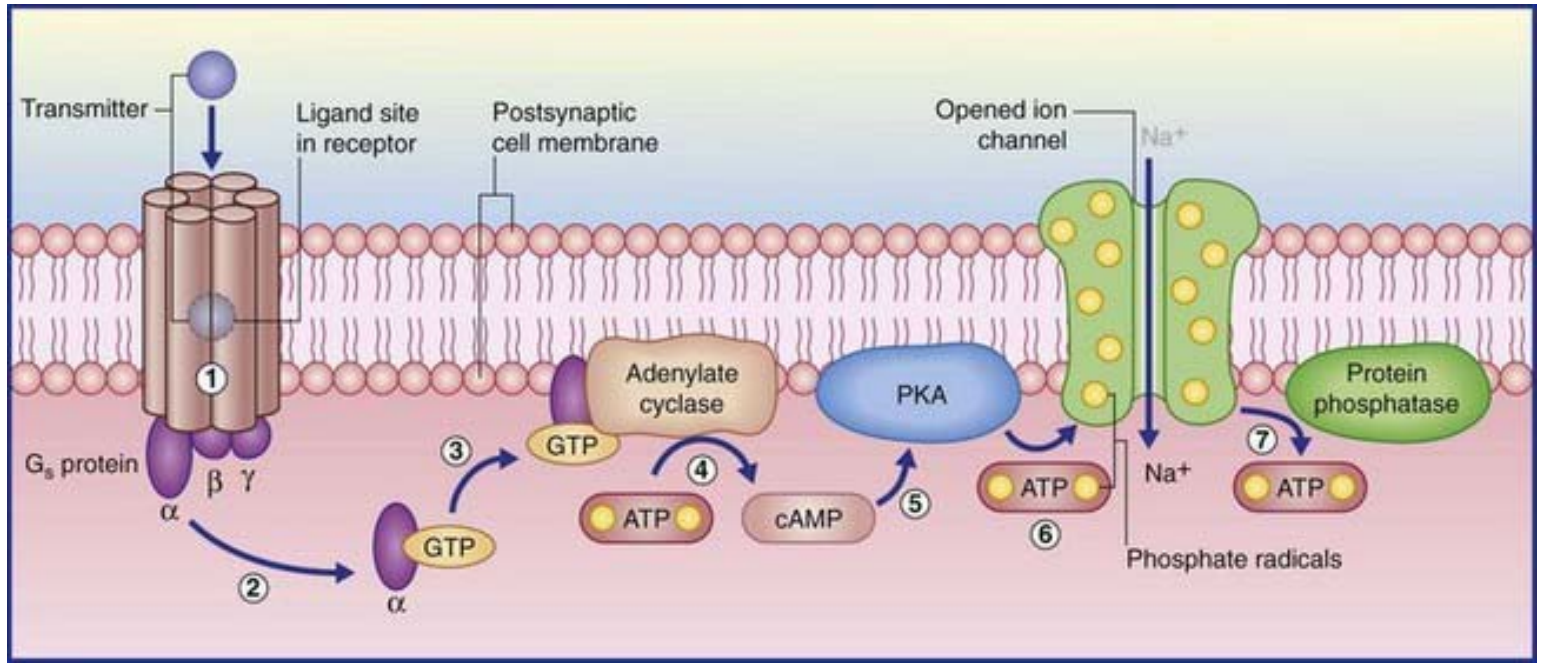
## Metabotropic receptors

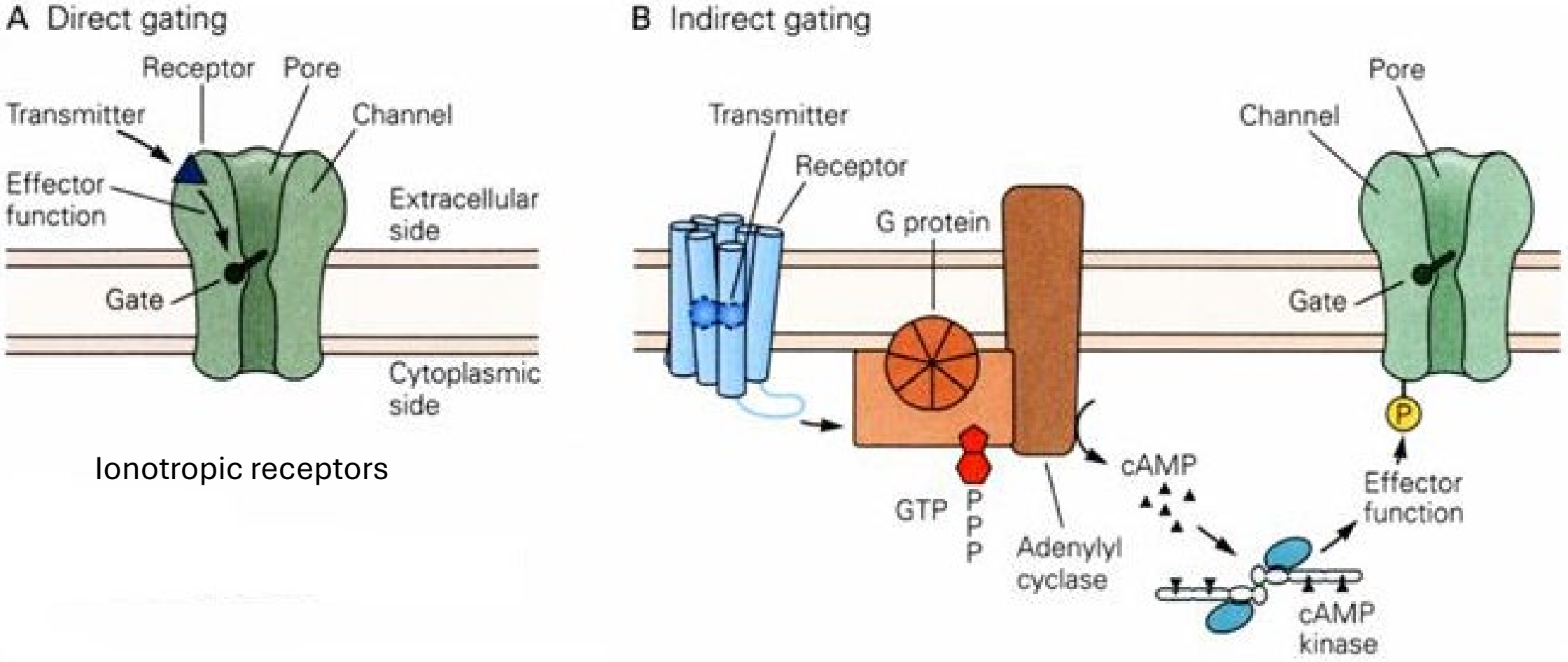
ligand receptor and ion channel have different types of integral proteins

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 system



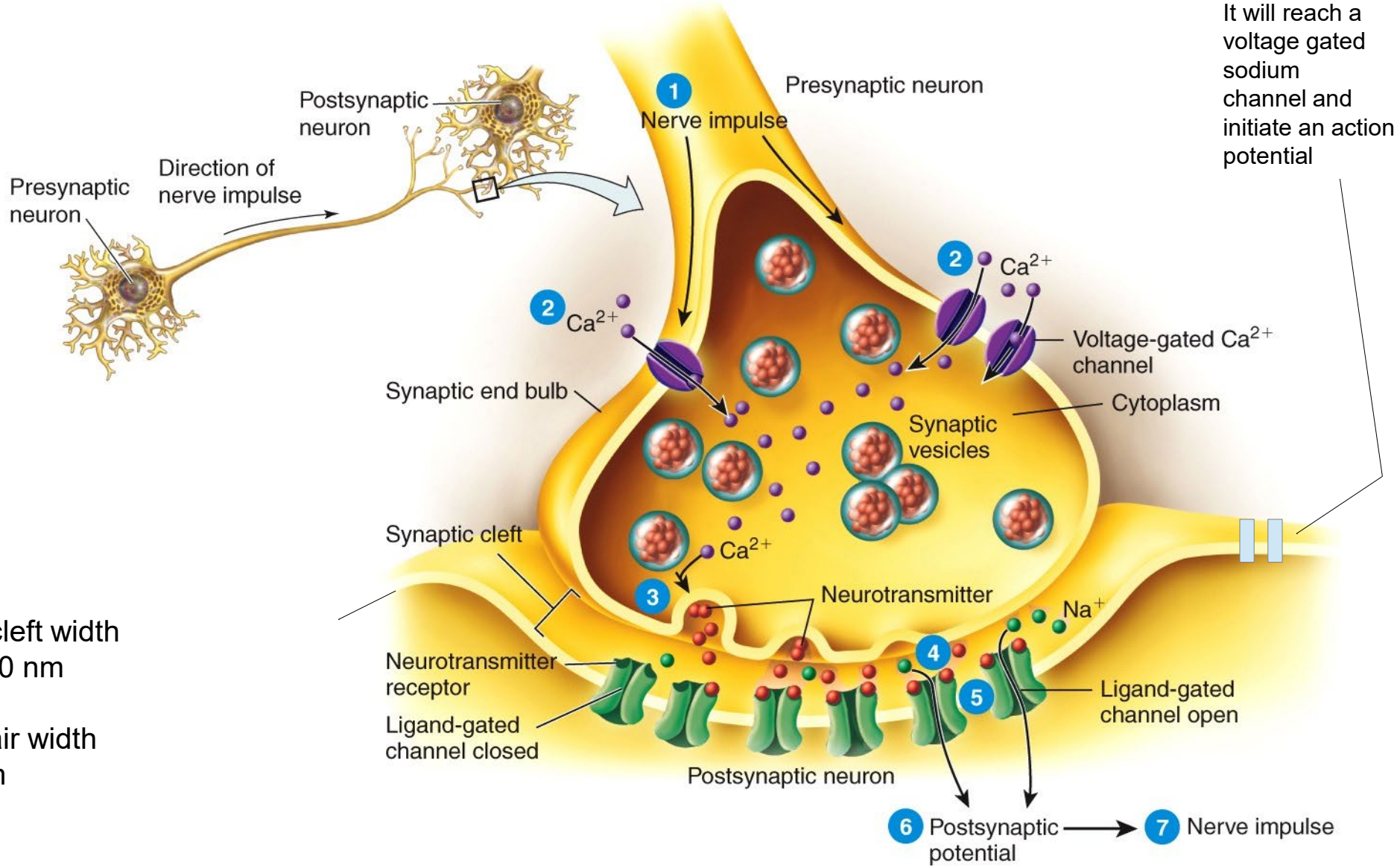



Ionotropic receptors

Metabotropic receptors

# Structure of a Chemical Synapse

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




Synaptic cleft width average 40 nm

Human hair width 80,000 nm

# 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

Diffusion of neurotransmitter across synaptic cleft // 0.5 msec

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

Significance?

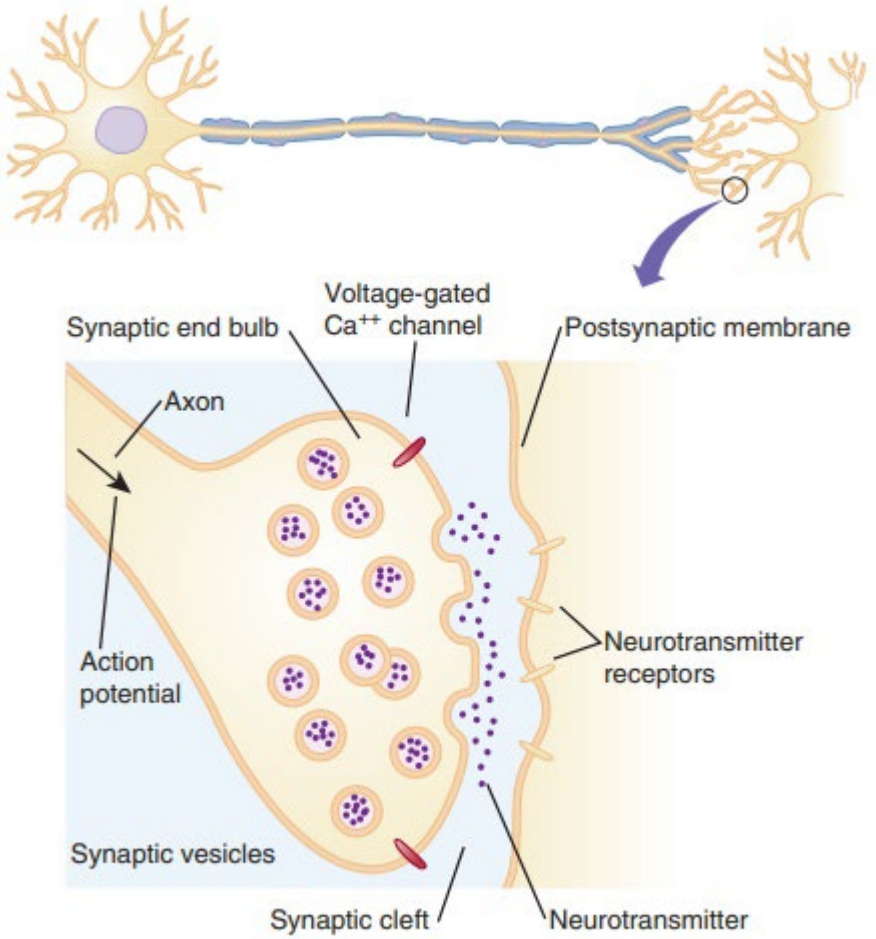



FIGURE 11-10 Chemical synapse.

# 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 post-synaptic membrane // moves resting membrane potential towards threshold or away from threshold

It is the receptor and not the neurotransmitter that determines  the outcome!!!

- For example: Dopamine has two main receptors
  - DA1-Receptor stimulates neuron (increases cAMP)
  - DA2-Receptor inhibits (decrease cAMP) // stop signal transmission.

# Effects of Neurotransmitters

The same neurotransmitter may have different effects on different target tissues

There are multiple receptors for some neurotransmitters /// 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 or 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 may function as a hormone, a neurotransmitter, or a neuromodulator!*

# Neurotransmitters and Related Messengers

**Monoamines (also called 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

–LSD and mescaline bind to monoamine 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)

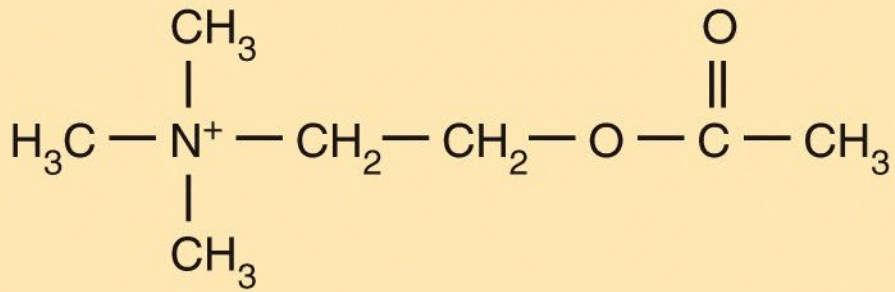
Pruines // adenosine triphosphate (ATP) / now recognized as major neurotransmitter in CNS and PNS

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

## SMALL-MOLECULE NEUROTRANSMITTERS

**Acetylcholine**



**Nitric oxide**

$N{=}O$

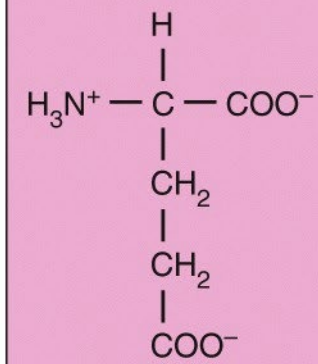
**Carbon monoxide**

$C{\equiv}O$

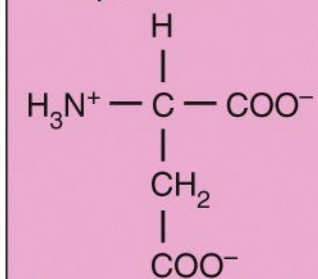
## SMALL-MOLECULE NEUROTRANSMITTERS

### Amino Acids

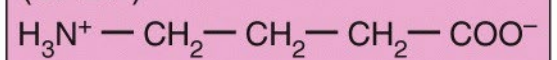
Glutamate



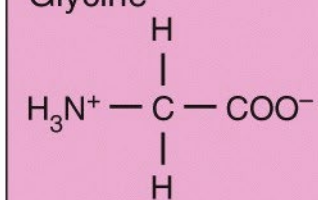
Aspartate



Gamma aminobutyric acid (GABA)



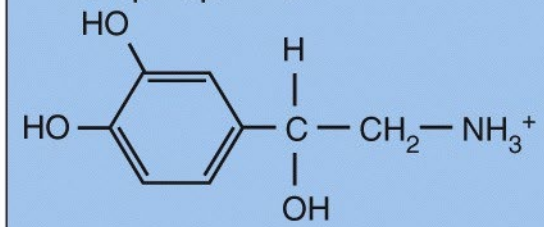
Glycine



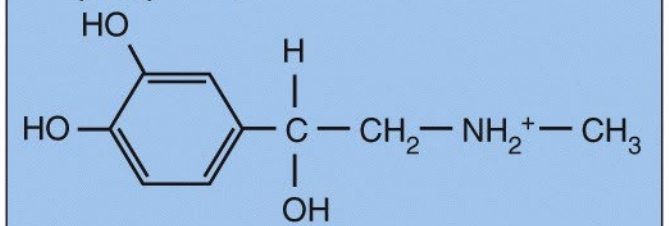
## SMALL-MOLECULE NEUROTRANSMITTERS

### Biogenic Amines

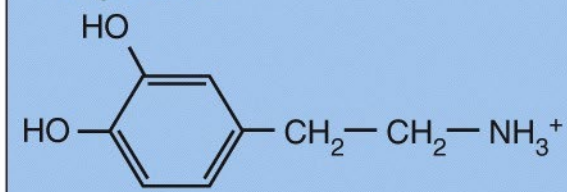
Norepinephrine



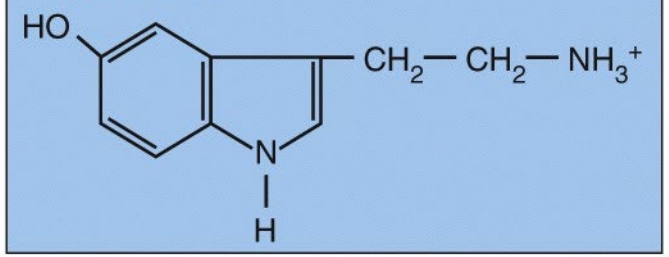

Epinephrine



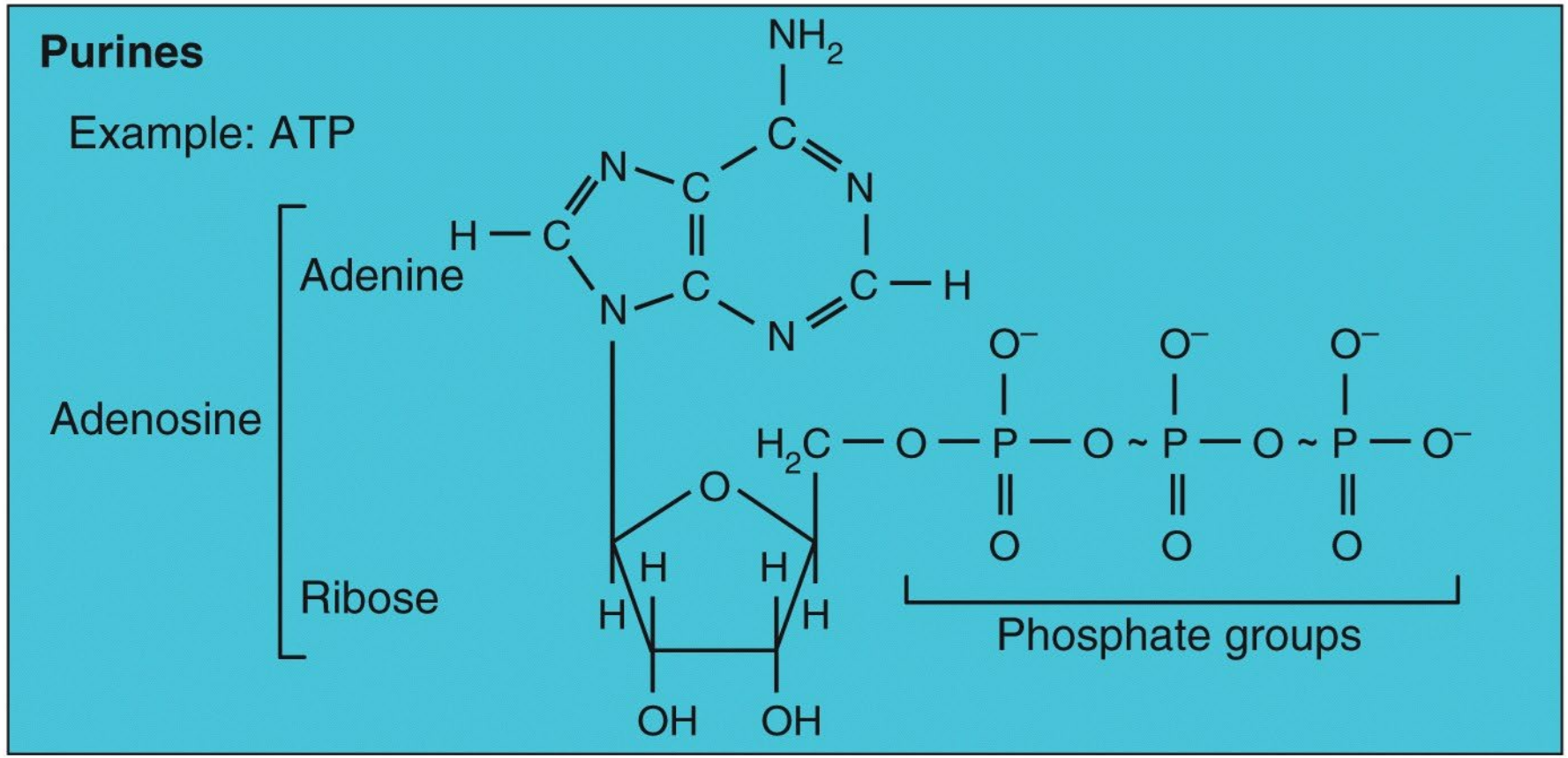

Dopamine



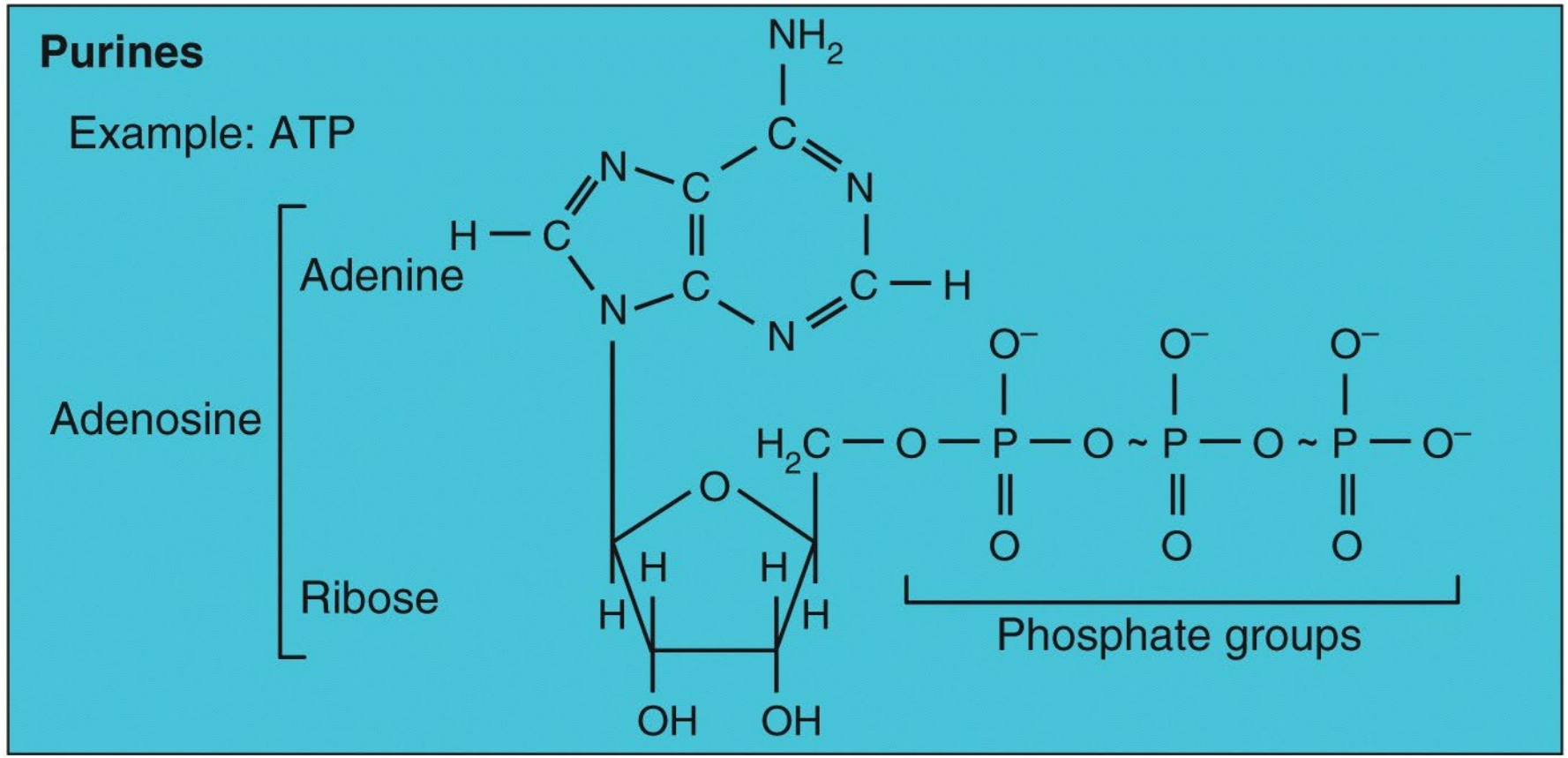

Serotonin



## SMALL-MOLECULE NEUROTRANSMITTERS

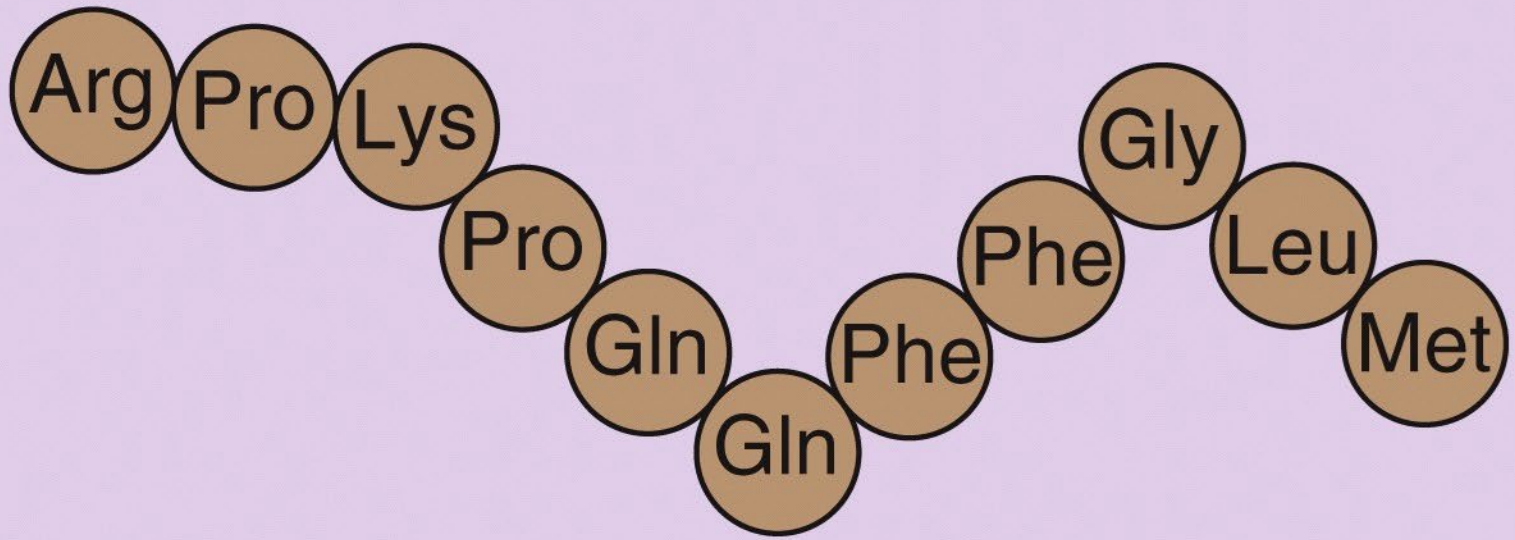


## SMALL-MOLECULE NEUROTRANSMITTERS



# 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 / uses both ionotropic and metabotropic receptors

## Monoamine

Norepinephrine – largely in ANS / in CNS area of brain stem called locus coeruleus sleep & wake cycles, attention, feeding behavior / activates sympathetic nervous system

Epinephrine – largely ANS similar effects as norepinephrine / more widely used as hormone

Dopamine – CNS / many CNS functions – coordinates movements, motivation, reward

# 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 – 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

Endogenous opioids – endorphins, dynorphins, and enkephalins / eliciting pain relief (analgesia) plus euphoria / 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

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

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

The excitatory junction's 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 (continue)

–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

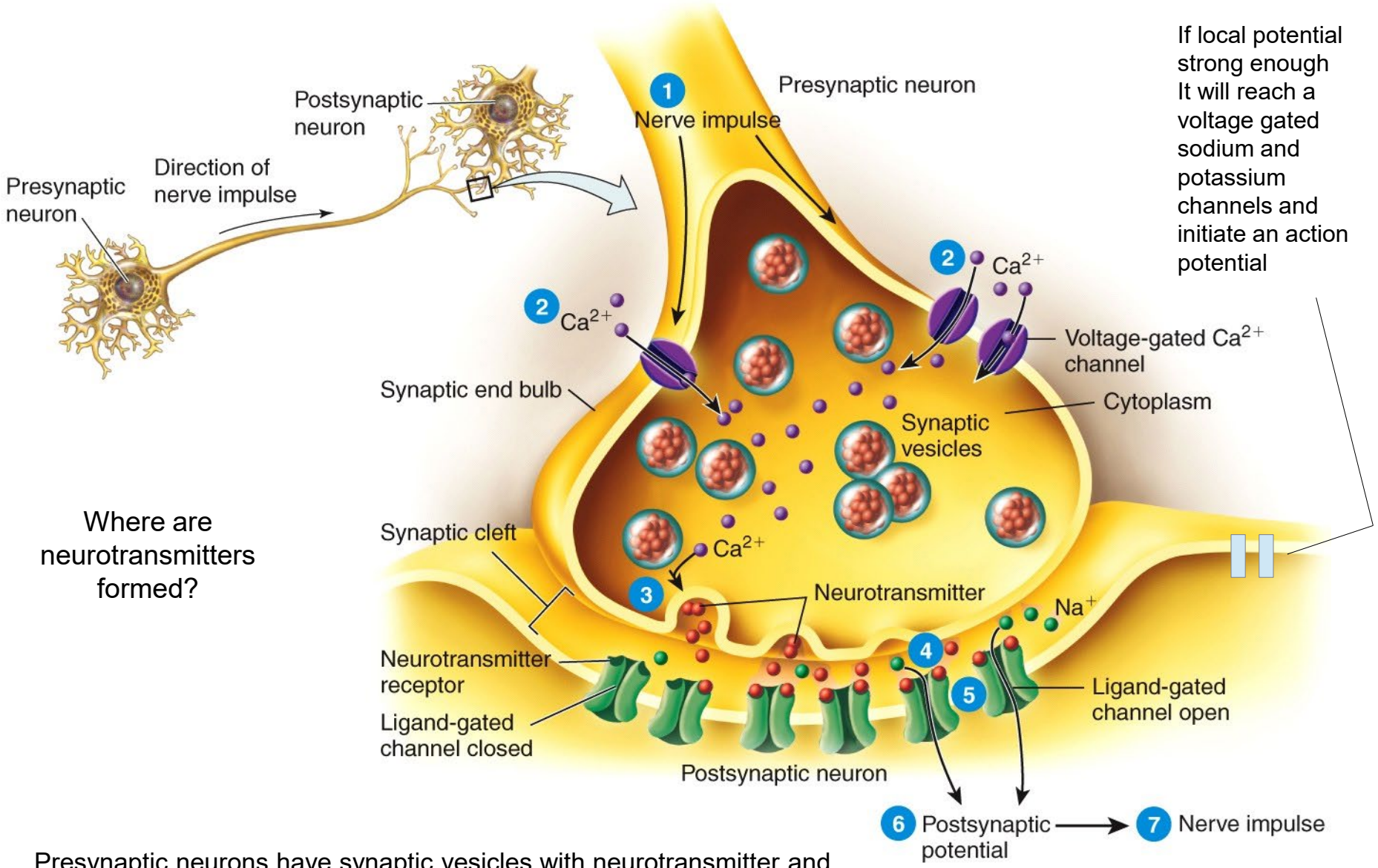
–as $Na^+$ enters the cell it spreads out along the inside of the plasma membrane and depolarizes it producing a local potential called the postsynaptic potential

–if it is strong enough and persistent enough

–it opens voltage-regulated ion gates in the trigger zone

–causing the postsynaptic neuron to fire

# 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

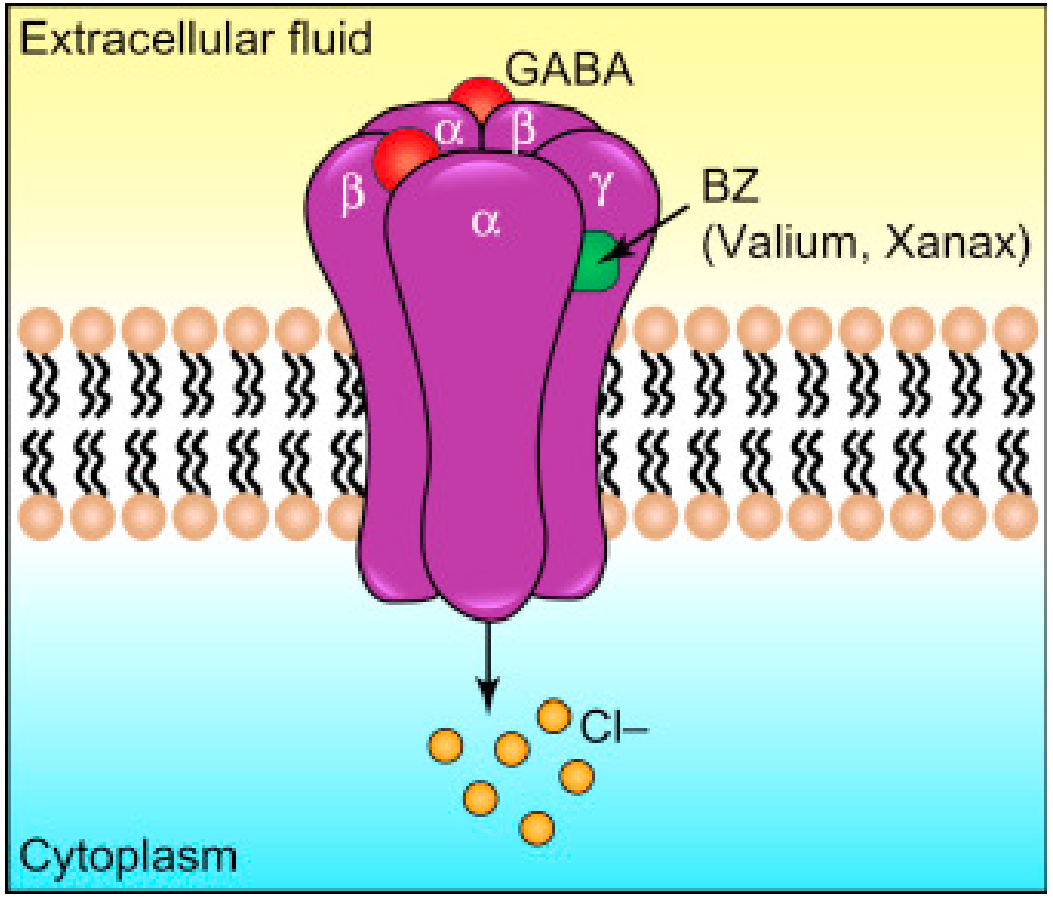
GABA-ergic synapse employs γ-aminobutyric acid as its neurotransmitter

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

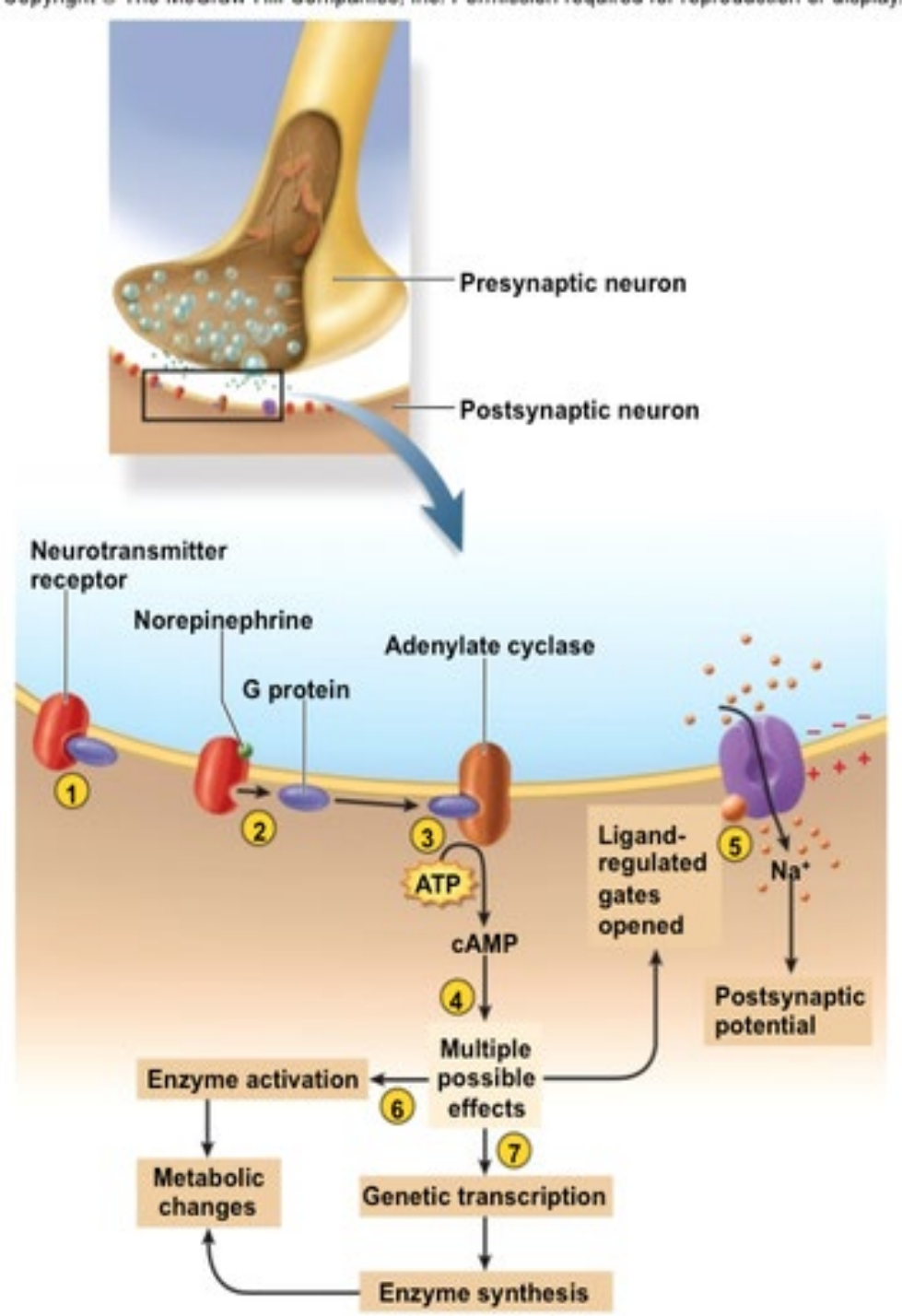


# Adrenergic Excitatory Synapse

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 Synapse



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

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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)

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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

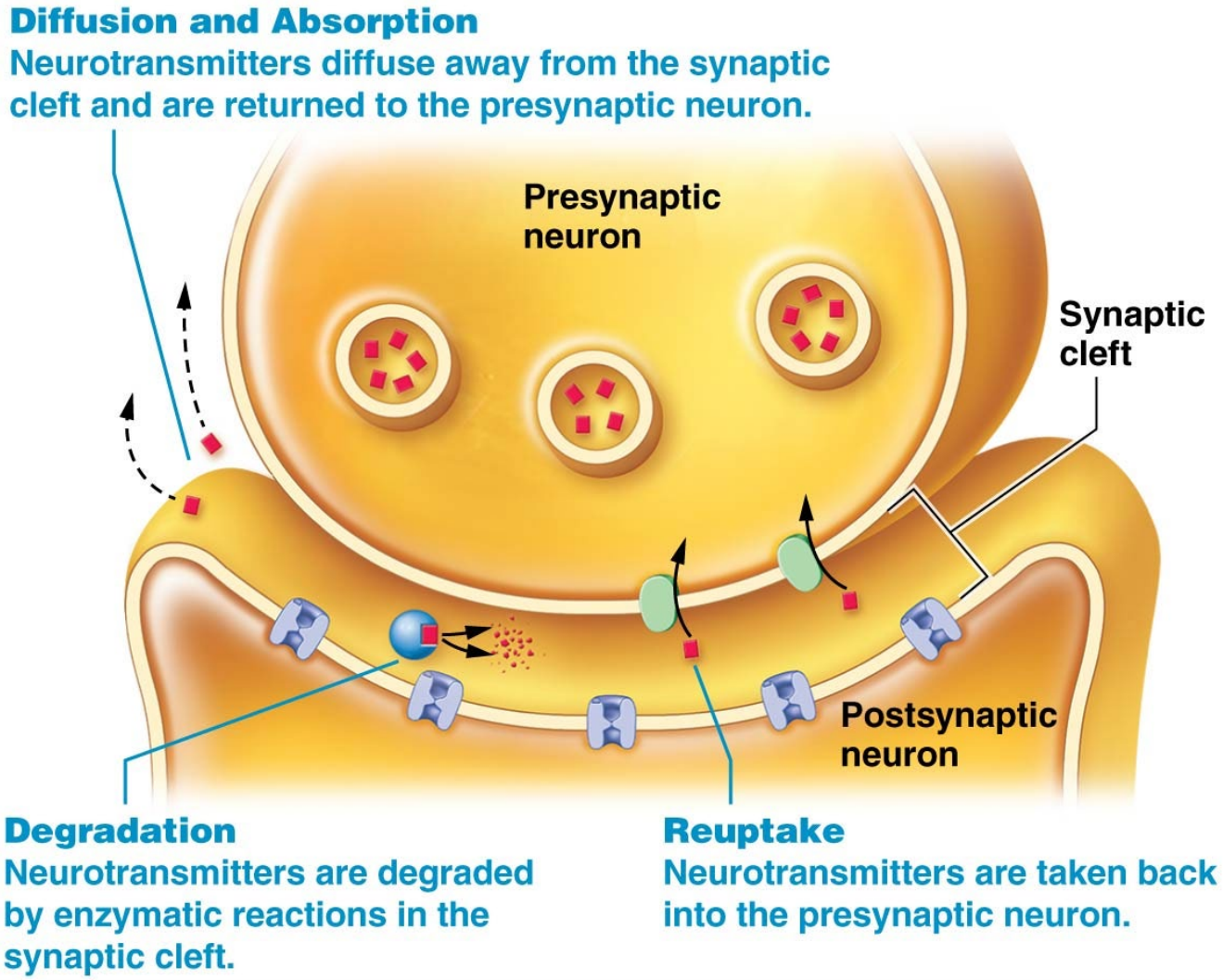
Remove neurotransmitter by:

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)* degraded by enzymes in synaptic cleft into acetate and choline // choline reabsorbed by synaptic knob

Catecholines 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

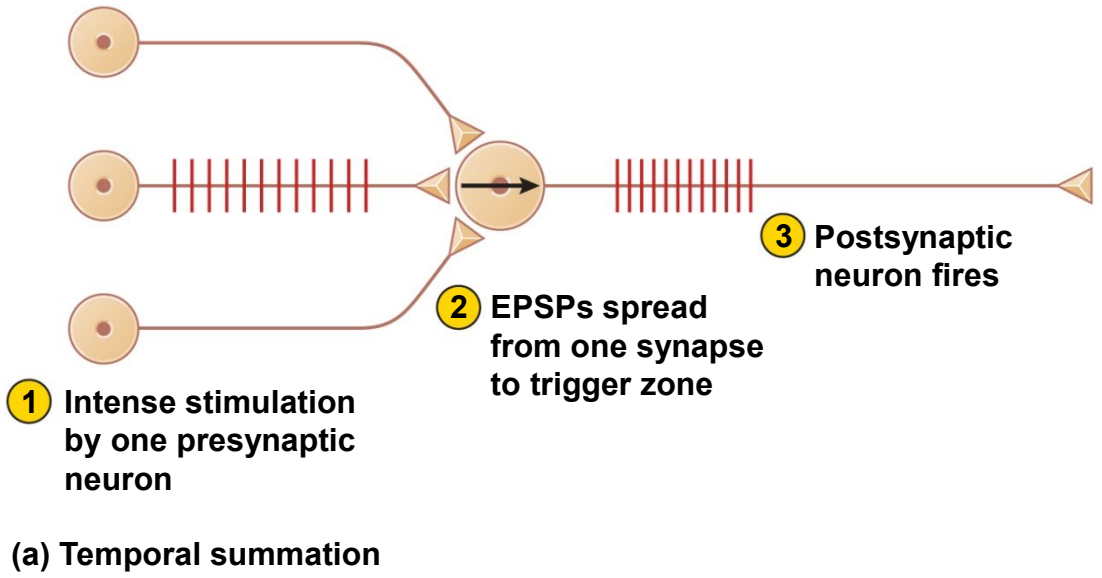
–allows EPSPs to add up over time to a threshold voltage that triggers an action potential

spatial summation – occurs when EPSPs from several different synapses add up to threshold at an axon hillock.

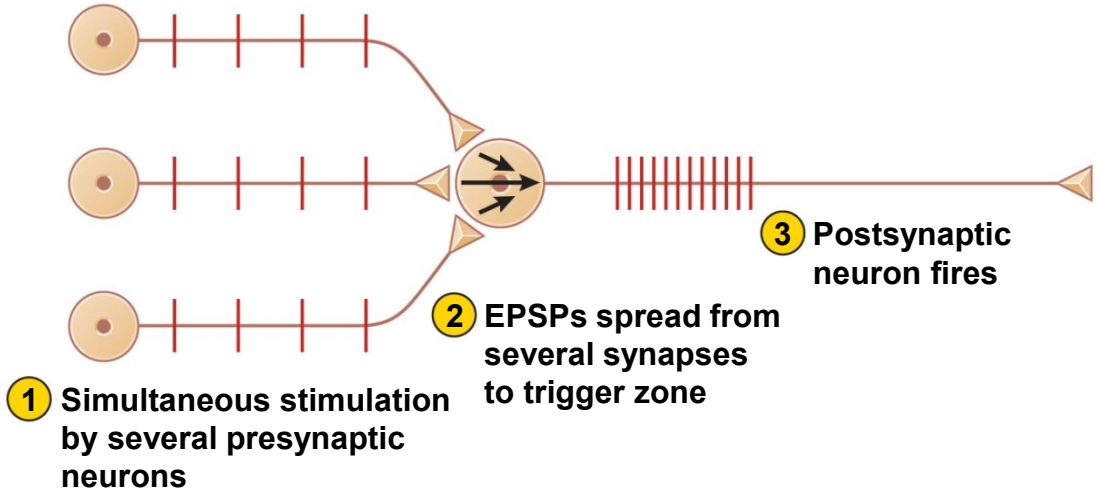
–several synapses admit enough $Na^+$ to reach threshold

–presynaptic neurons cooperate to induce the postsynaptic neuron to fire

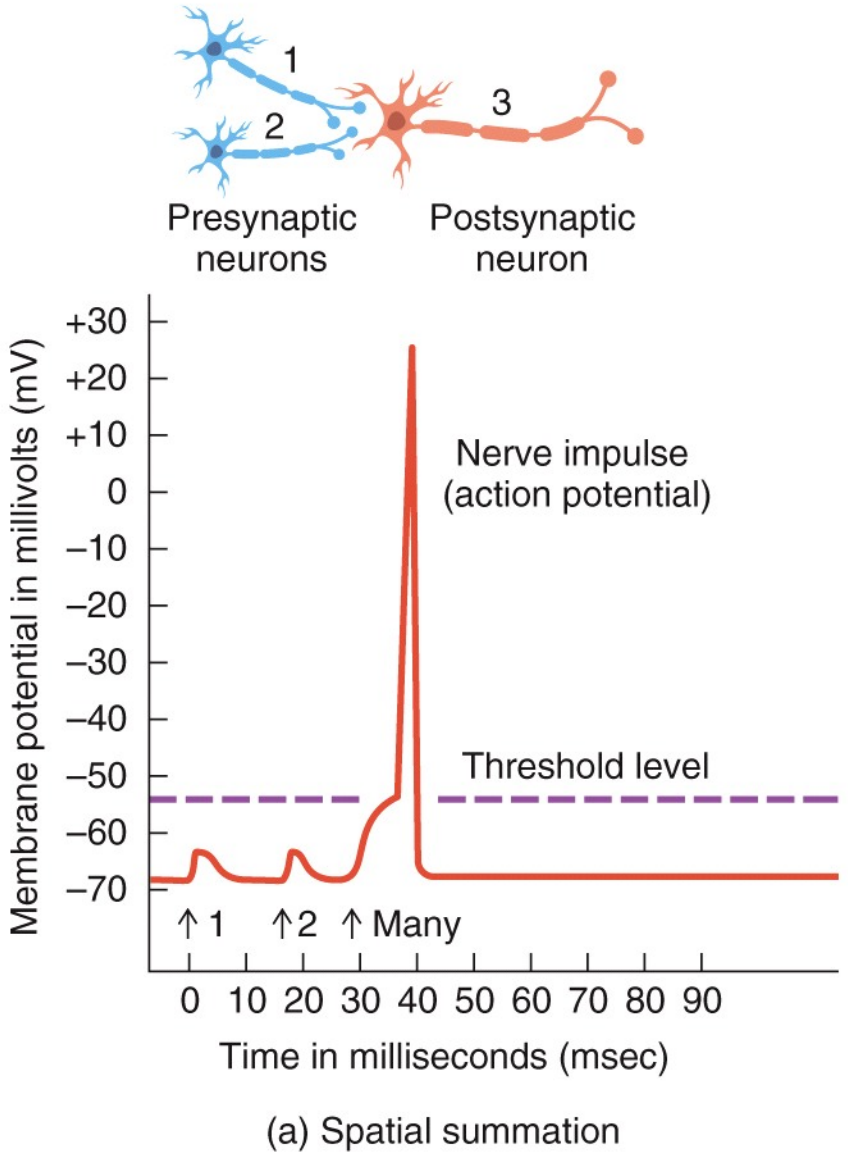
# Temporal and Spatial Summation



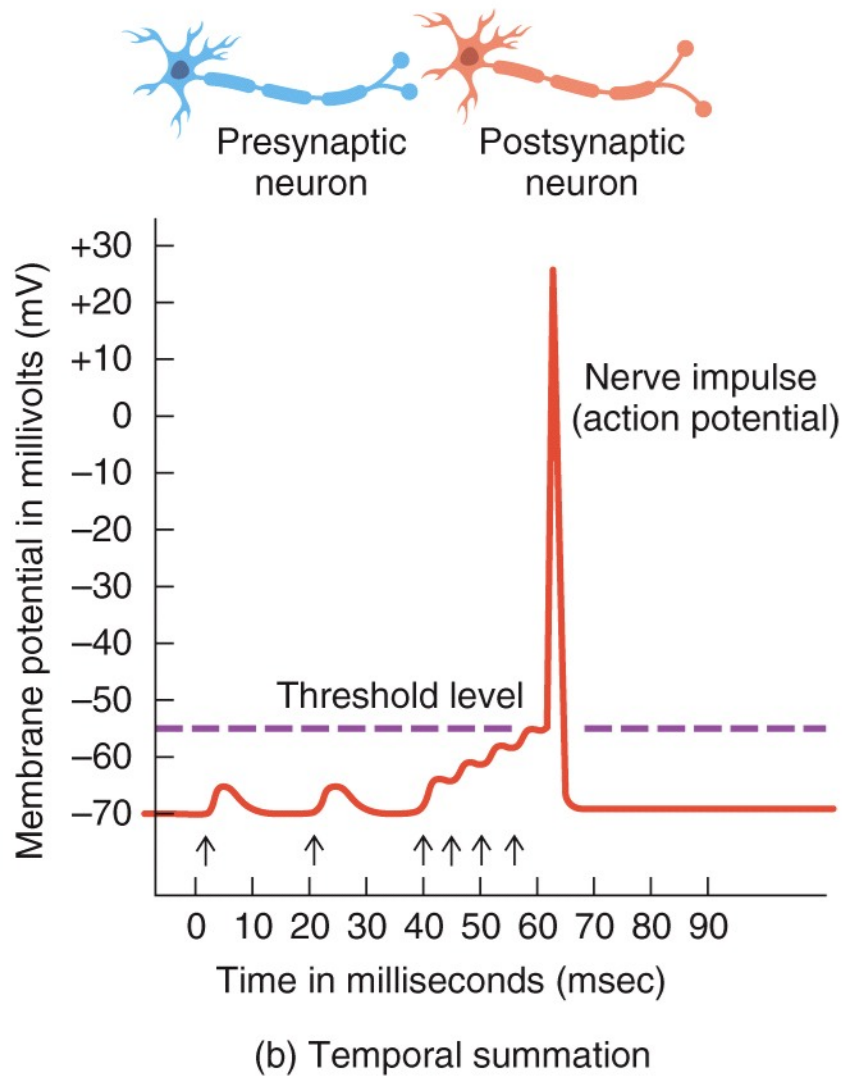

(a) Temporal summation




(b) Spatial summation



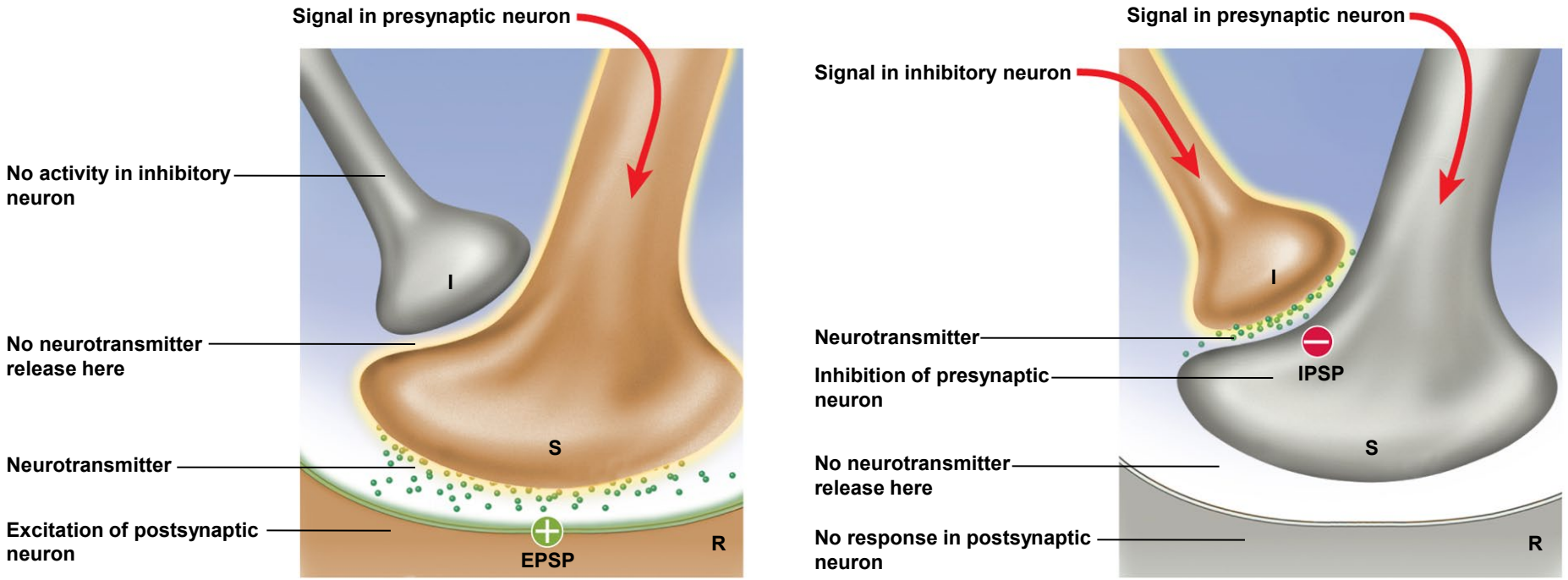

(a) Spatial summation




(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

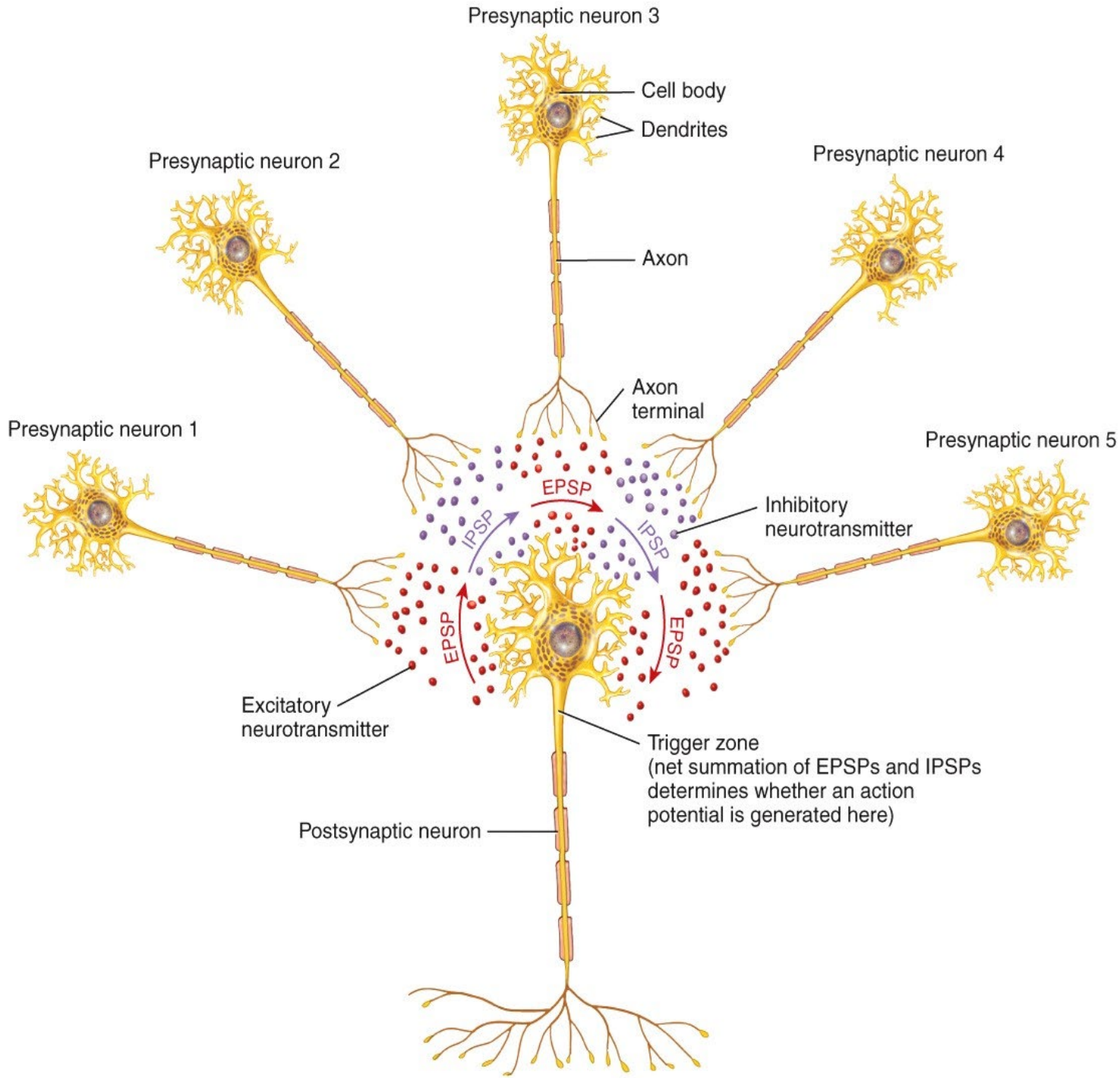
Glycine and GABA produce IPSPs /// move potential away from threshold /// inhibitory

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

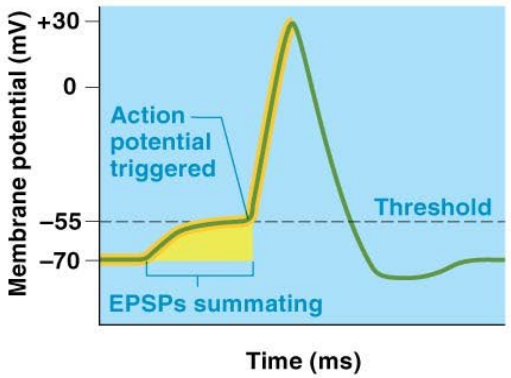
•depending on the *type of receptors* on the target cell

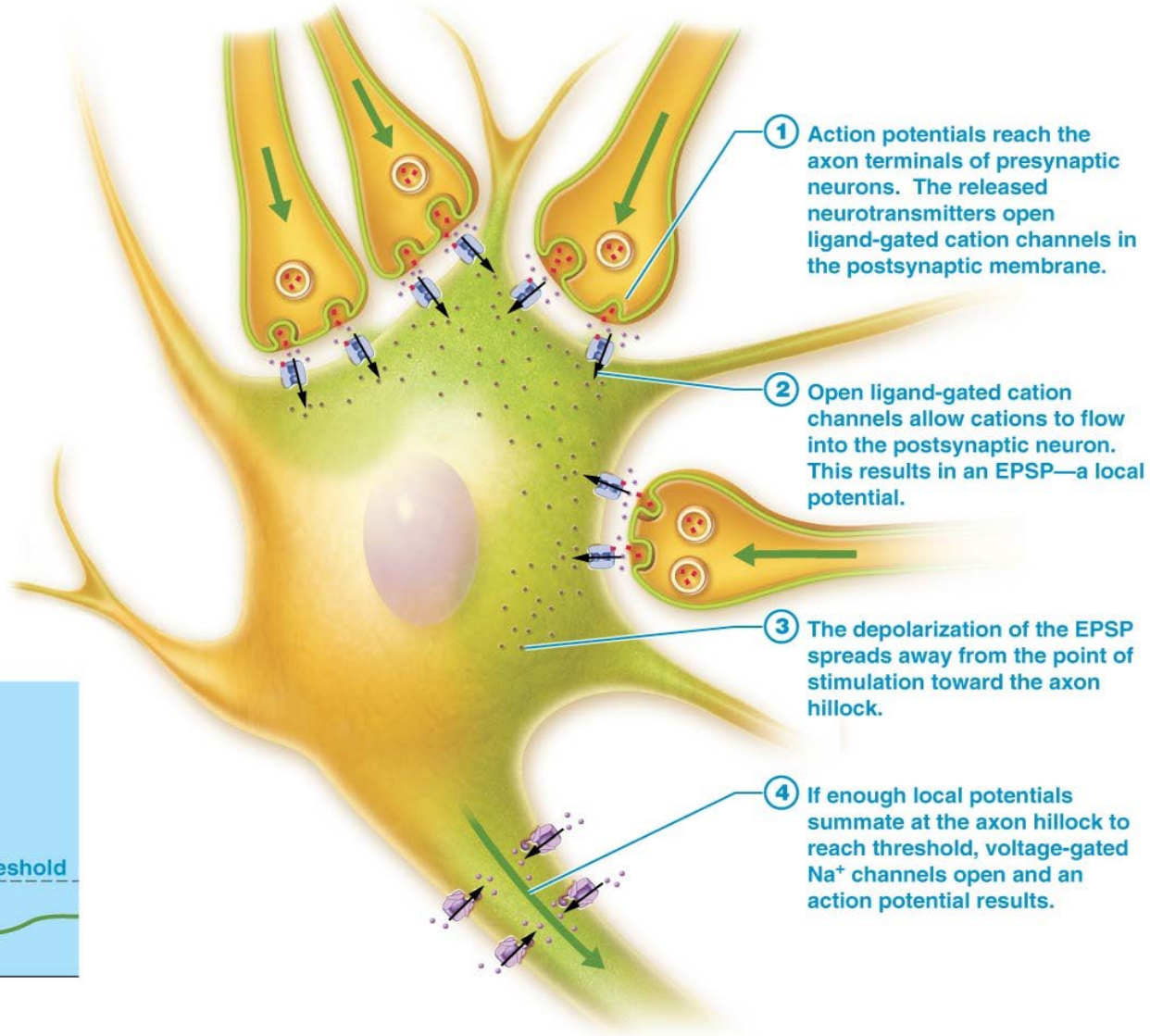
•*It is the receptor that has final say on the outcome!*

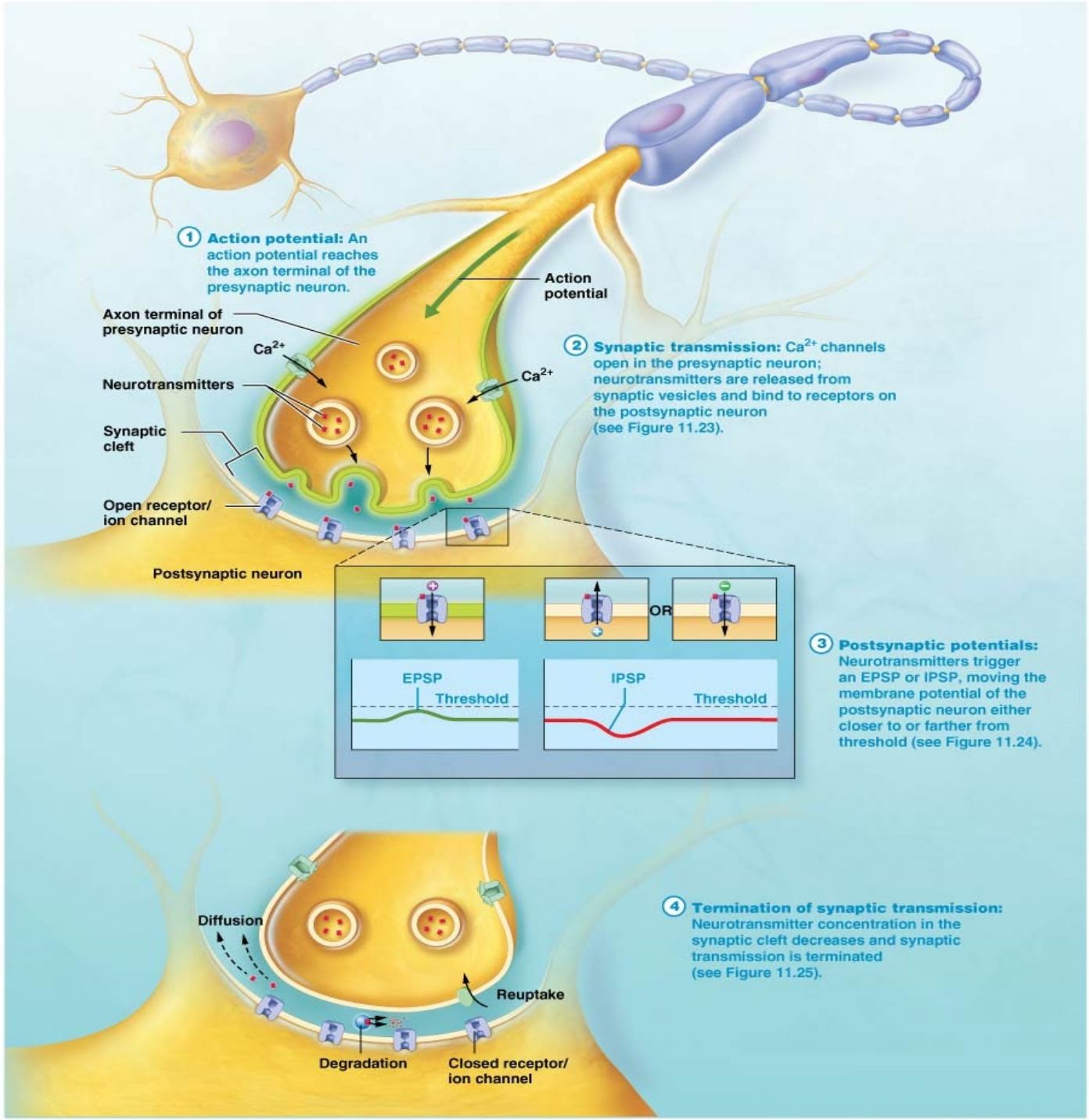
•Note: ACh excites skeletal muscle (inotropic receptor), but inhibits cardiac muscle (metabotropic receptor) due to the different type of receptors


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

Local potentials summating and leading to an action potential.



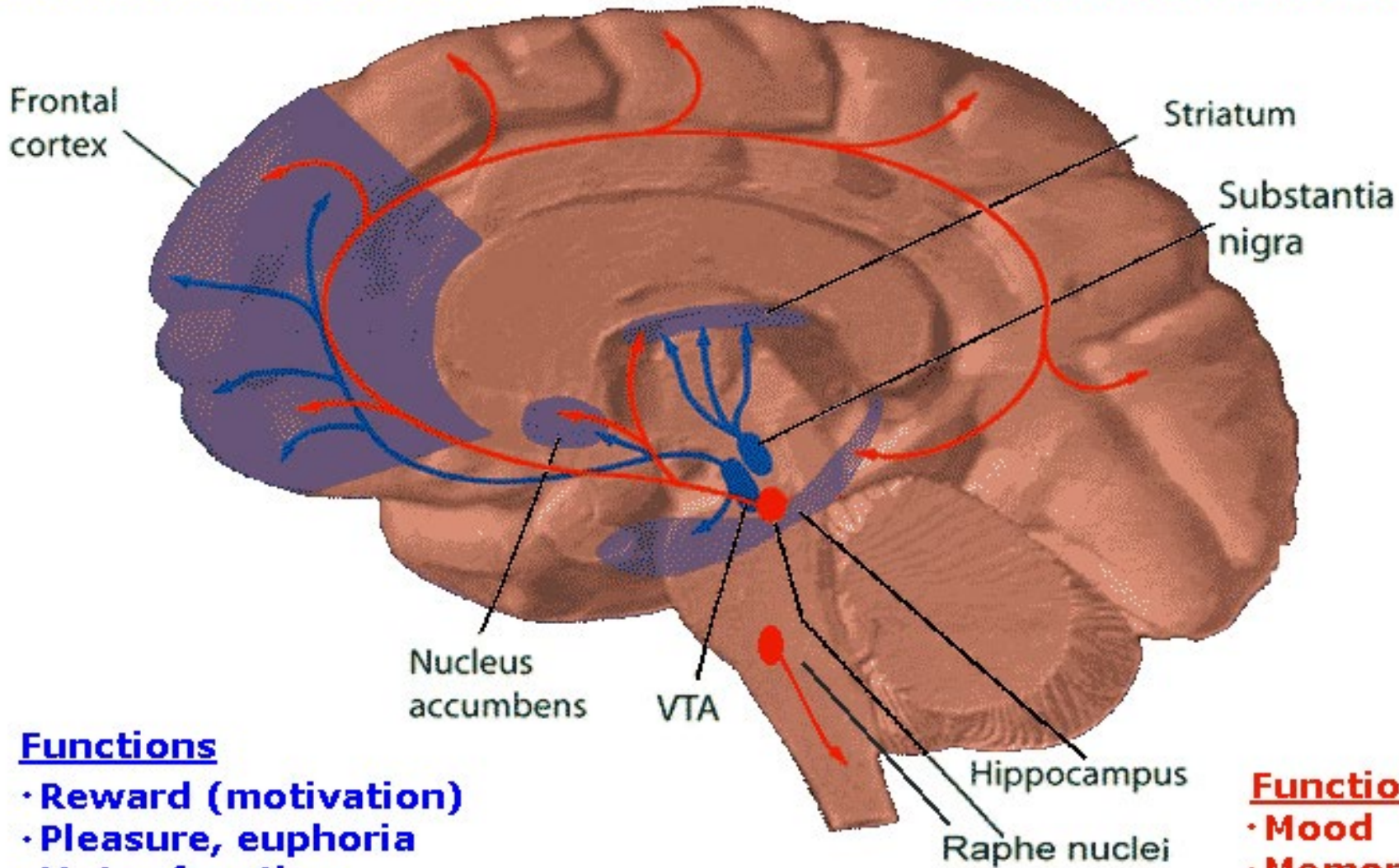






The Big Picture of Chemical Synaptic Transmission.

## Dopamine Pathways

## Serotonin Pathways

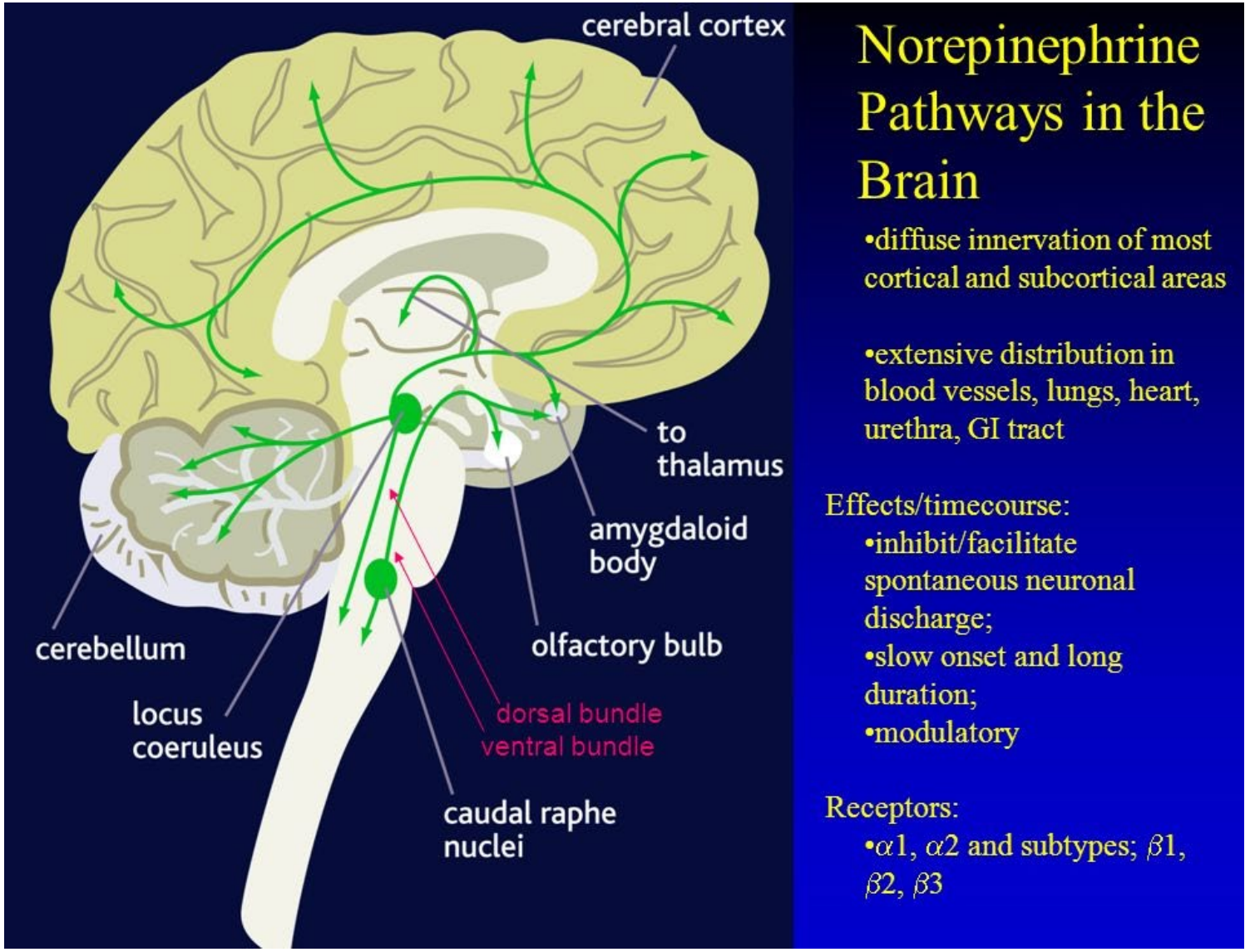



**Functions**

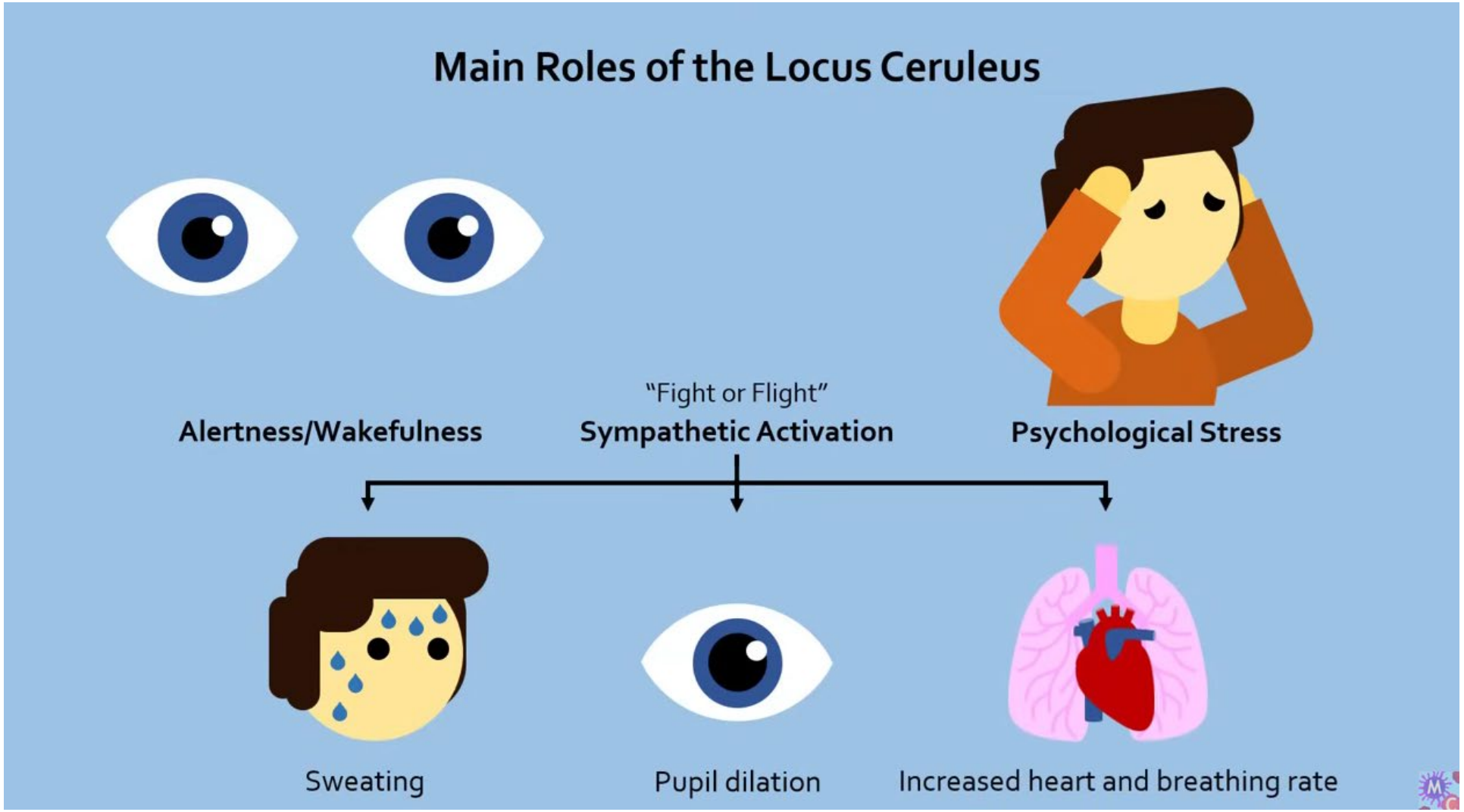
- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine tuning)
- Compulsion
- Perseveration

**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.




Locus ceruleus is the main source for CNS noradrenaline.  It projects this neurotransmitter throughout the brain and stimulates transmission between neurons.

# Main Roles of the Locus Ceruleus

## When opioids bind…

Opioid use symptoms are
**OPPOSITE OF**
normal Locus Ceruleus function

**Drowsiness**

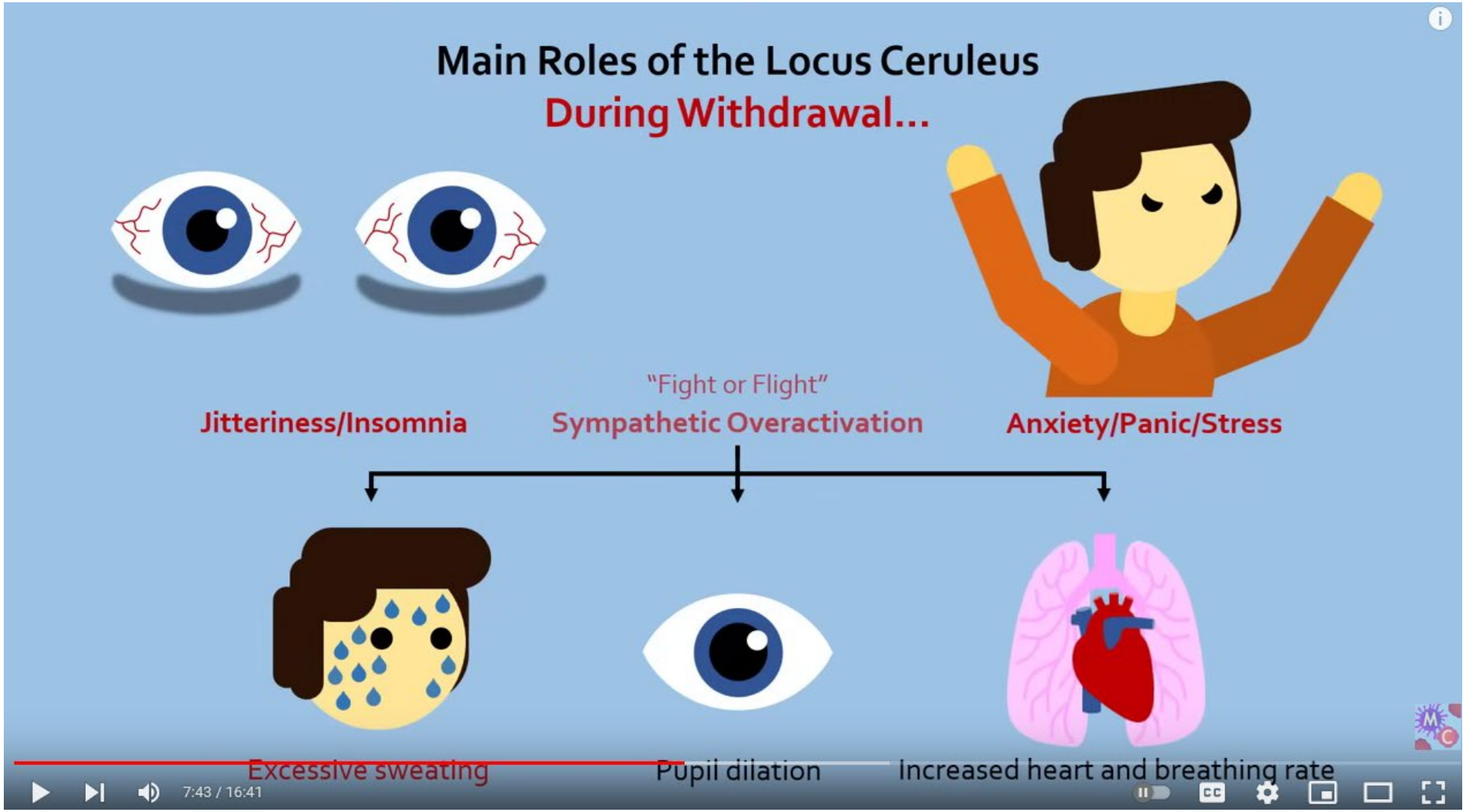
"Rest and Digest"
**Parasympathetic Activation**

**Sedation**

Reduced sweating

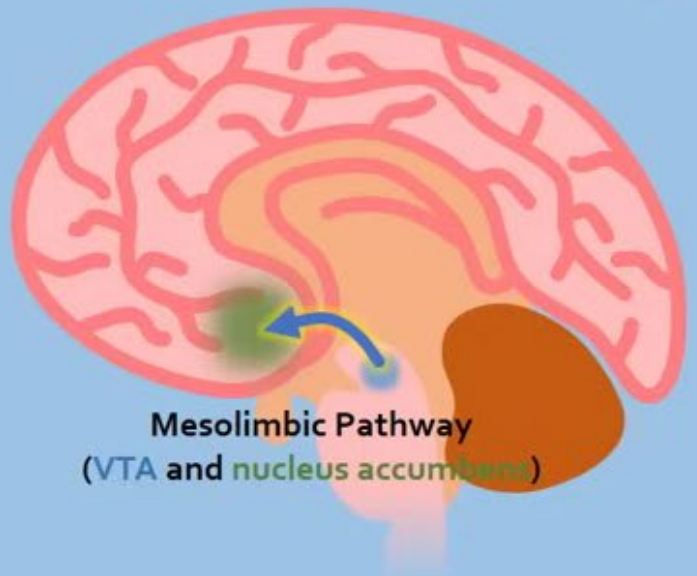
Pupil constriction
"Pinpoint pupils"

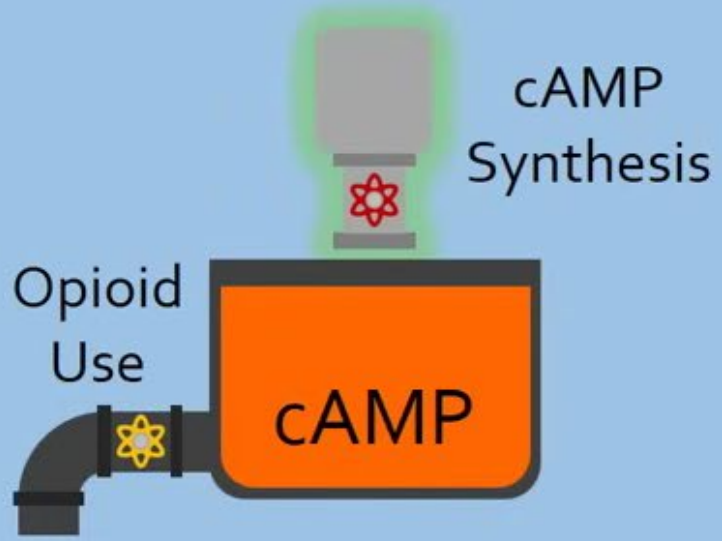
Decreased heart and breathing rate

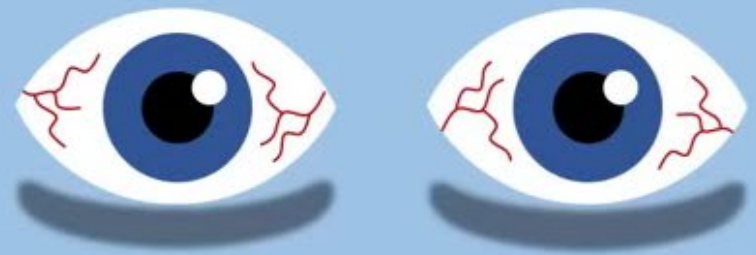

Main Roles of the Locus Ceruleus
During Withdrawal...
"Fight or Flight"
Jitteriness/Insomnia
Sympathetic Overactivation
Anxiety/Panic/Stress
Excessive sweating
Pupil dilation
Increased heart and breathing rate
7:43 / 16:41

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 and this then reduces locus ceruleus secretion of norepinephrine.

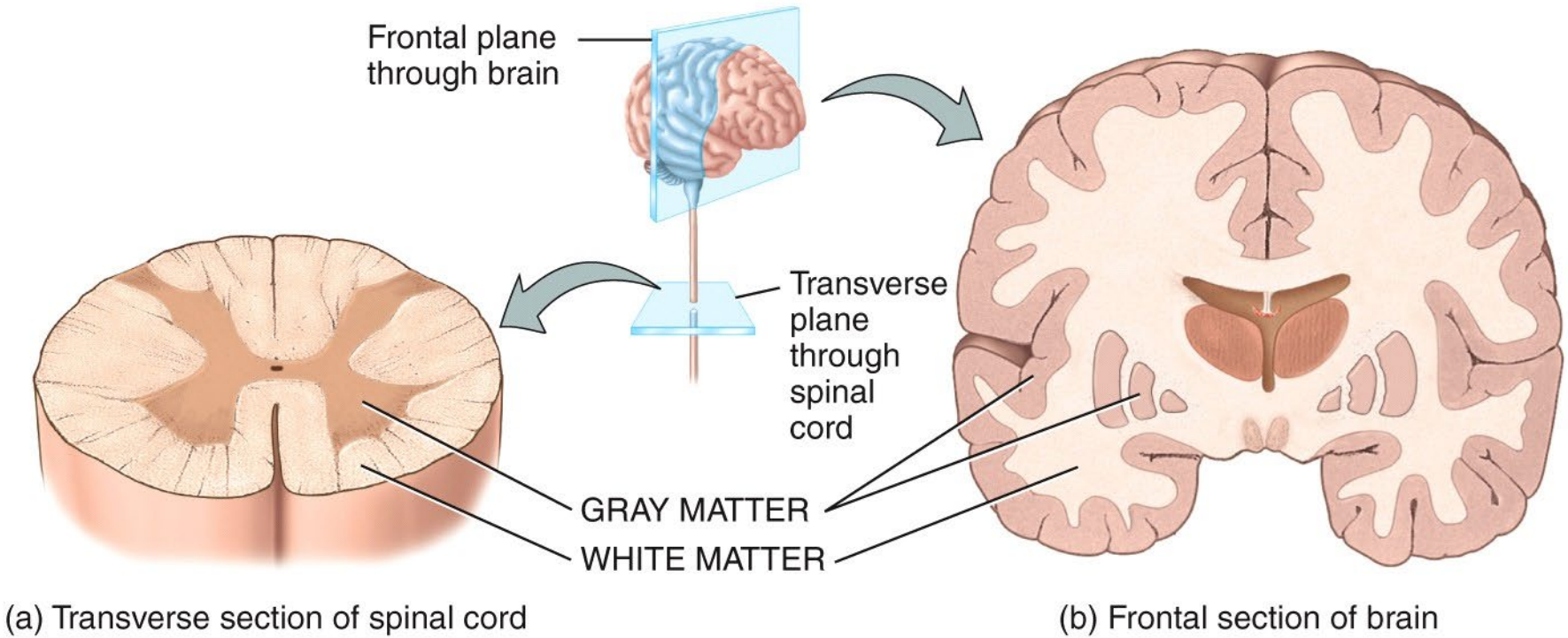
# Progression of Opioid Use Disorder



1. Association between drug and pleasure is formed after repeated opioid use
2. Tolerance results from pre-emptive cAMP increase due to repeated opioid use
3. Withdrawal symptoms prevent patient from stopping opioid use


Frontal plane through brain
Transverse plane through spinal cord
GRAY MATTER
WHITE MATTER
(a) Transverse section of spinal cord
(b) Frontal section of brain