
بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ
In the name of Allah, the most gracious, the most merciful


What is not
started today
is never
finished
tomorrow

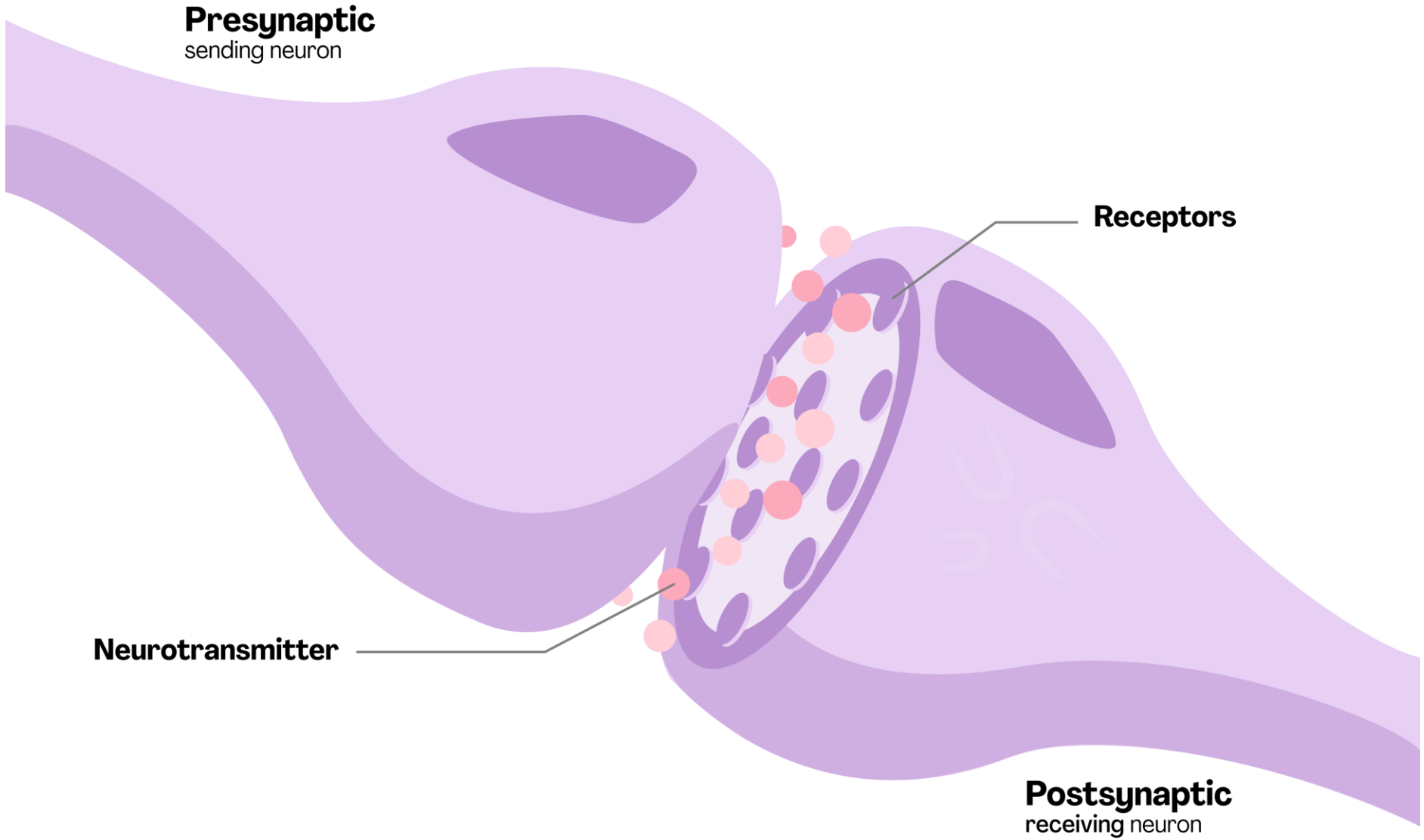
Function of Neurotransmitters

Learning Objectives

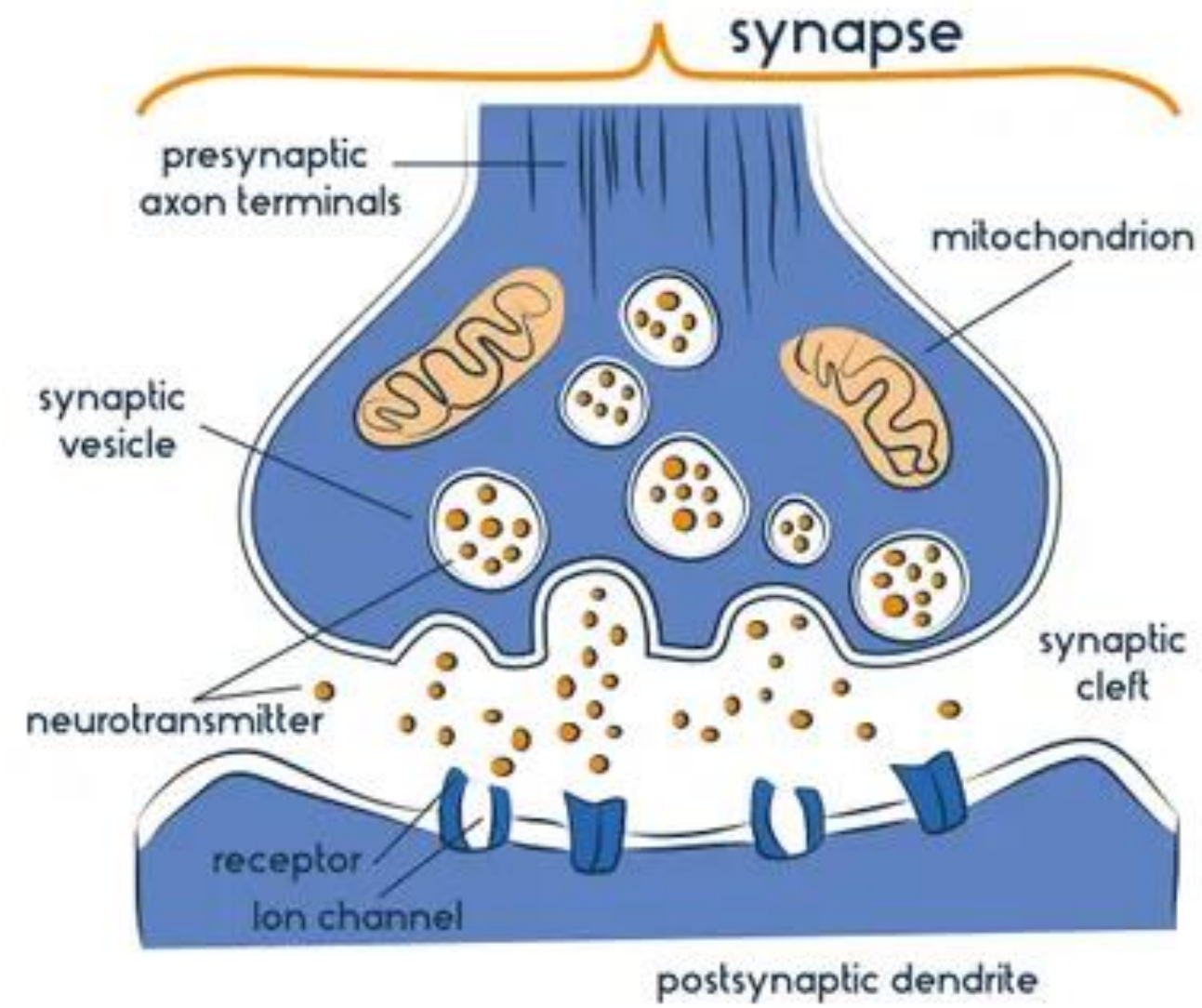
- Define the characteristics of a neurotransmitter.
- Enumerate the neurotransmitters involved in central nervous system.
- Classify neurotransmitters.
- Describe the action of some of the common neurotransmitters in central nervous system.

What is a Neurotransmitter?

- a chemical substance released at the end of a nerve fiber by the arrival of a nerve impulse and diffuses across the synapse or junction → transfer of the impulse to another nerve fiber


Presynaptic
sending neuron
Receptors
Neurotransmitter
Postsynaptic
receiving neuron

Characteristics of a Neurotransmitter


synapse
presynaptic
axon terminals
mitochondrion
synaptic
vesicle
synaptic
cleft
neurotransmitter
receptor
Ion channel
postsynaptic dendrite

Characteristics of a Neurotransmitter

influences a neuron in one of three ways:

- **Excitatory**
- **Inhibitory**
- **Modulatory**

An excitatory transmitter promotes the generation of an electrical signal called an action potential in the receiving neuron, while an inhibitory transmitter prevents it

Common Neurotransmitters

Acetylcholine	Histamine
Dopamine	Glycine
Norepinephrine	Glutamate
Epinephrine	Aspartate
Serotonin	Gamma-aminobutyric acid (GABA)

Classification of Neurotransmitters

Small molecule Rapidly Acting

Class I

Acetylcholine

Class II: The Amines

Norepinephrine
Epinephrine
Dopamine
Serotonin
Melatonin
Histamine

Class III: Amino Acids

Gamma-aminobutyric acid
Glycine
Glutamate
Aspartate

Class IV

ATP
Arachidonic acid
Nitric oxide
Carbon monoxide

Slowly Acting Neuropeptides

Hypothalamic-Releasing Hormones
Thyrotropin-releasing hormone
Luteinizing hormone–releasing hormone
Somatostatin (growth hormone inhibitory factor)
Pituitary Peptides
Adrenocorticotropic hormone
β-Endorphin
α–Melanocyte-stimulating hormone
Prolactin
Luteinizing hormone
Thyrotropin
Growth hormone
Vasopressin
Oxytocin

Peptides That Act on Gut and Brain
Leucine enkephalin
Methionine enkephalin
Substance P
Gastrin
Cholecystokinin
Vasoactive intestinal polypeptide
Nerve growth factor
Brain-derived neurotropic factor
Neurotensin
Insulin
Glucagon
Peptides from Other Tissues
Angiotensin II
Bradykinin
Carnosine
Sleep peptides
Calcitonin

Small molecule Rapidly Acting Neurotransmitters

- Mostly synthesized in the cytosol of the presynaptic terminal and absorbed via active transport into transmitter vesicles

- An action potential at the presynaptic terminal → a few vesicles at a time release their transmitter into the synaptic cleft

- acts on the postsynaptic neuron receptors to increase or decrease conductance through ion channels

- increase in Na+ conductance → excitation, or increase in K+ or Cl- conductance → inhibition

Slowly Acting Neuropeptides

- synthesized by ribosomes in the neuronal cell body
- The proteins enter the spaces inside the endoplasmic reticulum of the cell body and subsequently inside the Golgi apparatus, where two changes occur

1. neuropeptide-forming protein is enzymatically split into smaller fragments

2. Golgi apparatus packages them into minute transmitter vesicles that are released into the cytoplasm

- These vesicles are transported to the tips of the nerve fibers by axonal streaming of the axon cytoplasm
- Finally, the vesicles release their transmitter at the neuronal terminals in response to action potentials

Characteristic	Classical Neurotransmitters	Neuropeptides
Size	Small (one amino acid or similar chemical)	Large (2 to 40 amino acids)
Site of Synthesis	Cytosol of synaptic knob	Endoplasmic reticulum and Golgi complex in cell body; moved to synaptic knob by axonal transport
Site of Storage	Small synaptic vesicles in axon terminal	Large dense-core vesicles in axon terminal
Site of Release	Axon terminal	Axon terminal; may be co-secreted with neurotransmitter
Amount of Release	Variable, depending on synapse	Much lower concentration than classical neurotransmitter
Speed and Duration of Action	Rapid, brief response	Slow, prolonged response
Site of Action	Subsynaptic membrane of postsynaptic cell	Nonsynaptic sites on either presynaptic or postsynaptic cell
Effect	Usually alter potential of postsynaptic cell by opening specific ion channels	Modulate synaptic effectiveness by long-term changes in neurotransmitter synthesis or postsynaptic receptors

Neuropeptides

- Neuropeptides are small protein like molecules (peptides) used by neurons to communicate with each other. (Autocrine/paracrine).
- Neuronal signaling molecules(**not recycled back** into the cell once secreted, unlike glutamate, dopamine, serotonin etc.)
- Responsible for brain function:

- Analgesia.
- Food intake
- Learning & memory.
- Metabolism, reproduction.
- Social behaviors .

Eg: Neuropeptide Y(NPY), Cholecystokinin(CCK), Tachykinins(substance P, Neurokinin), Arginine Vasopressin(AVP), Corticotropin releasing factor(CRF)

KEY NEUROTRANSMITTERS AND THEIR MAIN FUNCTIONS

ADRENALINE/EPINEPHRINE

fight or flight
Produced in stressful situations. Increases heart rate and blood flow, leading to physical boost and hightened awareness.

NORADRENALINE/NOREPINEPHRINE

concentration
Affects attention and responding actions in the brain. Contract blood vessels, increasing blood flow.

DOPAMINE

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

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.

ACETYLCHOLINE

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

GLUTAMATE

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

Neuropeptides act primarily as Neuromodulators

Neuromodulators

- do not cause Excitatory or Inhibitory potentials but subtly modulate—**depress or enhance**—the action of the synapse
- do not directly alter membrane permeability and potential
- may act at either presynaptic or postsynaptic sites
- may influence the enzyme level involved in the synthesis of a neurotransmitter by a presynaptic neuron, or it may alter the sensitivity of the postsynaptic neuron to a particular neurotransmitter (number of subsynaptic receptors)

Action of Common Neurotransmitters

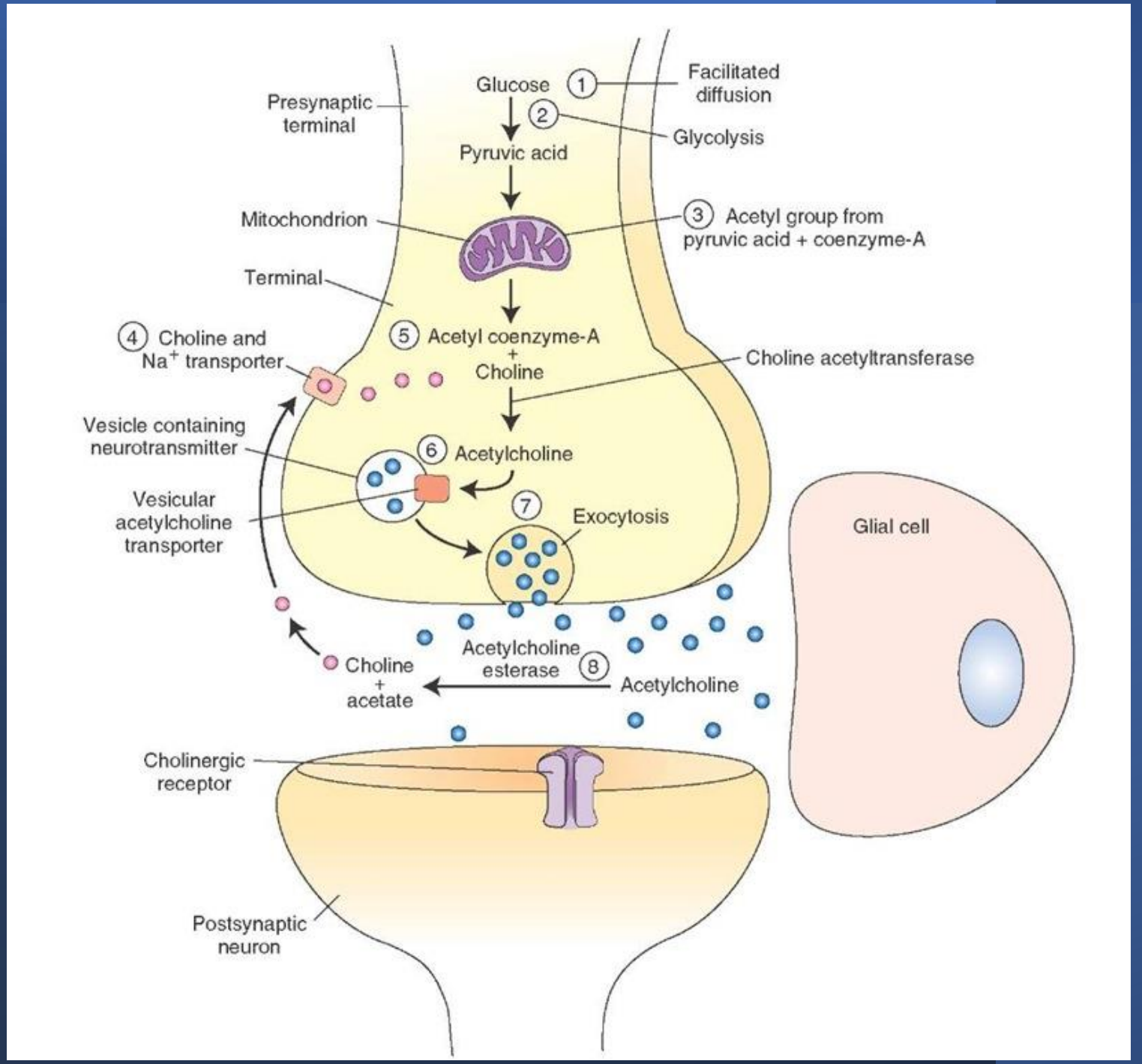
Small Molecule Neurotransmitters

1. Acetylcholine

secreted by neurons in many areas of the nervous system

- Large pyramidal cells from the motor cortex
- Neurons in the basal ganglia
- Motor neurons of skeletal muscles
- Preganglionic neurons of the autonomic nervous system
- Postganglionic neurons of the parasympathetic nervous system

Mostly has an excitatory effect; inhibitory effects at some peripheral parasympathetic nerve endings, such as inhibition of the heart by the Vagus nerves


Presynaptic terminal
Glucose
1
Facilitated diffusion
2
Glycolysis
Pyruvic acid
Mitochondrion
3
Acetyl group from pyruvic acid + coenzyme-A
Terminal
4
Choline and Na+ transporter
5
Acetyl coenzyme-A + Choline
Choline acetyltransferase
Vesicle containing neurotransmitter
6
Acetylcholine
Vesicular acetylcholine transporter
7
Exocytosis
Glial cell
Acetylcholine esterase
8
Choline + acetate
Acetylcholine
Cholinergic receptor
Postsynaptic neuron

2. Norepinephrine

- Secreted by neurons in the **brain stem and hypothalamus**
- **Locus Ceruleus-** Specific norepinephrine-secreting neurons located in the pons to help control overall activity, increasing the level of wakefulness
- Mostly activates **excitatory** receptors, but in a few areas activates inhibitory receptors
- **Postganglionic neurons** of the sympathetic nervous system, where it excites some organs but inhibits others

3. Dopamine

- secreted by neurons that originate in substantia nigra
- termination of these neurons is mainly in the basal ganglia
- usually, inhibitory

4. Glycine

- secreted mainly at synapses in the spinal cord
- It is believed to always act as an inhibitory transmitter

5. Gamma-aminobutyric acid (GABA)

- secreted by nerve terminals in the spinal cord, cerebellum, basal ganglia, and many areas of the cortex
- Primary inhibitory neurotransmitter
- In the early stages of brain development, it serves as an excitatory neurotransmitter

6. Glutamate

- secreted by the presynaptic terminals in many of the sensory pathways entering the central nervous system and in cerebral cortex

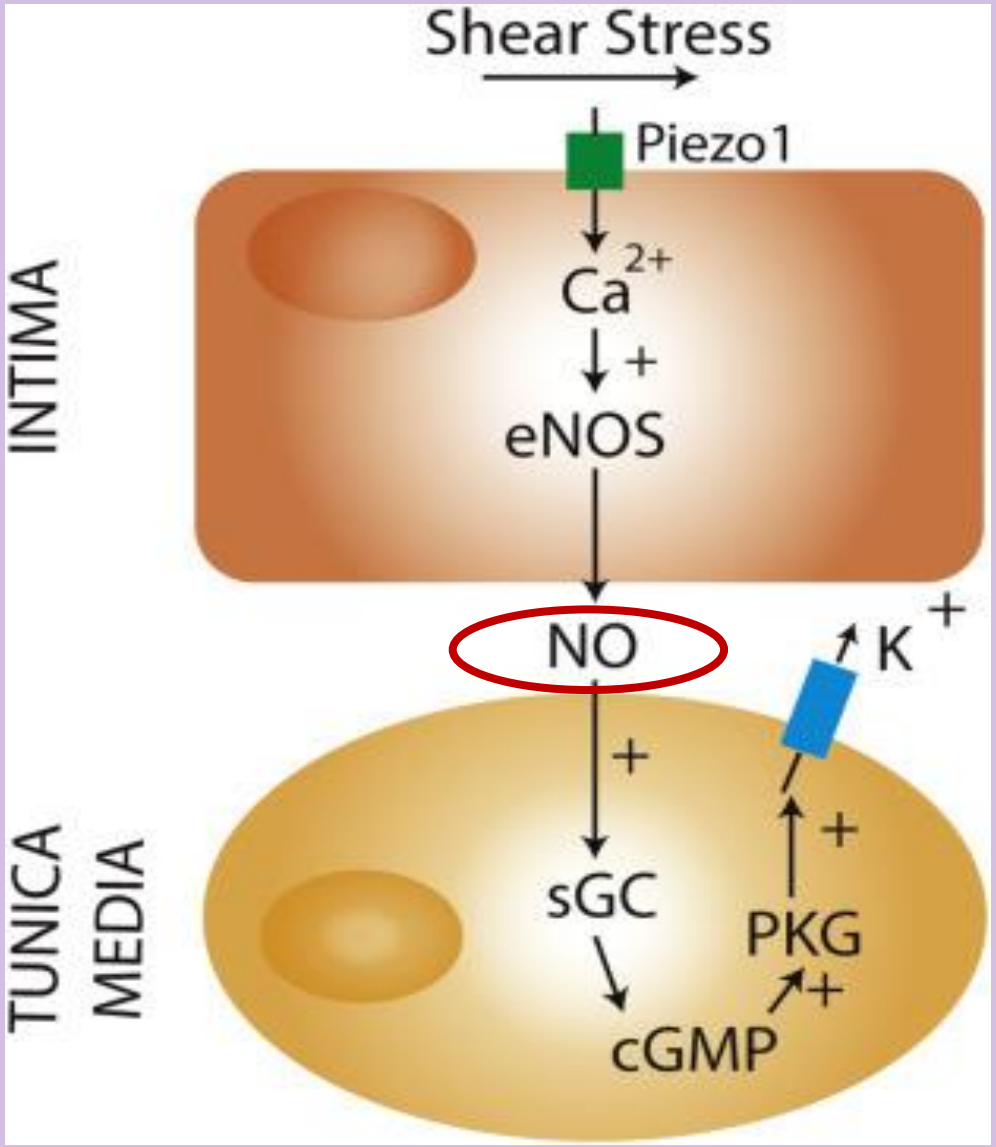
- Mostly excitatory

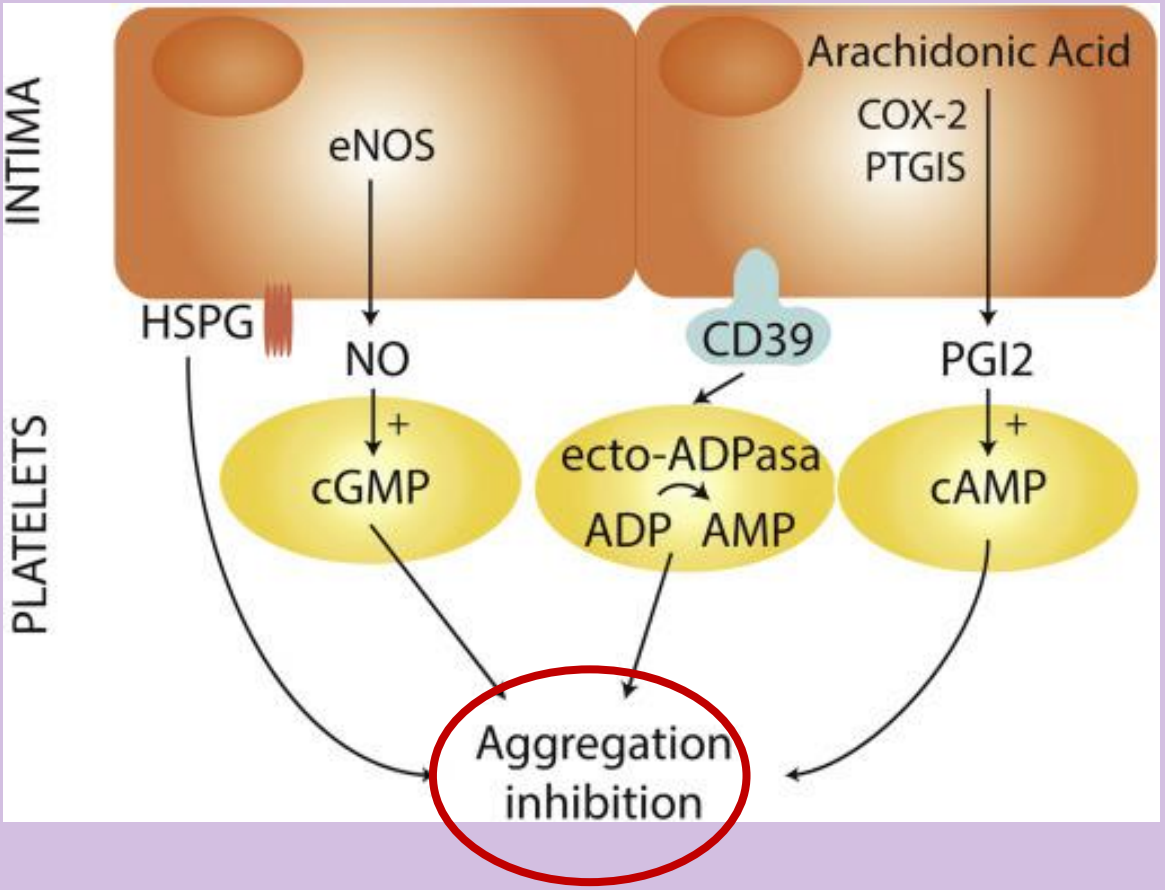
7. Serotonin

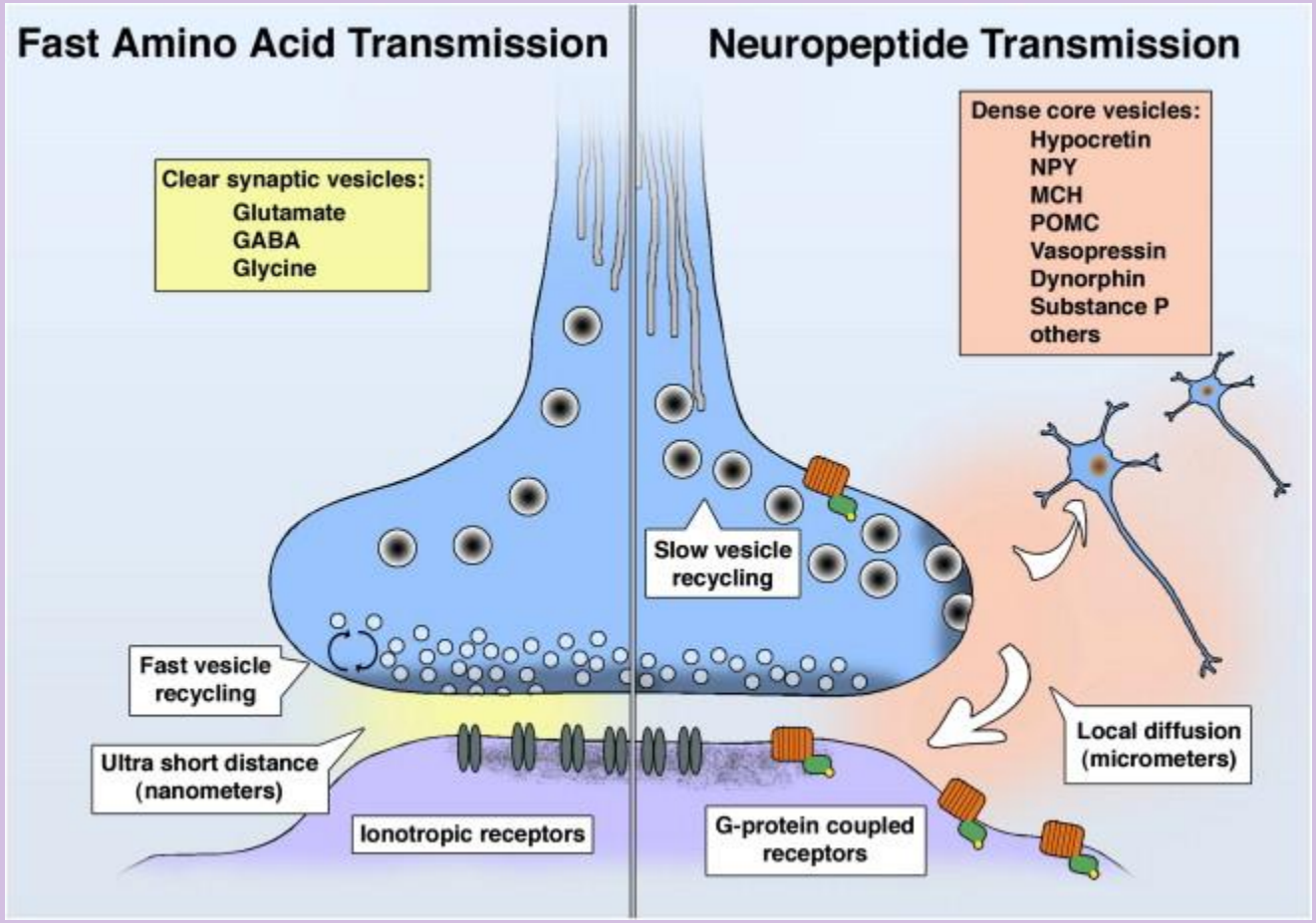
- Secreted by nuclei in the median raphe of the brain stem and project to many brain and spinal cord areas
- Acts as an inhibitor of **pain pathways** in the cord
- Inhibitory action in the higher regions of the nervous system helps control the **mood** of the person
- **Sleep induction**

8. Nitric oxide

- Produced by nerve terminals in areas of the brain responsible for long-term behavior and memory
- different from other small-molecule transmitters
- synthesized almost instantly as needed and then diffuses out of the presynaptic terminals
- → Diffuses into postsynaptic neurons where it changes intracellular metabolic functions that modify neuronal excitability


Shear Stress
Piezo1
INTIMA
Ca 2+
+
eNOS
NO
K +
+
+
sGC
PKG
+
cGMP
TUNICA MEDIA


INTIMA
eNOS
Arachidonic Acid
COX-2
PTGIS
HSPG
NO
CD39
PGI2
+
+
+
cGMP
ecto-ADPasa
ADP AMP
cAMP
PLATELETS
Aggregation inhibition

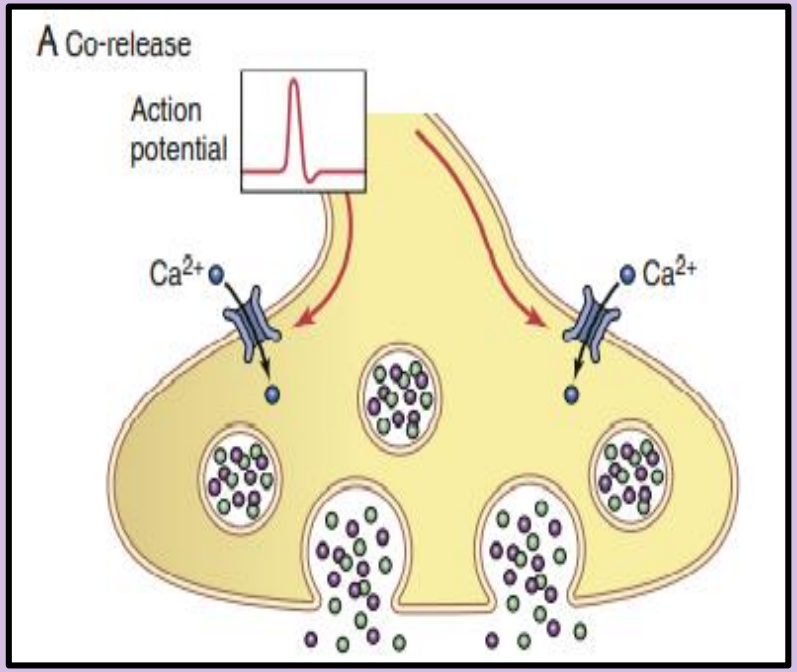


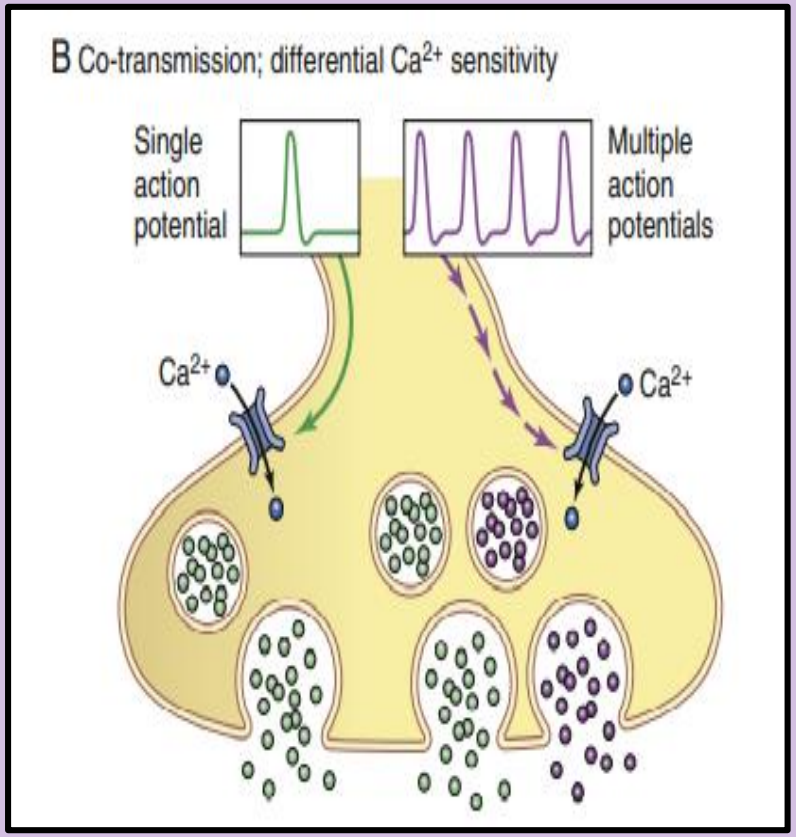
Neuropeptide Transmission in Brain Circuits, ScienceDirect Anthony, 2012

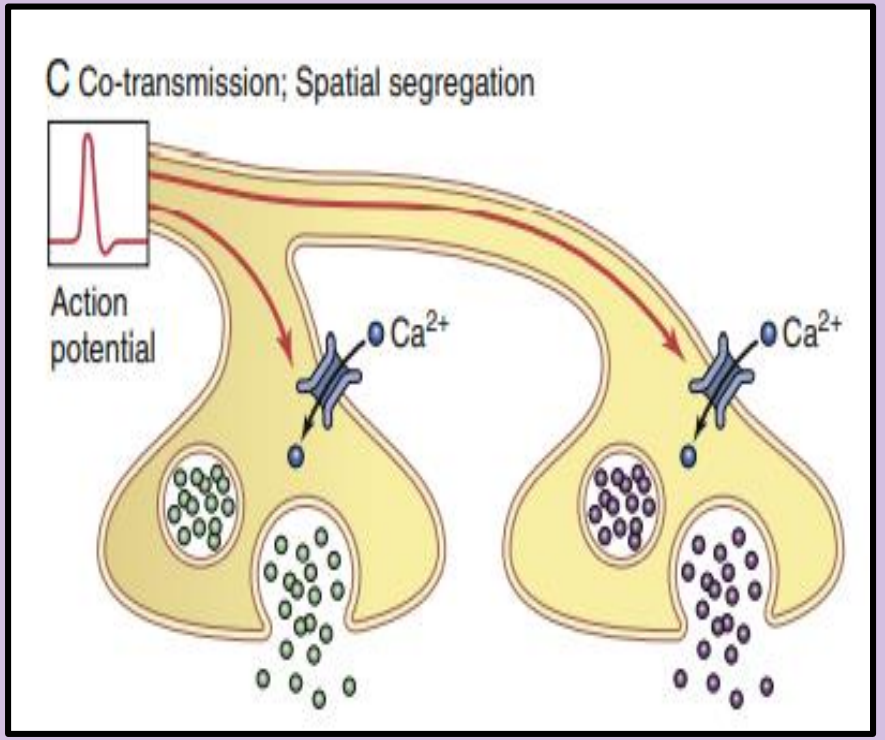
Table 9.1 Some Neurotransmitters and Their Functions

Neurotransmitter	Function	Examples of Malfunctions
Acetylcholine (ACh)	Enables muscle action, learning, and memory.	With Alzheimer's disease, ACh-producing neurons deteriorate.
Dopamine	Influences movement, learning, attention, and emotion.	Oversupply linked to schizophrenia. Undersupply linked to tremors and decreased mobility in Parkinson's disease.
Serotonin	Affects mood, hunger, sleep, and arousal.	Undersupply linked to depression. Some antidepressant drugs raise serotonin levels.
Norepinephrine	Helps control alertness and arousal.	Undersupply can depress mood.
GABA (gamma-aminobutyric acid)	A major inhibitory neurotransmitter.	Undersupply linked to seizures, tremors, and insomnia.
Glutamate	A major excitatory neurotransmitter; involved in memory.	Oversupply can overstimulate the brain, producing migraines or seizures (which is why some people avoid MSG, monosodium glutamate, in food).

Co-release of Neurotransmitters and Co-transmission of Neuronal Signals







Clinical Application

- some drugs work by interfering with removal of specific neurotransmitters from synapse

- **Selective serotonin reuptake inhibitors (SSRIs)** selectively block the reuptake of serotonin into presynaptic axon terminals prolonging the action of this neurotransmitter at synapses that use this messenger

- SSRIs, such as Prozac and Paxil, are prescribed to treat depression, characterized by a deficiency of serotonin, among other things

Clinical Application

- **Cocaine** blocks the reuptake of dopamine at presynaptic terminals by binding with the dopamine reuptake transporter

- dopamine remains in the synaptic cleft longer than usual → prolonged activation of neural pathways that use this chemical as a neurotransmitter, especially pathways that play a role in feelings of pleasure

Clinical Application

- **Tetanus toxin** prevents the release of GABA from inhibitory presynaptic inputs terminating at neurons that supply skeletal muscles →

- Unchecked excitatory inputs to these neurons → uncontrolled muscle spasms especially in the jaw muscles early in the disease (lockjaw)

- Later they progress to the muscles responsible for breathing, at which point death occurs

References

- Guyton and Hall Physiology
- Sherwood Physiology
- Ganong’s Physiology


ANY
QUESTIONS?


Thank
You