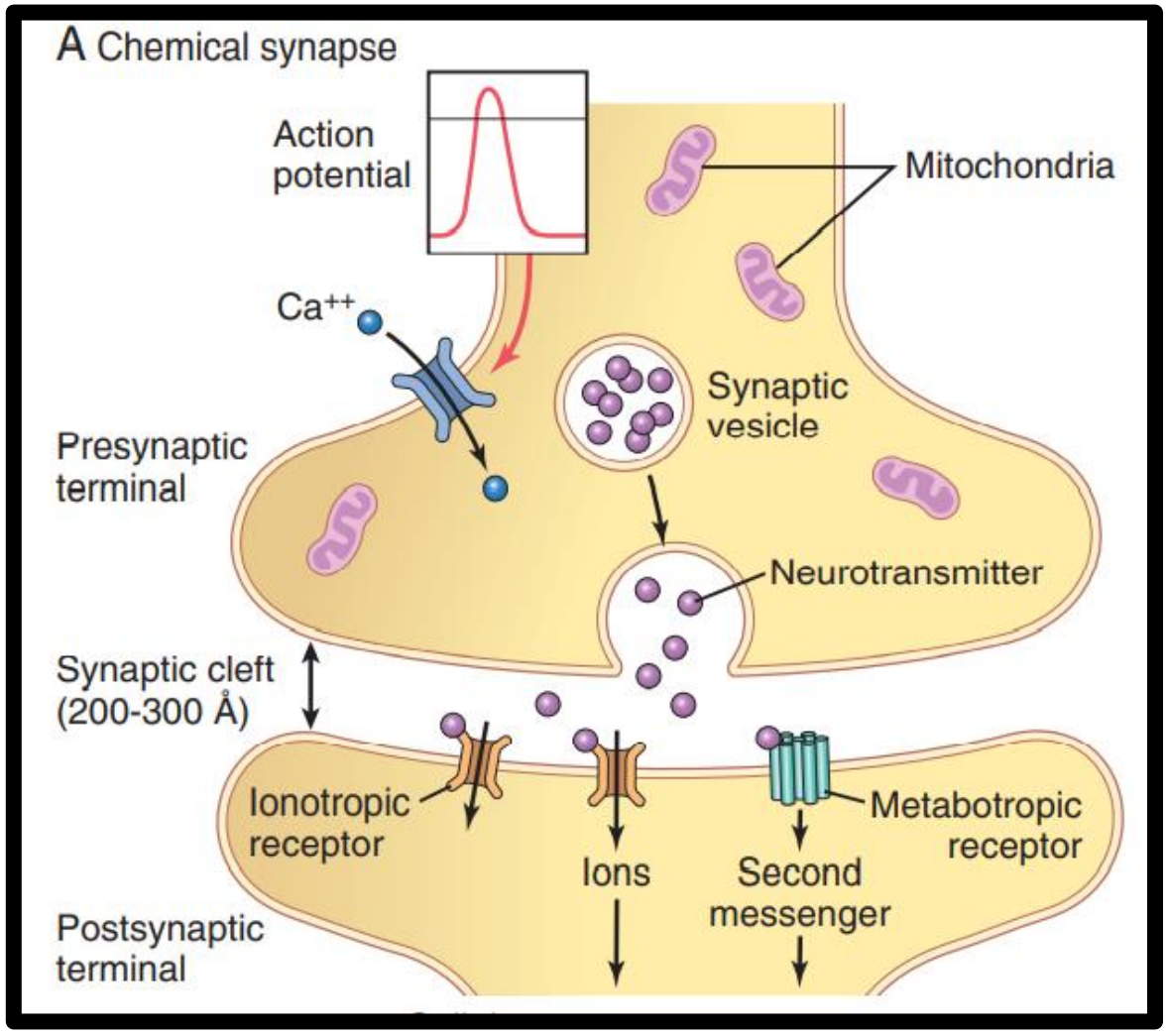
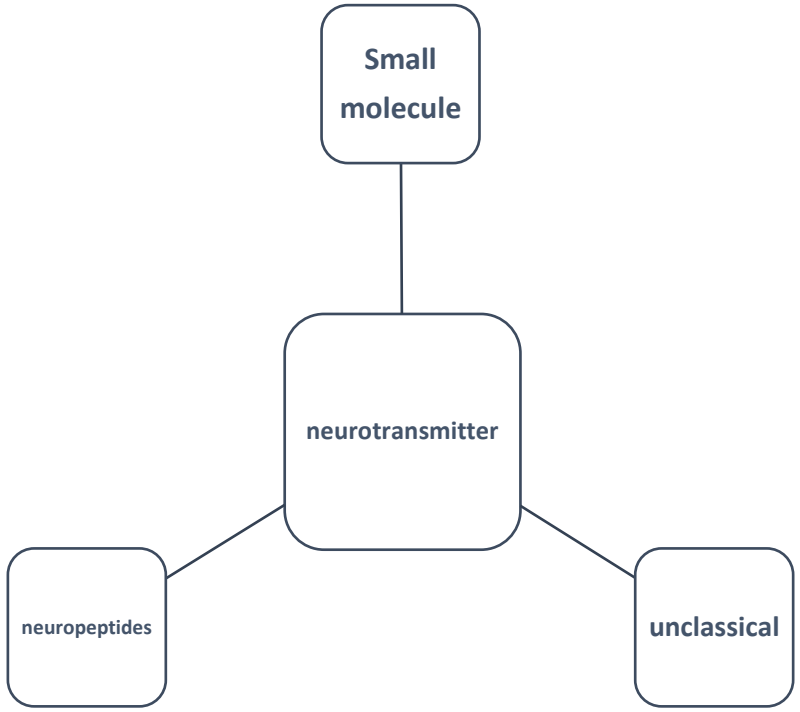
Introduction to Neurophysiology (lecture 3) Neurotransmitters

- **Fatima Ryalat, MD, PhD**
- **Assistant Professor, Physiology and Biochemistry Department, School of Medicine, The University of Jordan**

By Abdallah Al-Saraireh



Neurotransmitter are unique to chemical synapses; electrical synapses rely on direct ion flow through gap junctions instead



Small-Molecule, Rapidly Acting Transmitters
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

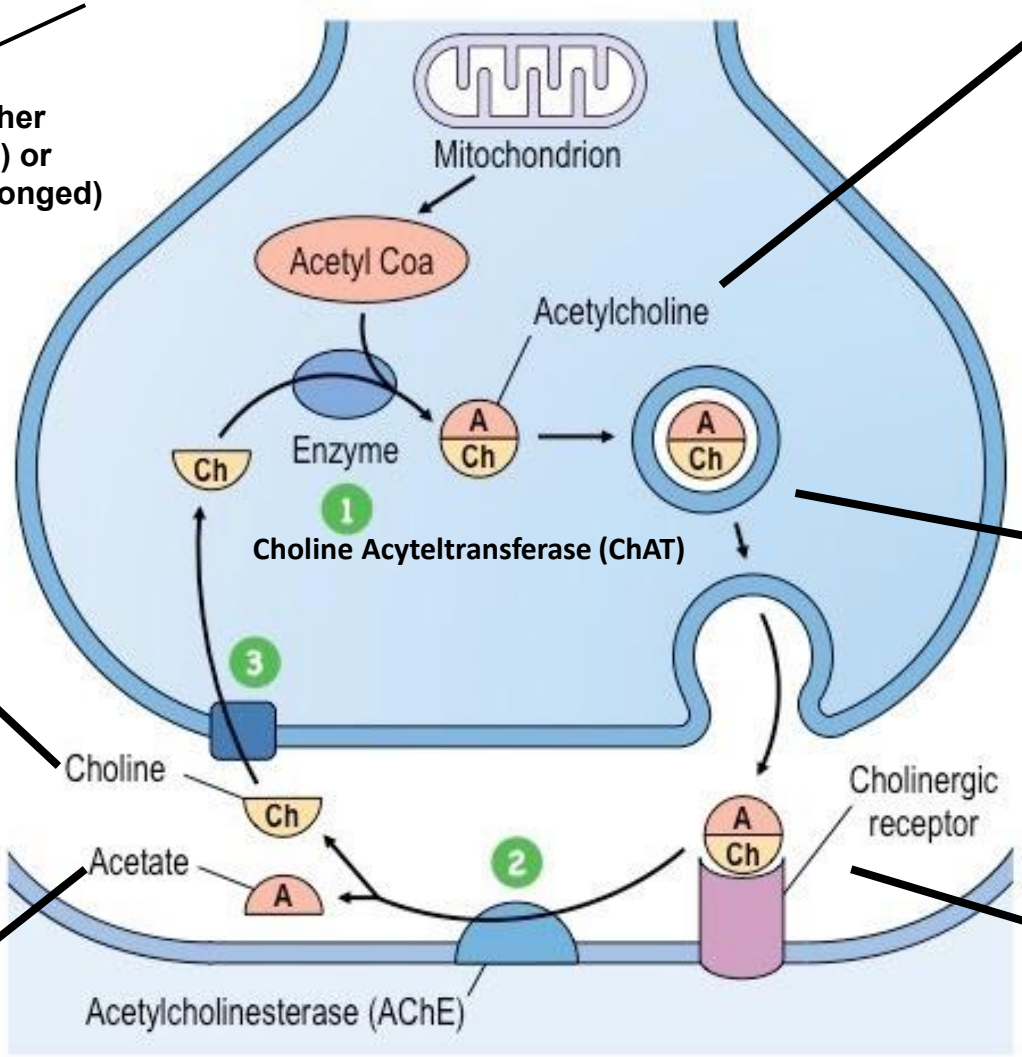
"The table classifies 'Small-Molecule, Rapidly Acting Transmitters' into four main classes based on their chemical structure. These neurotransmitters are responsible for most acute responses in the nervous system, such as sensory transmission to the brain and motor signals to the muscles."

Small-molecule

(rapid release)

Can bind to either Ionotropic (fast) or Metabotropic (prolonged) receptors.

Synthesis in presynaptic terminal (at the axon terminal)



1. Acetylcholine (ACh) is made from choline and acetyl CoA

2. In the synapse, ACh is rapidly broken down by the enzyme **acetylcholinesterase (AChE)**

Neurotransmitters are stored in vesicles to allow for quantal release (fixed amount)

3. Choline is transported back into the axon terminal and used to make more ACh

Choline is the component that undergoes recycling.

It is transported back into the axon terminal to be reused for synthesizing new Ach.

While choline is actively recycled back into the terminal, Acetate simply diffuses away into the surrounding environment.

Binding causes a conformational change in the receptor

Neuropeptides

→ The second type

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

From Other Tissues
Angiotensin II
Bradykinin
Carnosine
Sleep peptides
Calcitonin

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

Produced at the Soma (Cell Body).

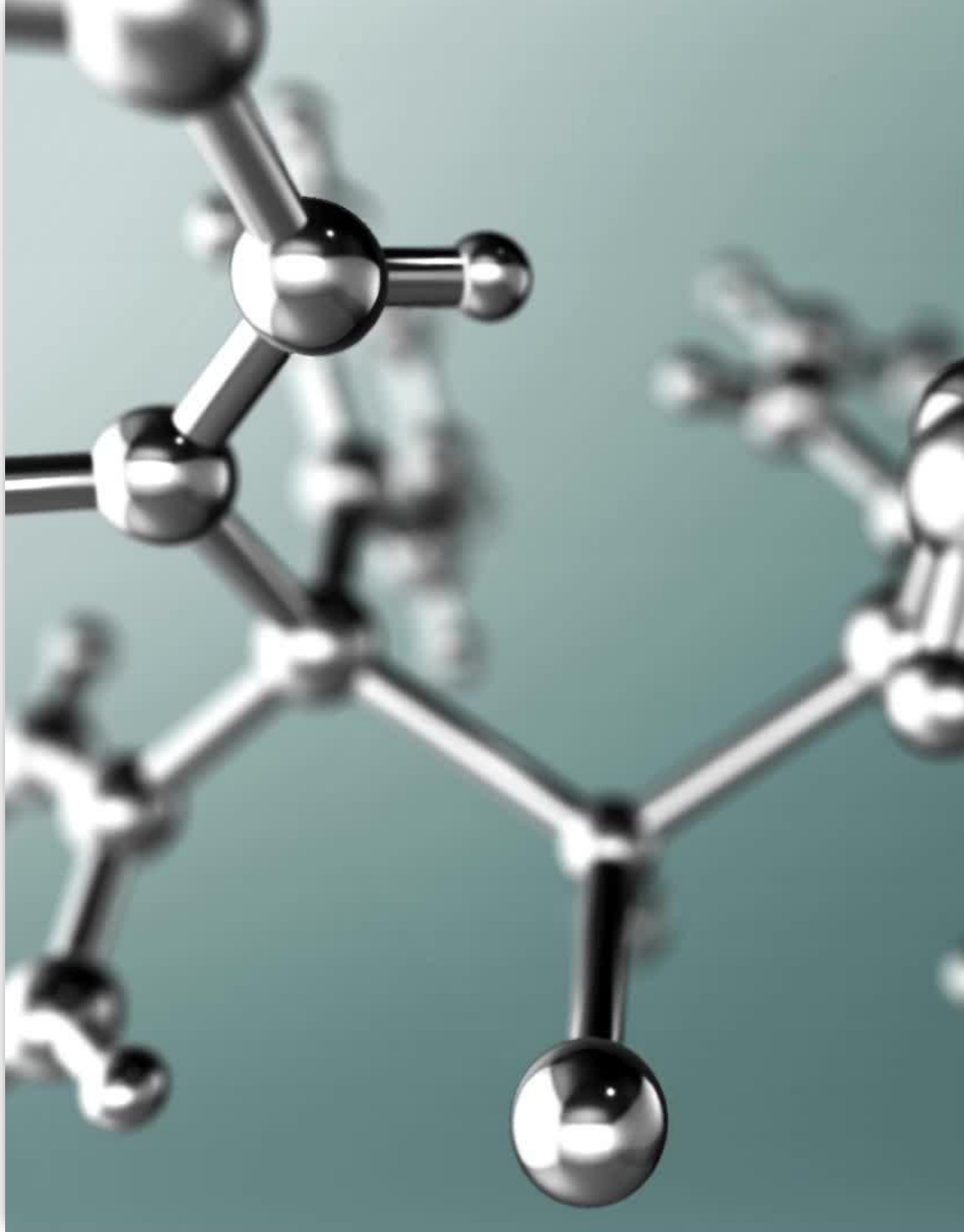
- **Packaging: Enclosed within vesicles inside the soma (specifically in the Golgi apparatus).**
- **Transport: Moved to the terminal via Axonal transport (which is slower than local synthesis).**
- **Receptors: Primarily act through GPCRs (Metabotropic receptors).**
- **Potency: Much more potent than small molecules; you need a smaller quantity to achieve the same effect.**
- **Mechanism: Cause Amplification of signals within the cell, leading to prolonged effects.**
- **Fate: Vesicles are not recycled; they undergo *autolysis* (digestion) after release.**

Neuropeptides

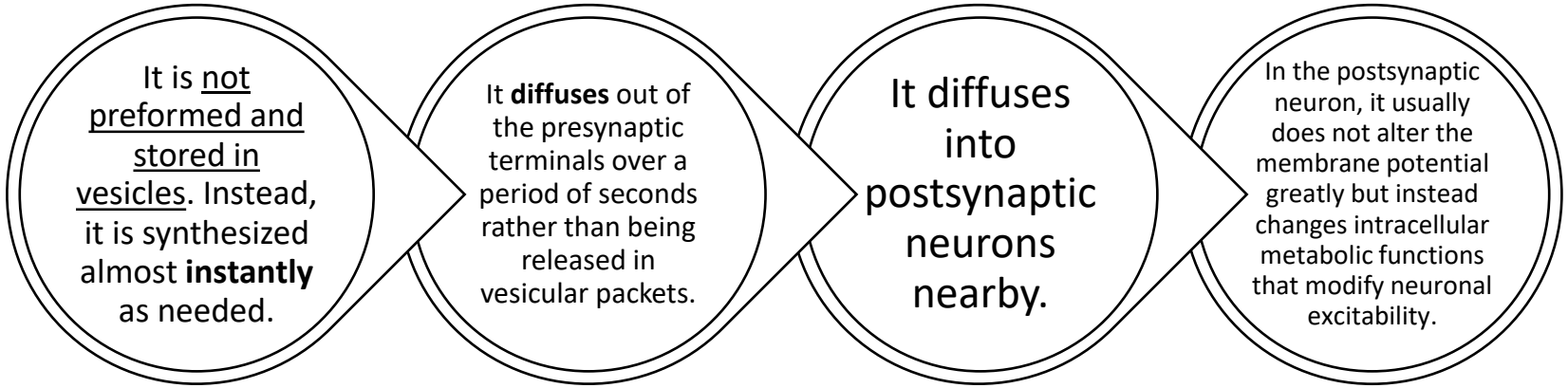
- synthesized in the **neuronal cell body**.
- packages into **vesicles**.
- transported along the axon to the axon terminals.
- traveling at the **slow rate**.
- vesicles release their transmitter at the neuronal terminals in response to action potential.
- Usually, the vesicle is autolyzed not reused.

Neuropeptides

- smaller quantities of neuropeptides are usually released.
- neuropeptides are generally more potent than the small-molecule transmitters.
- They often cause more prolonged actions.
- Metabotropic receptors



Nitric oxide (NO)



- **Not presynthesized (they are not made in advance)**
- **Not pre-vesicled (they are not stored in synaptic vesicles in the presynaptic terminal)**
- **Formed in the presynaptic neuron when needed (on demand)**
- **Synthesized by nitric oxide synthase (NOS) enzymes**

Types of NOS include:

- **nNOS (neuronal nitric oxide synthase)**
- **iNOS (includible nitric oxide synthase)**

The doctor said they are not included in the exam, but we will learn them in the next years, so why not memorize them now!

GABA

1. **GABA is the main "brake" that prevents Epilepsy, which occurs when low GABA levels cause uncontrolled electrical firing.**

2. **It functions via two receptors: GABA-A (fast Ionic channel) and GABA-B (slow Metabo-GPCR).**

- **Gamma-aminobutyric acid** (GABA).
- it is the main **inhibitory** neurotransmitter.

Very important

- **Receptors:** GABA-A (Cl- channel), GABA-B (GPCR)

G-protein Coupled Receptor

Ionic , fast , opens the Cl - channels

Metabo , slow , uses GPCR

- **Epilepsy** (uncontrolled electrical activity)

A chronic brain disorder

The doctor said that we don't have to memorize the receptors, but we will learn them in the next years!

Glycine

- Glycine is secreted mainly at synapses in the spinal cord > barin.

- It is almost always an inhibitory transmitter.

Very important

1. Glycine inhibits motor neurons to prevent over-contraction of muscles, ensuring smooth movement and relaxation.

2. It blocks the transmission of pain signals in the spinal cord before they reach the brain.

Quick question:

Which of the following is the primary inhibitory neurotransmitter in the spinal cord?

A) Glutamate
B) GABA
C) Glycine
D) Dopamine
E) Acetylcholine

The answer is (C)

Glutamate

Very important

- Glutamate is the main excitatory neurotransmitter.

- Receptors:

(ionotropic: AMPA, NMDA), metabotropic (mGluR)

Metabotropic Glutamate Receptor

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

N-methyl-D-aspartate

مو مطلوب حفظ أسماء المستقبلات ولا الاختصارات ، لكن حطيتهم عشان نمرّ على الاسم قبل ما نشوفه بالسنوات الجاي

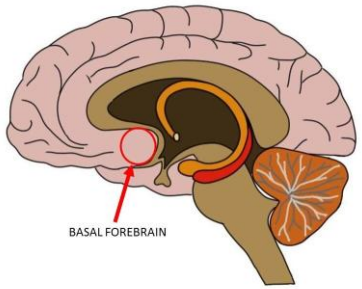
The doctor said that we don't have to memorize the receptors, but we will learn them in the next years!

Acetylcholine (ACh)

- **Acetylcholine is secreted by neurons in many areas of the nervous system such as:**
- **motor neurons** that innervate the skeletal muscles (**NMJ: neuromuscular junction**).
- **neurons of the autonomic nervous system.**
- **Basal forebrain**

Very important

Very important



Receptors are:

- **nicotinic (ionotropic)**
- **muscarinic (metabotropic: GPCR).**

- **In most cases, acetylcholine has an excitatory effect.** → Very important

Myasthenia gravis (loss of ACh receptors at the NMJ (Muscle weakness))

Alzheimer's disease (loss of ACh-producing neurons in the brain (memory loss))

→ Very important

Norepinephrine

- Norepinephrine is secreted by the terminals of many neurons whose cell bodies are in:
- the brain stem, specifically, locus ceruleus that plays a role in wakefulness and arousal. Very important
- also secreted by most postganglionic neurons of the sympathetic nervous system.

- **Depression** (low levels of it)
- **ADHD** (low levels of it) → Very important

Dopamine

Dopamine starts from the Brainstem (Nigra) and goes to the Striatum for movement, or to the Cortex for thinking and psychiatric control

- Dopamine is secreted by neurons in **nigrostriatal**, **mesolimbic, mesocortical**, and **tuberoinfundibular** pathways.
- Receptors: D1-D5

Controls movement; its destruction leads to Parkinson's disease

Regulate reward and emotion; overactivity is linked to psychiatric disorders (psychosis)

Inhibits prolactin secretion; blocking it causes high prolactin levels

D1-D5: Five types of receptors divided into Excitatory (D1, D5) and Inhibitory (D2, D3, D4) families.

- **Parkinson's disease**
- **Psychiatric disorders (motivation and emotions)**
- **Control prolactin secretion**

Dopamine from Hypothalamus acts on Anterior Pituitary to Reduce Milk (Inhibit Prolactin)

Serotonin

Serotonin, also known as 5-Hydroxytryptamine (5-HT), is secreted from the Raphe nucleus to regulate mood via 5-HT 1-7 receptors

Very important

- Secreted by **raphe nucleus** of the brainstem
- Control **mood**, **sleep**, **appetite**, **pain**.

- **Depression** **(low levels of serotonin)**

- **Receptors: 5-HT 1-7 (ionotropic and metabotropic)**

Substance P

- **Neuropeptide**
- Sensory neurons, **spinal cord**, hypothalamus

Pain transmission (chronic pain), inflammation and stress.

Hypothalamus: Releases Substance P during stress and emotional pain responses

Sensory Neurons: Use Substance P to transmit pain signals from the body to the Spinal Cord

Oxytocin

- **Neuropeptide**
- Produced in **hypothalamus** and Released from **posterior pituitary**.

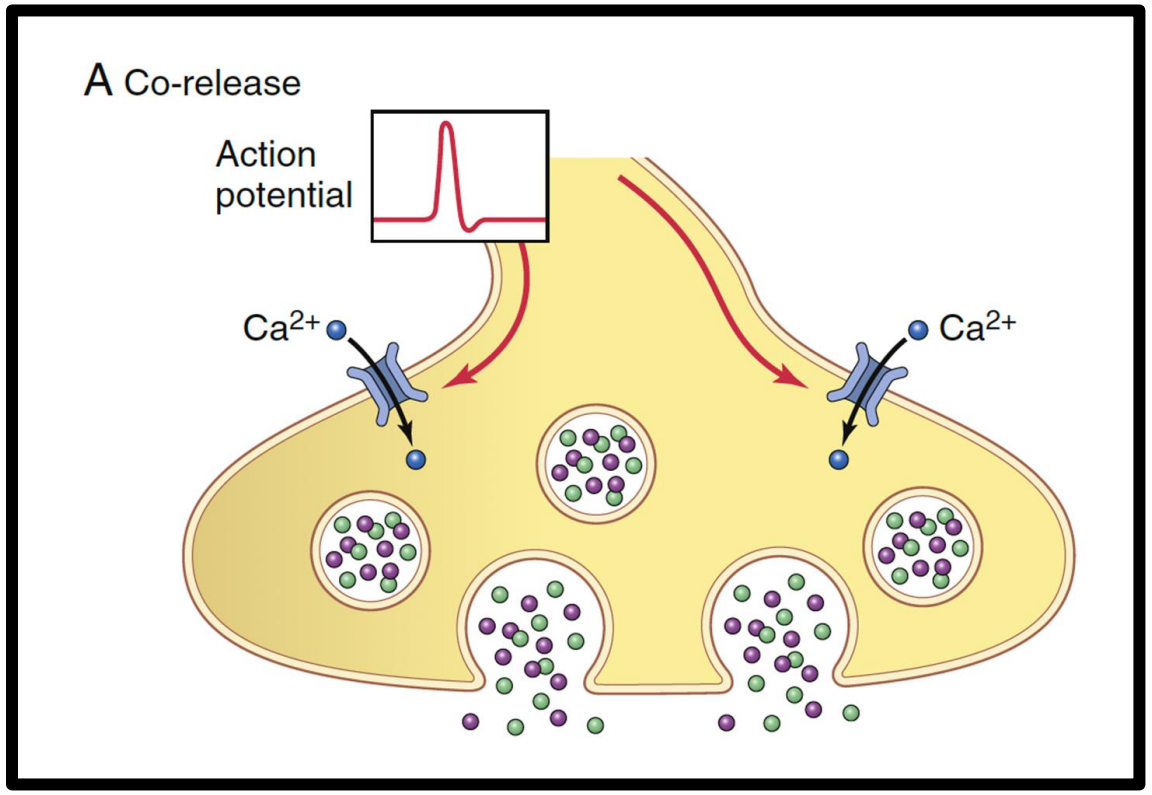
- Control **contractions** of **uterus** during labor
- **Ejection of milk** during lactation
- **Social bonding** and **emotional behavior**

Co-transmission

Co-release

- **Slowly acting neuropeptide transmitters and rapidly acting, small-molecule transmitters are often stored and released from the same neurons.**

- **In some cases, two or more of these transmitters are co-localized in the same synaptic vesicles and are co-released when an action potential reaches the presynaptic terminal.**



Quick question:

In the context of neuronal communication, which of the following best describes the physiological phenomenon of "Co-release"?

A) The activation of multiple postsynaptic neurons by a single neurotransmitter type.
B) The simultaneous discharge of different neurotransmitters stored within the same synaptic vesicle.
C) The release of neuropeptides from one neuron and small-molecule transmitters from a neighboring neuron.
D) The enzymatic breakdown of neuropeptides in the synaptic cleft to produce small-molecule transmitters.
E) The inhibition of (Ca ++) channels to prevent the release of multiple neurotransmitter types.

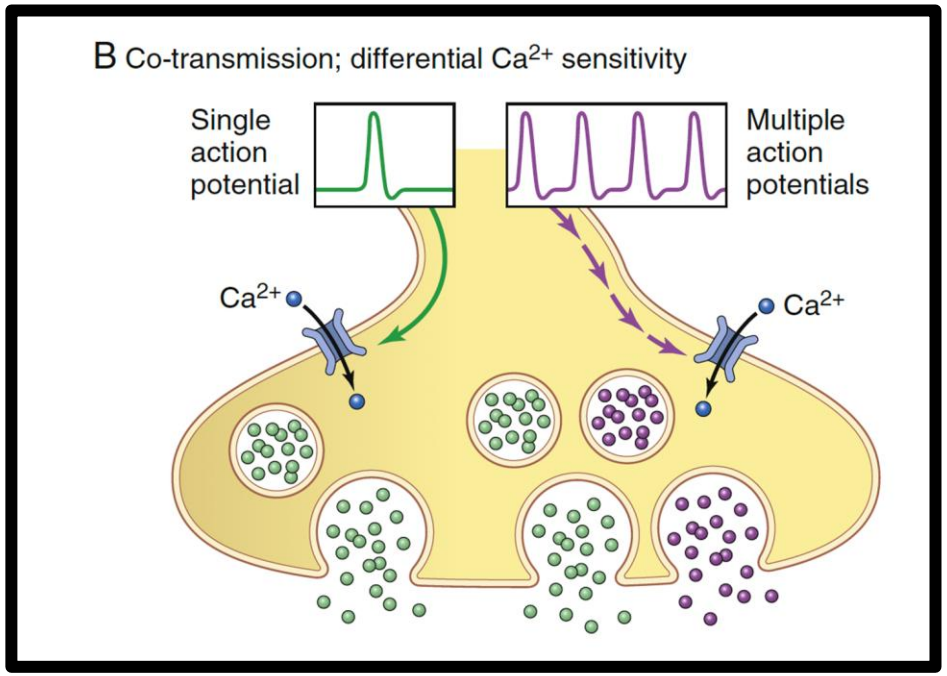
The answer is (B)

Co-transmission

Differential regulation

- **In other cases, these transmitters may be localized in different synaptic vesicles of the same neuron and contribute to co-transmission of signals to a postsynaptic neuron.**

- **Moreover, their release may be differentially regulated because of different calcium ion sensitivities**



Quick question:

In neurons utilizing co-transmission from distinct vesicle populations, how does the firing frequency of action potentials achieve differential regulation of neurotransmitter release?

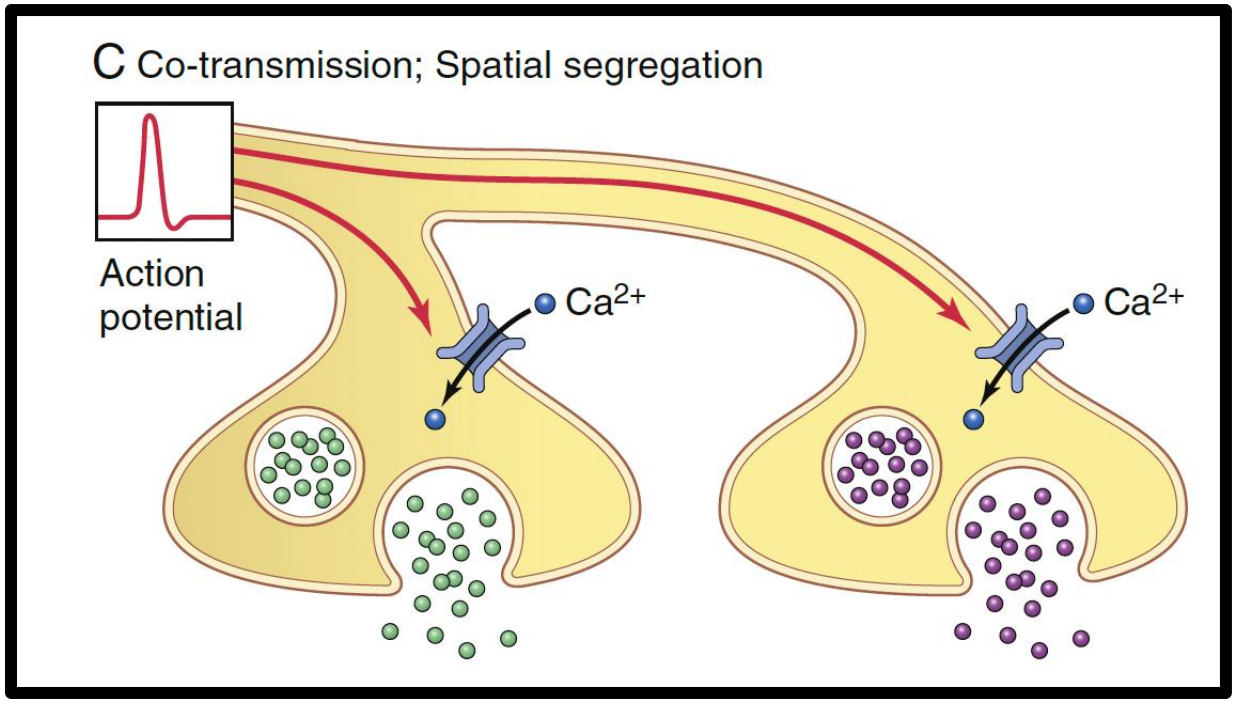
A) By altering the chemical structure of neuropeptides to fit into small-molecule vesicles.
B) By increasing the size of the synaptic cleft to accommodate multiple transmitter types.
C) By reversing the direction of (Ca++) efflux during high-frequency stimulation.
D) By modulating the concentration of intracellular (Ca++) to meet different vesicular sensitivities.
E) By activating postsynaptic receptors only when a single action potential occurs.

The answer is (D)

Co-transmission

Spatial segregation

- **Or spatial segregation of the vesicles on different boutons**



Quick question:

Which of the following best characterizes "Spatial Segregation" as a mechanism of neuronal co-transmission?

A) The release of different neurotransmitters from the same synaptic vesicle into the cleft.
B) The distribution of distinct neurotransmitter types into separate axonal terminals (boutons) of a single neuron.
C) The requirement of high-frequency action potentials to release all transmitter types from a single bouton.
D) The conversion of neurotransmitters from inhibitory to excitatory depending on the target site.
E) The storage of all neurotransmitter types in a single, large dense-core vesicle at the main axon hillock.

The answer is (B)

Summary

Feature	Co-release	Differential regulation	Spatial segregation
Storage strategy	Same synaptic vesicles	Different vesicles in the same terminal	Different vesicles in different terminals (boutons)
Release mechanism	Simultaneous (Always together)	Frequency-dependent (low vs. high)	Branch-specific release
Ca++ sensitivity	Uniform for all transmitters	Different sensitivities between vesicles	Location-specific sensitivity
Action potential (AP)	Single AP triggers both	Low frequency = one type of neurotransmitters High frequency = both types	AP reaches different branches to release specific types
Main advantage	Guaranteed dual signal (وصول إشارة مزدوجة للخلية المستهدفة في وقت واحد)	Temporal control (Time-based)	Target-specific control (spatial – based)

1. Which of the following neurotransmitters is unique because it is synthesized on demand (not pre-stored in vesicles) and acts by modifying intracellular metabolic functions rather than membrane potential?

A) Acetylcholine
B) Gamma-aminobutyric acid (GABA)
C) Nitric oxide (NO)
D) Substance P
E) Serotonin

The answer is (C)

2. A patient presents with progressive memory loss. Clinical investigation suggests a loss of neurons in the basal forebrain. Which neurotransmitter system is most likely affected?

A) Dopaminergic system in the substantia nigra
B) Cholinergic system (Acetylcholine)
C) Noradrenergic system in the locus ceruleus
D) Serotonergic system in the raphe nucleus
E) GABAergic system in the spinal cord

The answer is (B)

3. In the clinical context of "Epilepsy", which neurotransmitter is often referred to as the main "brake" of the brain, where its deficiency leads to uncontrolled electrical firing?

A) Glutamate
B) Dopamine
C) Glycine
D) GABA
E) Norepinephrine

The answer is (D)

4. Regarding the potency and fate of Neuropeptides compared to small-molecule transmitters, which statement is correct?

A) Neuropeptides are less potent and released in larger quantities
B) Neuropeptide vesicles are recycled and reused multiple times
C) Neuropeptides are more potent and their vesicles typically undergo autolysis after release
D) Neuropeptides are synthesized locally at the axon terminal
E) Neuropeptides cause rapid, acute responses that last for milliseconds only

The answer is (C)

5. Destruction of dopamine-producing neurons in the nigrostriatal pathway is the primary pathophysiological hallmark of which disorder?

A) Alzheimer's disease
B) Depression
C) Parkinson's disease
D) ADHD
E) Psychosis

The answer is (C)

6. A scientist is studying a neurotransmitter secreted by the Raphe nucleus that regulates mood, sleep, and appetite. Low levels of this transmitter are clinically linked to depression. Identify this transmitter:

A) Norepinephrine
B) Epinephrine
C) Serotonin (5-HT)
D) Oxytocin
E) Dopamine

The answer is (C)