Physiology Team

LECTURE : 1

Physiology of synapses and receptors

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OBJECTIVES

At the end of this lecture, student should be able to know:

- Define synapses
- Functions of synapses
- Structures of synapses
- Types of synapses: Anatomical & Functional
- Synaptic transmission & neurotransmission
- Fate of neurotransmitters
- Electrical events at synapses (EPSPs & IPSPs)
- Properties of synaptic transmission
- Factors affecting synaptic transmision

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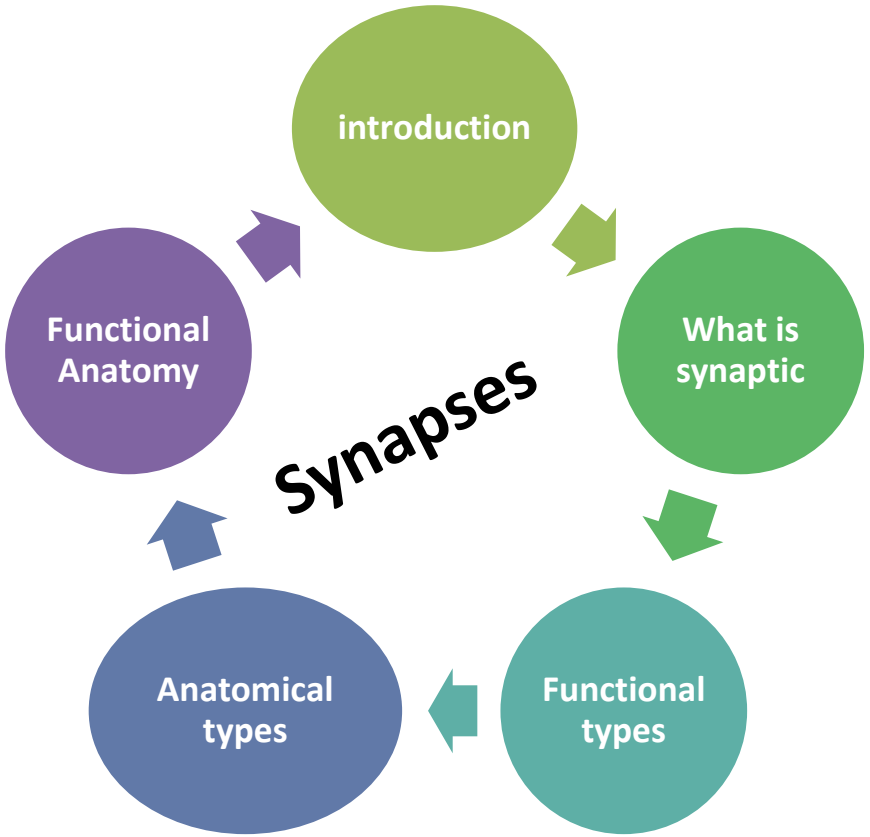
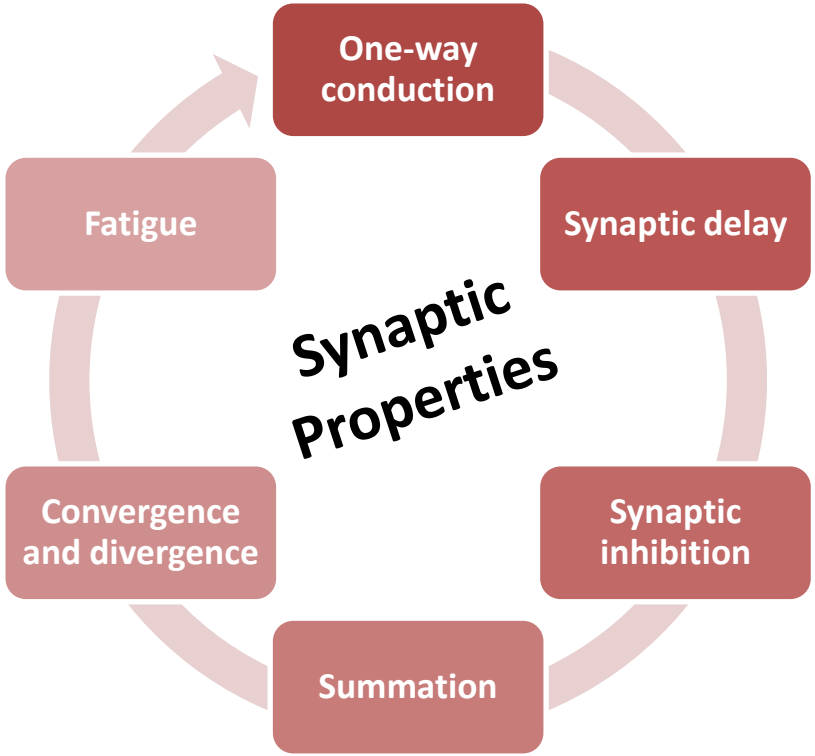
MIND MAP





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Synapse

So, the # of synapses will be more than # of neurons.

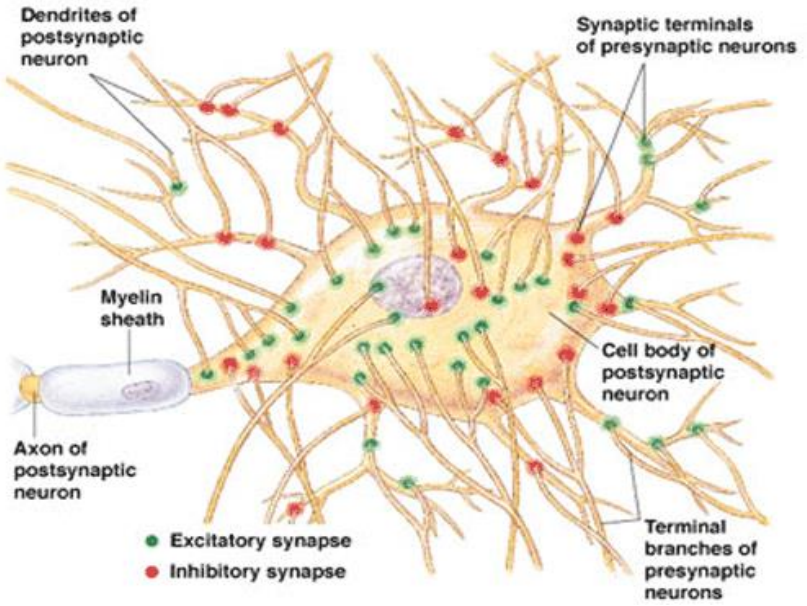
- The CNS contains more than **100 billion neurons**.
- Incoming signals enter the neuron through synapses *located* mostly on the **neuronal dendrites**, but also on the **cell body**.
- *For different types of neurons, there may be only a few hundred or as many as 200,000 such synaptic connections from input fibers*.

Conversely, the **output** signal travels by way of a single axon **leaving** the neuron.

What is Synapse

junction where the axon or some other portion of one cell (= presynaptic cell) terminates on the dendrites, soma, or axon of another neuron (post synaptic cell).

In the synapses the membranes of adjacent cells are in close apposition (contiguity=contact, not continuity).

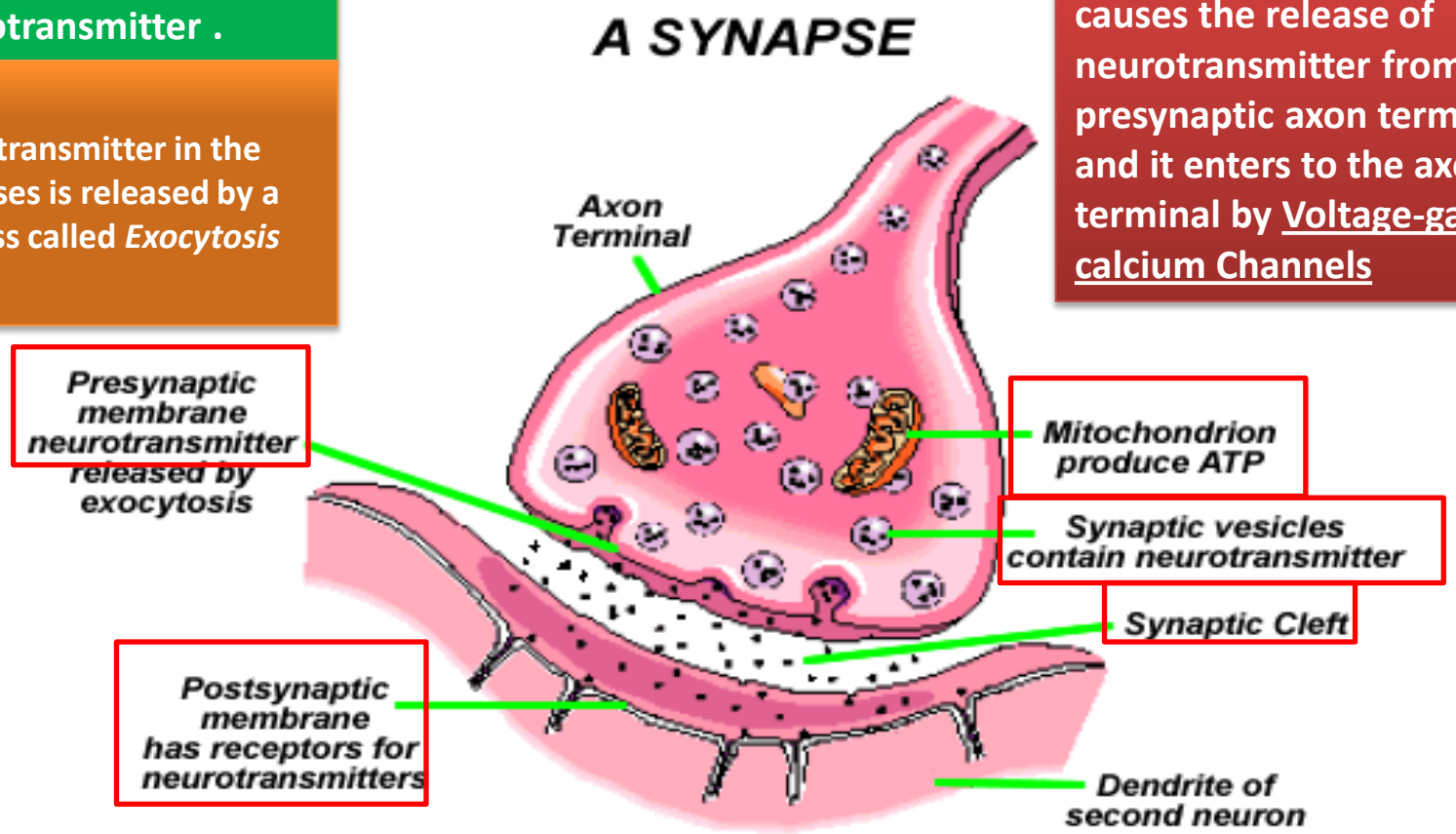


Functional Anatomy of a synapse

There is inhibitory & excitatory neurotransmitter .

neurotransmitter in the synapses is released by a process called *Exocytosis*

Calcium is the ion that causes the release of neurotransmitter from the presynaptic axon terminal, and it enters to the axon terminal by Voltage-gated calcium Channels



Ligand gated channel Receptors

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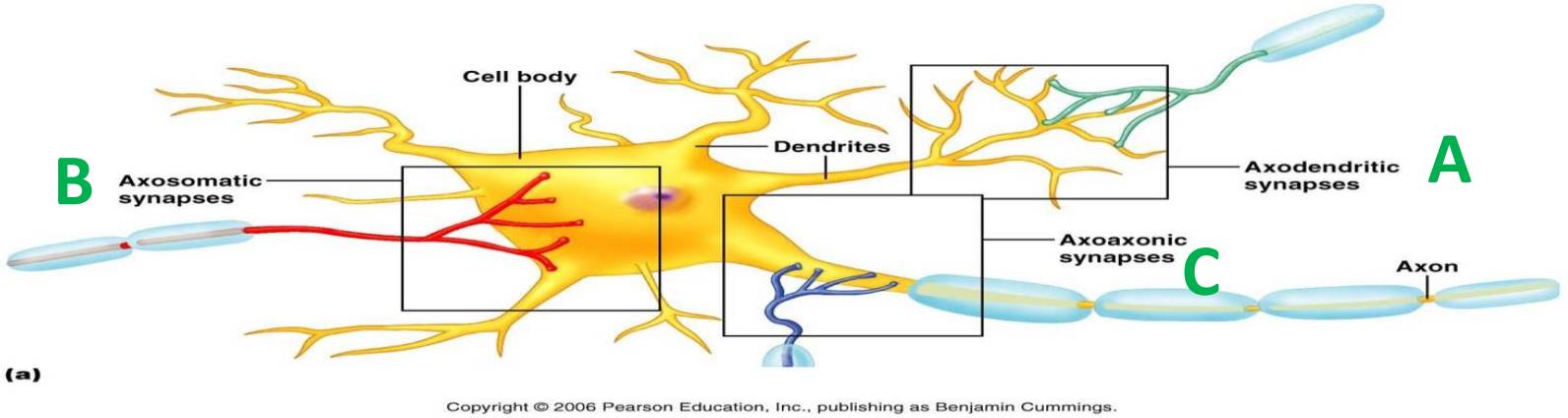
Anatomical types of synapses

- **A- Axodendritic :** synapses between the axon of one neuron and the dendrite of another
- **B- Axosomatic :** synapses between the axon of one neuron and the soma of another
- **C- Other types of synapses include:**
  - **– Axoaxonic** (axon to axon)
  - **– Dendrodendritic** (dendrite to dendrite)
  - **– Dendrosomatic** (dendrites to soma)
  - -- **Somato-somatic**



Functional types of synapses

Chemical synapses	Electrical synapses	Conjoint synapses
Almost all synapses used for signal transmission in the CNS of human being are chemical synapses. **(most common)** i.e. first neuron secretes a chemical substance called neurotransmitter at the synapse to act on receptor on the next neuron to excite it, inhibit or modify its sensitivity. **Slower than electrical synapses in conduction of nerve Impulses.**	Membranes of the pre- and post-synaptic neurons come close together and gap junctions forms low membrane borders which allow passage of ions. • Are less common than chemical synapses Correspond to gap junctions found in other cell types Are important in the CNS in: • Arousal from sleep • Mental attention, Emotions and memory • Ion and water homeostasis	Both electrical and chemical. E.X: neurons in lateral vestibular nucleus.

In this type of synapses, there is One-way conduction , since that the neurotransmitter is released by the presynaptic neuron to act on the postsynaptic neuron, and cannot be in the opposite way.

Gap junctions are formed in the cell membranes of the two neurons in the synapse (why?) > to allow the easy passage of ions across the membranes, which explains why the electrical synapses are much more faster in conduction of nerve impulses, compared to the chemical synapses. Therefore, it is required in process such as mental attention and arousal from sleep.

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EXPLANATION

The Neurotransmitters

Neurotransmitter is a chemical substance released by a neuron (called presynaptic cell), crosses the synaptic cleft, and binds to a receptor located on the membrane (postsynaptic membrane) of another cell

What are the types of transmitters?

- **Excitatory neurotransmitter**: It's a transmitter that produces excitatory postsynaptic potential (EPSP) on the postsynaptic neuron.
- **Inhibitory neurotransmitter**: It's a transmitter that produces inhibitory postsynaptic potential (IPSP) on the postsynaptic neuron.

In what location the neurotransmitter synthesized?

All the neurotransmitters which are peptides are synthesized in the cell body, but all those which have small molecular weight are synthesized in the nerve ending (e.g ACH)

In what location the transmitter vesicle synthesized? Neuron cell body.

What happens at the synapses

Information is transmitted in the CNS mainly in the form of Action Potentials "=nerve impulse", which pass from one neuron to another.

Each impulse through its way from one neuron to another may be:-

1. **blocked** in its transmission from one neuron to another
2. **changed** from single impulse to **repetitive impulses**.

Synaptic transmission is a complex process that permits grading and adjustment of neural activity necessary for normal function.

E.X. of synapses outside CNS:

1.NMJ = Neuromuscular Junction

2.Contact between: autonomic neurons and smooth , cardiac muscles, and other effector cells

Structure & function of synapse

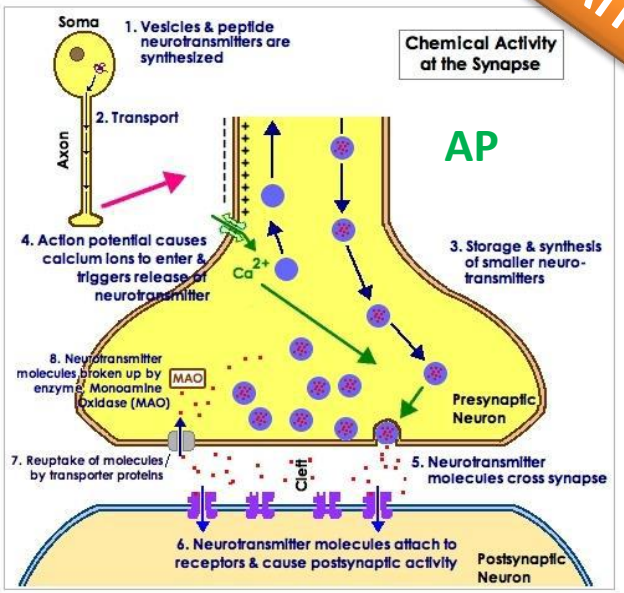
Synaptic cleft: This the space between the axon terminal and sarcolemma. It has a width of 200-300 angstroms.
It contains enzymes that destroy neurotransmitters.

Synaptic knobs (presynaptic terminal) cover about 40% of soma and 70% of dendritic membrane
It contains neurotransmitters and mitochondria to provide ATPs for the synthesis and secretion of the neurotransmitters.

Mechanism of synaptic Transmission

EXPLANATION

1. Synthesis of Neurotransmitter peptides and the vesicles in the cell body, and then they will be transferred to the Axon terminal.
2. In the Axon terminal, the neurotransmitter will be stored in those small vesicles.
3. Action potential will be traveling along the axon until it reaches the axon terminal where it causes the opening of VoltAge-gated Calcium channel, allowing the influx of the Ca++.
4. The entry of Ca++ will cause the release of neurotransmitter in the synaptic cleft.

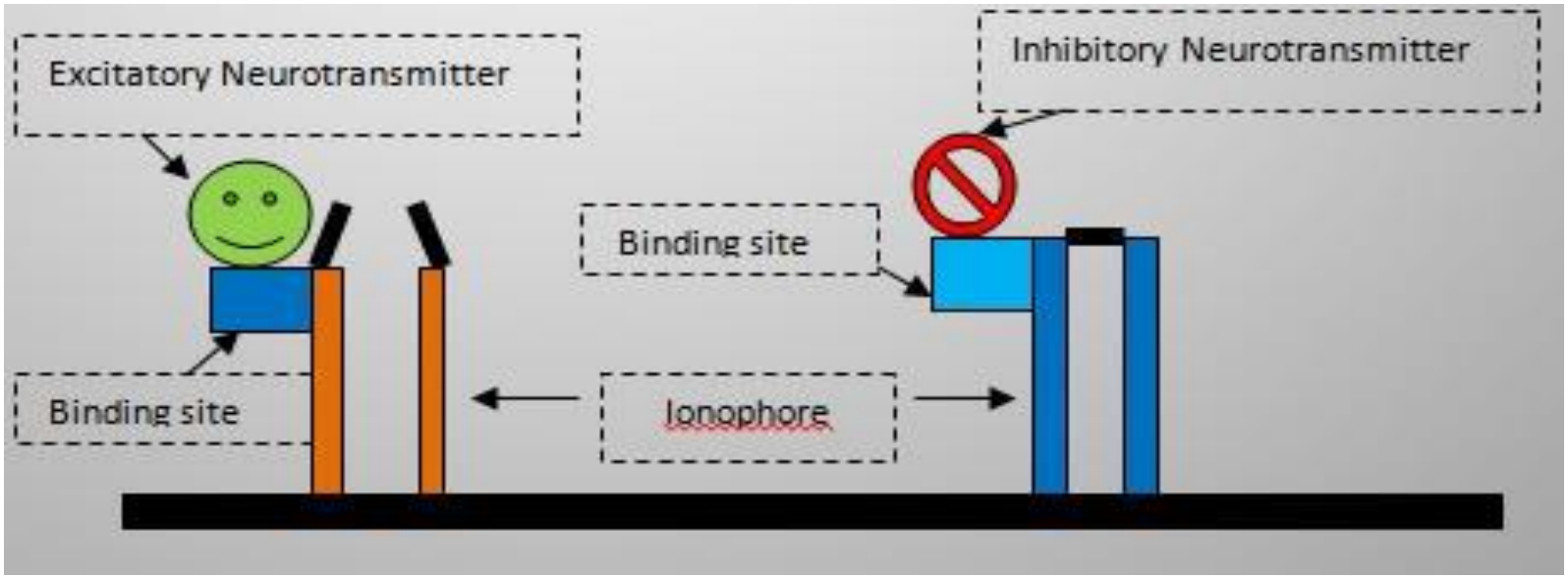


5. Neurotransmitter will act on the postsynaptic cell receptors and cause an activity there (according to the type of neurotransmitter)
6. After acting on the receptors, the neurotransmitter will be either: diffused to the fluid outside the synaptic cleft, undergone enzymatic destruction, or uptaken by Active transport to the presynaptic axon terminal where it will be stored again in vesicles.

Calcium is the ion that causes the release of neurotransmitter from the presynaptic axon terminal, and it enters to the axon terminal by Voltage-gated calcium Channels

Action of the transmitter substance on post-synaptic neuron

At the synapse, the membrane of post-synaptic neuron contains large number of receptor proteins. Binding of the neurotransmitter to its receptor will result in **inhibition** **or** **excitation** of the post-synaptic membrane **depending on the type of the neurotransmitter** **i.e. excitatory or inhibitory.**



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These receptors have two components

1. Binding site that face the cleft to bind the neurotransmitter

2. Ionophore: It passes all the way through the membrane to the interior. It is of two types

Opening of K channels >> K go out of the cell carrying +ve charge , leaving – ve charge behind it >> causing hyperpolarization

Ion channels

Cation channels Na+
(most common) K+ Ca++
Opening of Na+ channels>> ↑membrane potential in positive direction toward threshold level of excitation >> (+) neuron

Anion channels Cl^- (mainly)
Opening of Cl^- channels diffusion of negative charges into the membrane membrane potential making it more negative >> away from threshold level >> (-) neuron

- **2nd messenger system** in the post-synaptic membrane.
- This mechanism is important where prolonged post-synaptic changes are needed to stay for days, months . . Years (**memory**).

Effects: intracellular enzymes activation, gene transcription, etc…

Fate of neurotransmitter

After a transmitter substance is released at a synapse, it must be removed by:-

- **Diffusion** :out of synaptic cleft into surrounding fluid
- **Enzymatic destruction** :e.g. Ach esterase for Ach
- **Active transport** : back into pre-synaptic terminal itself (**re-uptake**) e.g. norepinephrine

Electrical events in post-synaptic neurons

1. RMP of neuronal soma:

Like In ventricular muscles of the heart

- ≃ - 65 mV i.e. less than **Skeletal Muscles** [**-70** to **-90mV**]
- - If the voltage is less negative (**towards positivity**) >> the neuron is **excitable**

Causes of RMP:

1. Leakage of K+ (high K+ permeability)
2. Large number of negative ions inside: proteins, phosphate
3. Excess pumping of Na+ out by **Na+-K+ pump**

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2. Effect of synaptic excitation on post-synaptic membrane

(Excitatory post-synaptic potential [**EPSPs**])

- When excitatory neurotransmitter binds to its receptor on post-synaptic membrane,(it will cause opening of Na+ channels & there will be influx of sodium , [↑Na influx] of post-synaptic cell membrane. So, there will be increase in the positivity inside the cell.
- causing >> partial depolarization **immediately** under presynaptic ending. i.e. **EPSPs.**
- If this potential rises enough to threshold level >> **AP** will develop and excite the neuron (via central or neuronal summation).
- This summation will cause the membrane potential to increase from -65mV to -45mV.

So, **EPSPs** = **+20mV** which makes the membrane **reach the firing level** >> **AP** develops at **axon hillock.**

N.B. Discharge of a **single** pre-synaptic terminal can **never** increase the neuronal potential from -65mV to -45mV (**resting**) to the firing level, so to raise it up to the threshold level; it requires the process of summation.

we said "immediately under the presynaptic endings" because EPSP is not propagated

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THE DIFFERENCE BETWEEN EPSP & AP

Characteristics	EPSP	Action Potentials
ORIGIN	Arise mainly in dendrites and cell bodies	Arise at trigger zones and propagate along axon
TYPES OF CHANNELS	CHEMICAL, mechanical, or light	Voltage gated ion channels
CONDUCTION	Not propagated, Localized, thus permit communication over a few mm	Propagated, thus permit communication over long distances
POLARITY	May be hyperpolarizing (inhibitory to generation of action potential) or depolarizing (excitatory to generation of action potential)	Always consist of depolarizing phase followed by repolarizing phase and then return to resting membrane potential
summation	Can be summated (temporal & spatial)	Can not be summated
Graded	Can be graded	Can not be graded

In contrast of EPSP, if IPSPs is graded & summated it will not lead to AP

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3. Inhibitory post-synaptic potentials (IPSPs)

- When an inhibitory neurotransmitter binds to its receptor on post-synaptic membrane, it causes hyperpolarization of the post-synaptic membrane which is the IPSP.

- **Causes:**

1. **An increase in membrane permeability to Cl^- of post-synaptic membrane**. **(produced by inhibitory neurotransmitter)** >> ↓ excitability and membrane potential becomes away from firing level.

2. **Also IPSP can be produced by:-**

-Opening of K+ channels >> outward movement of K+

-Closure of Na+ or Ca++ channels

-IPSP = **- 5mV**

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Synaptic Properties

Properties	Definition
One-way conduction	➢ Synapses generally permit conduction of impulses in one-way i.e. from pre-synaptic to post-synaptic neuron. Because most of synapses are chemical so it has to pass from presynaptic membrane to the cleft then to the post synaptic membrane.
Synaptic delay	➢ Is the minimum time required for transmission across the synapse. ➢ It is **0.5 ms** for transmission across one synapse. ➢ This time is taken by : ▪ Discharge of transmitter substance by pre-synaptic terminal ▪ Diffusion of transmitter to post-synaptic membrane ▪ Action of transmitter on its receptor ▪ Action of transmitter to ↑ membrane permeability ▪ Increased diffusion of Na+ to ↑ post-synaptic potential ➢ Electrical neurotransmitters is faster than the chemical one. ➢ To know the type of the synapse either it is monosynaptic or polysynaptic, you have to calculate the number of synapses by this equation: $\frac{total\ time\ of\ reflex}{required\ time\ for\ 1\ synapse}$
Fatigue	It is due to exhaustion of neurotransmitter. If the pre synaptic neurons are continuously stimulated there may be an exhaustion of the neurotransmitter. Resulting in stoppage of synaptic transmission. This will results in epileptic convulsions.

Synaptic Properties

Properties	Definition
Convergence and Divergence	**Convergence :** الحصر والتجميع When many pre-synaptic neurons converge on any single post-synaptic neuron. **Divergence :** الانتشار والتوزيع Axons of pre-synaptic neurons divide into many branches that diverge to end on many post-synaptic neurons.
Summation	a. **Spatial summation.** When EPSP occurs in more than one synaptic knob at the same time. b. **Temporal summation.** If EPSPs in a pre-synaptic knob are successively repeated (sequentially) without significant delay so the effect of the previous stimulus is summated to the next. ➢ If IPSPs are summated, there is no AP even if it reaches the firing level. (From its name ACTION, and we inhibit here → No AP) ➢ EPSPs and IPSPs have local response till they reach the firing level.

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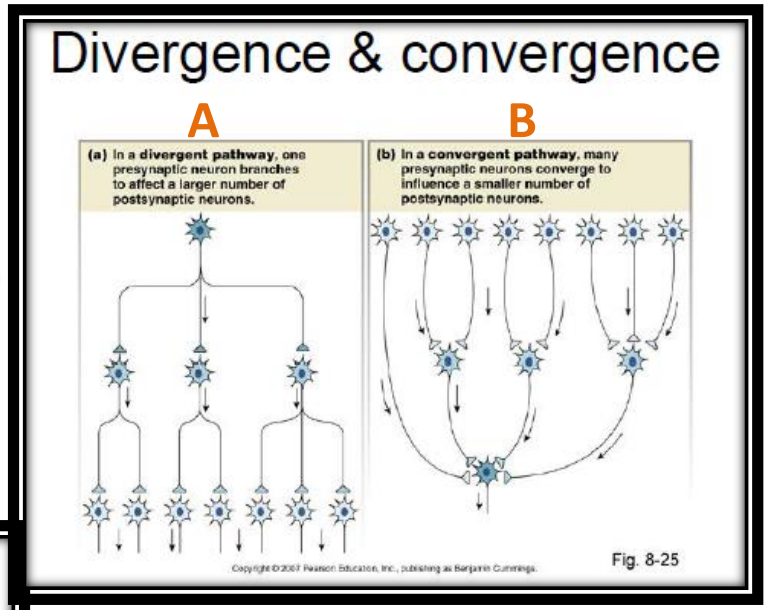
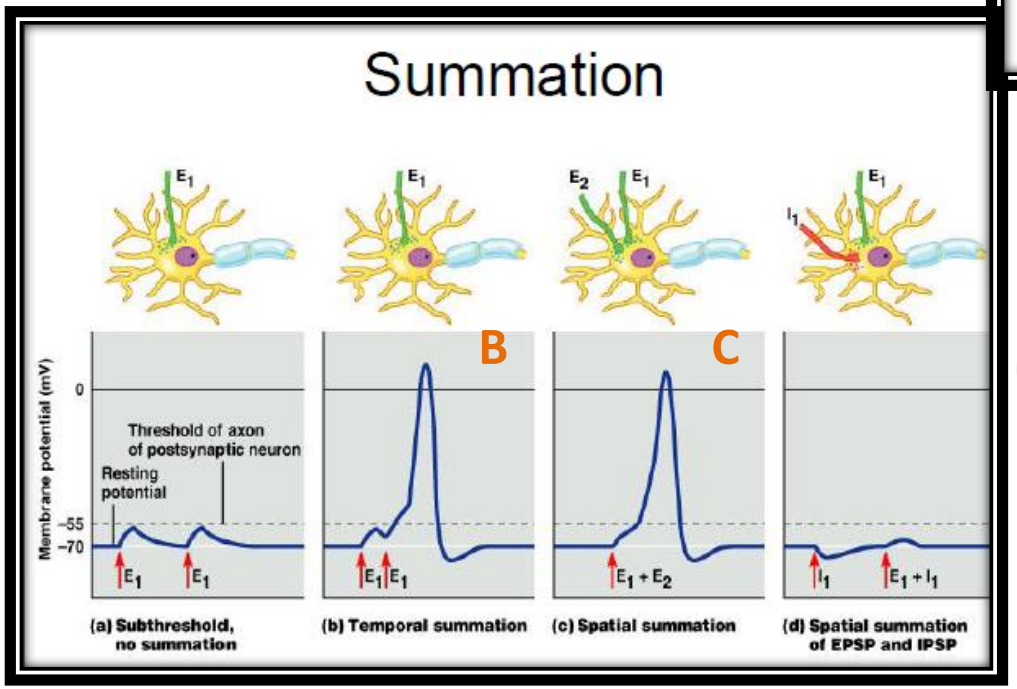
A) One to Many
B) Many to One





B) Temporal: after each other time → firing level and depolarization

C) Spatial: at the same time → firing level and depolarization

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Synaptic Properties

Properties	Definition
Synaptic Inhibition When you walk and there is harmful thing near your left leg, you stand on your right leg in response to that stimulus	**A. Direct inhibition:** Occurs when an inhibitory neuron (releasing inhibitory substance) acts on a post-synaptic neuron leading to → its hyperpolarization due to opening of Cl^- [IPSPs] and/or K+ channels. - Example : Glycine at the level of the spinal cord to block pain impulses. **B. Indirect inhibition: (=Pre-synaptic inhibition).** This happens when an inhibitory synaptic knob lie directly on the termination of a pre-synaptic excitatory fiber. - The inhibitory synaptic knob release a transmitter which inhibits the release of excitatory transmitter from the pre-synaptic fiber. - The transmitter released at the inhibitory knob is GABA (gamma-Aminobutyric acid) - The inhibition is produced by ↑ Cl^- and ↑ K+. e.g. occurs in dorsal horn → pain gating. **C. Reciprocal inhibition** Inhibition of antagonist activity is initiated in the spindle in the agonist muscle. Impulses pass directly to the motor neurons supplying the same muscle and via branches to inhibitory interneurones that end on motor neurones of antagonist muscle. (release of neurotransmitters on the other side) **D. Inhibitory interneuron (Renshaw cells خلايا وسيطة) : Negative feedback inhibitory interneuron of a spinal motor neuron .**

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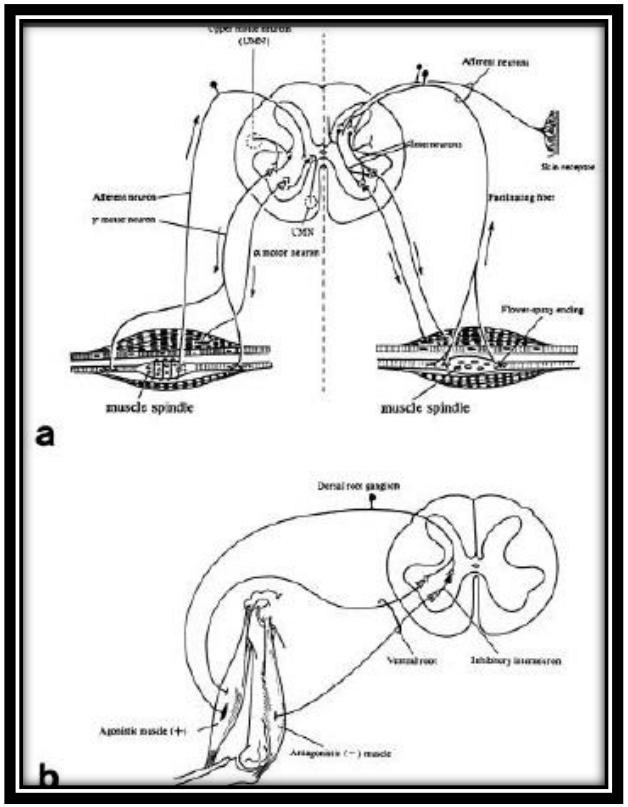
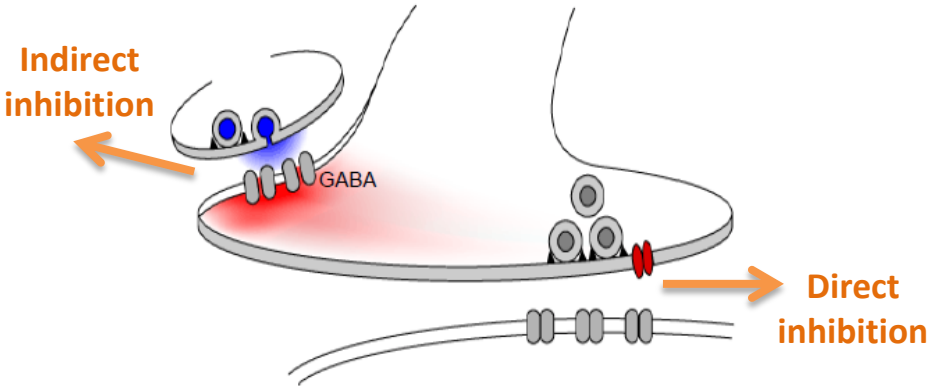
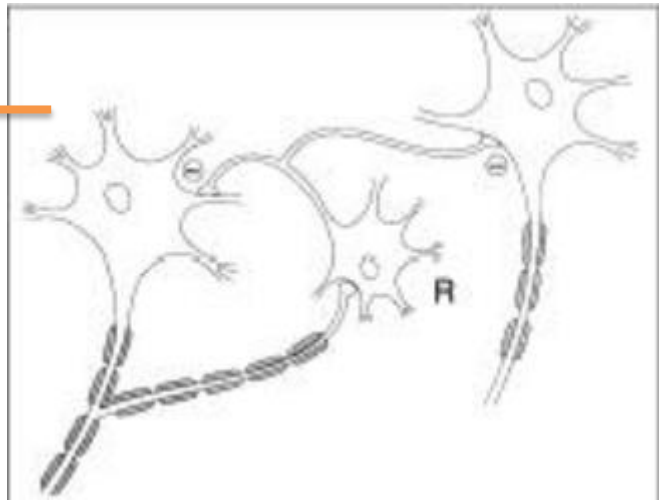
Pre-synaptic inhibition



Reciprocal inhibition



Inhibit both neurons → inhibit transmission of impulses through both of them in one time



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Factors affecting synaptic transmission

Alkalosis:

- Normally, alkalosis greatly **increases neuronal excitability**.
- For instance, a rise in arterial blood pH from the 7.4 norm to 7.8 to 8.0 often causes cerebral epileptic seizures because of increased excitability of some or all of the cerebral neurons.
- This can be demonstrated by asking a person who is predisposed to epileptic seizures to over breathe.
- The over breathing blows off carbon dioxide and therefore elevates the pH of the blood momentarily.

Acidosis:

- Conversely, acidosis greatly **depresses neuronal activity**.
- A fall in pH from 7.4 to below 7.0 usually causes a comatose state.
- For instance, in very severe diabetic or uremic acidosis, coma virtually always develops.

Drugs:

- Many drugs are known to increase the excitability of neurons, and others are known to decrease excitability.
- **Caffeine** found in coffee, tea, **increases neuronal excitability**, by reducing the threshold for excitation of neurons.
- **Strychnine:** Is one of the best known of all agents that **increase excitability of neurons**. It inhibits the action of some normally inhibitory transmitter substances, especially glycine in the spinal cord. Therefore, the effects of the excitatory transmitters become overwhelming, and the neurons become so excited that they go into rapidly repetitive discharge, resulting in severe tonic muscle spasms and convulsions.

Hypoxia:

- **Depression of neurons**

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SUMMARY

- **Anatomical types of synapses:** Axodendritic, Axosomatic, Axoaxonic, Dendrodendritic & dendrosomatic.
- **Functional types of synapses:** chemical synapse, electrical synapse & conjoint synapse.
- **At the synapse** the information are transmitted in the CNS mainly in the form of A.P. passing from one neuron to another.
- **One-way conduction** especially seen in the **Chemical Synapses** .
- **RMP (-65mv)** >> **EPSP (-45mv)** by Na+ influx, if it reaches the **firing level (+20mv)** → **AP** will develop → Nerve is **excited.**
- **Synaptic Properties :**
  - **One-way conduction**
  - **Synaptic delay**
  - **Synaptic inhibition**
  - **Summation**
  - **Convergence and divergence**
  - **Fatigue**

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QUESTIONS

A = D B = D C = A

1- The cause\s of the RMP in post-synaptic neurons is\are:

A. leakage of K+
B. Excess pumping of (Na+ - K+ pump)
C. Large number of (–ve ions) inside
D. All of the above

2- _____mv makes the membrane of EPSP reach the firing level and develops A.P.

A. -45
B. -65
C. -20
D. +20

3- It takes _____ for the transmission across one synapse:

A. 0.5 ms
B. 5.0 ms
C. 50 ms
D. 0.05 ms

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THE END

If there are any Problems or Suggestions,
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THANK YOU