

Chapter 12.3

Synapses and Neurotransmitters



The Discovery of the Synaptic Cleft

Early physiologists 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 1890'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 10⁻⁹ meters)

–In the 1970s Dr. Eric Kandel demonstrated how the **synapse changes during learning**. He also showed 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)

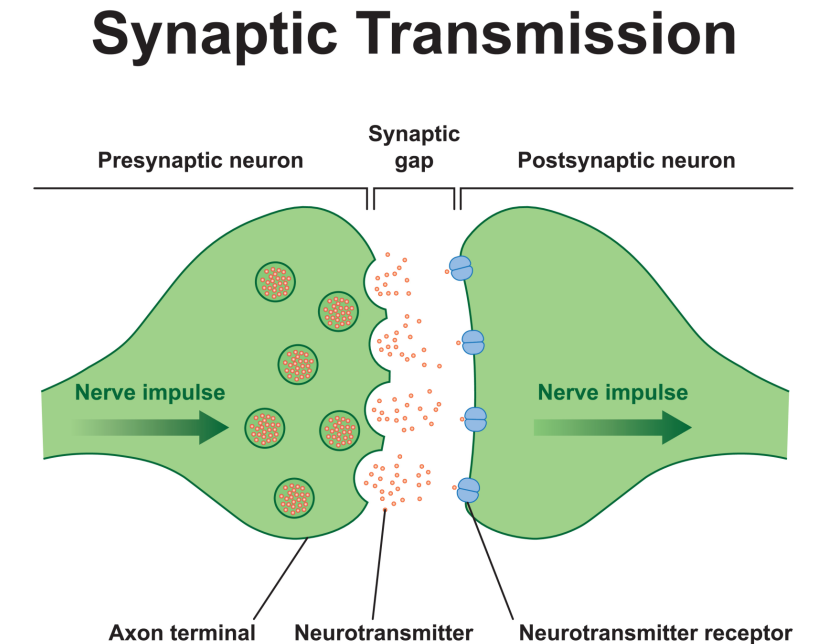
A chemical synapse consist of three components

- **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?



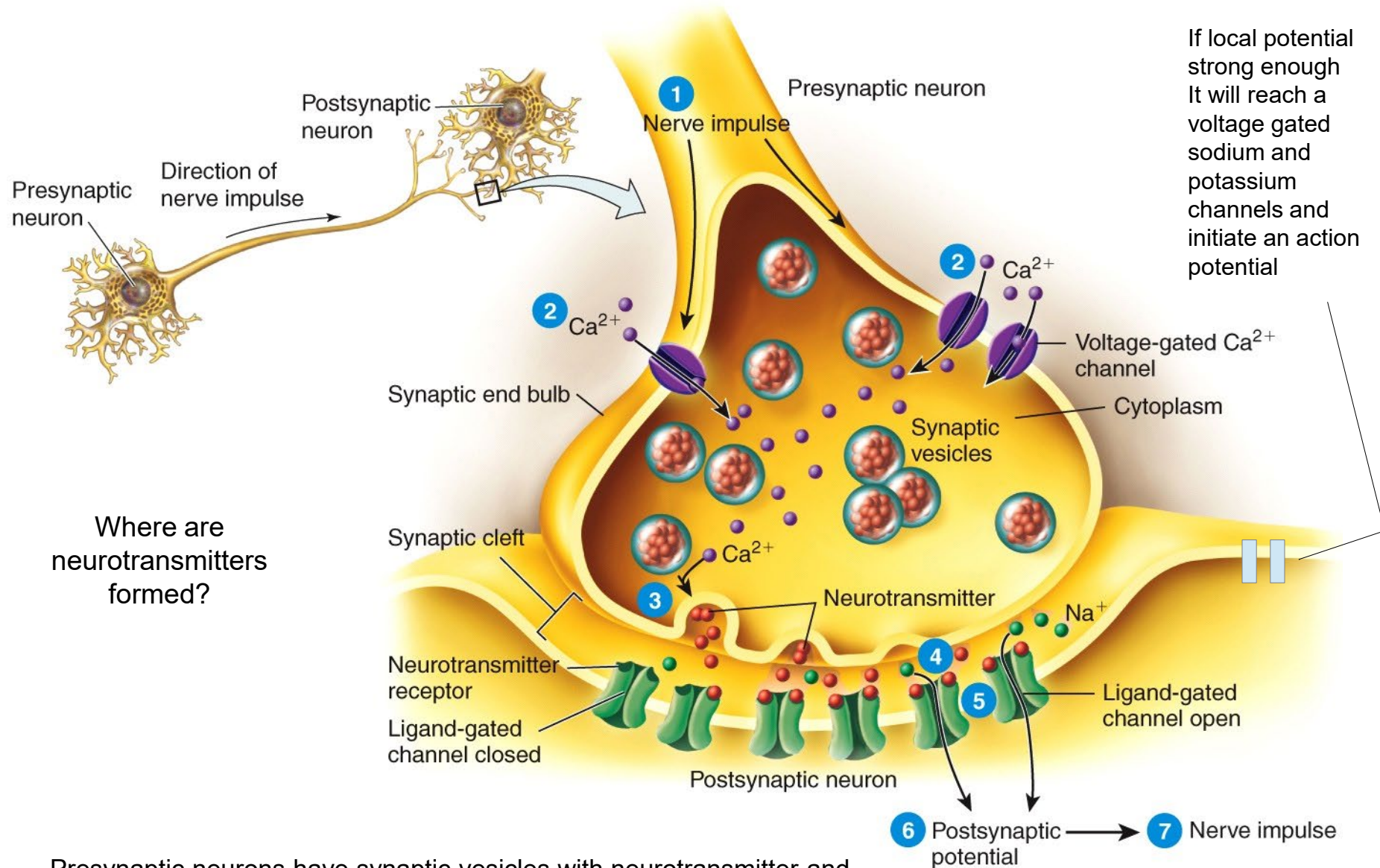
The Synapse

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



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

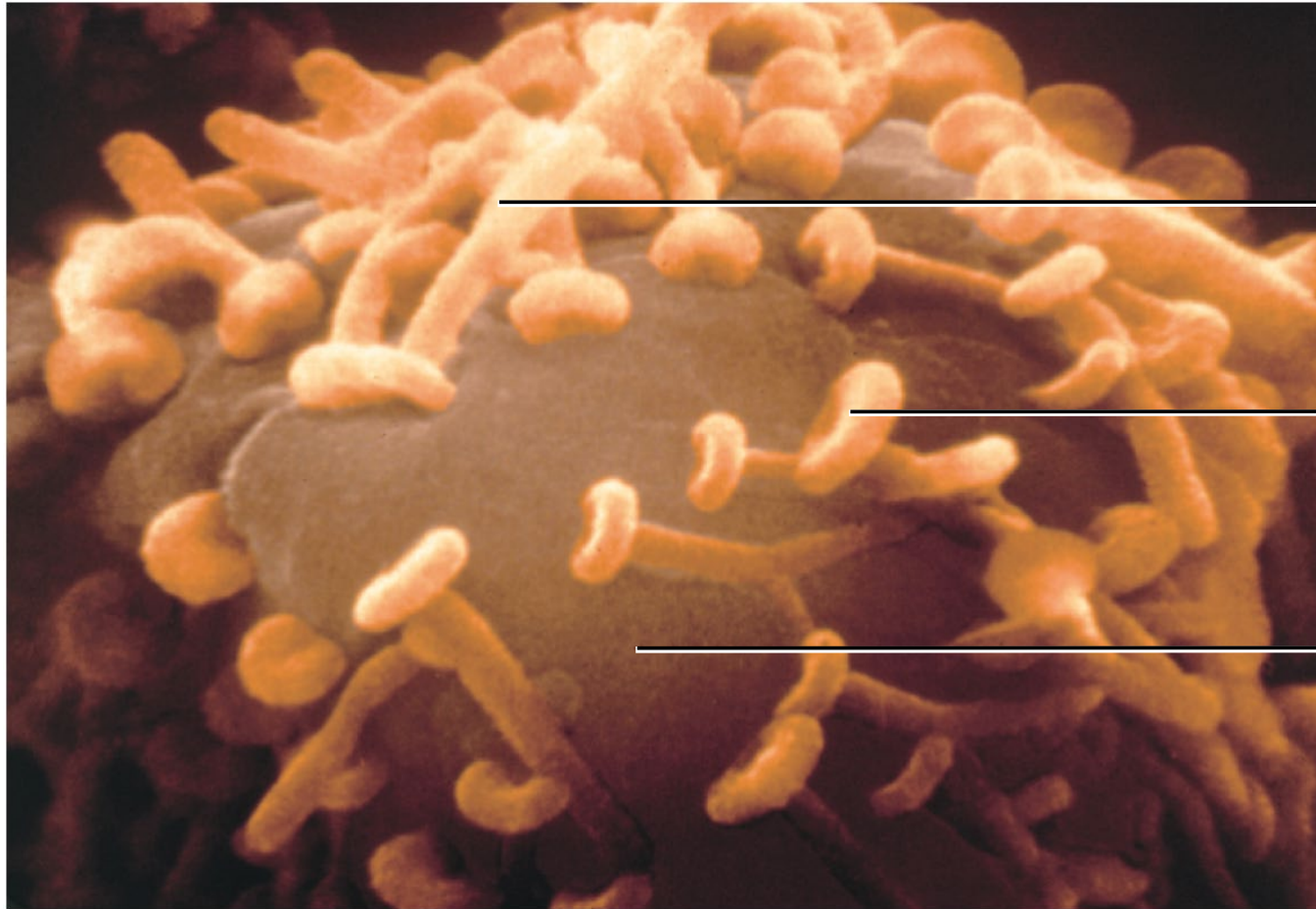
a reserve pool of synaptic vesicles are located further away from inner face of synaptic knob's membrane

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



**Axon of
presynaptic
neuron**

**Synaptic
knob**

**Soma of
postsynaptic
neuron**

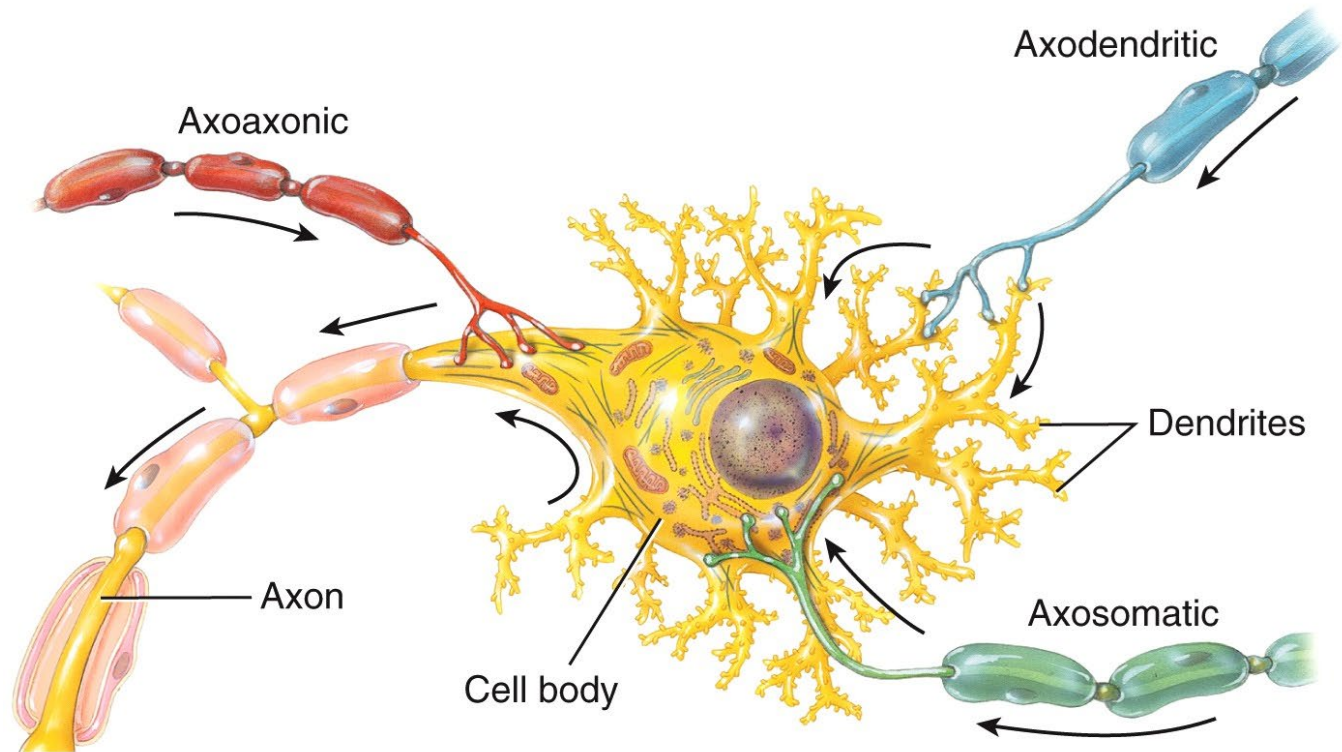
Where May A Synapse Occur?

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”?

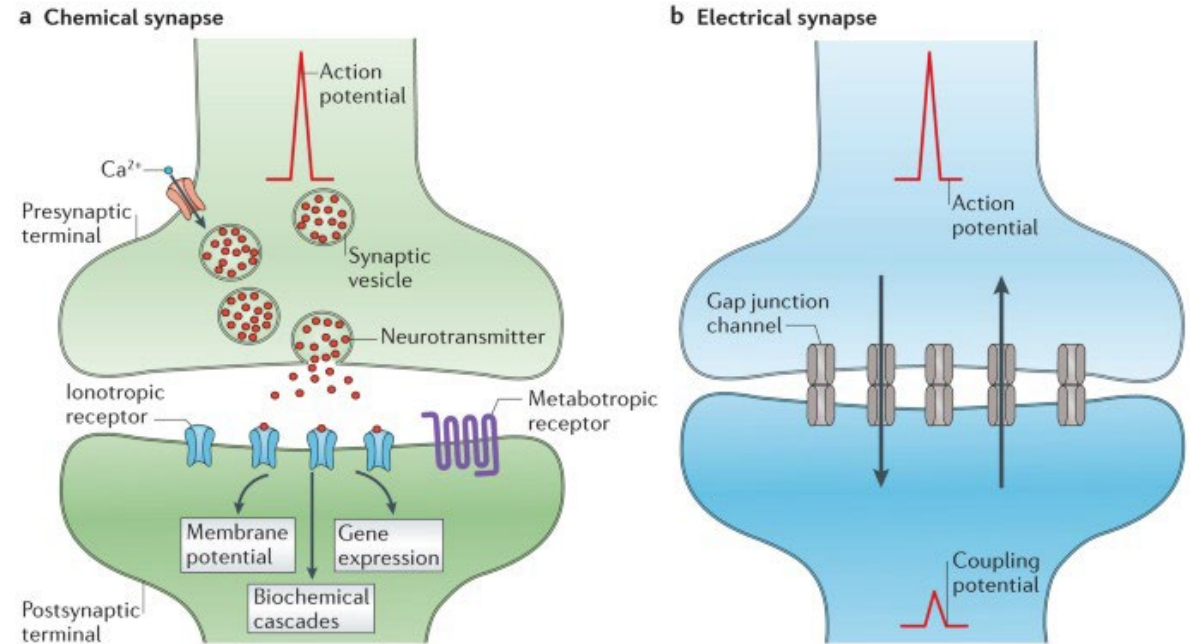
It is a gap junction! Gap junctions allow action potentials to move rapidly between adjacent cells!
// no neurotransmitter

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 can not integrate information and can not be used in making decisions



Two Types of Neurotransmitter Receptors: Ionotropic VS Metabotropic

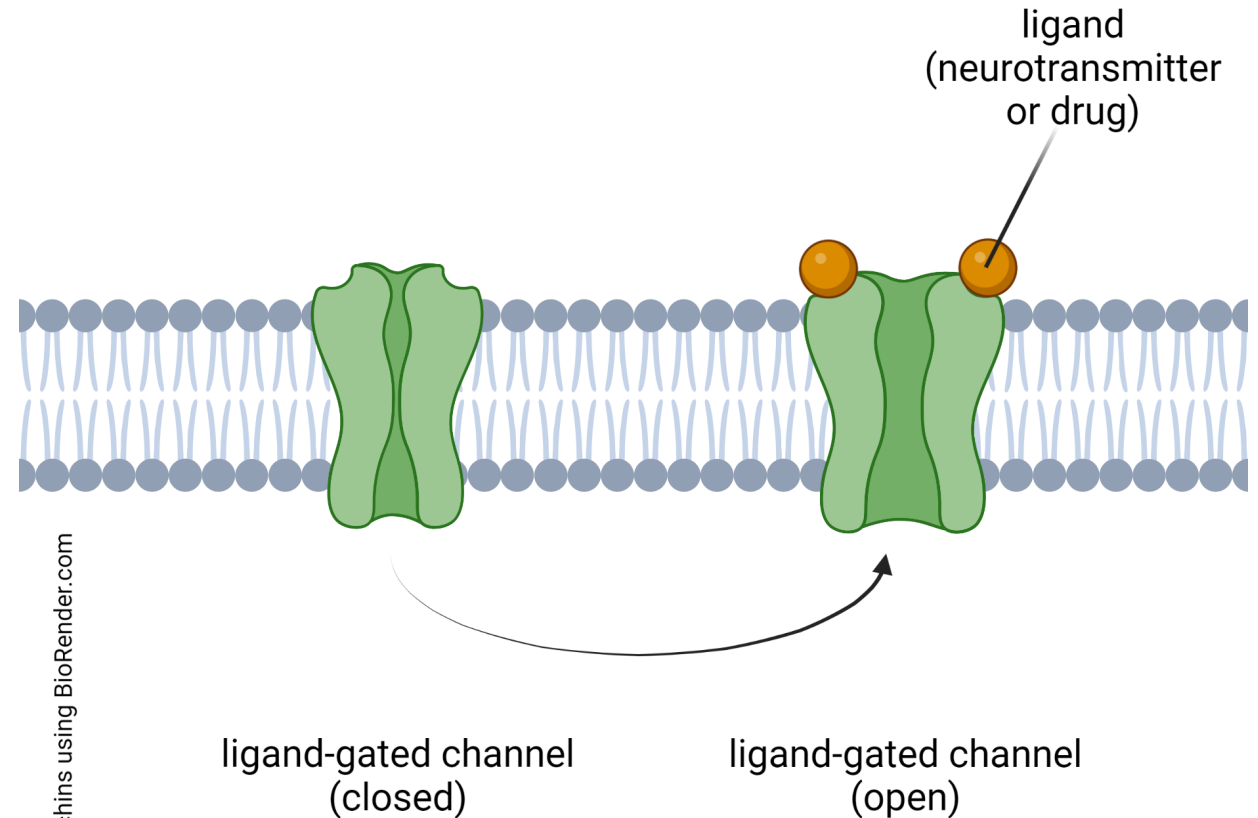
Ionotropic receptors

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

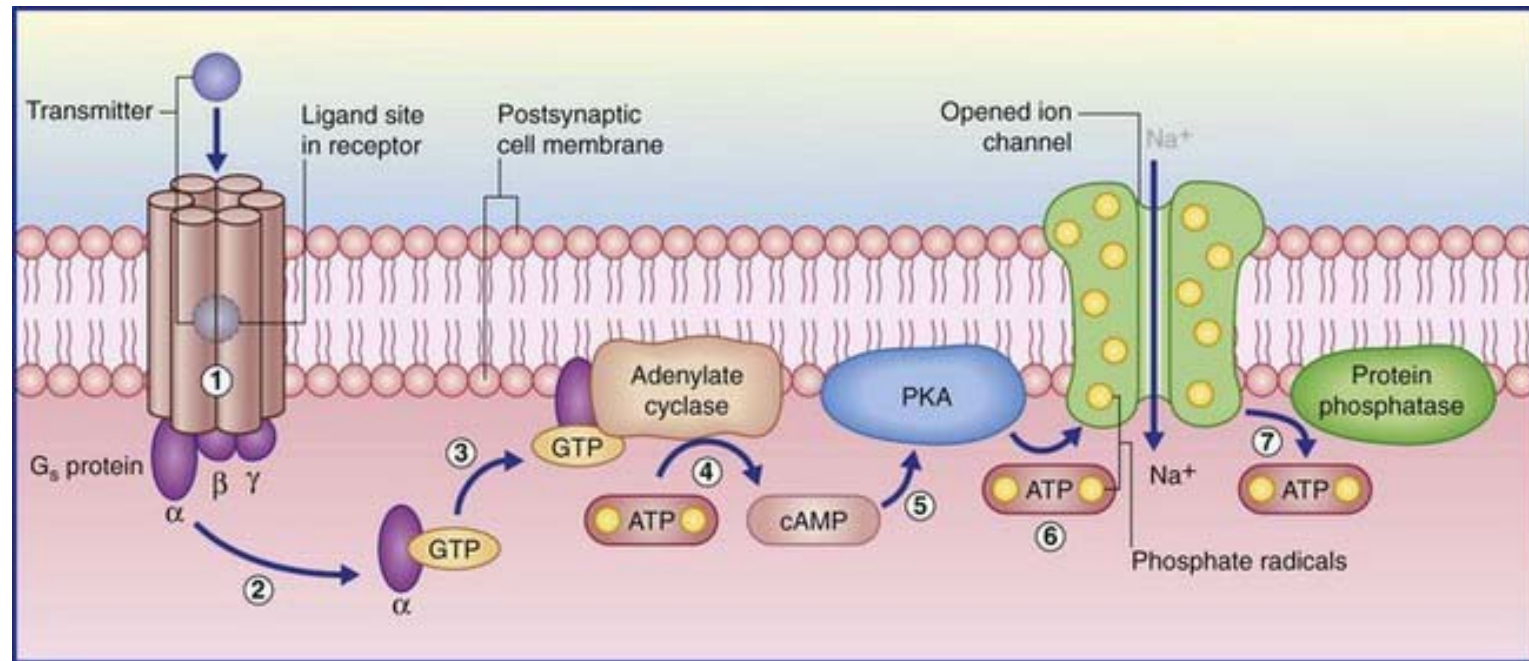
Metabotropic receptors

ligand receptor and ion channel have different types of integral proteins

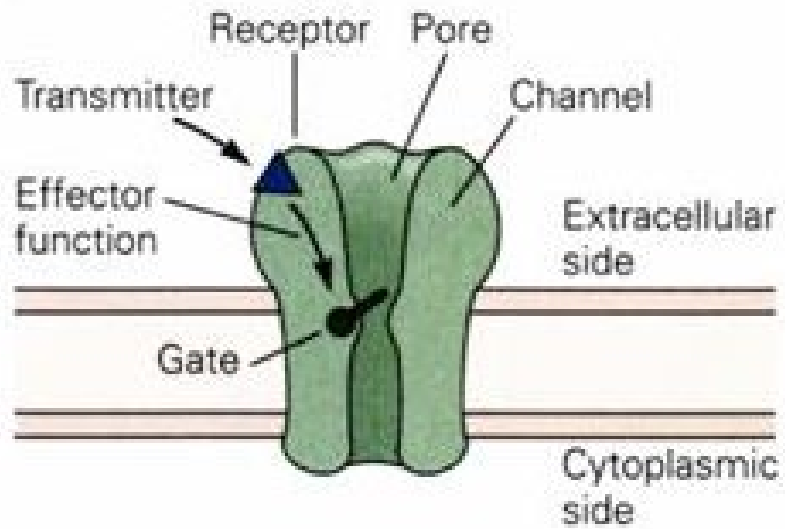
metabotropic receptors are “ligand receptors” on external face of membrane that releases “G protein” on their internal face of membrane

G protein travels to a second integral protein and this integral protein then functions as the ion channel

this is Second messenger system

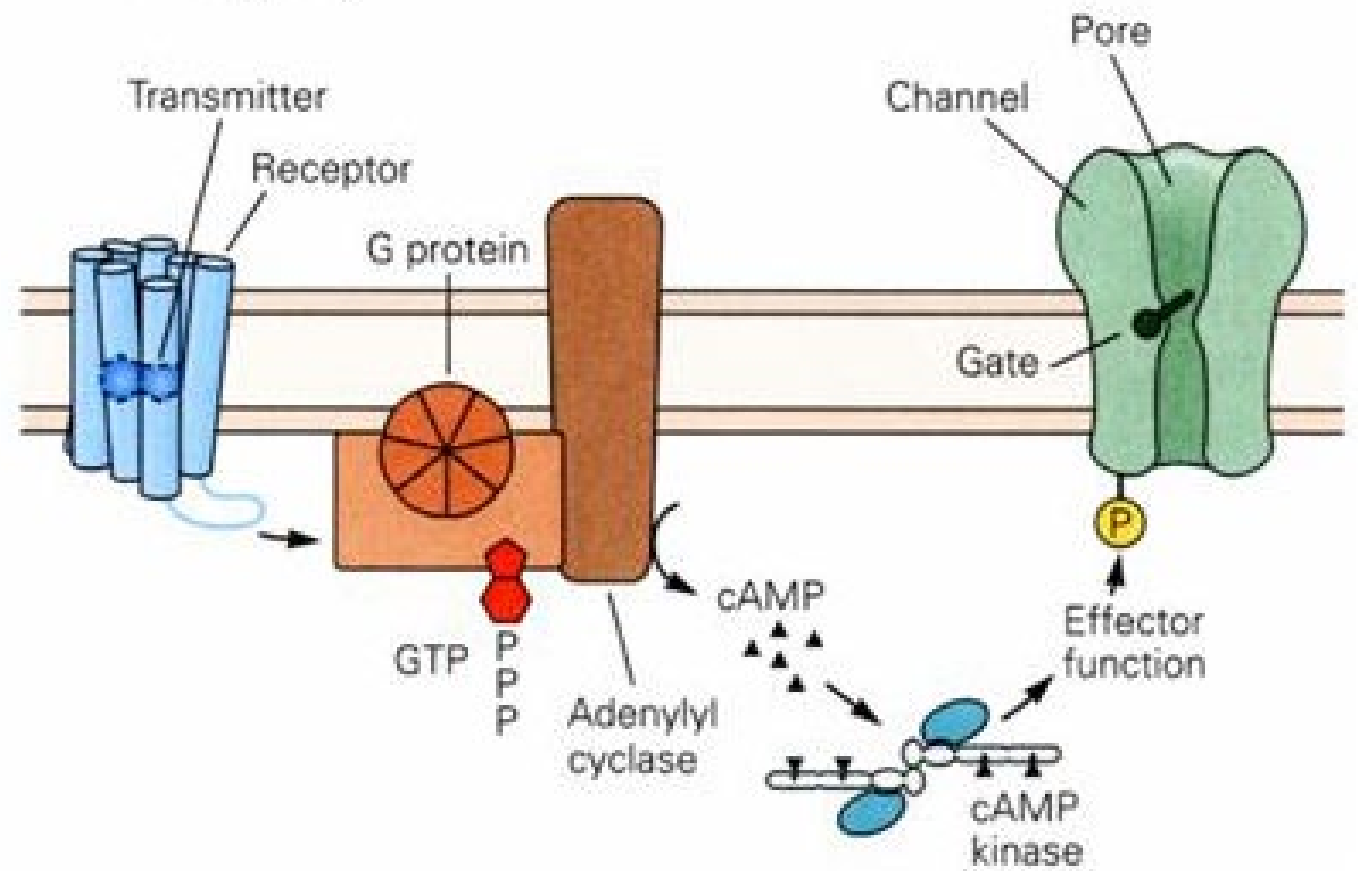


A Direct gating



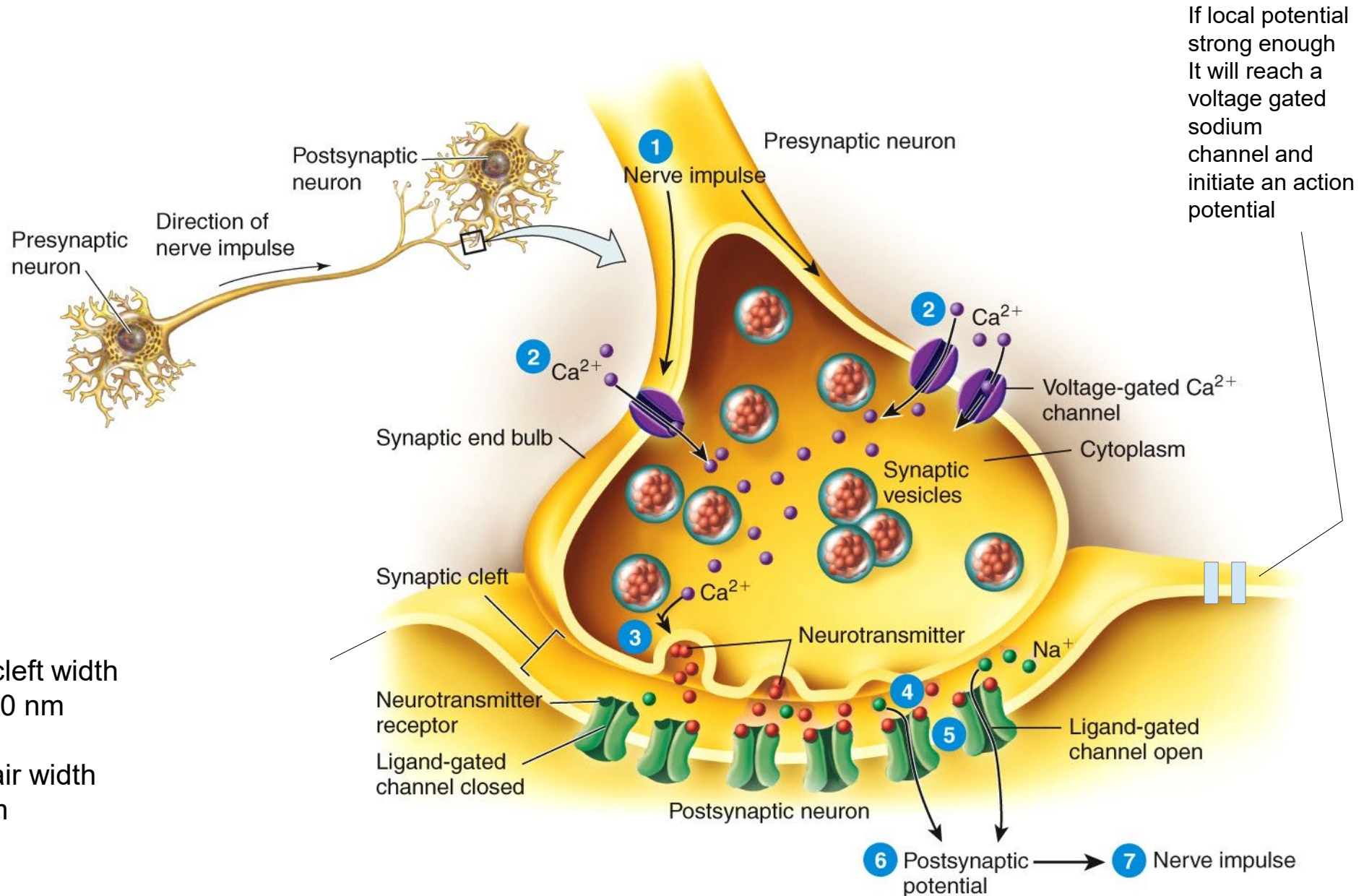
Ionotropic receptors

B Indirect gating



Metabotropic receptors

Structure of a Chemical Synapse



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?

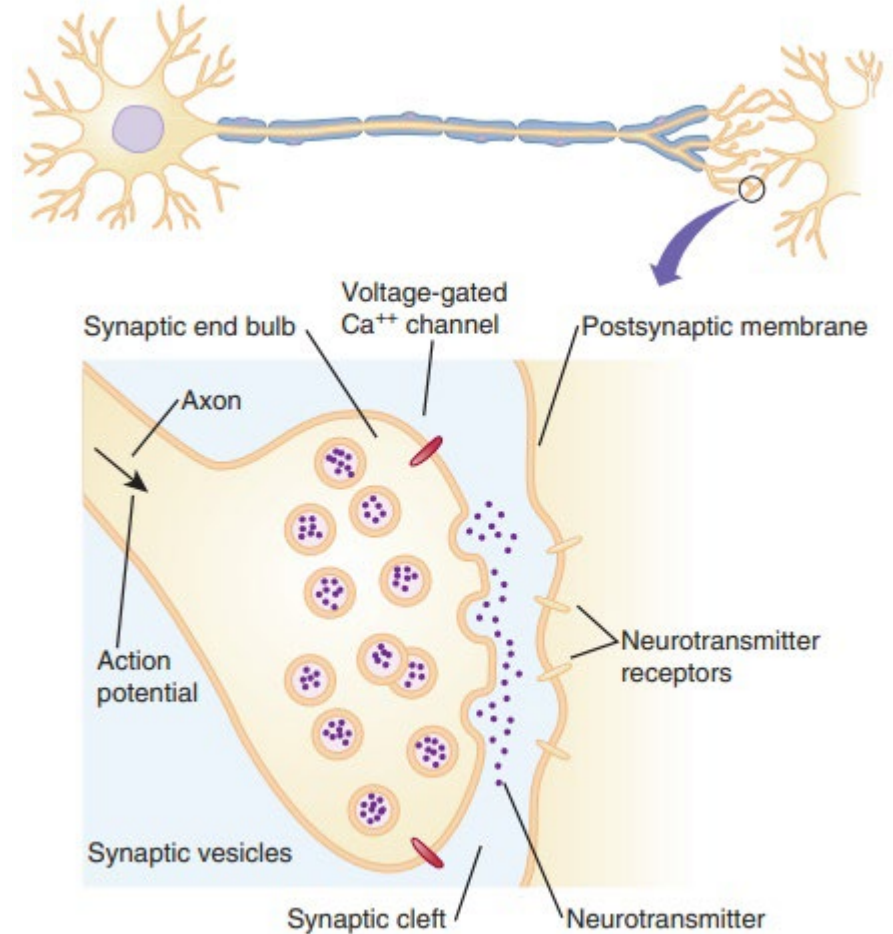


FIGURE 11-10 Chemical synapse.

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 neurotransmitter 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)

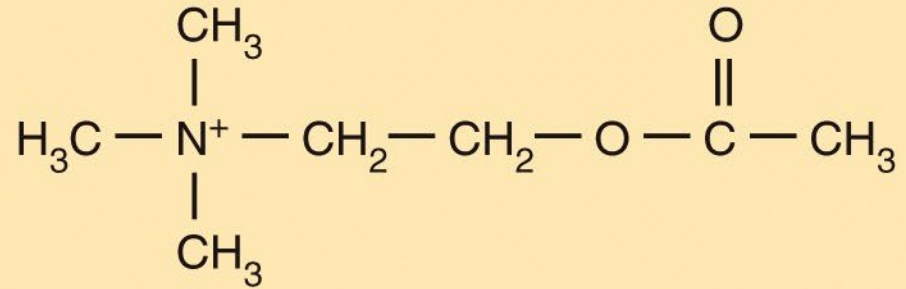
Pruines // adenosine triphosphate (ATP) / now recognized as major neurotransmitter in CNS and PNS

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 / tetrahydrocannabinol (THC) interacts with the endocannabinoid receptors

SMALL-MOLECULE NEUROTRANSMITTERS

Acetylcholine



Nitric oxide



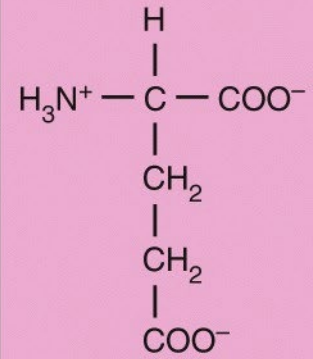
Carbon monoxide



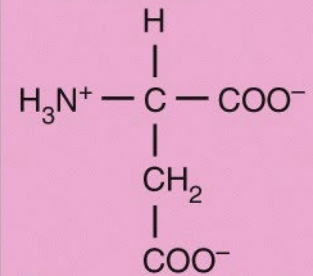
SMALL-MOLECULE NEUROTRANSMITTERS

Amino Acids

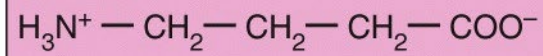
Glutamate



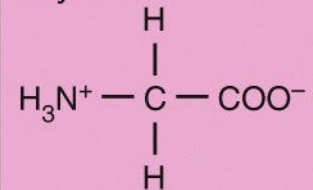
Aspartate



Gamma aminobutyric acid
(GABA)



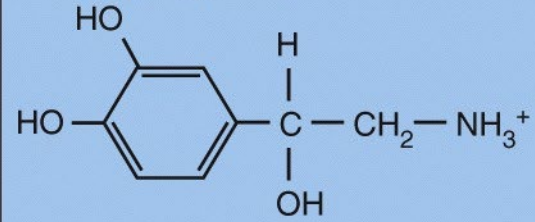
Glycine



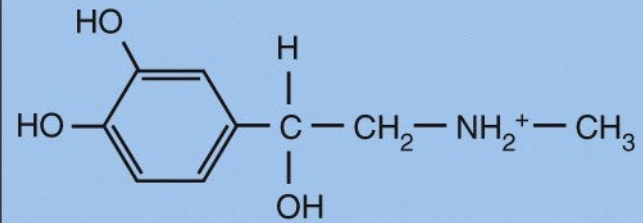
SMALL-MOLECULE NEUROTRANSMITTERS

Biogenic Amines

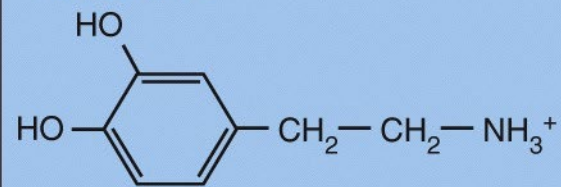
Norepinephrine



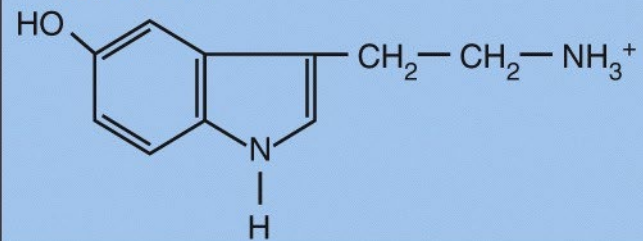
Epinephrine



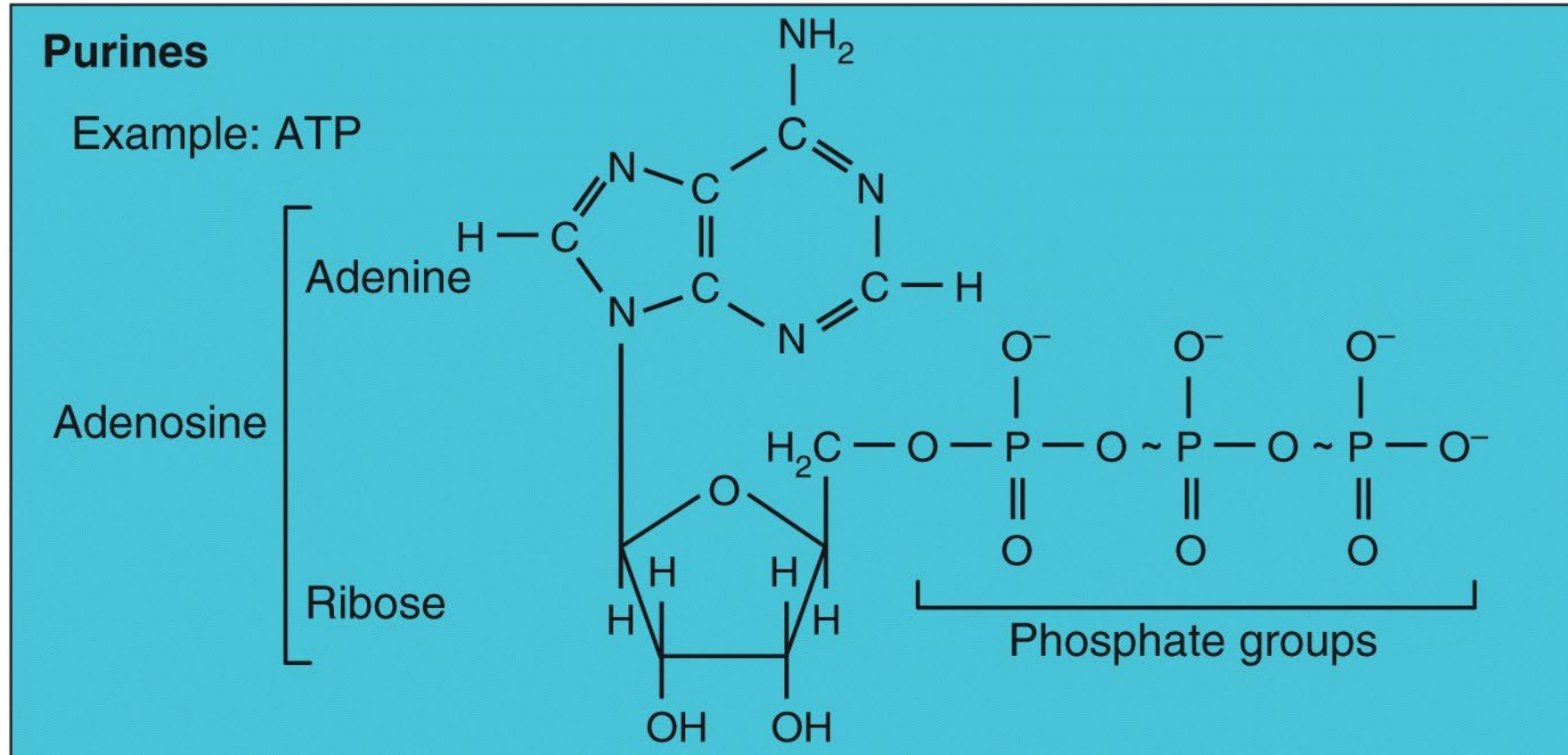
Dopamine



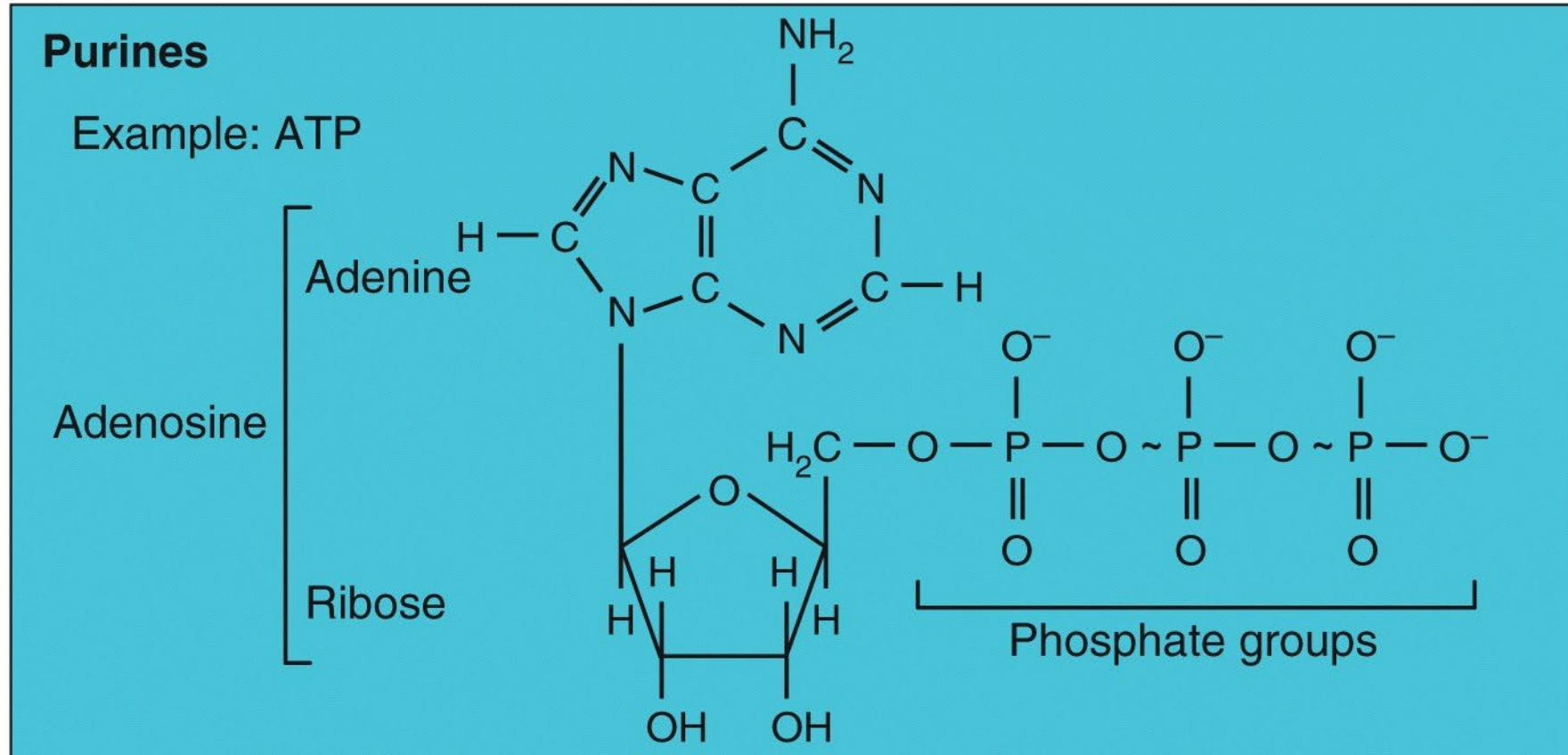
Serotonin



SMALL-MOLECULE NEUROTRANSMITTERS

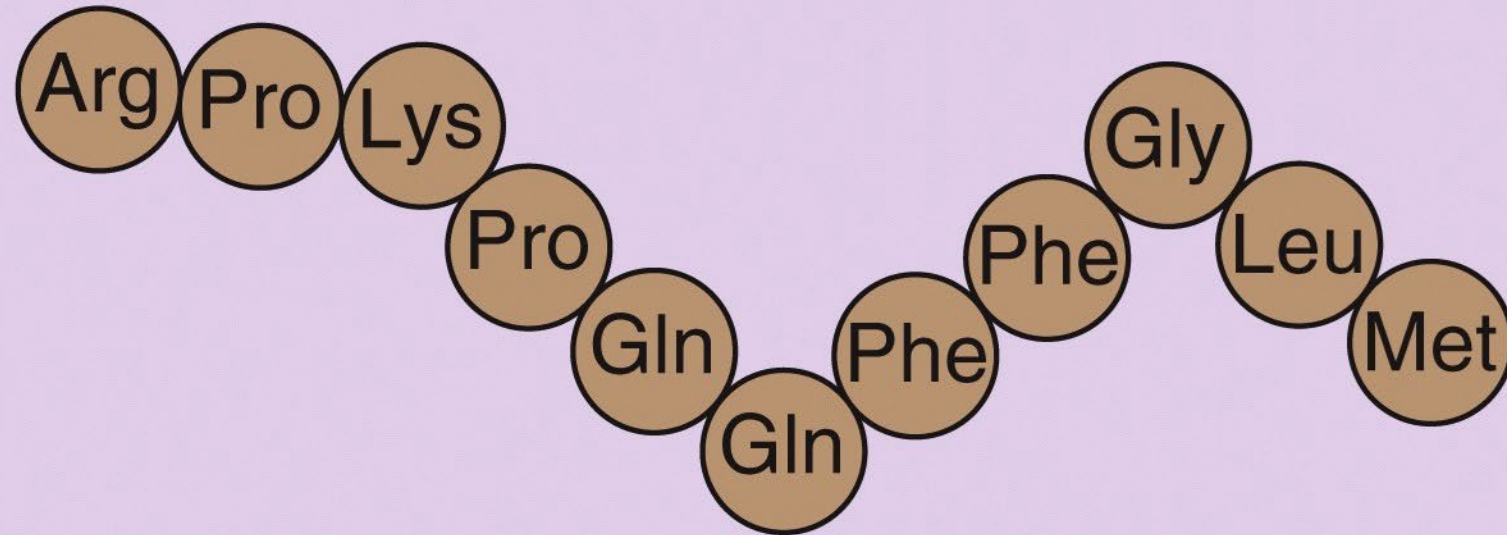


SMALL-MOLECULE NEUROTRANSMITTERS



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 important excitatory CNS – half of all CNS synapses release glutamate!

Glycine & GABA – two of the major inhibitory neurotransmitters

- GABA – very important in CNS

- Glycine – 1/2 synapses in spinal cord release glycine other 1/2 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 metabotropic 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

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

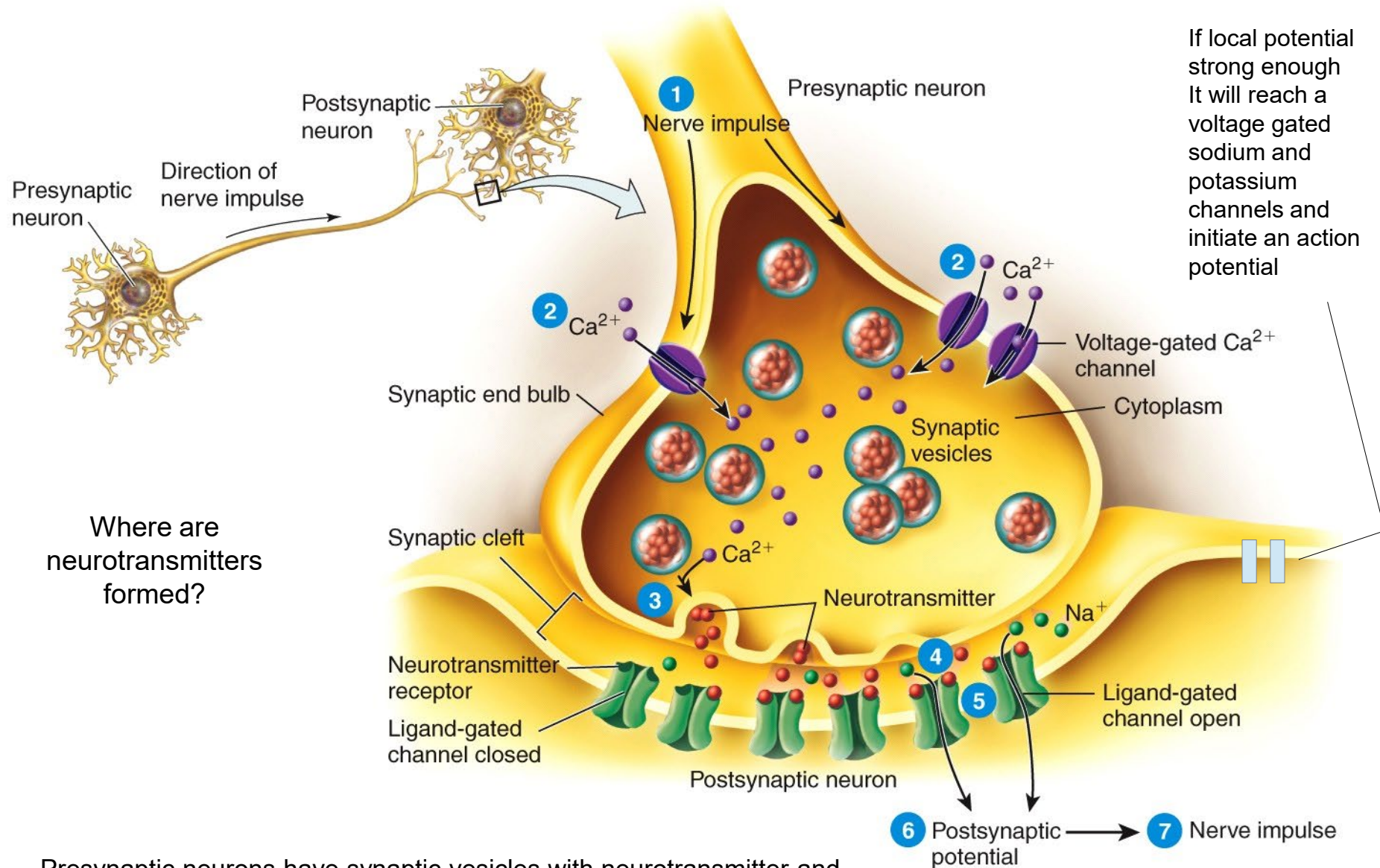
as Na^+ enters the cell it spreads out along the inside of the plasma membrane and depolarizes it producing a local potential called the postsynaptic potential

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



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

Inhibitory GABA-ergic Synapse

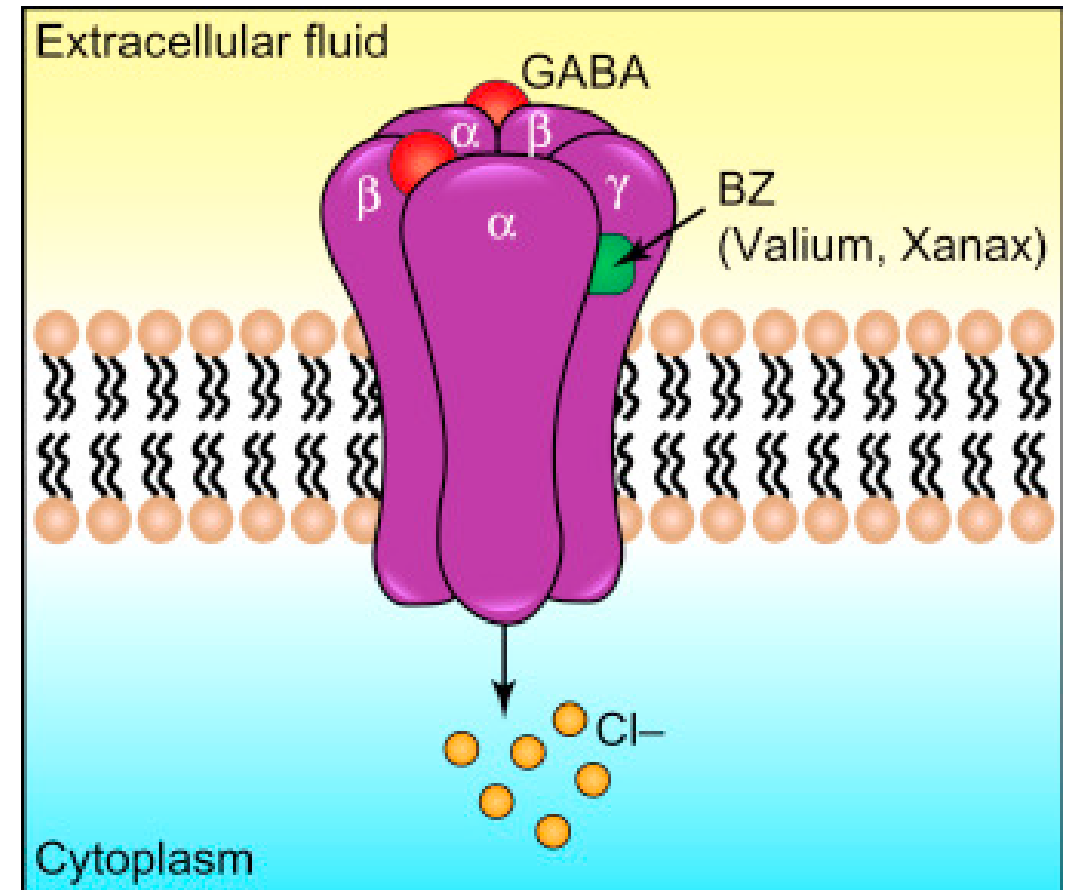
GABA-ergic synapse employs γ -aminobutyric acid as its neurotransmitter

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

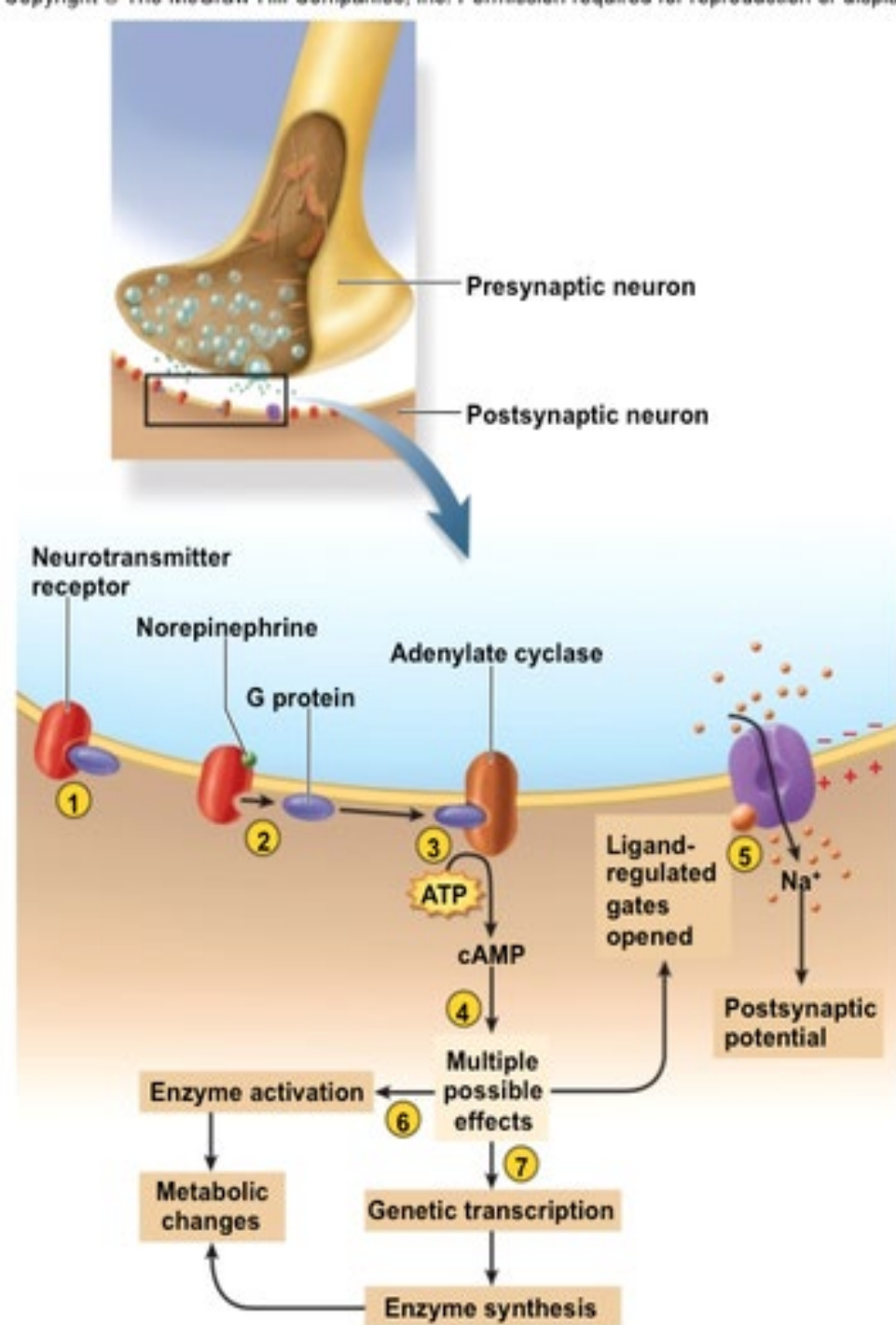
The receptor on post synaptic membrane for the adrenergic synapses is a metabotropic type receptor

Not an ion gate but a second messenger system

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

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

Adrenergic Synapse



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)

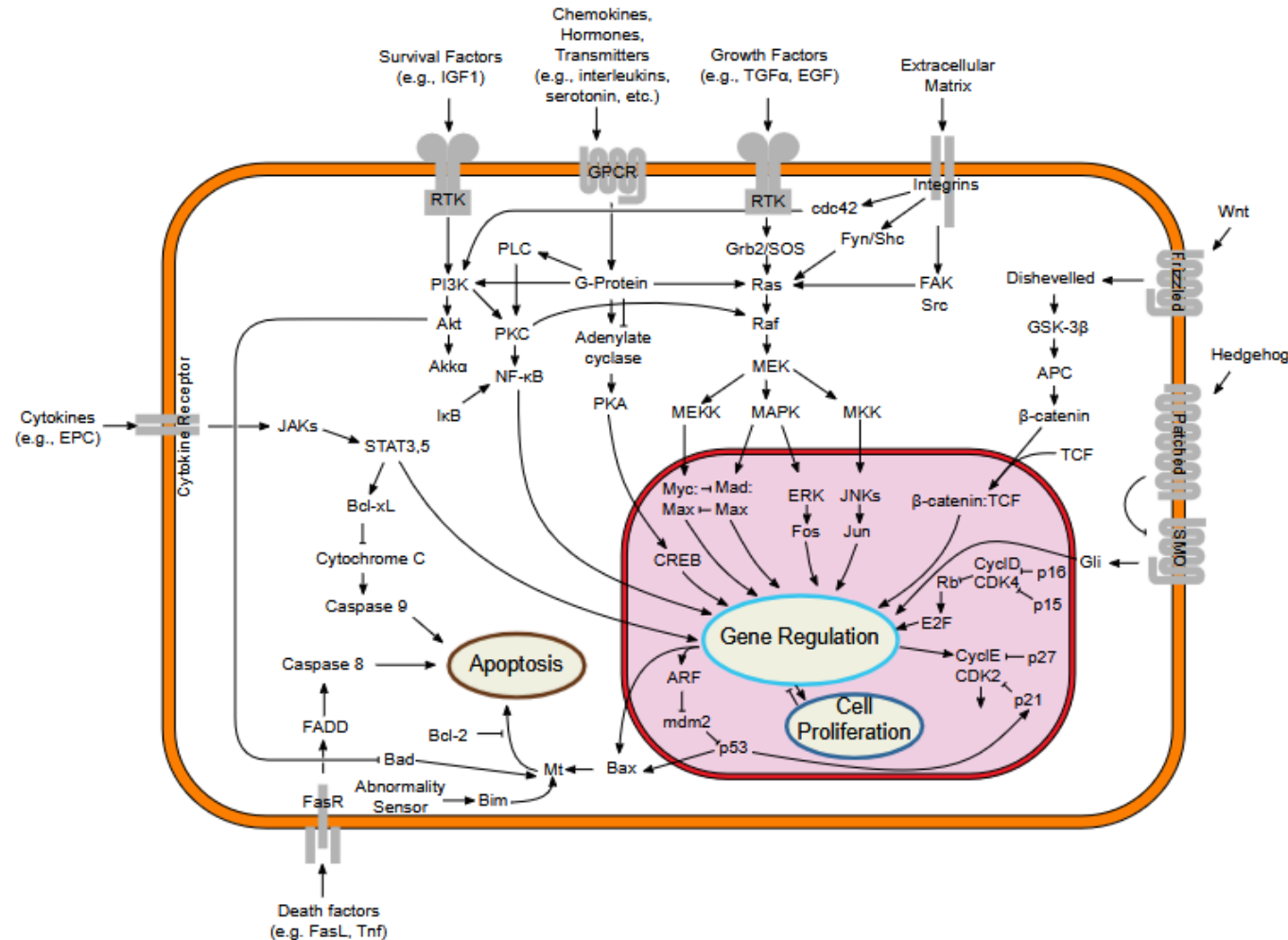
The second messenger cyclic AMP may cause many different outcomes in the cell

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**

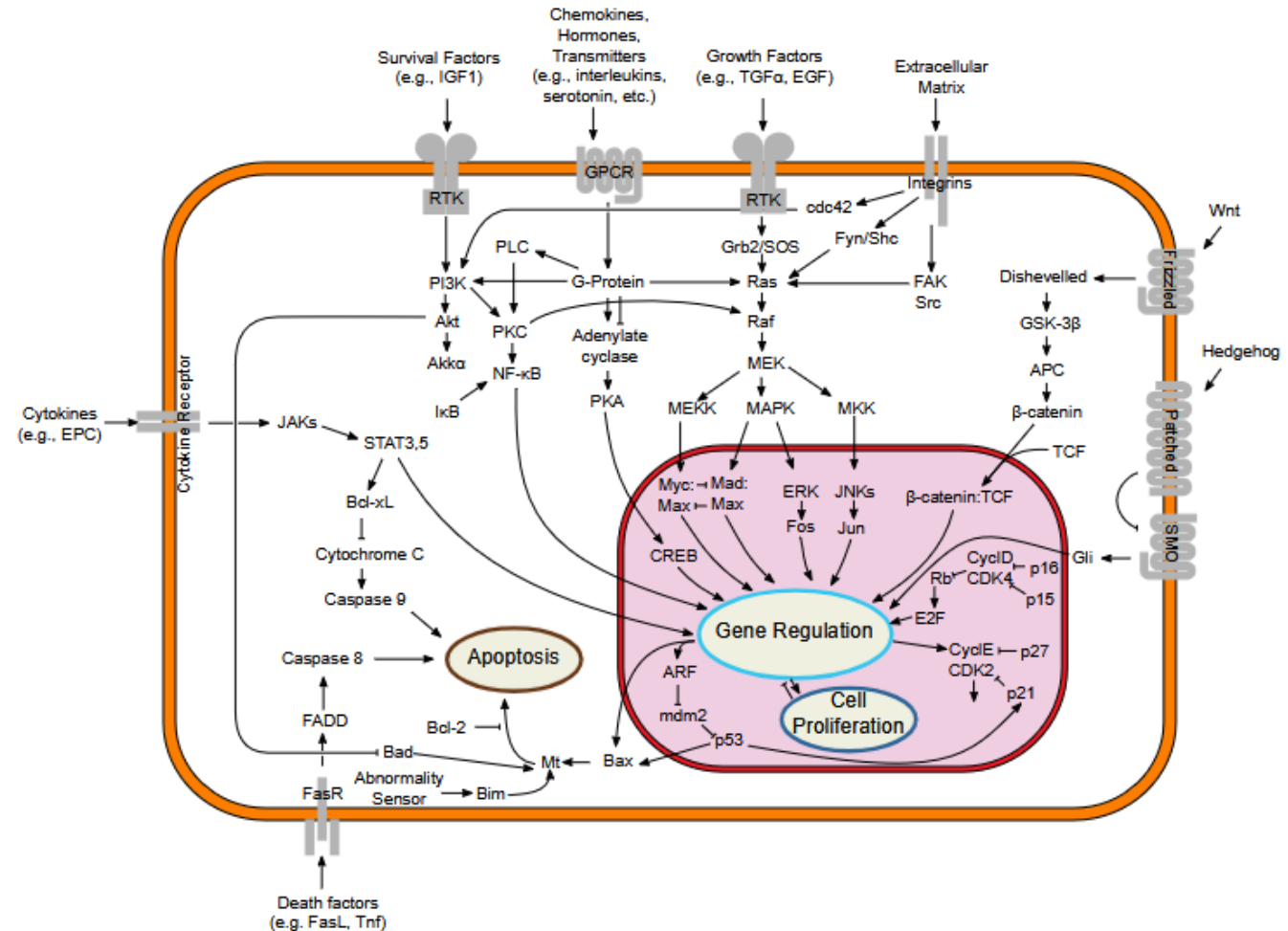
can activate preexisting **cytoplasmic enzymes** that lead to diverse metabolic changes

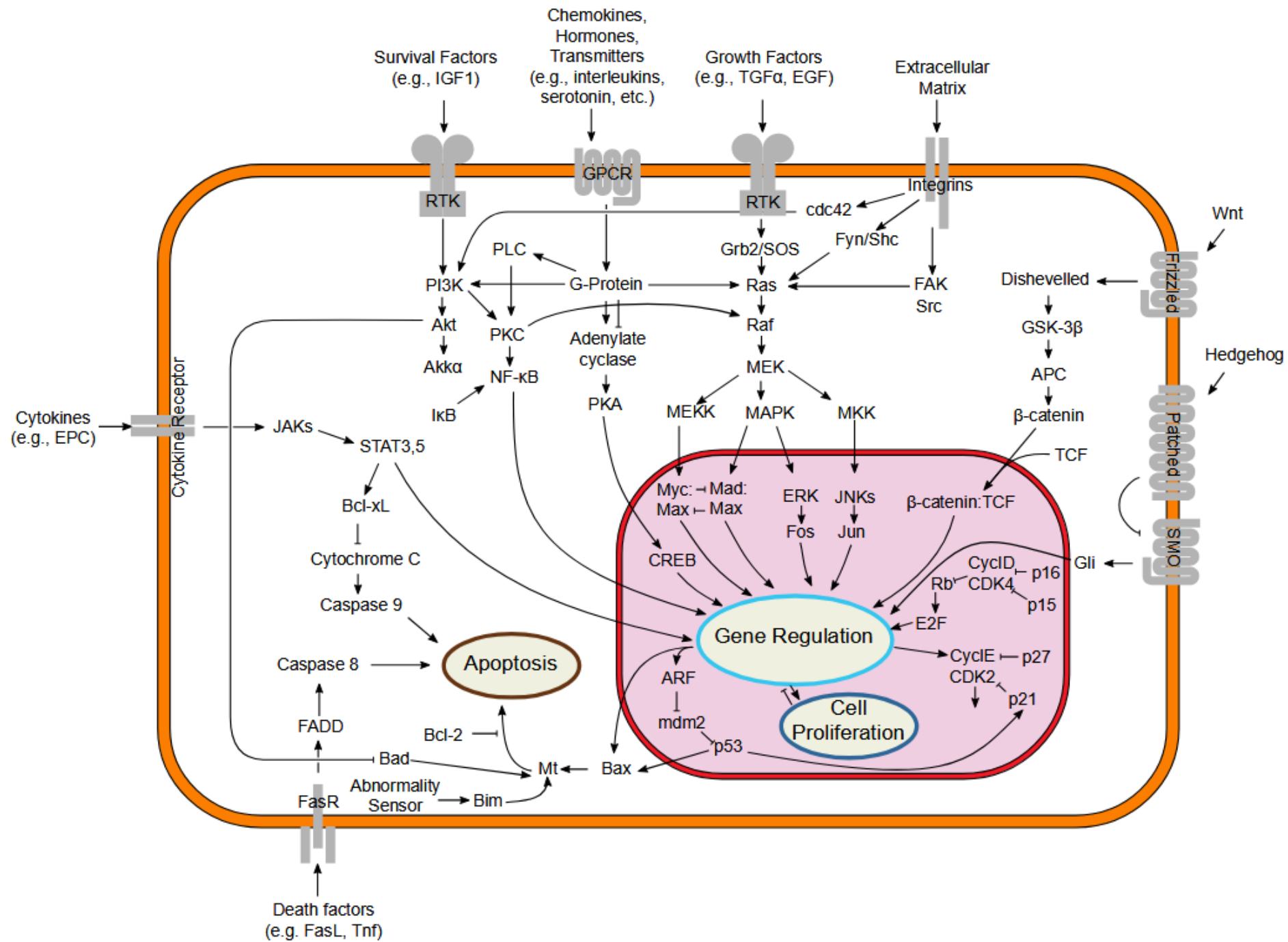
can induce **genetic transcription**, so that the cell produces new cytoplasmic enzymes that can lead to diverse metabolic effects

Signal transduction is the process by which a chemical or physical signal is transmitted through a cell as a series of molecular events. Proteins responsible for detecting stimuli are generally termed receptors, although in some cases the term sensor is used. The changes elicited by ligand binding (or signal sensing) in a receptor give rise to a biochemical cascade, which is a chain of biochemical events known as a signaling pathway.



When signaling pathways interact with one another, they form networks, which allow cellular responses to be coordinated, often by combinatorial signaling events. At the molecular level, such responses include changes in the **transcription or translation** of genes, and **post-translational** and conformational changes in proteins, as well as changes in their location. These molecular events are the basic mechanisms controlling **cell growth, proliferation, metabolism** and many other processes. In multicellular organisms, signal transduction pathways regulate **cell communication**.





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

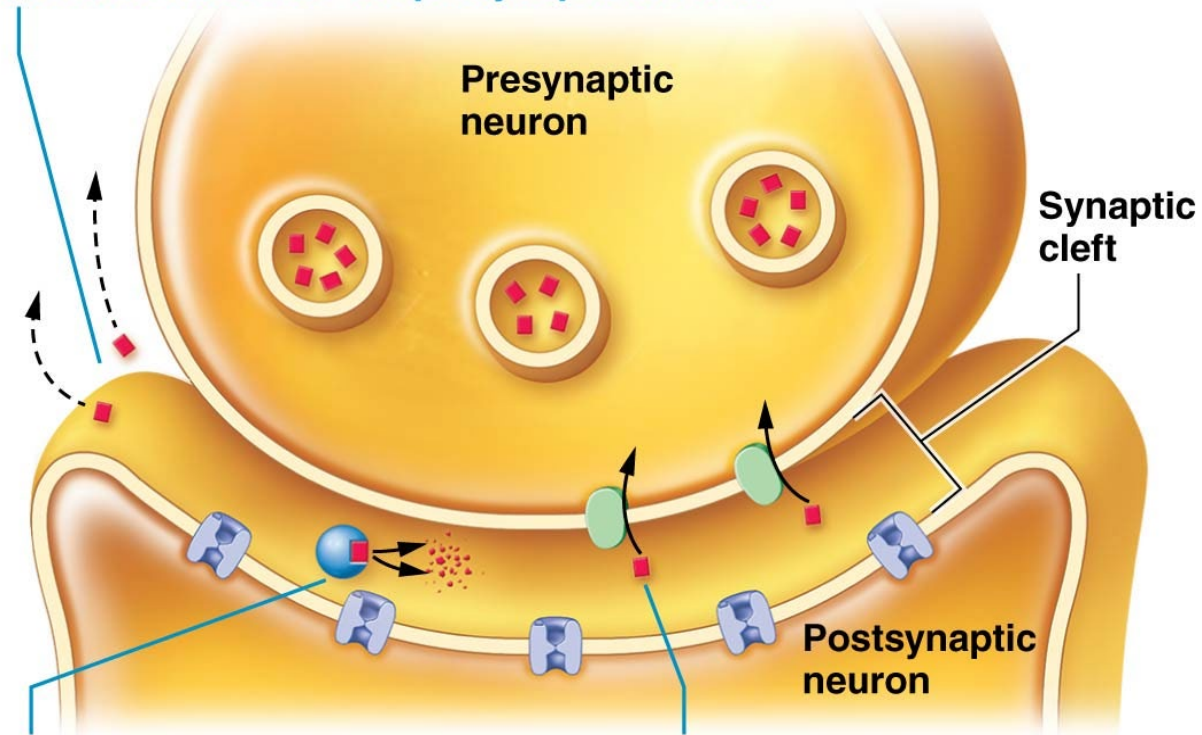
re-uptake // synaptic knob reabsorbs amino acids and monoamines by endocytosis //

degradation by enzymes // see next slide

Methods of termination of synaptic transmission.

Diffusion and Absorption

Neurotransmitters diffuse away from the synaptic cleft and are returned to the presynaptic neuron.



Degradation

Neurotransmitters are degraded by enzymatic reactions in the synaptic cleft.

Reuptake

Neurotransmitters are taken back into the presynaptic neuron.

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

catechol-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

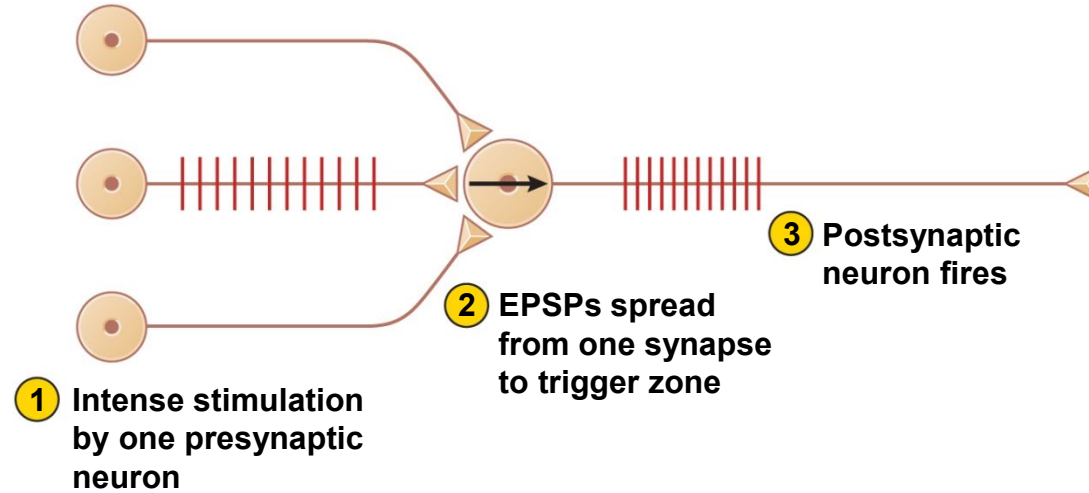
–allows EPSPs to add up over time to a threshold voltage that triggers an action potential

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

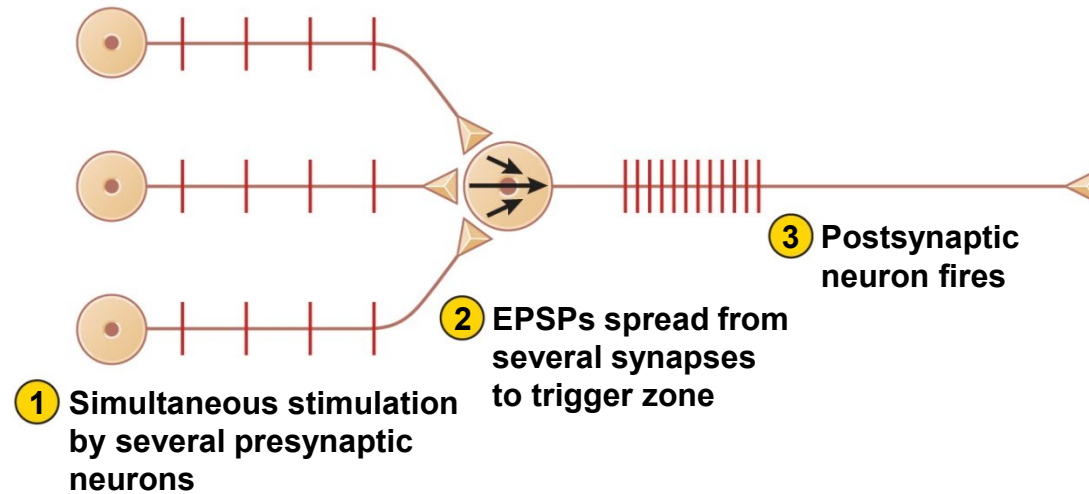
–several synapses admit enough Na^+ to reach threshold

–presynaptic neurons cooperate to induce the postsynaptic neuron to fire

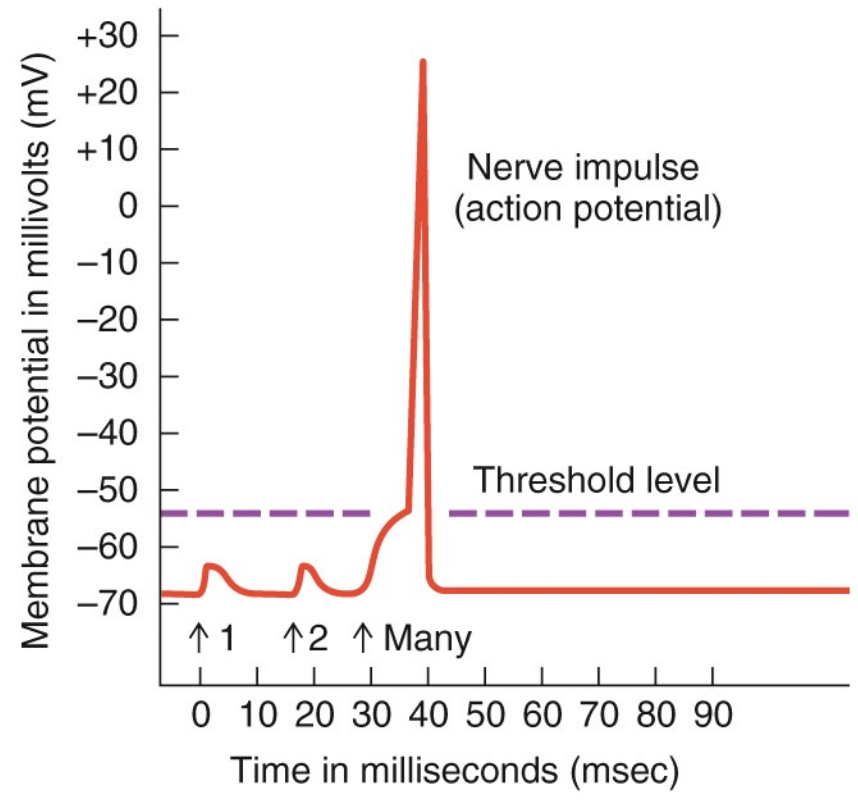
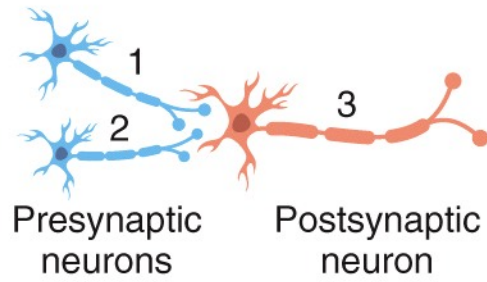
Temporal and Spatial Summation



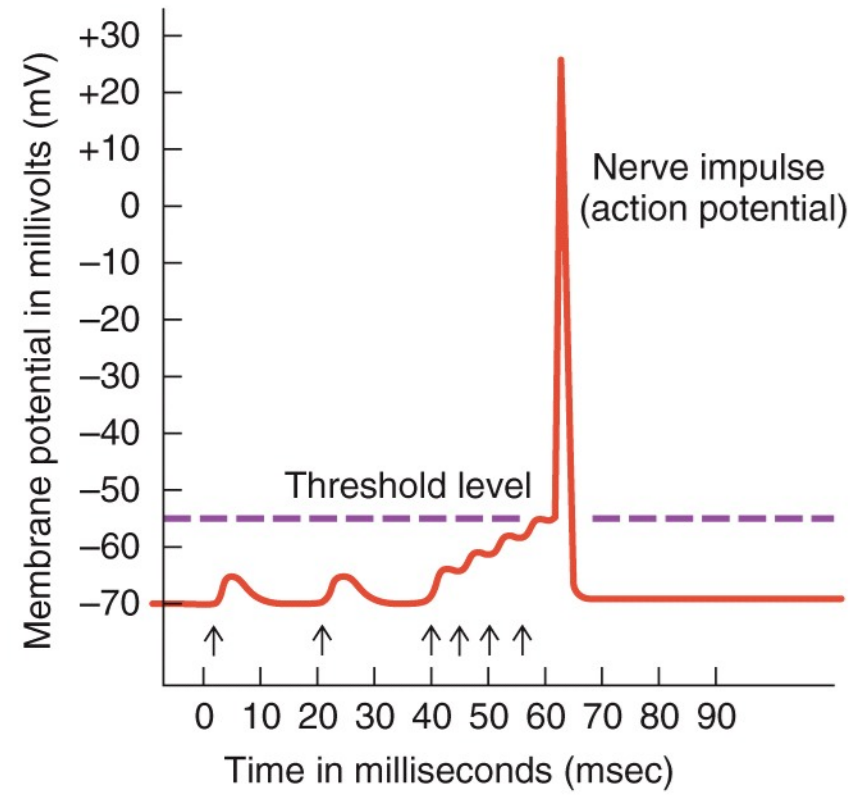
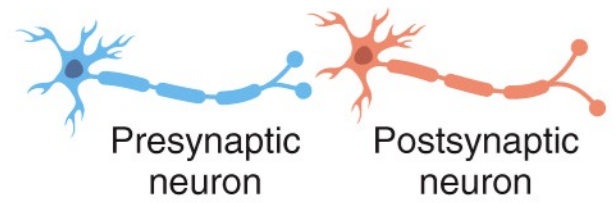
(a) Temporal summation



(b) Spatial summation



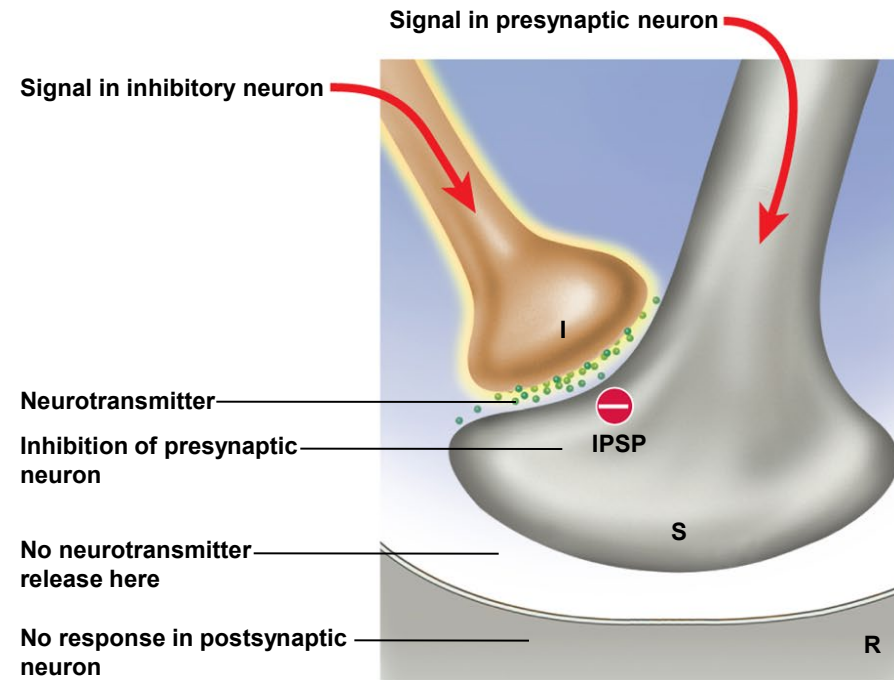
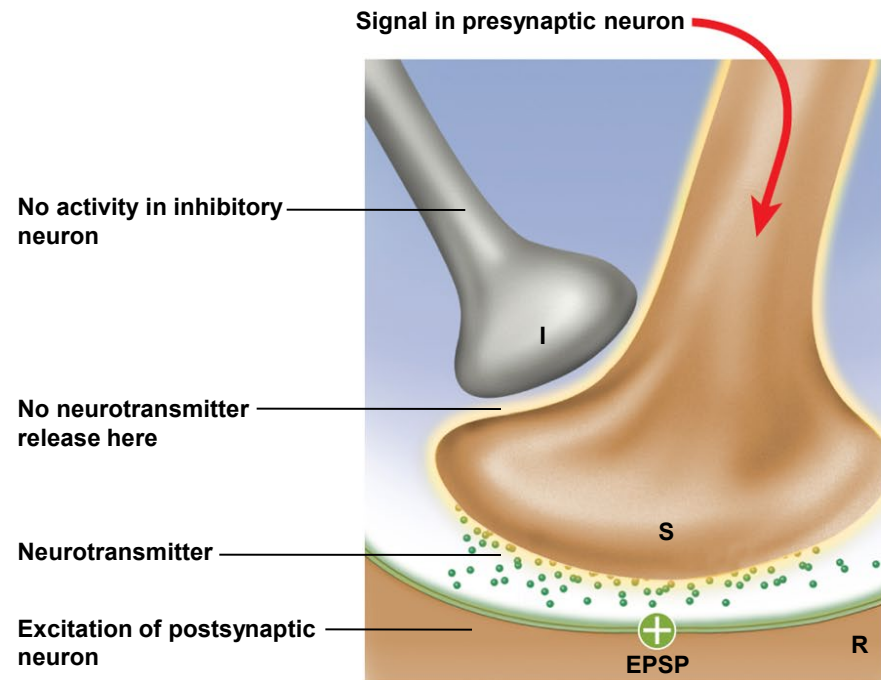
(a) Spatial summation



(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

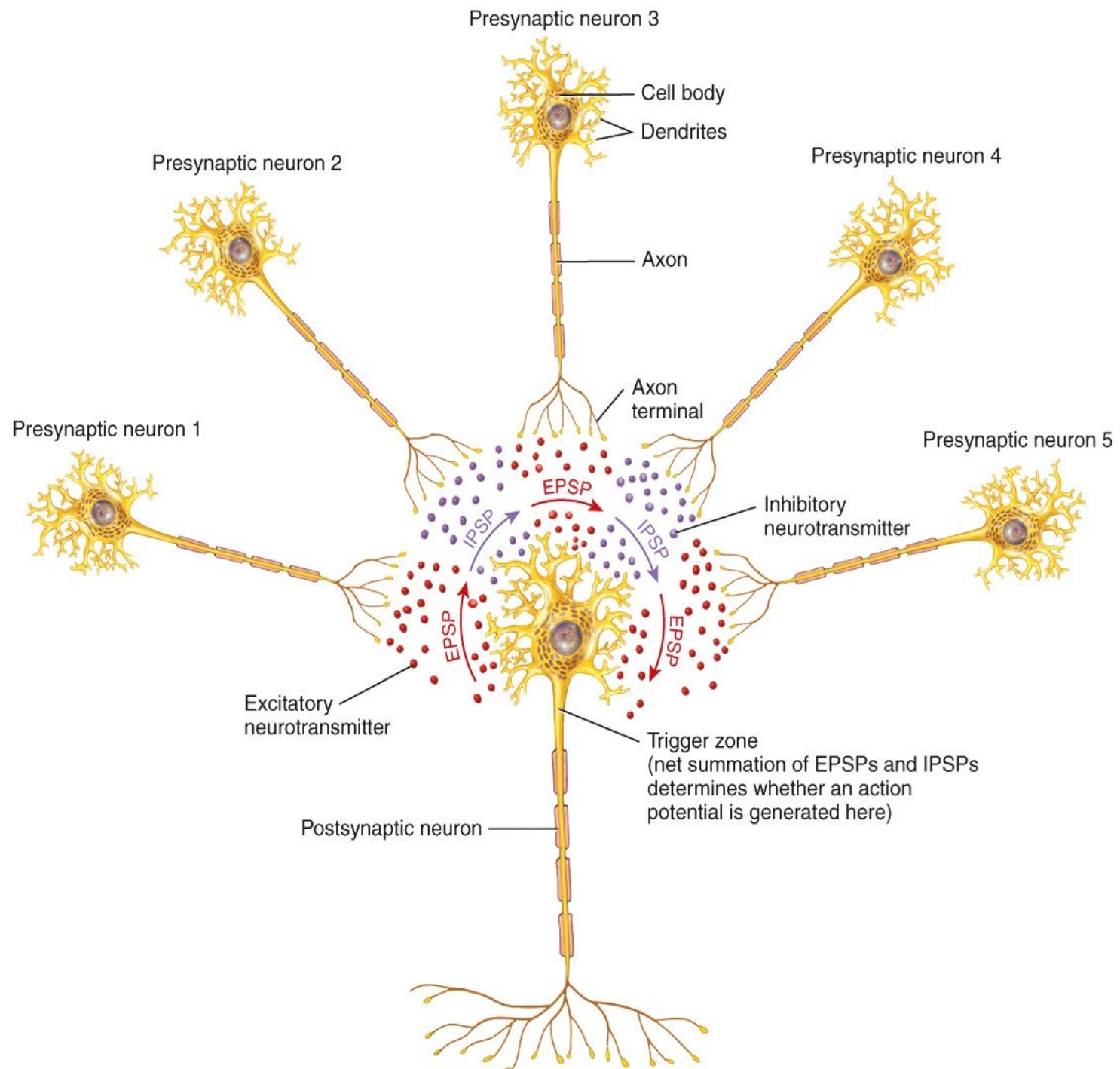
Glycine and GABA produce IPSPs /// move potential away from threshold /// inhibitory

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

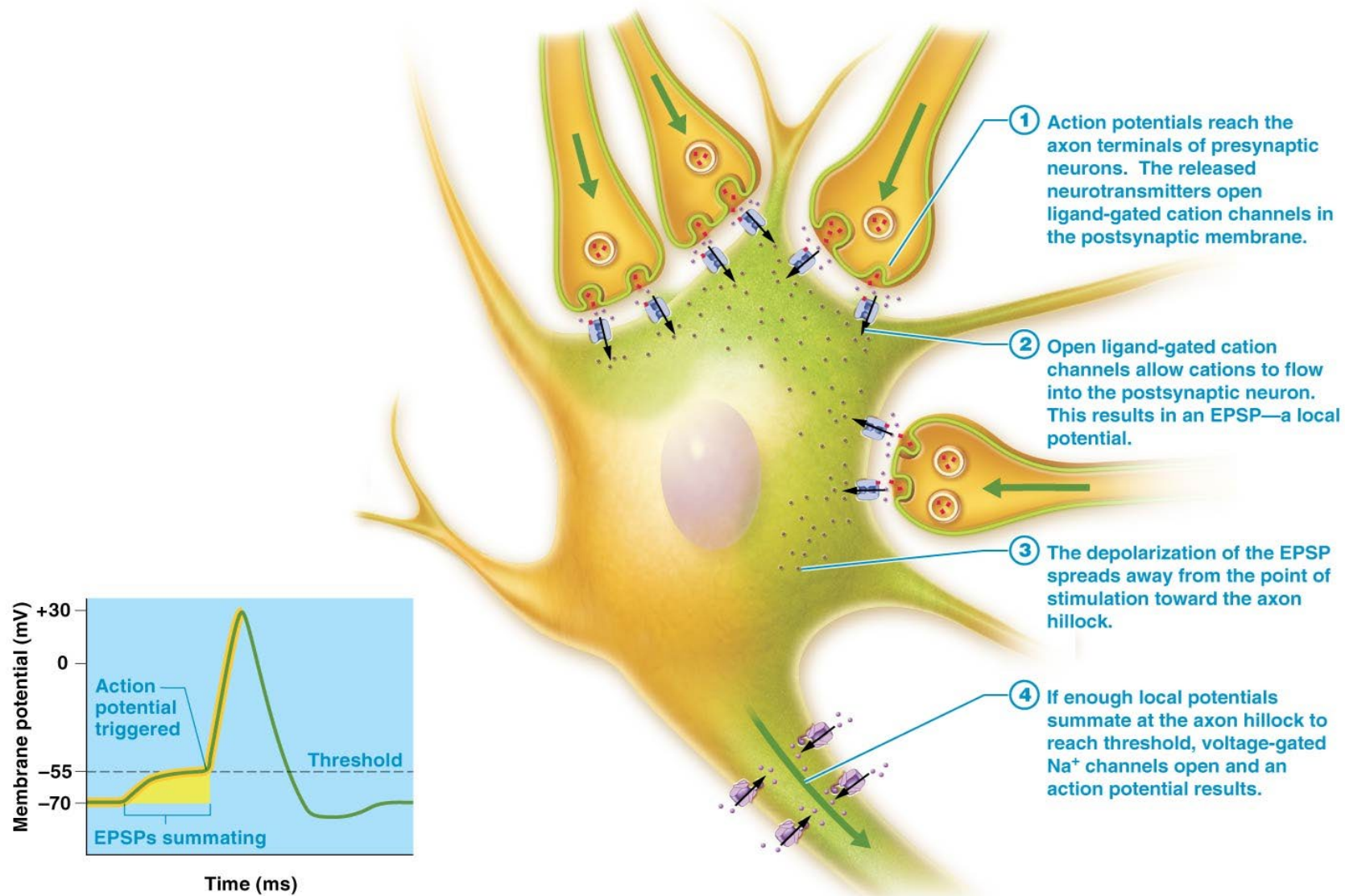
- depending on the type of receptors on the target cell

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

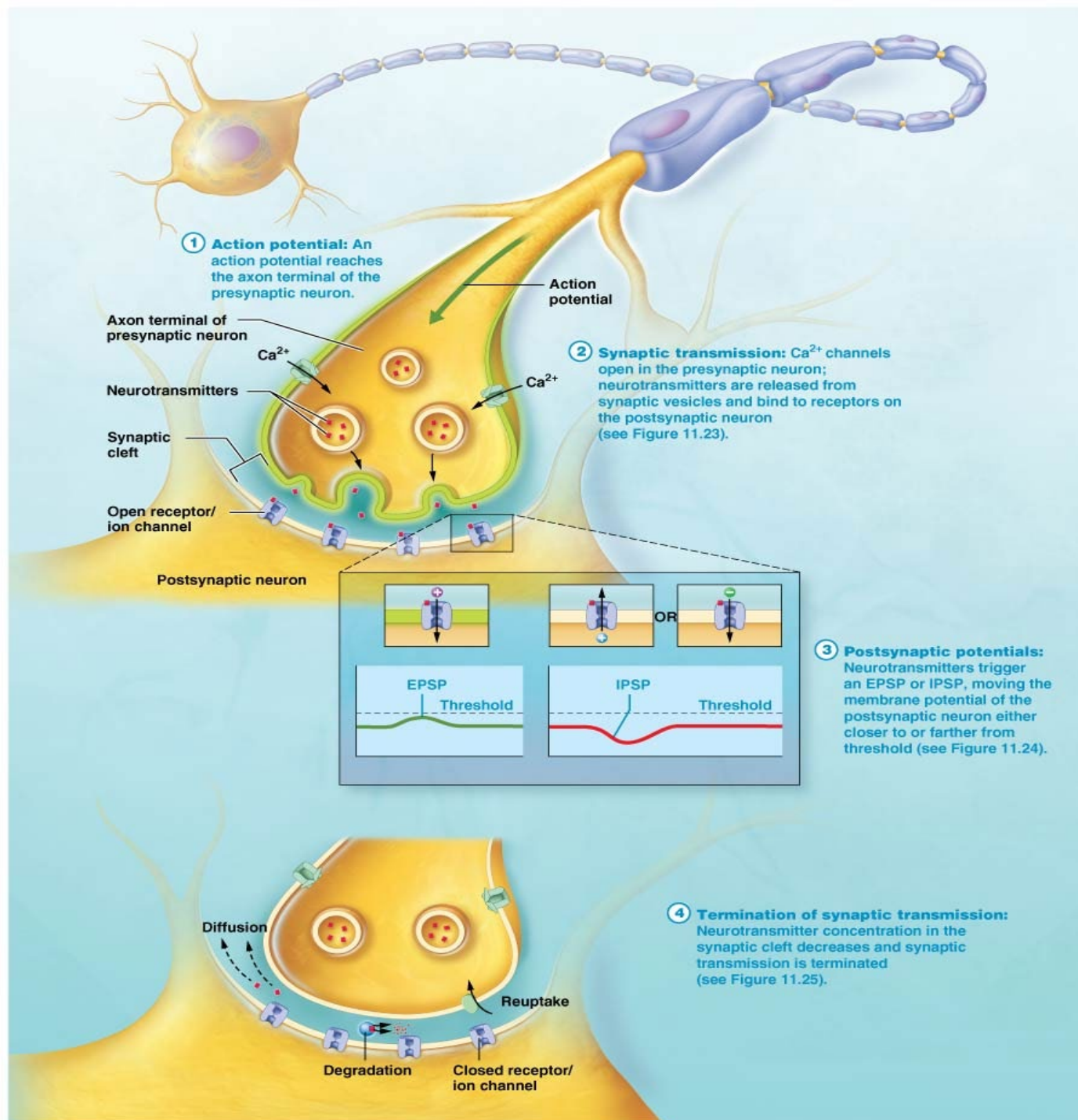
- Note: ACh excites skeletal muscle (inotropic receptor), but inhibits cardiac muscle (metabotropic receptor) due to the different type of receptors**



Local potentials summing and leads to an action potential.

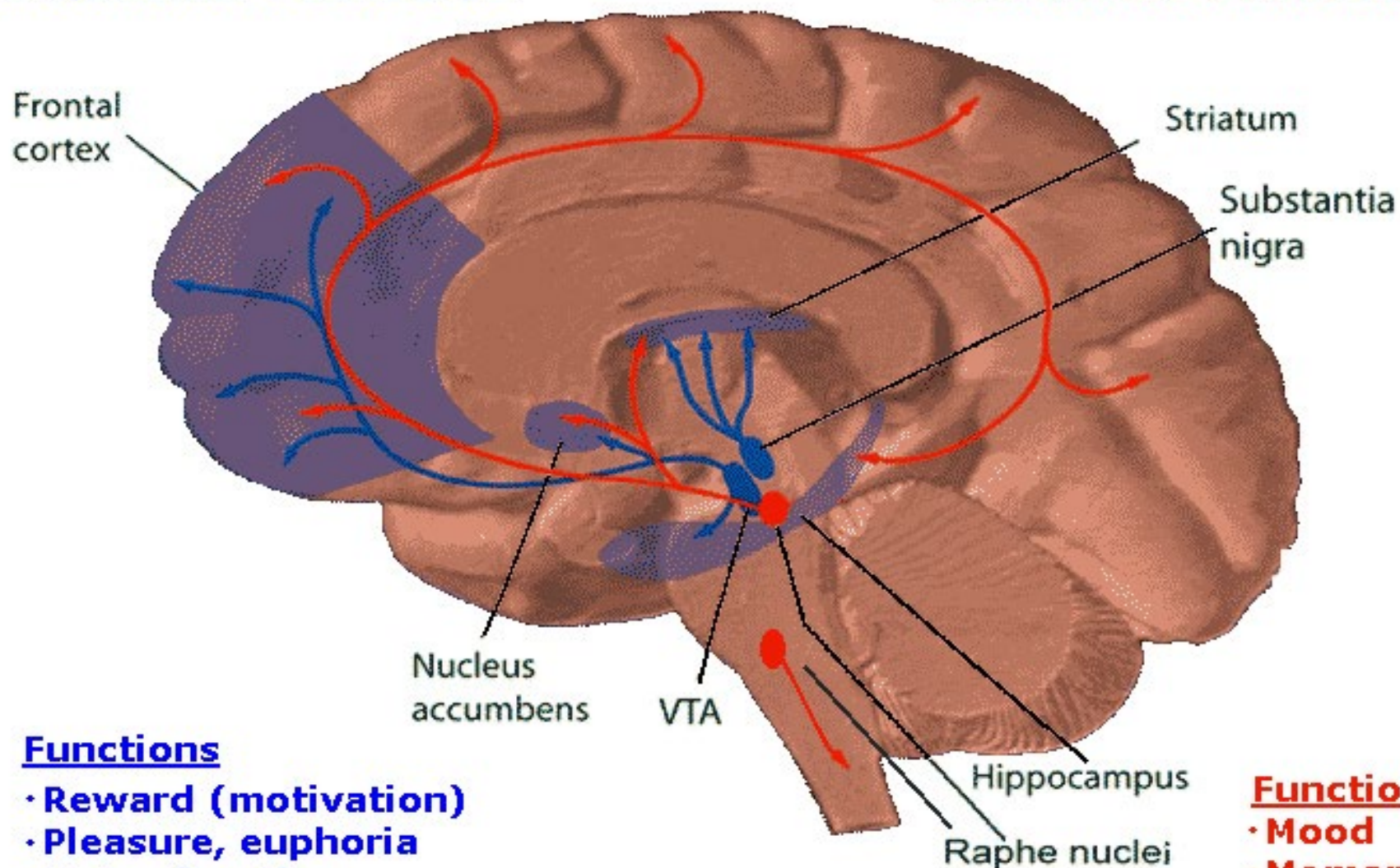


The Big Picture of Chemical Synaptic Transmission



Dopamine Pathways

Serotonin Pathways



Functions

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

Functions

- Mood
- Memory processing
- Sleep
- Cognition

What is the difference between dopamine and serotonin?

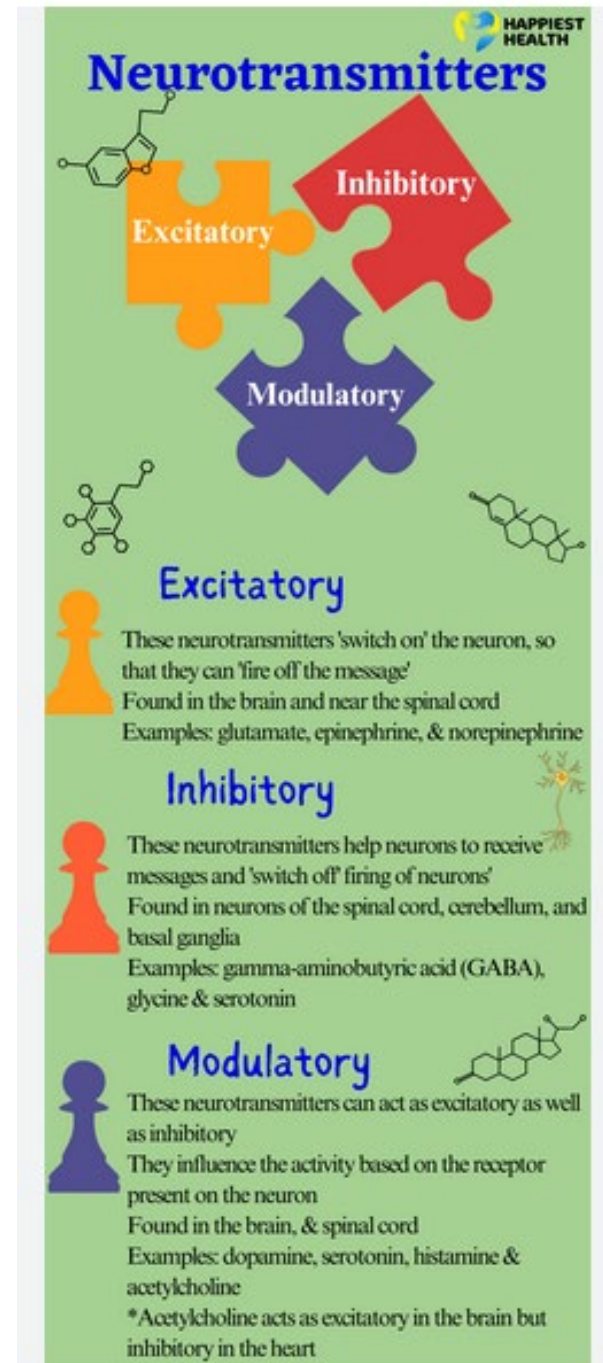
The brain says I like dopamine and I want more.
Dopamine is pleasure.

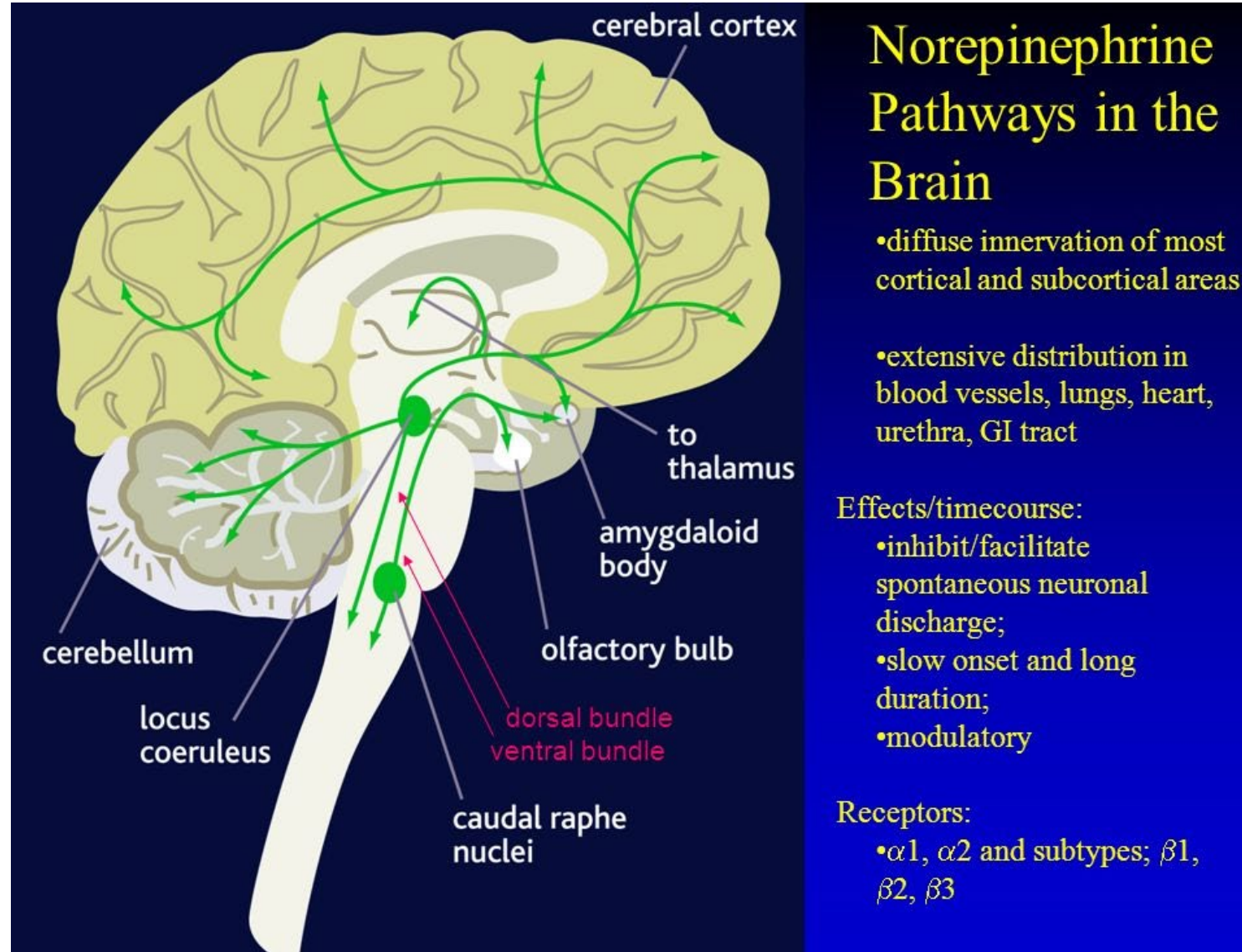
The brain says I like serotonin, but I don't want more.
Serotonin is happiness.

Pleasure and happiness are not the same.

Pleasure is achieved by taking something, like a substance. It is receiving something. You may get pleasure from gambling if you win.

Happiness is achieved by giving something. You may achieve happiness by attending helping someone or going to a birthday party.





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.

SEROTONIN

TOO LITTLE

Sadness
Fatigue
Suicidal thoughts
Anxiety
Overeating
Insomnia
Increased pain
sensation



Happiness
Contentment
Relaxed

TOO MUCH

Irritability
Agitation
Restlessness
Tremors
Muscle spasms
Rapid heartbeat
High blood pressure
Sweating

Neurotransmitters

```
graph TD; A[Neurotransmitters] --> B[Inhibitory]; A --> C[Excitatory]; B --- B_list["GABA<br/>Serotonin<br/>Glycine<br/>Taurine<br/>Dopamine<br/>Agmatine"]; C --- C_list["Glutamate<br/>Epinephrine<br/>Histamine<br/>Aspartic Acid<br/>Dopamine<br/>Glycine<br/>Norepinephrine<br/>Phenylethylamine"];
```

Inhibitory

GABA
Serotonin
Glycine
Taurine
Dopamine
Agmatine

Excitatory

Glutamate
Epinephrine
Histamine
Aspartic Acid
Dopamine
Glycine
Norepinephrine
Phenylethylamine

Serotonin (5-HT) primarily acts as an **inhibitory neurotransmitter** within the central nervous system, helping to regulate mood, sleep, appetite, and pain by balancing excessive excitatory signals. While often classified as inhibitory, it can exert both excitatory and inhibitory responses depending on the specific receptor subtype (G-protein coupled receptors or ligand-gated ion channels). [Cleveland Clinic +3](#)

- **Inhibitory Function:** It is essential for curbing excessive nervous system activity, which helps regulate mood and anxiety.
- **Action Mechanism:** Serotonin acts on various receptors to cause either excitatory or inhibitory postsynaptic potentials.
- **Key Regulation:** It modulates excitatory and inhibitory inputs, frequently regulating GABAergic (inhibitory) neurotransmission.
- **Balance:** Serotonin works in conjunction with excitatory neurotransmitters to stabilize brain activity. [National Institutes of Health \(.gov\) +3](#)

In summary, while widely known for its inhibitory role in regulating mood and behavior, serotonin's effects are highly receptor-dependent. [National Institutes of Health \(.gov\)](#)

This is for informational purposes only. For medical advice or diagnosis, consult a professional. AI responses include mistakes. [Learn more](#)

Negative feedback

NEUROTRANSMITTERS

ADRENALINE fight or flight

produced in stressful situations. Increases heart rate and blood flow, leading to physical boost and heightened awareness.

GABA calming

Calms firing nerves in the central nervous system. High levels improve focus, low levels cause anxiety. Also contributes to motor control and vision.

NORADRENALINE concentration

affects attention and responding actions in the brain. Contracts blood vessels, increasing blood flow.

ACETYLCHOLINE learning

Involved in thought, learning and memory. Activates muscle action in the body. Also associated with attention and awakening.

DOPAMINE pleasure

feelings of pleasure, also addiction, movement and motivation. People repeat behaviors that lead to dopamine release.

GLUTAMATE memory

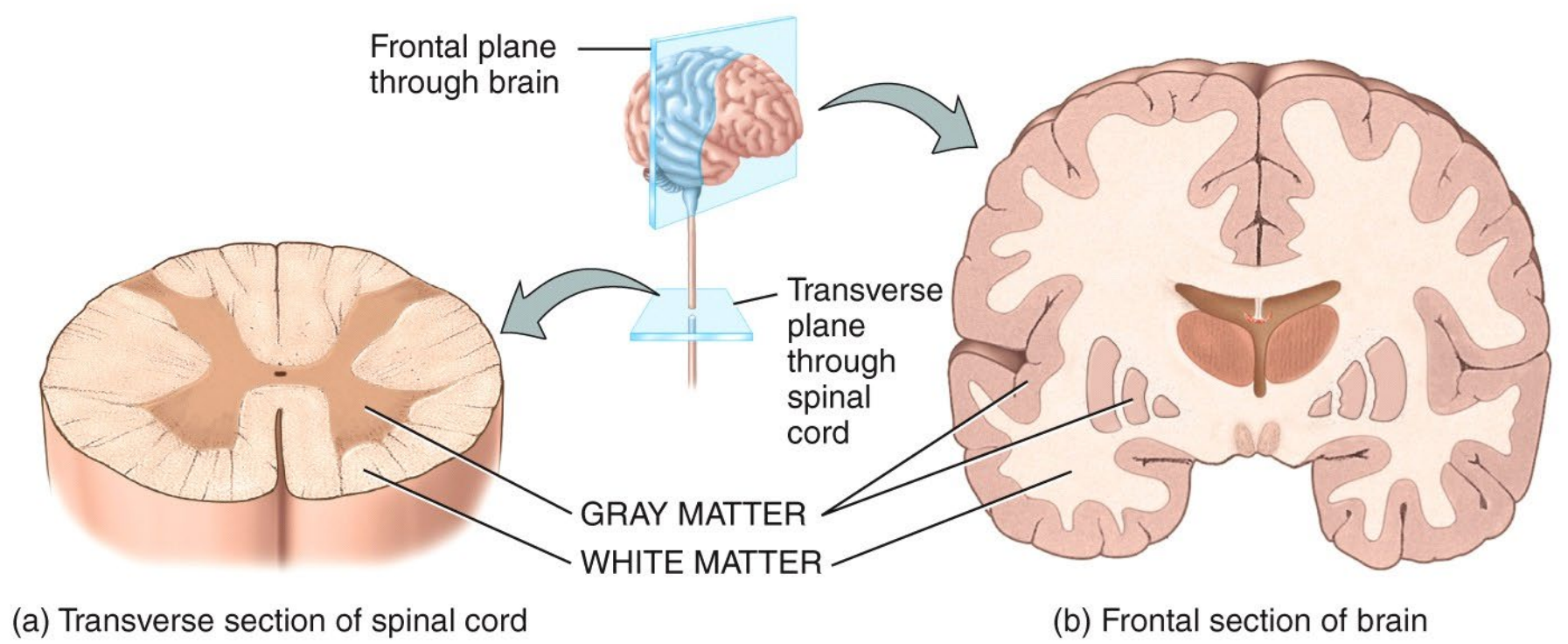
Most common neurotransmitter. Involved in learning and memory, regulates development and creation of nerve contacts.

SEROTONIN mood

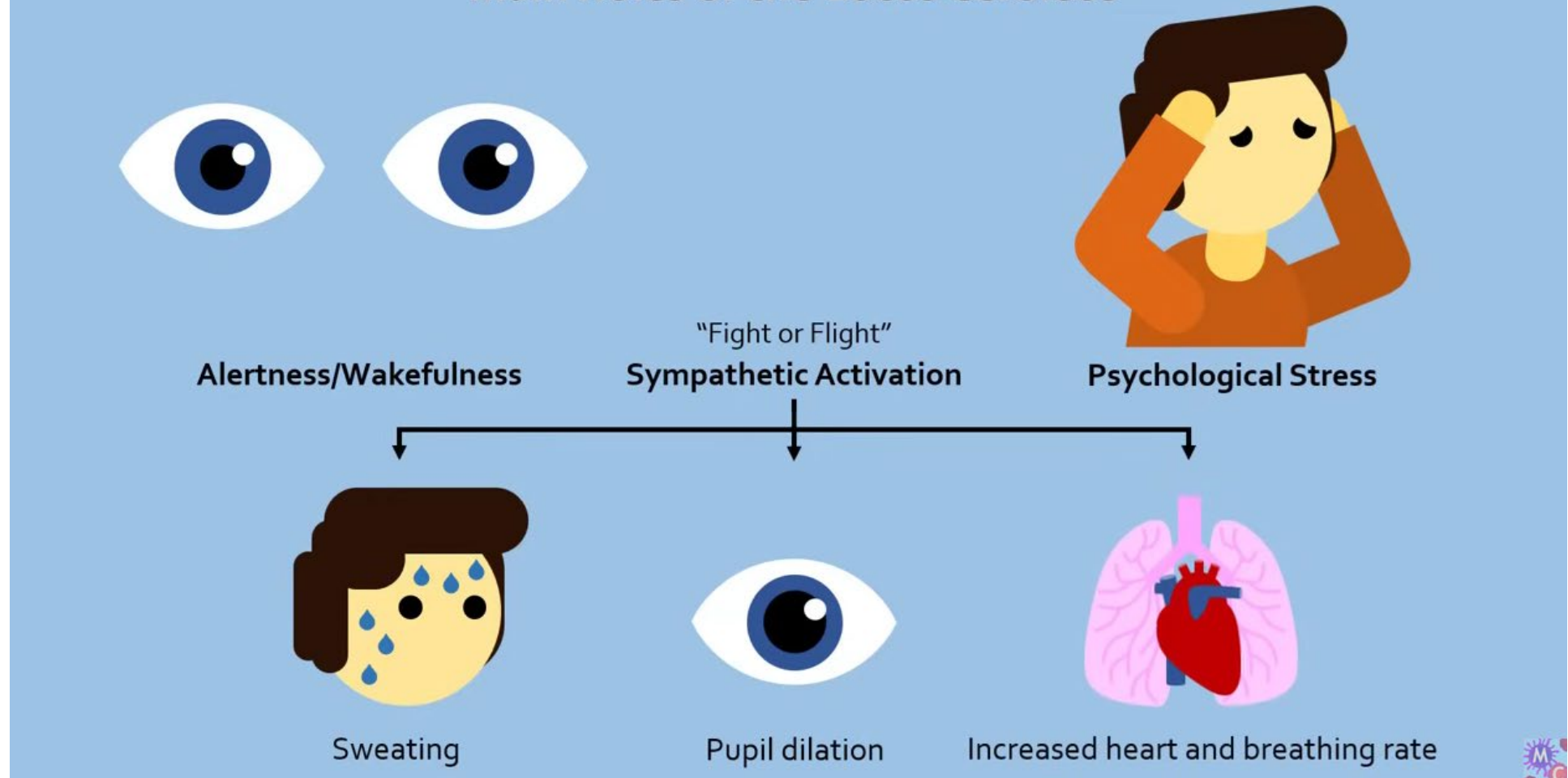
contributes to well-being and happiness. Helps sleep cycle and digestive system regulation. Affected by exercise and light exposure.

ENDORPHINS euphoria

Released during exercise, excitement and sex, producing well-being and euphoria, reducing pain



Main Roles of the Locus Ceruleus



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...



Jitteriness/Insomnia

"Fight or Flight"
Sympathetic Overactivation

Anxiety/Panic/Stress



Excessive sweating

Pupil dilation

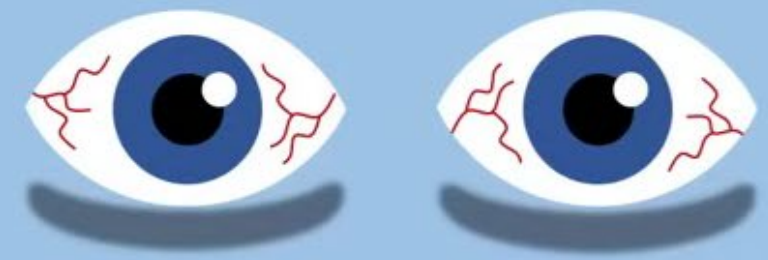
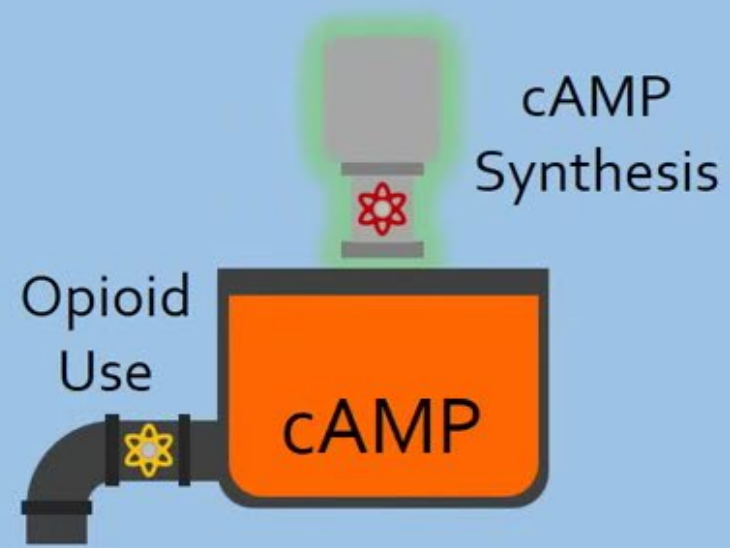
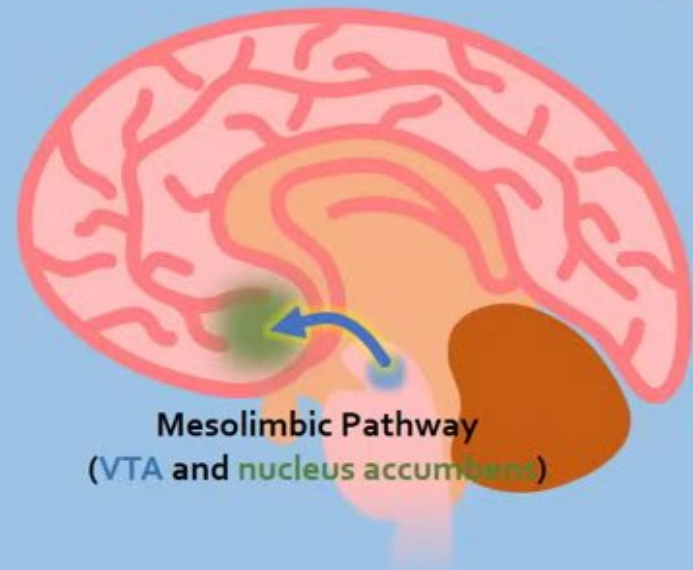
Increased heart and breathing rate

Opioid Mu receptors (DA 2R) are on locus ceruleus neurons. When opioids bind to the G protein linked receptor (second messenger/ metabotropic) it lowers the cytoplasmic cAMP. This then reduces locus ceruleus secretion of norepinephrine.

Behavior



Progression of Opioid Use Disorder



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