بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

PHYSIOLOGY

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MID | Lecture 9

Neurotransmitters and changes in membrane potential

Reviewed by : Hamzeh
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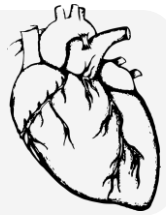

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Introduction to Neurophysiology 3

Neurotransmitters

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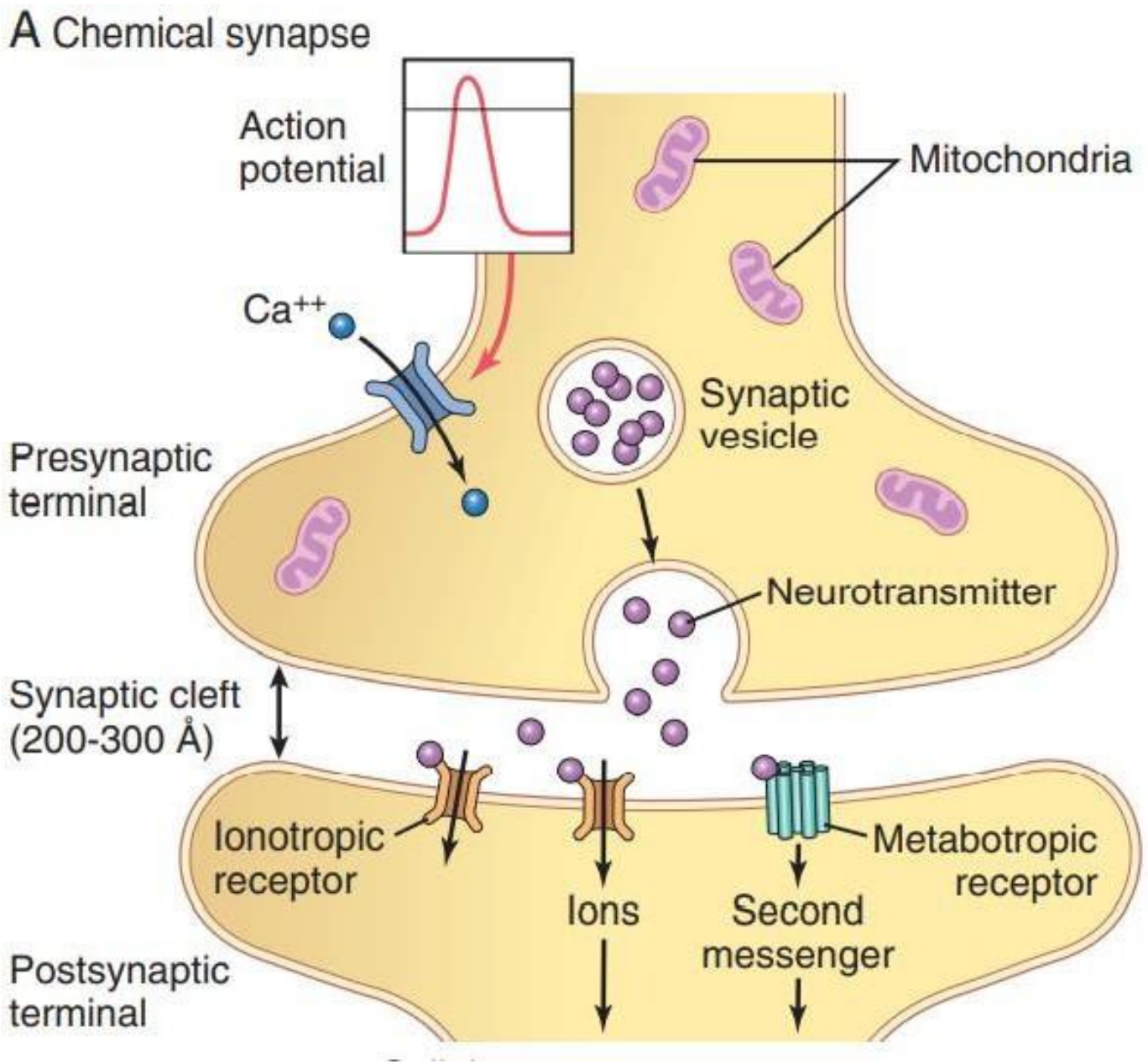


Neurotransmitters are the chemicals that will be released from through the presynaptic neuron through the synaptic cleft toward the postsynaptic cleft where we have receptors for these neurotransmitters

The word "neuro" means that these chemicals are released by neuronal cells, specifically from the presynaptic neuron. The word "transmit" refers to their role in transmitting signals from one neuron to another

Neurotransmitters can be classified in several ways; however, according to *Guyton*, they are broadly divided into **rapidly acting small-molecule neurotransmitters** and **neuropeptides**.

Small-Molecule, Rapidly Acting Transmitters

are a type of neurotransmitters. They are also called neuromodulators, because rather than changing the permeability of the postsynaptic neuron, they may cause different metabolic effects, thus modulating the function of the postsynaptic neuron.

This type is divided into subclasses:

Class I

Acetylcholine (a choline derivative)

Class II: The Amines (amino derivatives.)

- Norepinephrine
- Epinephrine
- Dopamine
- Serotonin

→ These neurotransmitters can act as either inhibitory or excitatory, depending on the type of receptors they bind to on the postsynaptic neuron.

- Melatonin
- Histamine

Class III: Amino Acids

- Gamma-aminobutyric acid (GABA)
- Glycine

→ Inhibitory neurotransmitters

- Glutamate
- Aspartate

→ Excitatory neurotransmitters

Class IV → Different molecules

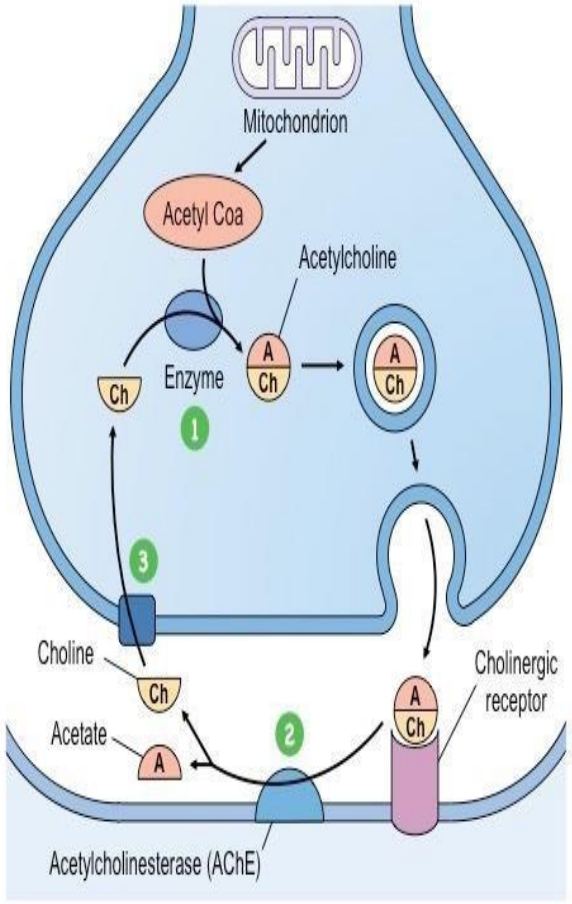
- ATP
- Arachidonic acid
- Nitric oxide
- Carbon monoxide

→ Gases

Neurotransmitters can be classified into two main categories: **classical neurotransmitters** and **neuropeptides**. Common examples of classical neurotransmitters include **acetylcholine** and **serotonin**, which will be discussed further in this file.
To understand neurotransmission, it is important to first examine the **small-molecule neurotransmitters**. These molecules may belong to several chemical groups, including **amino acids, amines, or other small molecular compounds**. Despite their structural differences, they share several common characteristics in their **synthesis, storage, release, and recycling**.

Acetylcholine (ACh) is one of the most common neurotransmitters. As mentioned in the previous lecture, the substrates required for its synthesis are present in the **axon terminal**, meaning that **acetylcholine is synthesized at the same site where it is released**.
The synthesis of acetylcholine requires two components: **acetyl-CoA and choline**. These substrates are combined by the enzyme **choline acetyltransferase**, which catalyzes their reaction to produce **acetylcholine**.
After synthesis, acetylcholine is **packaged into synaptic vesicles**

. Vesicular packaging serves several important functions:
It **protects the neurotransmitter from enzymatic degradation** within the cell.
It allows the release of **quantified amounts** of neurotransmitter.
The amount released depends on the **intracellular calcium concentration**.
For example, the entry of **one calcium ion may trigger the release of one vesicle**, and each vesicle contains multiple neurotransmitter molecules. A stronger stimulus leads to **greater calcium influx**, resulting in the release of **more vesicles and a larger amount of neurotransmitter**.

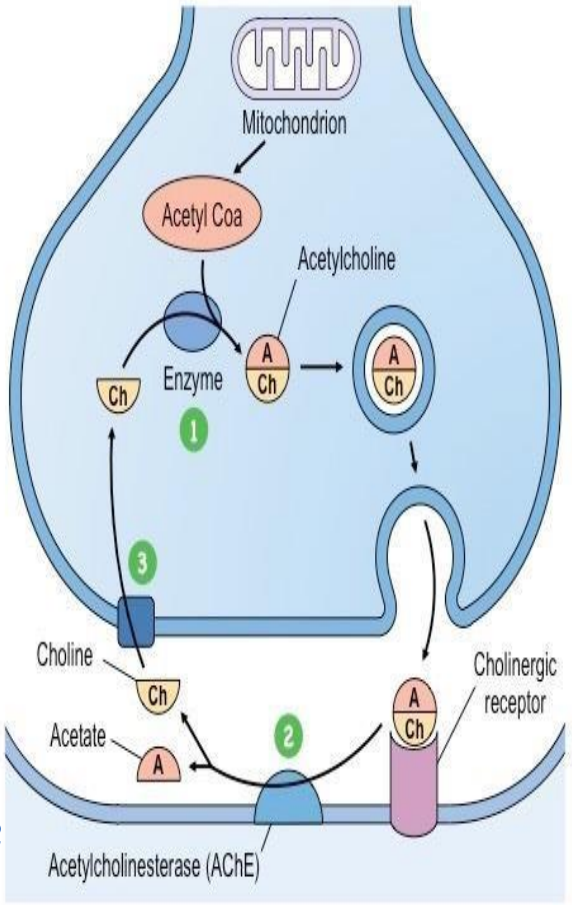


1 Acetylcholine (ACh) is made from choline and acetyl CoA

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

3 Choline is transported back into the axon terminal and

These vesicles remain stored in the presynaptic terminal until needed. When an **action potential arrives**, calcium enters the terminal, triggering **vesicle fusion with the membrane and exocytosis**, releasing acetylcholine into the **synaptic cleft**.
Once released, acetylcholine diffuses across the synaptic cleft and binds to **receptors on the postsynaptic neuron**. However, not all neurotransmitter molecules bind to receptors. Some may **diffuse away from the synaptic cleft**, while others are rapidly **degraded by the enzyme acetylcholinesterase (AChE)** into **choline and acetate**.
After receptor activation, acetylcholine also quickly **dissociates from the receptor**, allowing ion channels to return to their resting state. The **choline produced by degradation is transported back into the presynaptic neuron**, where it is reused for **acetylcholine resynthesis**



1. Acetylcholine (ACh) is made from choline and acetyl CoA
2. In the synapse, ACh is rapidly broken down by the enzyme **acetylcholinesterase (AChE)**
3. Choline is transported back into the axon terminal and used to make more ACh

Key Feature of Small-Molecule Neurotransmitters

Small-molecule neurotransmitters are characterized by their **rapid action**. In the presynaptic terminal, they undergo a continuous cycle consisting of:

1.Synthesis
2.Packaging into vesicles
3.Rapid release
4.Enzymatic degradation or reuptake
5.Recycling and resynthesis

These processes allow them to function as **fast-acting chemical signals in synaptic transmission.**

Neuropeptides(Large molecules)

Hypothalamic-Releasing Hormones	Peptides that Act on Gut and Brain	From Other Tissues
Thyrotropin-releasing hormone	Leucine enkephalin	Angiotensin II
Luteinizing hormone–releasing hormone	Methionine enkephalin	Bradykinin
Somatostatin (growth hormone inhibitory factor)	Substance P	Carnosine
Pituitary Peptides	Gastrin	Sleep peptides
Adrenocorticotropic hormone	Cholecystokinin	Calcitonin
β-Endorphin	Vasoactive intestinal polypeptide	
α-Melanocyte-stimulating hormone	Nerve growth factor	
Prolactin	Brain-derived neurotropic factor	
Luteinizing hormone	Neurotensin	
Thyrotropin	Insulin	
Growth hormone	Glucagon	
Vasopressin		
Oxytocin		

Neuropeptides differ from small-molecule neurotransmitters primarily in their **site and mechanism of synthesis.** Unlike small-molecule neurotransmitters, which are synthesized in the **axon terminal**, neuropeptides are synthesized in the **neuronal cell body (soma).** This is because neuropeptides are **large and structurally complex molecules** that require the full processes of **gene expression**, including **transcription in the nucleus and translation on the rough endoplasmic reticulum**.
After synthesis, neuropeptides undergo **post-translational processing and packaging in the Golgi apparatus**. Because of their complexity, they **axon terminal**. Instead, once synthesized and packaged, they are transported from the **cecannot be synthesized locally at the ll body to the axon terminal through axonal transport** within specialized vesicles.
Axonal transport is a **relatively slow process**, resulting in a delay between the **synthesis of neuropeptides in the soma and their arrival at the nerve terminal for release**. Consequently, neuropeptides are generally **released in smaller quantities** compared with small-molecule neurotransmitters.
Despite their lower quantity, neuropeptides produce **stronger and longer-lasting physiological effects**. They are considered **highly potent**, meaning that even a small number of molecules can generate a significant response in the postsynaptic neuron.
Regarding receptor interaction, **small-molecule neurotransmitters can act on both ionotropic and metabotropic receptors**, whereas **neuropeptides mainly act through metabotropic receptors**. Activation of these receptors produces **slower but prolonged effects**, including modulation of synaptic transmission, changes in membrane potential, and regulation of **gene transcription and receptor expression**.

Key differences between **small-molecule neurotransmitters** and **neuropeptides** include:

Feature	Small-Molecule Neurotransmitters	Neuropeptides
Site of synthesis	Axon terminal	Cell body (soma)
Speed of synthesis	Rapid	Slow
Packaging	Synaptic vesicles in terminal	Vesicles formed in soma
Transport	Local synthesis	Axonal transport to terminal
Quantity released	Relatively large	Small
Duration of effect	Short-acting	Long-lasting
Receptors	Ionotropic and metabotropic	Mainly metabotropic

Functional and Clinical Importance

Understanding the differences between neurotransmitters is essential for determining their **functional roles and localization within the nervous system**. Neurotransmitters may exert **excitatory or inhibitory effects**, and their actions may be mediated through **ionotropic or metabotropic receptors**.

This distinction is particularly important in **clinical medicine**, as many neurological disorders arise from an **imbalance between excitatory and inhibitory neurotransmission**. Knowledge of these mechanisms allows for **targeted pharmacological interventions**, where drugs are designed to enhance or suppress specific neurotransmitter systems.

Furthermore, identifying whether a neurotransmitter acts through **ionotropic receptors (rapid responses)** or **metabotropic receptors (slower, longer-lasting effects)** is critical for understanding **neural signaling, synaptic modulation, and disease mechanisms**, as well as for developing effective therapeutic strategies.

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

is a gas, and mostly it is kind of a neuromodulator, rather than just binding to ionotropic receptors and changing the permeability. It can do more structural changes within the postsynaptic neuron.

- It is not preformed and stored in vesicles in the presynaptic terminal as are other transmitters.
- Instead, it is synthesized almost instantly as needed and then diffuses out of the presynaptic terminals over a period of seconds rather than being released in vesicular packets.
- Next, it diffuses into postsynaptic neurons nearby.
- In the postsynaptic neuron, it usually does not greatly alter the membrane potential but instead changes intracellular metabolic functions that modify neuronal excitability for seconds, minutes, or longer.

Key Points in Studying Neurotransmitters

- Identify the **name of the neurotransmitter** and the **site of its release.**
For example, if acetylcholine is released at the **neuromuscular junction**, this indicates that neurotransmission occurs at that junction.
- If a neurotransmitter is described as being released from a **specific brain region** (e.g., the **brainstem**), this means that the **cell bodies of the neurons producing that neurotransmitter are located in that region.**
- Determine the **type of receptor** on which the neurotransmitter acts: **ionotropic, metabotropic, or both**.
- Identify the **functional effect** of the neurotransmitter: **excitatory, inhibitory, or both**, depending on the receptor and location.
- Recognize the **most common neurological disorders associated with dysfunction of that neurotransmitter.**

Acetylcholine

Acetylcholine is secreted by neurons in many areas of the nervous system such as:

- motor neurons that innervate the skeletal muscles form a synapse known as the **neuromuscular junction** (NMJ), where acetylcholine is released to transmit signals from the nerve to the muscle. Therefore, dysfunction of motor neurons may lead to **impaired release of acetylcholine**. Therapeutic strategies may involve **administration of acetylcholine or inhibition of its degradation at the neuromuscular junction,** produces an **excitatory effect**, particularly at the neuromuscular junction where muscle contraction is required.
- neurons of the autonomic nervous system, and dysfunction in this system may result in **disturbances in internal organ regulation**.
- Basal forebrain, **including the frontal cortex**, which is involved in **thinking and judgment**. Degeneration of cholinergic neurons in these regions is associated with **Alzheimer's disease**, which affects memory and cognitive function. Research is ongoing to better understand and treat this condition.

In most cases, acetylcholine has an excitatory effect

Acetylcholine

Receptors are nicotinic (ionotropic) which produce rapid responses, such as those required at the neuromuscular junction, muscarinic (metabotropic: GPCR).

- Mysthenia gravis.
- Alzheimer's disease

Norepinephrine

- A Norepinephrine is secreted by the terminals of many neurons whose cell bodies are located in:
- the brain stem, specifically, locus ceruleus that plays a role in wakefulness and arousal.
- also secreted by most postganglionic neurons of the sympathetic nervous system.
- Abnormalities in norepinephrine signaling are associated with conditions such as: Depression & ADHD, where alterations in arousal and excitability occur.
- Therapeutic interventions may involve drugs that influence **norepinephrine signaling**.

Dopamine

- Dopamine is secreted by neurons that originate in the substantia nigra, forming the nigrostriatal pathway, which is involved to control movement of muscles.
- Dopamine is present in pleasure pathways (reward and motivation pathways (mesolimbic pathway)).
- The effect of dopamine can be inhibitory or excitatory depends on the type of the receptor.

Disorders in the dopaminergic neurons at the level of the substantia nigra, which is in the brainstem, affect the control of muscle movement, as this area is considered part of the basal nuclei. So, this impairment will affect our muscle movement, and this is most specifically related to a common disease that we know of, which is Parkinson's disease.

Also, dopamine is related to the pleasure sensation pathway. One example of the implication of that is cocaine. Cocaine actually works to prevent the reuptake of dopamine, and consequently, dopamine will accumulate in the synaptic cleft. So, it will continue binding to the postsynaptic neuron and act on these postsynaptic neurons.
And as we said, it is part of the pleasure pathway, so that's why cocaine uptake will give this kind of pleasure sensation. But later on, that will cause addiction and the consequences of addiction.

- Nigrostriatal pathway → movement (Parkinson's)
- Mesolimbic pathway → reward/pleasure

Glycine

- A Glycine is secreted mainly at synapses in the spinal cord.
- It is almost always an inhibitory transmitter.

GABA

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

- R: GABA-A (Cl channel) **ionotropic chloride channels** producing rapid inhibition through **hyperpolarization**.
  GABA-B (GPCR); which are **metabotropic receptors** producing more **prolonged inhibitory effects**.

- Epilepsy

Glutamate

- A Glutamate is the main excitatory neurotransmitter.
- R : (ionotropic: AMPA, NMDA), metabotropic (mGluR)

Serotonin

- ASecreted by raphe nucleus of the brain stem.
- plays an important role in Control mood, sleep, appetite, pain.
- Abnormal serotonin signaling is associated with Depression, For this reason, antidepressant therapy commonly involves **selective serotonin reuptake inhibitors (SSRIs)**, which increase serotonin availability. Patients with depression often present with **depressed mood, sleep disturbances, appetite changes, and chronic discomfort or pain**..
- R: 5-HT1-7 (ionotropic and metabotropic)

Substance P

- Neuropeptide
- Sensory neurons, spinal cord, hypothalamus.
- Pain transmission (chronic pain), inflammation and stress.

It is released from **sensory neurons transmitting pain signals** and is particularly associated with **chronic pain**, often accompanied by **inflammatory processes and physiological stress.**

Oxytocin

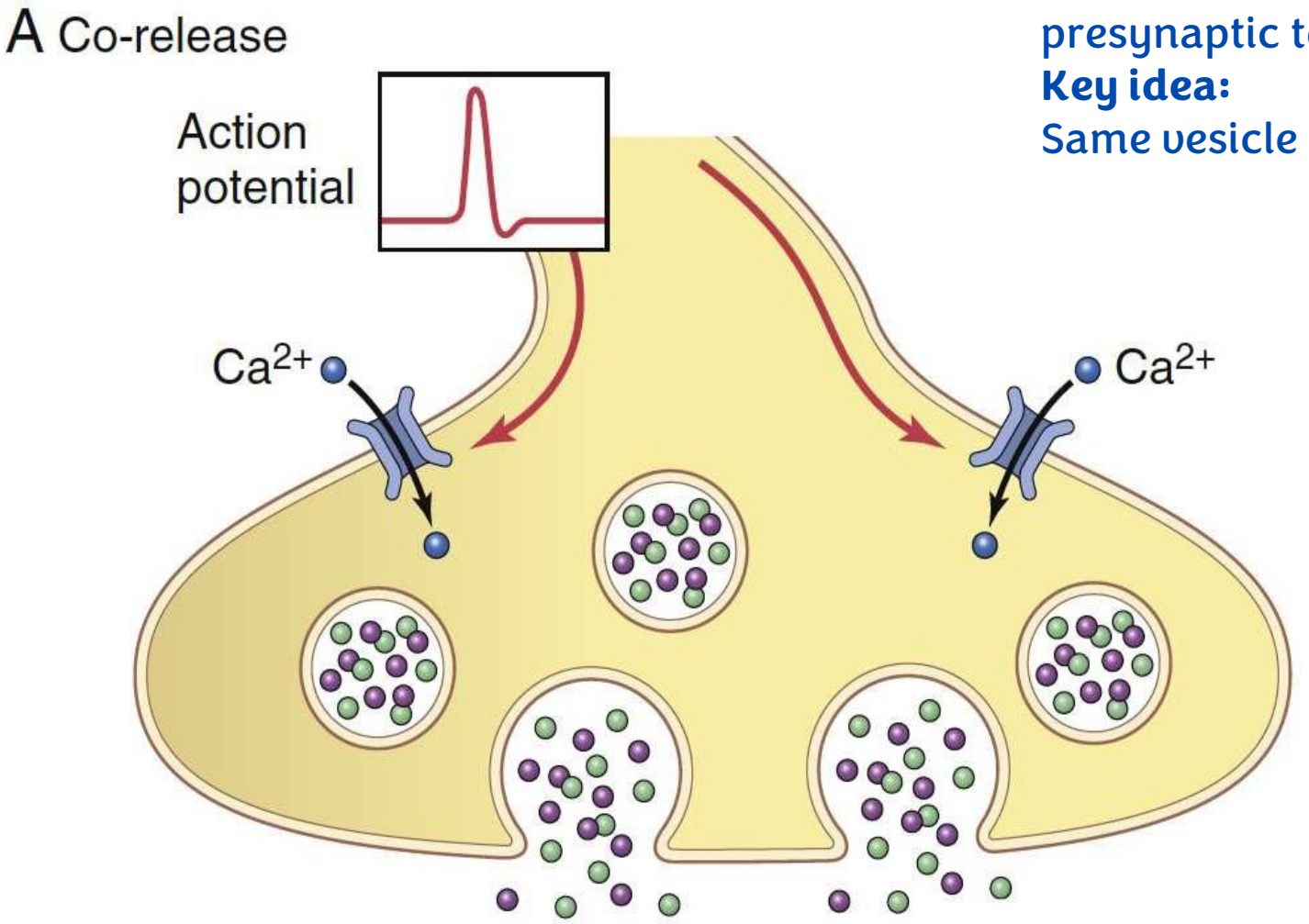
- Neuropeptide
- Produced in hypothalamus and Released from posterior pituitary **into the bloodstream**.
- Control contractions of uterus during labor
- Ejection of milk during lactation
- Social bonding and emotional behavior

- **Reproductive system:**
  - Stimulates **uterine contractions** during labor.
  - Promotes **milk let-down reflex** during breastfeeding.
- **Behavioral effects:**
  - Enhances **bonding** between mother and child.
  - Increases **trust, empathy, and social connection**.
  - Released during **hugging, touch, music, and exercise**.

Co-transmission

- 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.



1. Co-release

Two or more neurotransmitters are **co-localized within the same synaptic vesicles** and are **released simultaneously** when an action potential reaches the presynaptic terminal.

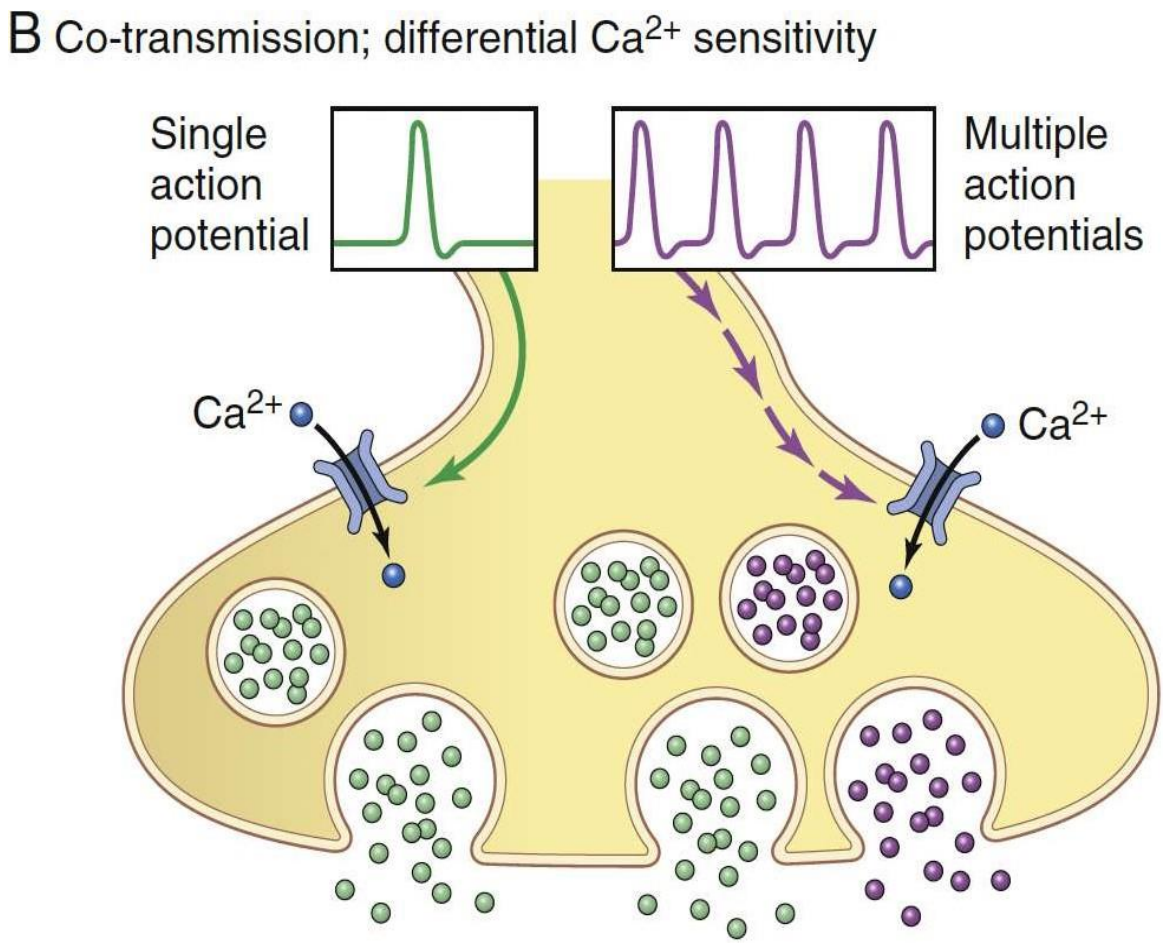
Key idea:

Same vesicle → same release.

Co-transmission

- 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

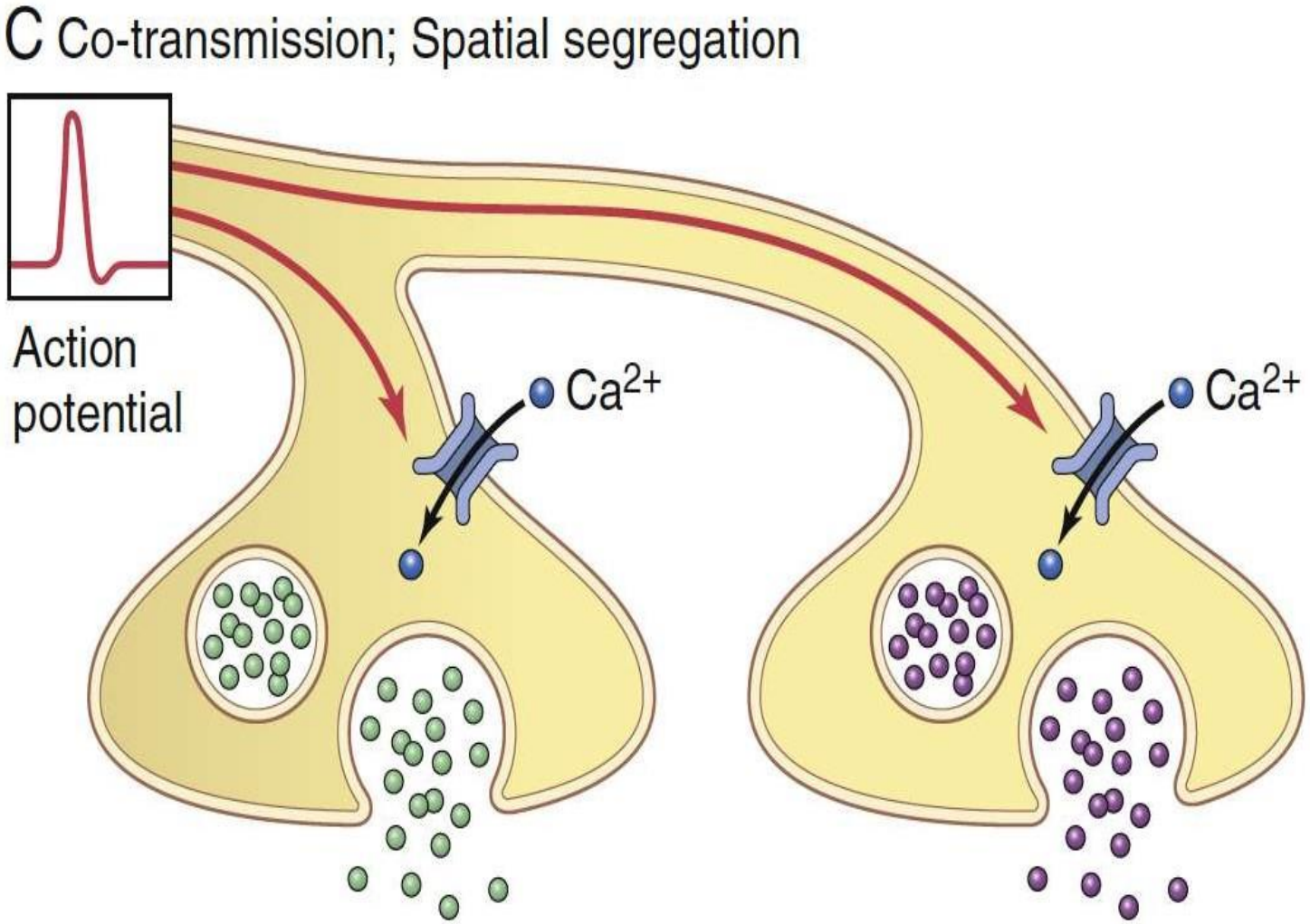


2. Differential release (different Ca^{2+} sensitivity)
Different neurotransmitters may be **stored in separate vesicles within the same neuron.**
Their release can be **differentially regulated depending on calcium ion sensitivity.**
- **Single action potential → release of one transmitter**
- **Multiple action potentials → release of additional transmitters**

Key idea:
Different vesicles → release depends on stimulation intensity.

Co-transmission

- Or spatial segregation of the vesicles on different boutons



Different neurotransmitters may be **stored in vesicles located at different presynaptic boutons of the same neuron**, allowing release at **different synaptic sites**.

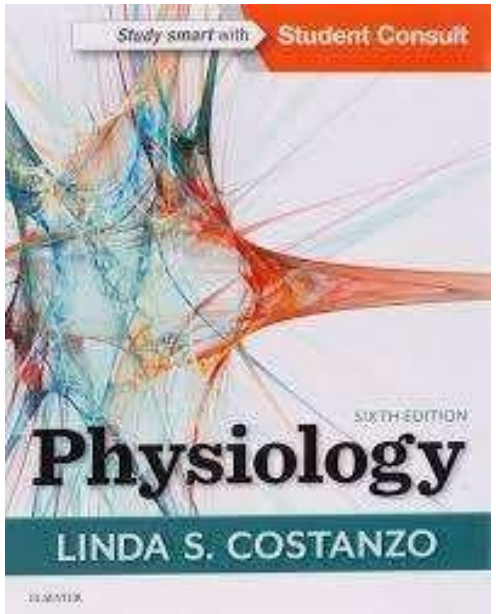
Key idea:

Different terminals → different transmitters.

Summary table to recap your info

وفقكم الله

Neurotransmitter	Main Location / Source	Receptor Type	Main Effect	Key Functions	Clinical Association
Acetylcholine (ACh)	Motor neurons (NMJ), Autonomic nervous system, Basal forebrain	Nicotinic (ionotropic), Muscarinic (metabotropic)	Mostly **excitatory**	Muscle contraction, autonomic regulation, cognition	Myasthenia gravis, Alzheimer's disease
Norepinephrine (NE)	**Locus coeruleus** (brainstem)	Metabotropic (adrenergic)	Excitatory or inhibitory	Arousal, attention, wakefulness	Depression, ADHD
Dopamine (DA)	**Substantia nigra**, mesolimbic & mesocortical pathways	Metabotropic (D receptors)	Excitatory or inhibitory	Movement control, reward, motivation	Parkinson's disease, schizophrenia
Glutamate	Widely distributed in CNS	Ionotropic (NMDA, AMPA, kainate), Metabotropic	**Main excitatory neurotransmitter**	Learning, memory, synaptic plasticity	Excitotoxicity, stroke, neurodegeneration
GABA	Widely distributed in CNS	GABA A (ionotropic Cl^-), GABA B (metabotropic)	**Main inhibitory neurotransmitter**	Reduces neuronal excitability	Anxiety disorders, epilepsy
Glycine	**Spinal cord** and brainstem	Ionotropic (Cl^- channels)	Inhibitory	Spinal cord inhibition	Startle disorders
Serotonin (5-HT)	Raphe nuclei (brainstem)	Mostly metabotropic (some ionotropic)	Excitatory or inhibitory	Mood, sleep, appetite	Depression, anxiety
Substance P	Sensory neurons (pain pathways)	Metabotropic	Excitatory	Pain transmission, inflammation	Chronic pain
Oxytocin	Hypothalamus → Posterior pituitary	Metabotropic	Modulatory	Uterine contraction, milk ejection, behavior	Labor regulation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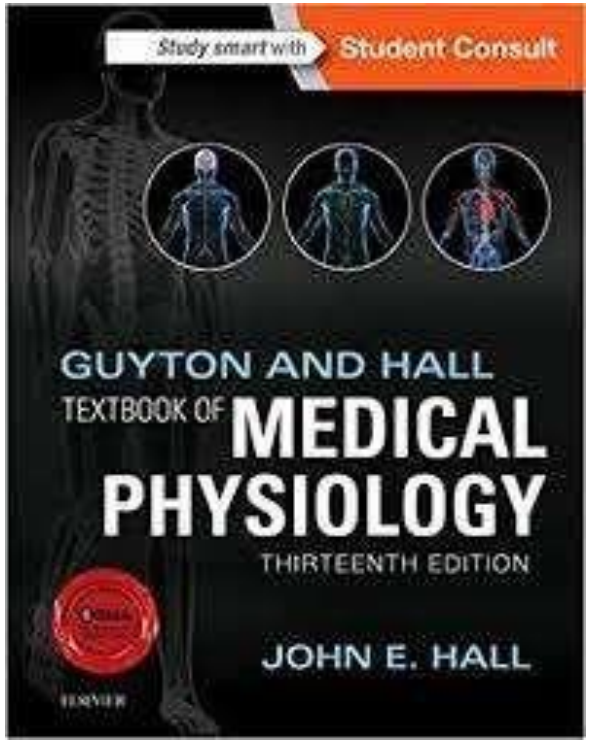
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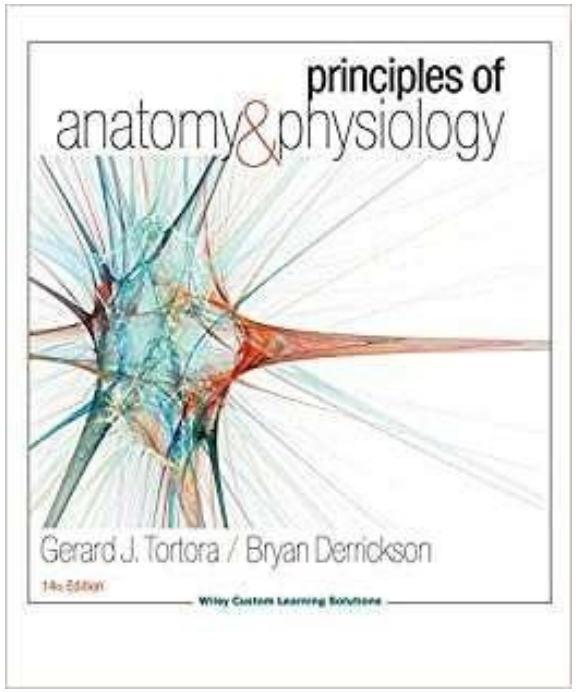
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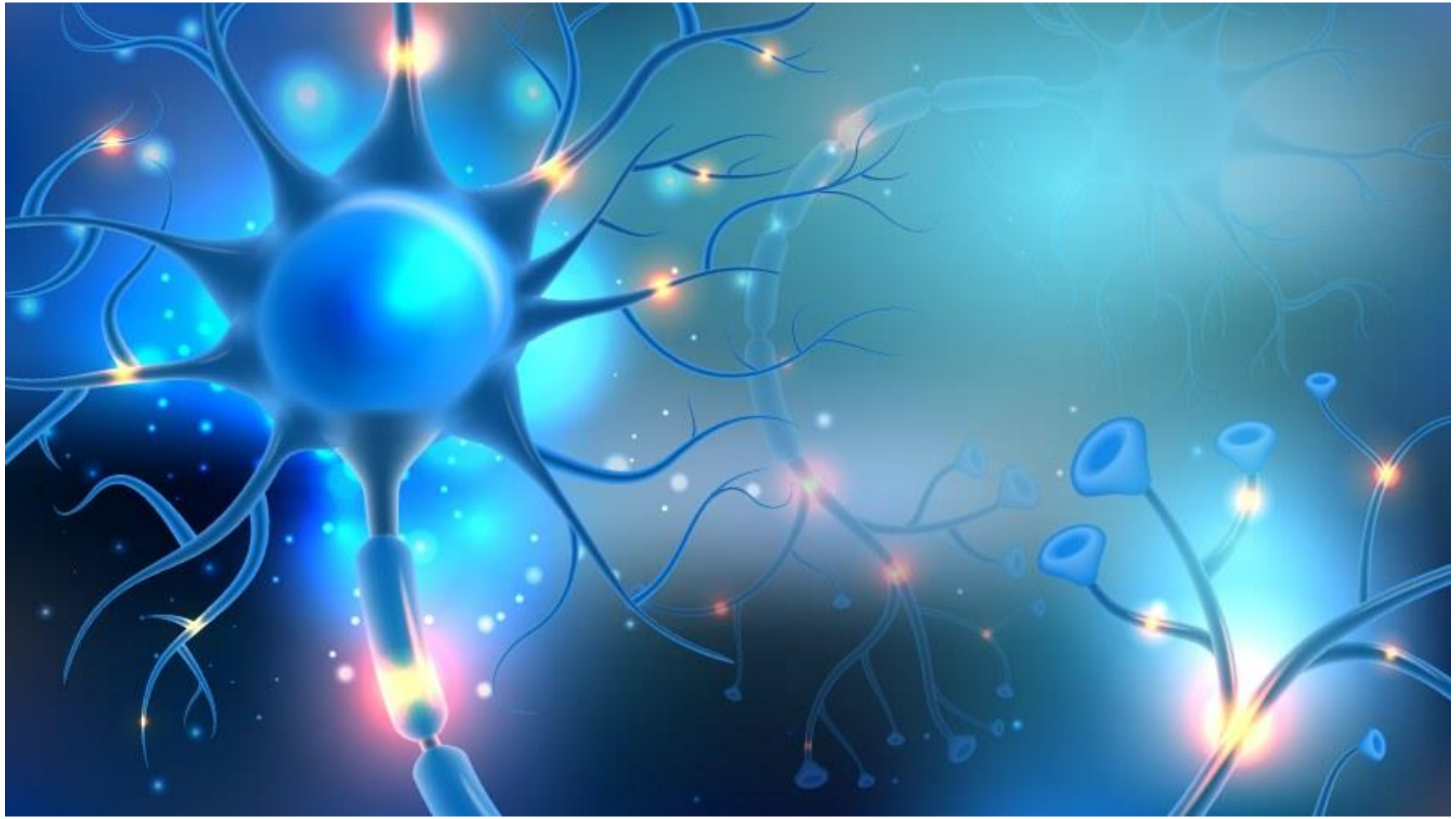

Additional Resources:

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"رَبِّ إِنِّي لِمَا أَنْزَلْتَ إِلَيَّ مِنْ خَيْرٍ فَقِيرٌ) "سورة القصص(24 :

لا تنسَ احتساب أجر تعبك وقت الدراسة لله ، وتأكد أنَ الله لا يضيع تعب من سعى ، فعلينا السعي والله يتولى النتائج .
ولا تقارن نفسك بأحد ، وتوكل على الله وتأكد أن كل علامة هي رزق ومقدّر عند الله سبحانه وتعالى .
واجعل همّك في دراستك رفع الأمة وليس علامة تنالها في امتحان
قال الإمام الشافعي : «لَيْسَ العِلْمُ مَا حُفِظَ، إنَّما العِلْمُ مَا نَفَعَ»

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