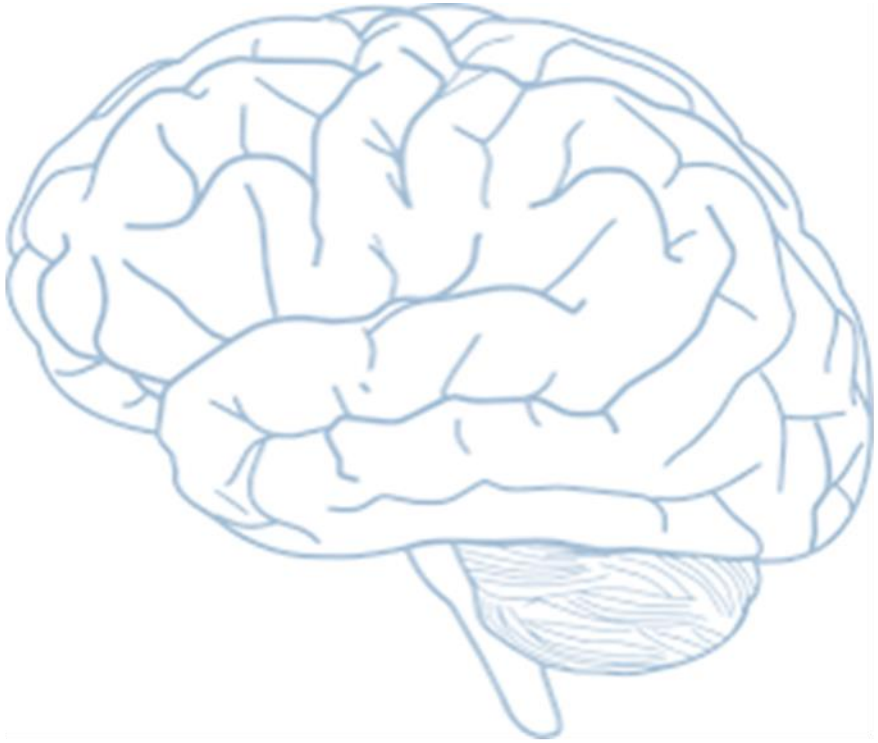
MEDICINE
KING SAUD UNIVERSITY

تمت المراجعة
شوق الأحمري & عبدالعزيز العنقري

Physiology Team 436



CNS PHYSIOLOGY

- Text.
- Important
- Formulas
- Numbers
- Doctor notes
- Extra notes and explanation

Lecture No. I

« وإن الملائكة لتضع أجنحتها
لطالب العلم رضاً بما يصنع »

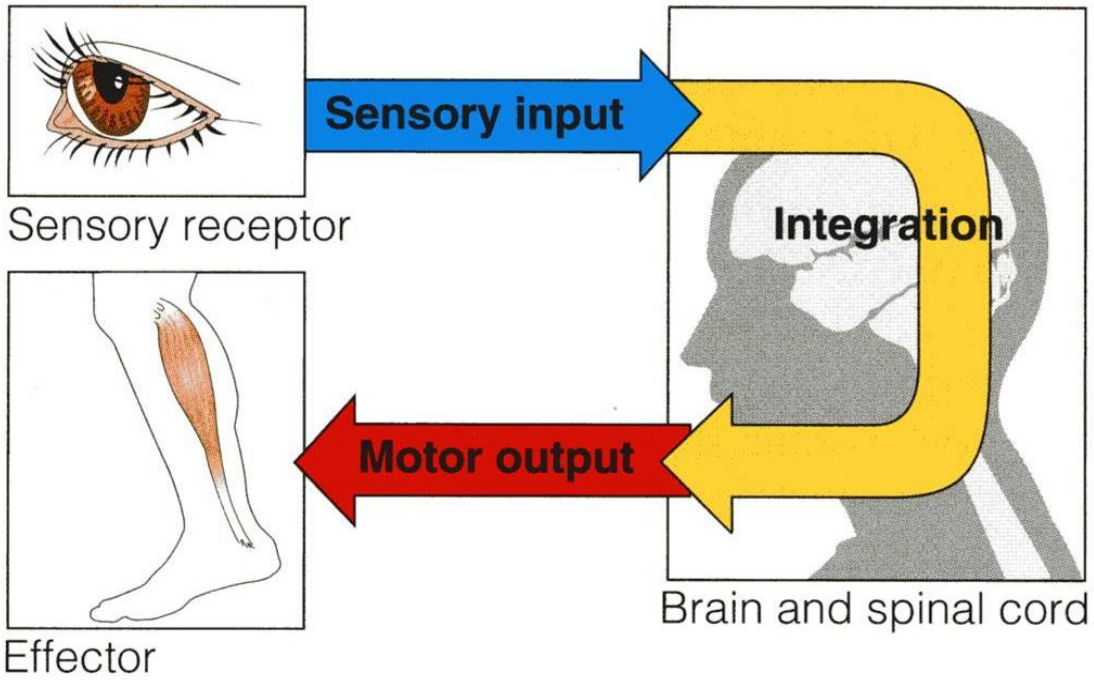
Physiology of Synapses &Receptors

Objectives:

1. Define a synapse and describe the structure and function of chemical and electrical synapses.
2. Define what neurotransmitters are, and how they are released and act on their receptors, and
3. how they are removed.
4. Differentiate between ionotropic receptors and metabotropic receptors
5. Differentiate between postsynaptic and presynaptic inhibition, and between excitatory and
6. inhibitory postsynaptic potentials (EPSPs and IPSPs).
7. Describe properties of synapses and explain the nature of temporal and spatial summation.
8. Appreciate that effectiveness of neurotransmitters can be modified by drugs and diseases.

How brain functions?

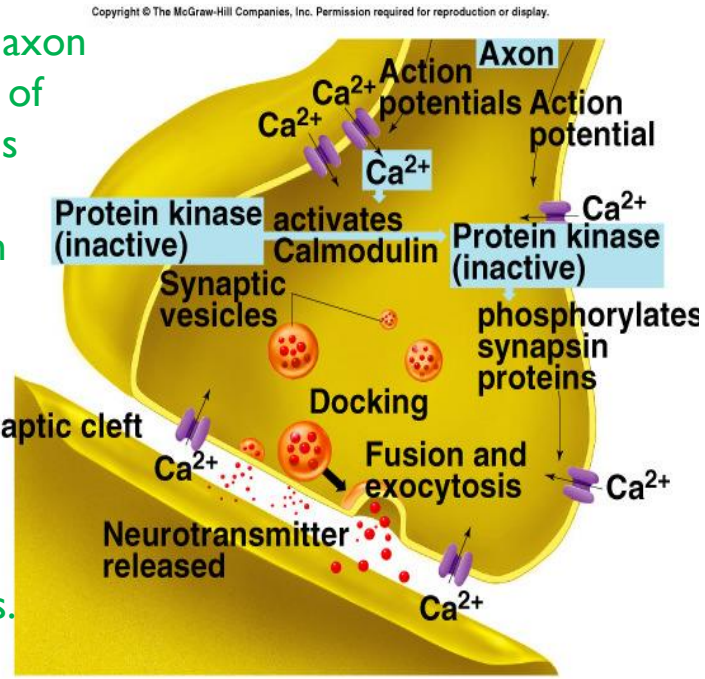
- Collection of sensory input.
- Central Integration.
- Motor output.



Synaptic transmission, neurotransmitters

Information is transmitted in the central nervous system mainly in the form of nerve action potentials, called nerve impulses, through a succession of neurons, one after another.

Propagation of AP in the axon will result in the opening of voltage-gated Ca channels → Calcium activates calmodulin → calmodulin activates protein kinase → PK exposes syntaxin and Synaptobrevin causing the vesicle to become "sticky"→ vesicles fuse in docking site and NTs are releases.



syntaxin and synaptobrevin are proteins found in the membranes of synaptic vesicles. They play a role in vesicle fusion to the " docking " site.

Synapse

What is it?

- It is a 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).
- The CNS contains more than 100 billion neurons.

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- The brain has 86 billion neurons.
- Some CNS neurons receive 20,000 synapses.
- Synaptic input is converted to a nerve impulse (ap) at the axon hillock.
- The output signal (AP) travels by way of a single axon leaving th e neuron.
- The synapse is present in the CNS. And the Junction is present outside it.
- The brain only uses glucose for Energy.
- Unlike muscles that can sustain no blood supply for 2 hours, the brain can only last a few seconds before serious damage is inflicted.

Structure of chemical synapses

1. Synaptic knob (presynaptic terminal):

It has synaptic vesicles (neurotransmitter vesicles).

2. Synaptic cleft (gap):

- The space between the axon terminal and sarcolemma where neurotransmitters release into.
- It has a width of 200-300 angstroms.

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3. Postsynaptic membrane:

It has receptors for neurotransmitters or ion channels.

- Damage in Wernicke's area that is located on the union of parietal and occipital lobe will result in loss of comprehension. E.g. when asked about their name, patients will reply with something unrelated like "the weather is cold"

Synapse

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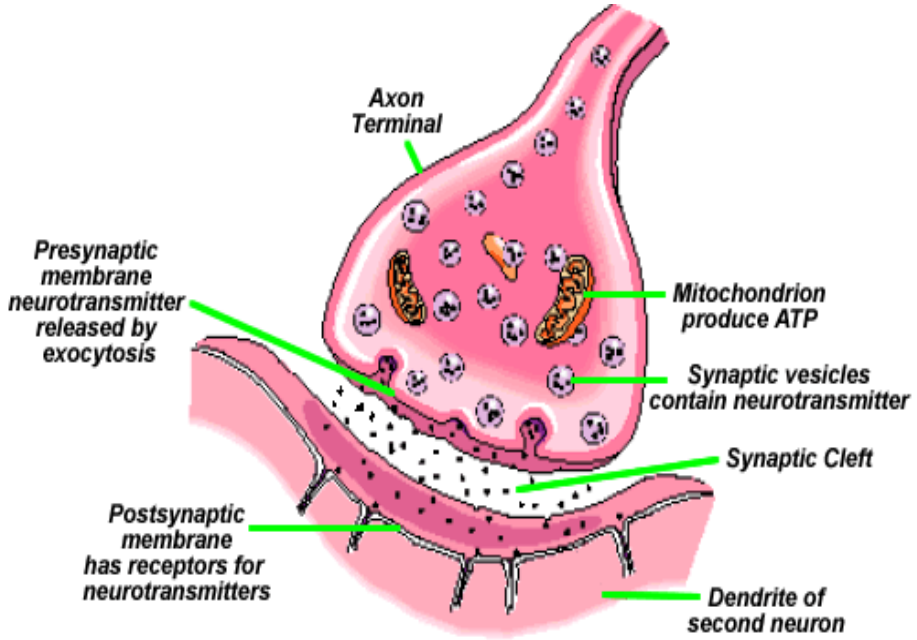
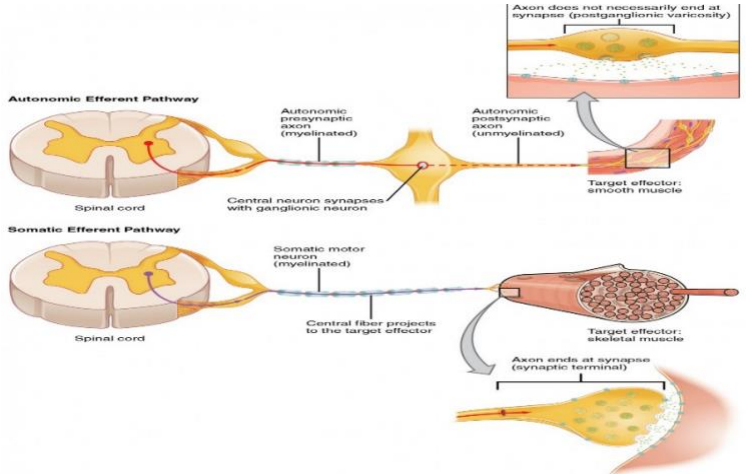
- A synapse is the connection between a neuron and a second cell.
- In the CNS, this other cell is also a neuron.
- In the PNS, the other cell may be either a neuron or an effector cell e.g. gland or muscle.



Examples of Junctions outside the CNS

- Neuromuscular junction
- Contact between: autonomic neurons and smooth, cardiac muscles and any other effector cells.



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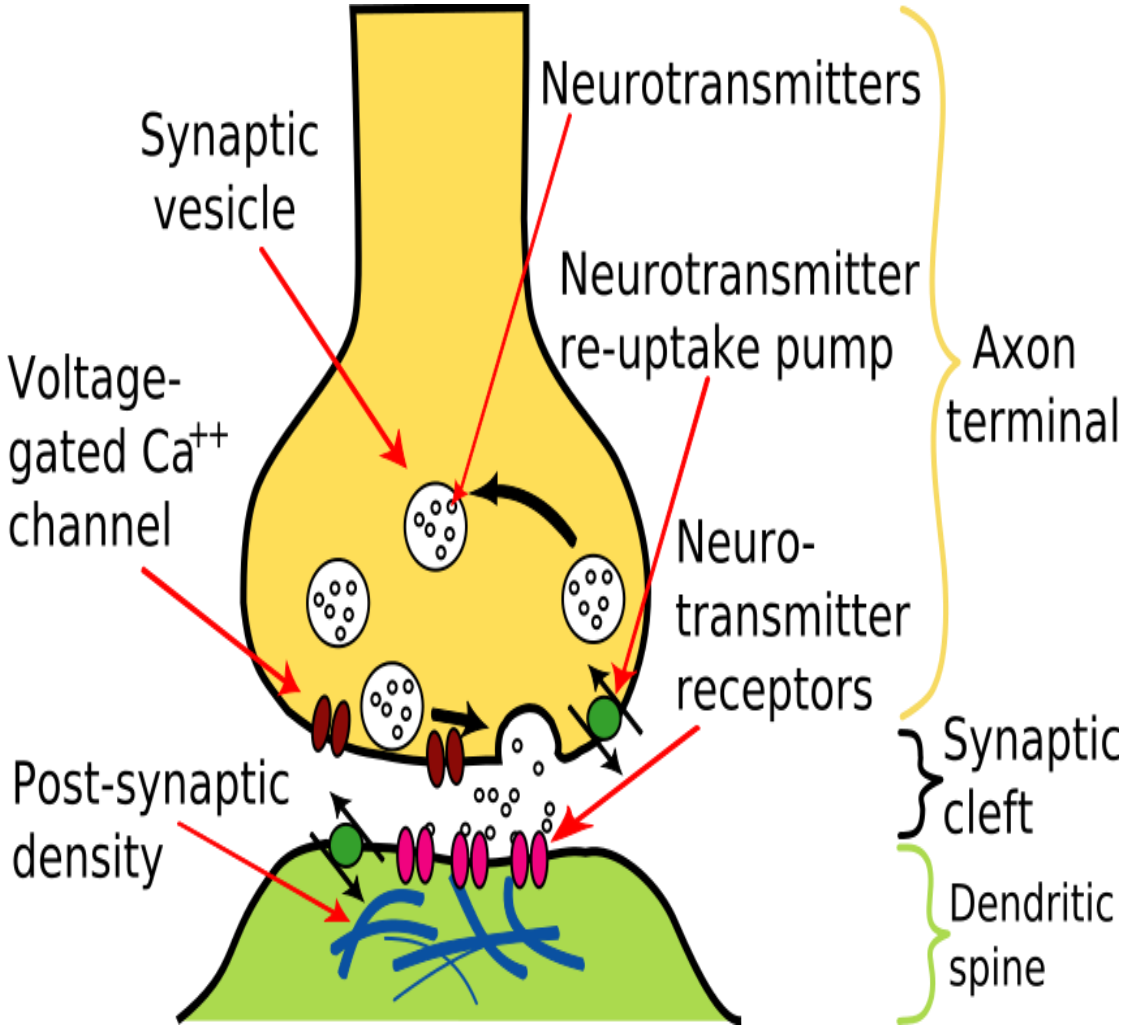
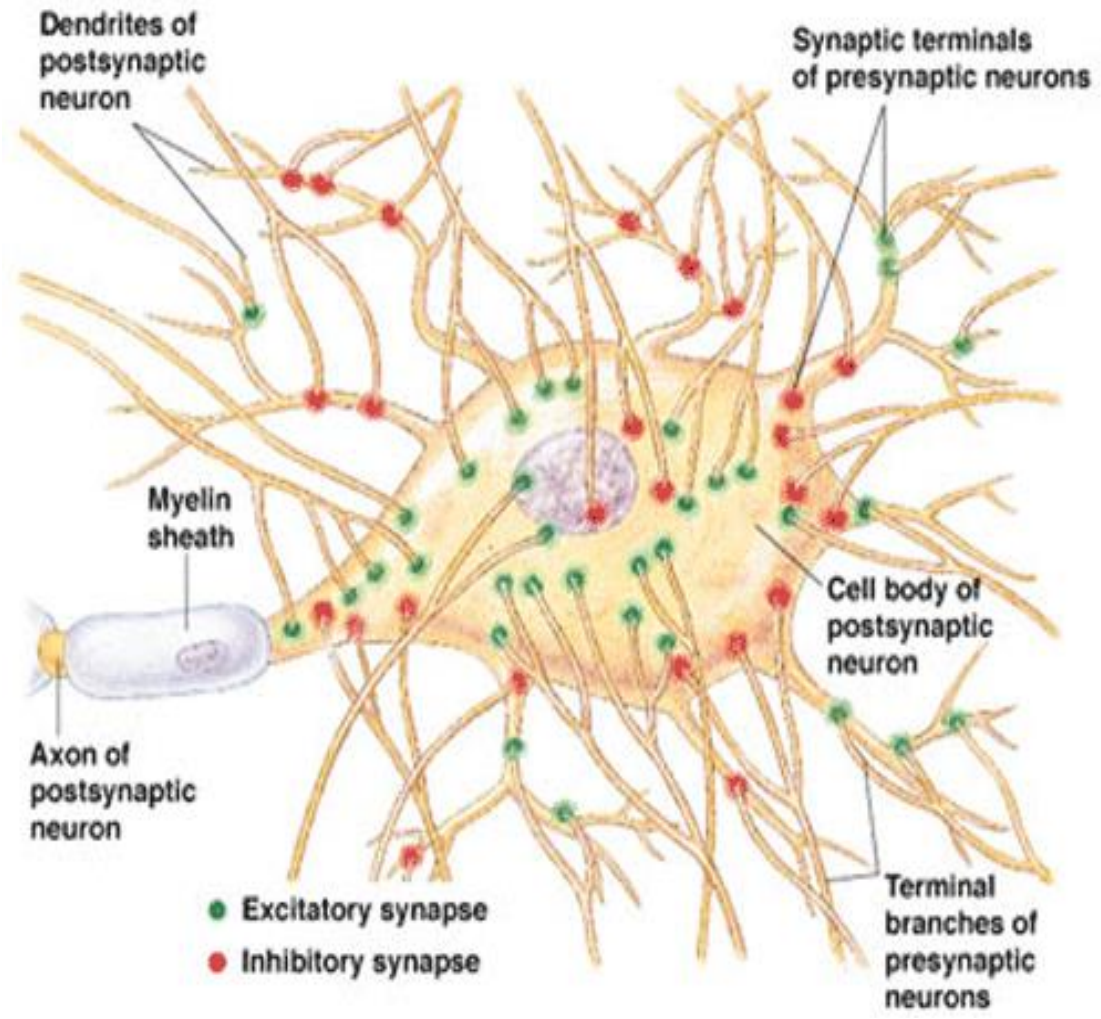
Synapse

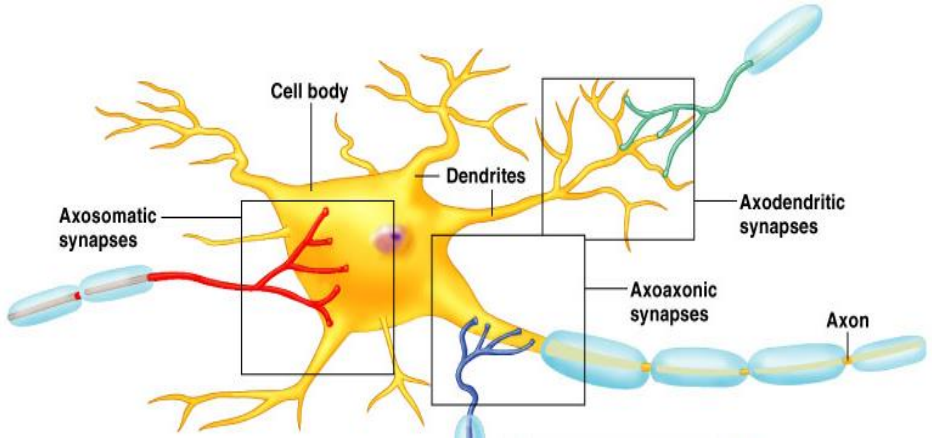


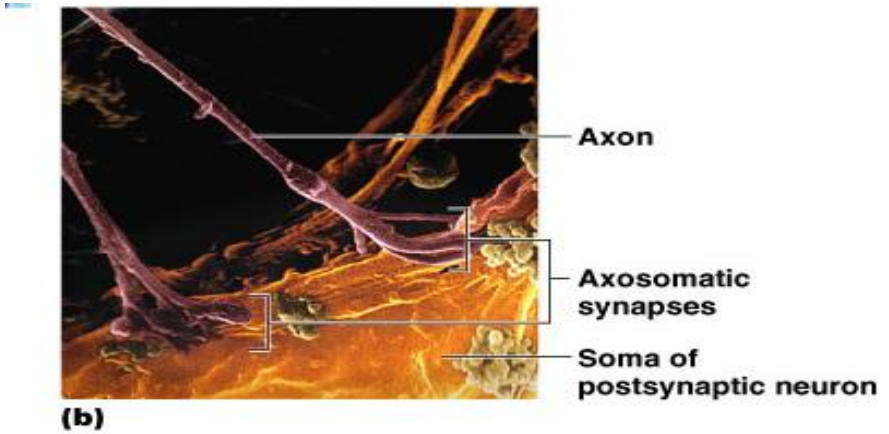
Structure of chemical synapses



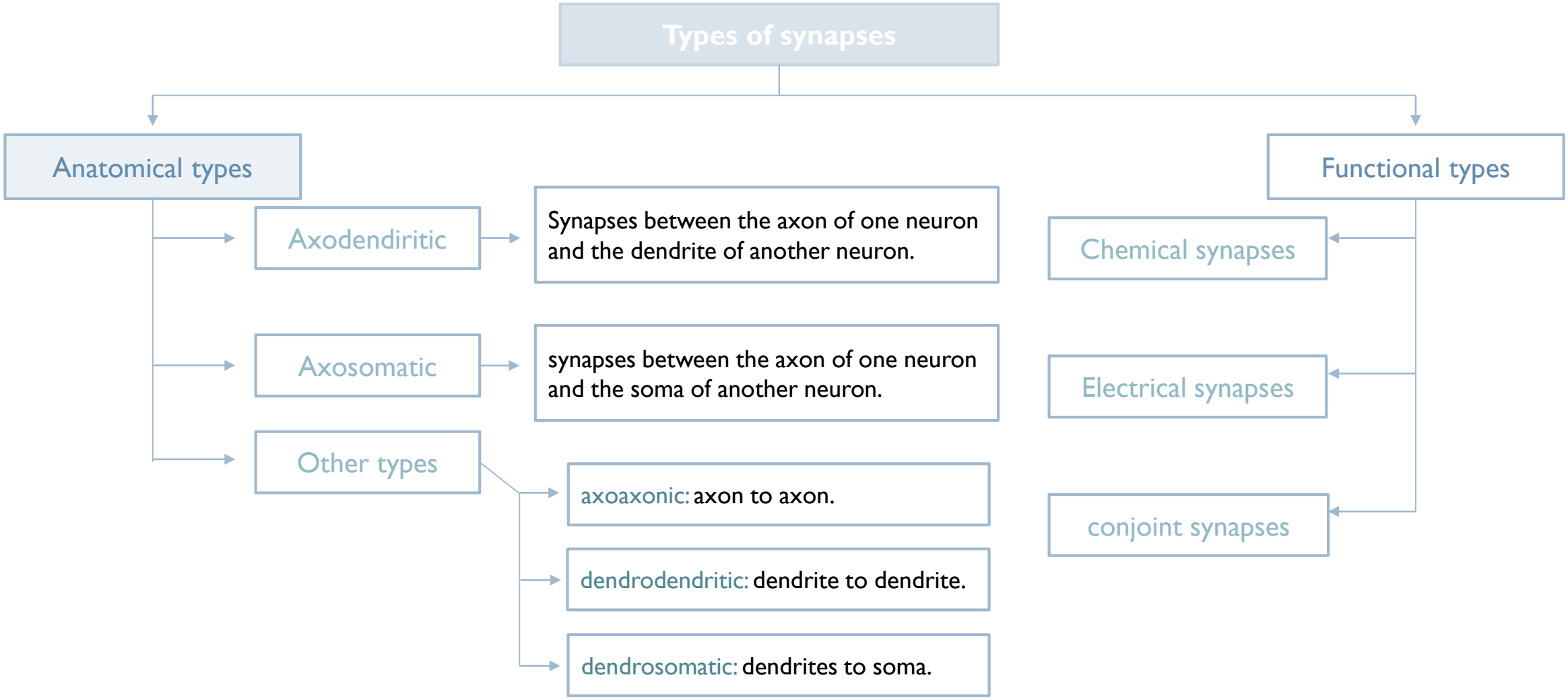
Functional anatomy: Types of synapses

- Types of synapses
  - Anatomical types
    - Axodendiritic
    - Axosomatic
    - Other types
  - Functional types
    - Chemical synapses
    - Electrical synapses
    - conjoint synapses

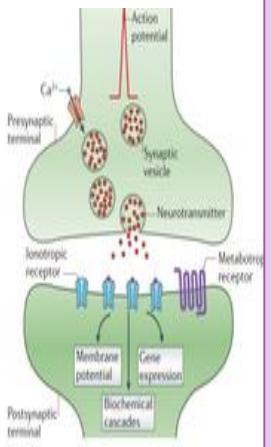
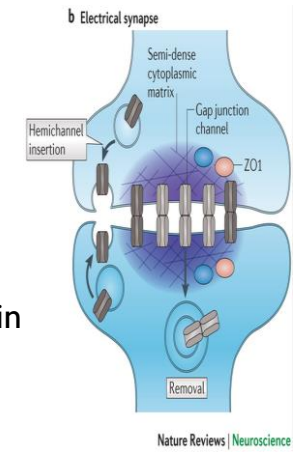




Anatomical types



Functional types

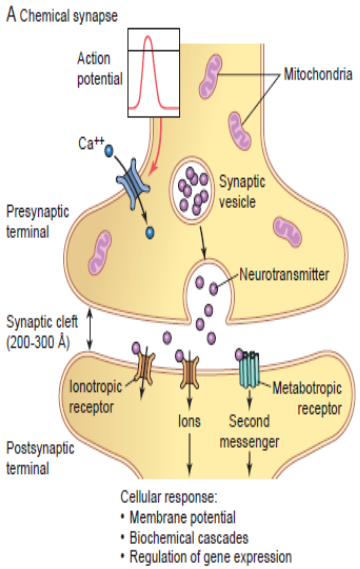
Functional types		
Chemical synapses	Electrical synapses	conjoint synapses
Via Neurotransmitters.	Ion exchange via Gap Junctions. **ONLY IN MALES' SLIDES**	Both electrical and chemical.
20-30 nm.	2-4 nm.	
One-direction transmission. **ONLY IN MALES' SLIDES** الإتجاه واحد، لأن النيوروترانسمتر لازم يرتبط بالمستقبل، والمستقبل يكون في البوست سينابتك فقط.	Bi-direction transmission. **ONLY IN MALES' SLIDES** بإتجاهين، لأن الأيونات لا تتطلب مستقبل.	
Almost all synapses in the CNS. (Most common type)	less common than Chemical synapses, and are very rare in the brain.	Example: neurons in the lateral vestibular nucleus
A neuron secretes a chemical substance called **neurotransmitter** at the synapse to act on the next neuron (by binding to a specific receptor enabling an electrical signal "postsynaptic potential or action potential") to excite it, inhibit or modify its sensitivity.  **ONLY IN FEMALES' SLIDES**	• membrane of the pre and postsynaptic neurons come close together. • Gap junctions form. • low membrane borders, which allows direct passage of ions and small molecules. • Correspond to gap junctions found in other cell types • if present, they are Important in the **CNS** in - Mental attention. - Emotions & Memory. - Arousal from sleep.  **ONLY IN FEMALES' SLIDES**	

Cont.

Functional types

Chemical synapses

- Terminal bouton is separated from postsynaptic cell by synaptic cleft.
- NTs are released from synaptic vesicles.
- Vesicles fuse with axon membrane and NT released by exocytosis.
- Amount of NTs released depends upon **frequency** of AP.



Electrical synapses

Impulses can be regenerated without interruption in adjacent cells.

Gap junctions:

- Adjacent cells electrically coupled through a channel.
- Each gap junction is composed of 12 connexin proteins.

- The bidirectional transmission of electrical synapses permits them to help coordinate the activities of large groups of interconnected neurons.
- Promotes synchronous firing of a group of interconnected neurons.

For example in:

- Mental attention.
- Emotions and Memory
- Arousal from sleep

Examples: Smooth and cardiac muscles, brain, and glial cells.

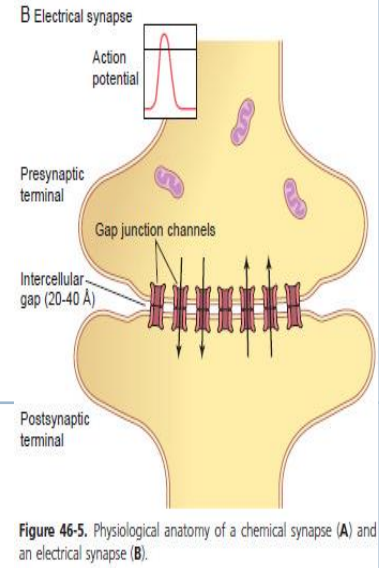
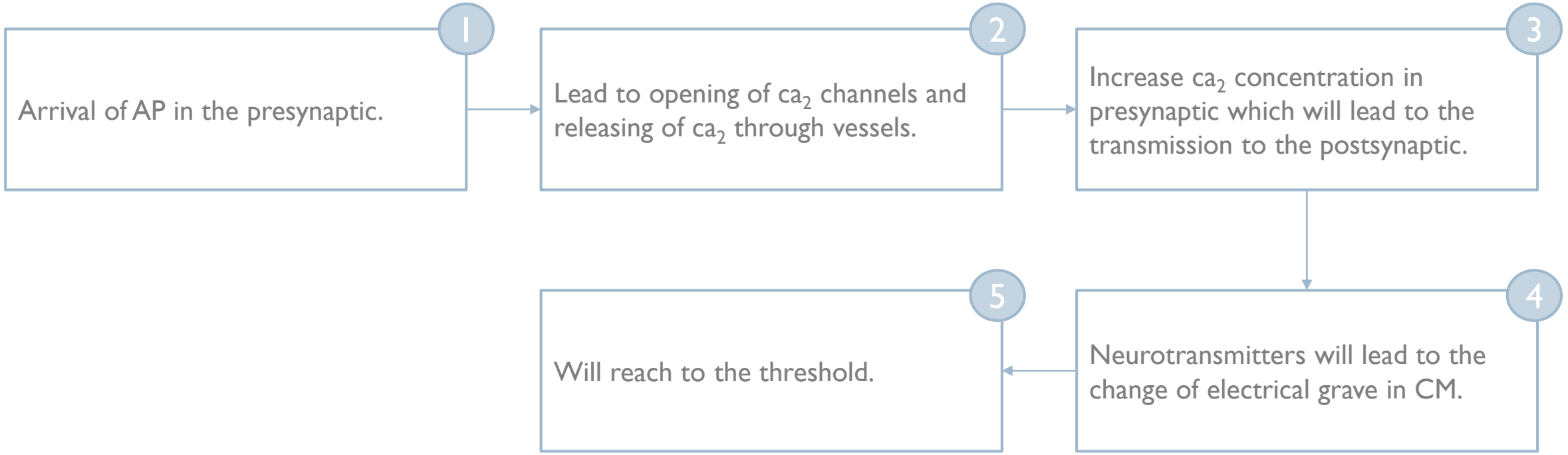


Figure 46-5. Physiological anatomy of a chemical synapse (**A**) and an electrical synapse (**B**).

- In the Electrical synapses there is a direct contact between pre synaptic and post synaptic.
- No delay occurs in Electrical synapses (unlike chemical synapses).
- As you see in the picture, the space between pre synapse and post synapse in the chemical is larger than electrical.

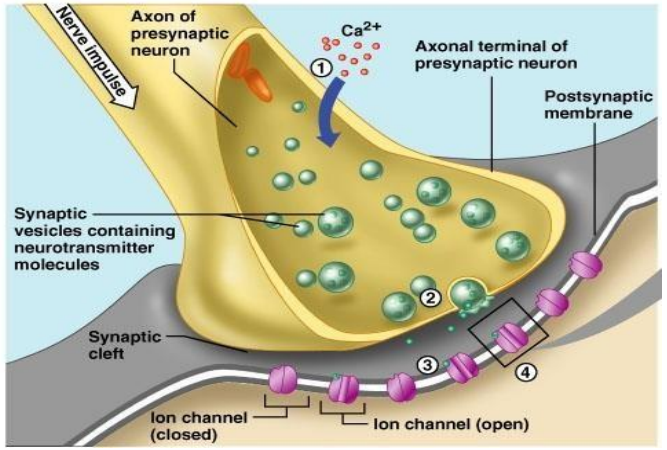
Recall

Recall what you studied in MSK block about neurotransmitters:



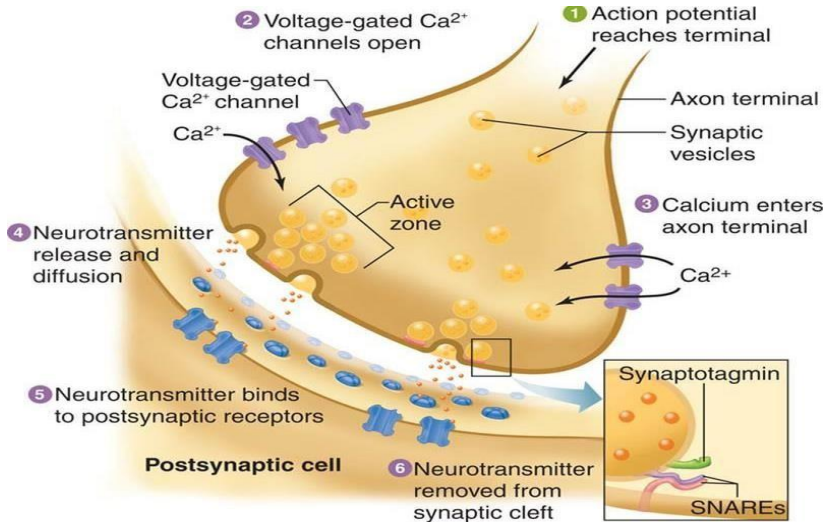
Synaptic Vesicle

- An abundant organelle with a diameter of 40 nm.
- Can accommodate only a limited number of neurotransmit ters.
- Each vesicle contain only one type of neurotransmitters.
- Different vesicles containing different NTs are often found in a single synaptic knob.
- There are over 100 Neurotransmitter.
- Synaptotagmin and SNAREs are proteins involved in the vesicle fusion.



Synaptic vesicular membrane

- Synaptotagmin (protein on the vesicle involved in vesicle fusion) helps the vesicle to bind to the terminal membrane without Ca.
- When Ca binds to synaptotagmin it starts the interaction with SNARE proteins (on the presynaptic membrane) causing exocytosis.
- Exocytosis occurs only in vesicles close to the terminal me mbrane.



Mechanism of a synaptic transmission

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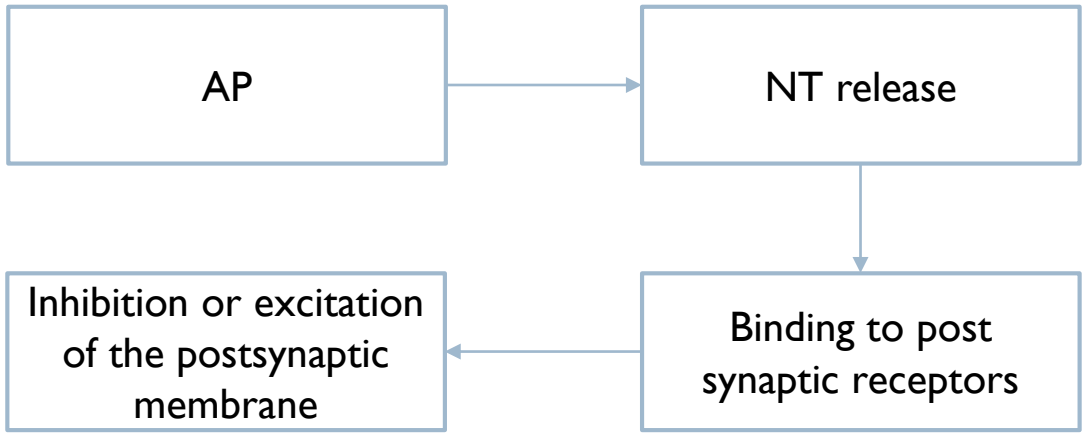
1. NT release is rapid because many vesicles form fusion-complexes at "docking site."
2. AP travels down axon to bouton.
3. VG Ca^{2+} channels open.
4. Ca^{2+} enters bouton down concentration gradient.
5. Inward diffusion triggers rapid fusion of synaptic vesicles and release of NTs.
6. Ca^{2+} activates calmodulin, which activates protein kinase.
7. Protein kinase aid in the fusion of synaptic vesicles.
8. NTs are released and diffuse across synaptic cleft.
9. NT (ligand) binds to specific receptor proteins in postsynaptic cell membrane.
10. NT effects are produced



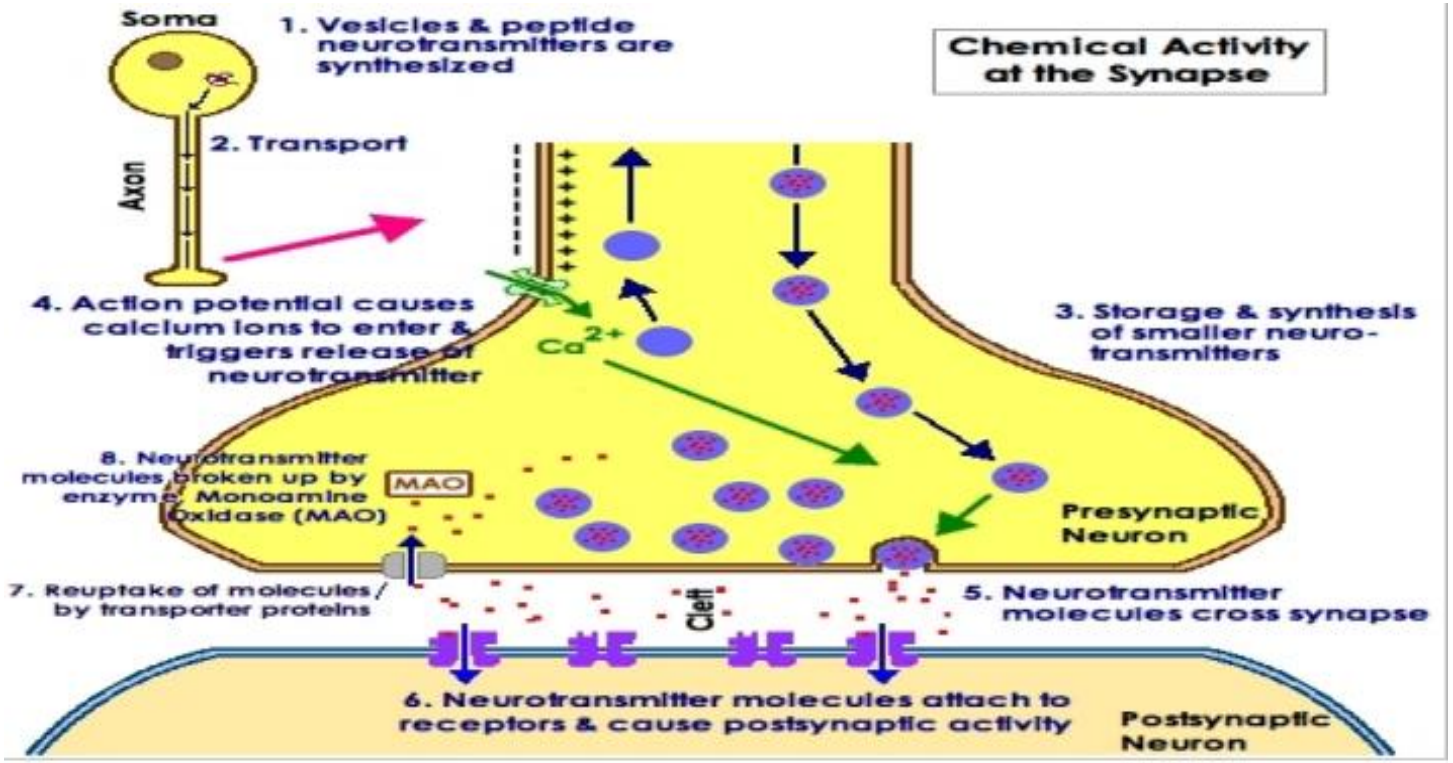
- depending on the type of the neurotransmitter

  i.e. excitatory or inhibitory))

Fate of neurotransmitter

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

- Diffusion out of synaptic cleft into surrounding fluid.
- Enzymatic destruction: e.g. Ach esterase for Ach.
- Active transport (reuptake) back into presynaptic terminal itself . e.g. Norepinephrine.



Postsynaptic receptors

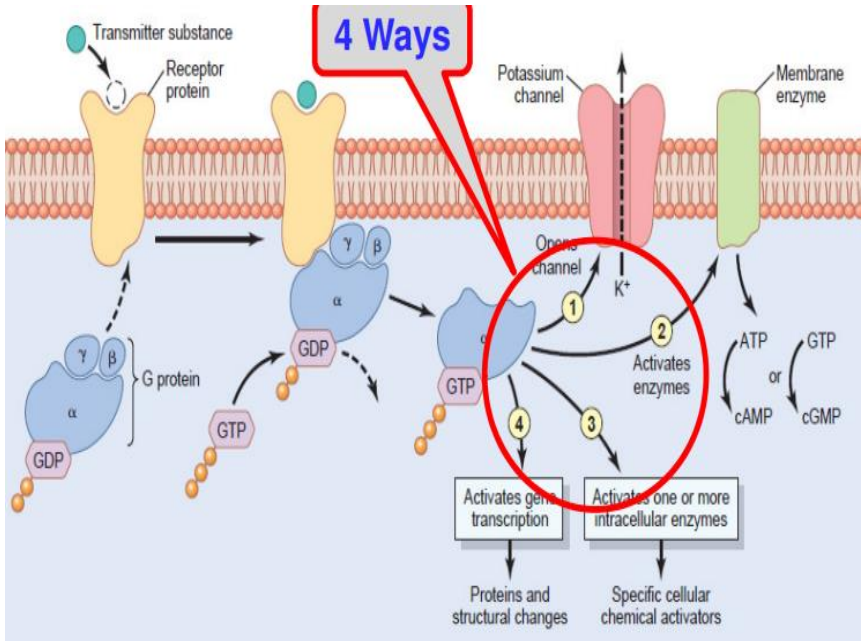
- Transmitter Substance acts on the Postsynaptic Neuron via "Receptor Proteins".
- Have binding & intracellular component.

Receptor activation acts in one of two ways:

1. By gating ion channels directly and allowing passage of specified types of ions through the membrane (ionotropic receptors)

2. By activating a "second messenger" that is not an ion channel but a molecule that protrudes into the cell cytoplasm and activates one or more substances inside the postsynaptic neuron (metabotropic receptors)

"Second Messenger" System in the Postsynaptic Neuron acts in 4 Ways:



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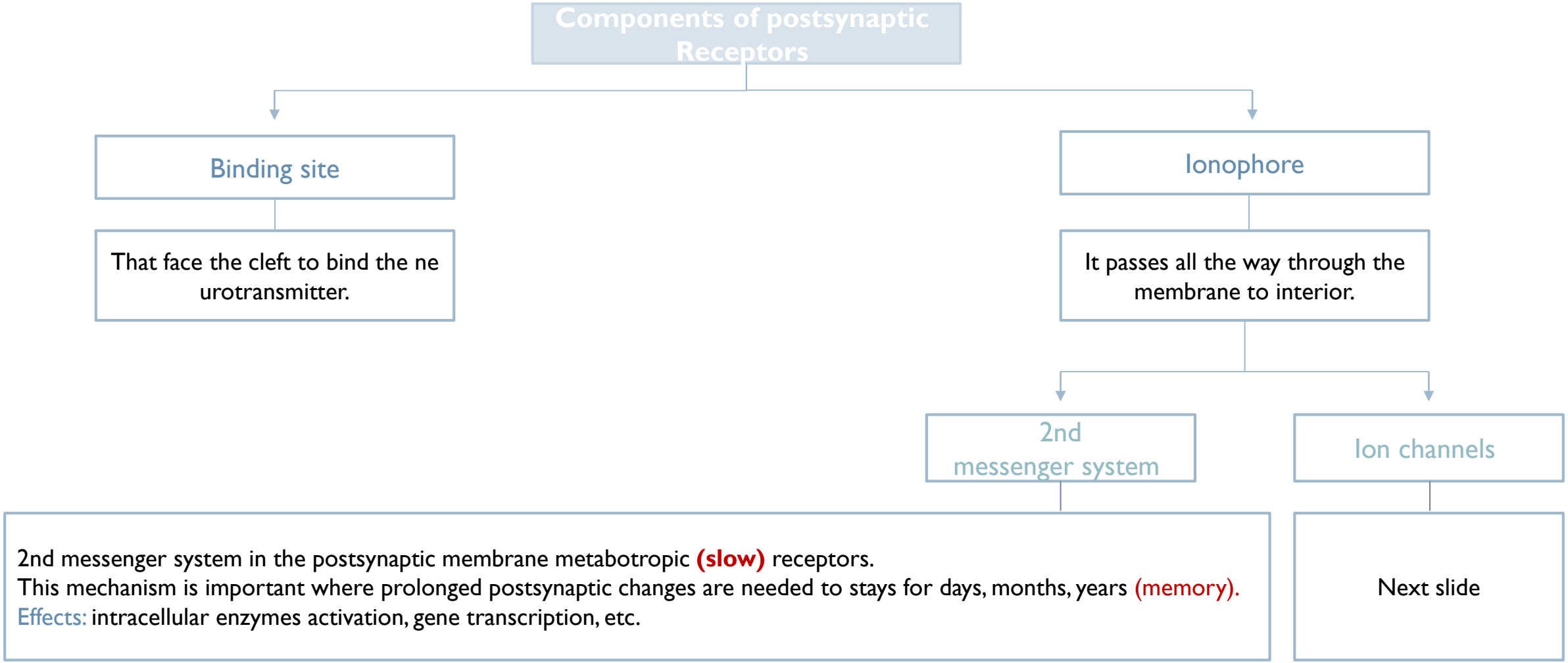

Components of postsynaptic Receptors
Binding site
That face the cleft to bind the ne urotransmitter.
Ionophore
It passes all the way through the membrane to interior.
2nd messenger system
Ion channels
2nd messenger system in the postsynaptic membrane metabotropic (slow) receptors.
This mechanism is important where prolonged postsynaptic changes are needed to stays for days, months, years (memory).
Effects: intracellular enzymes activation, gene transcription, etc.
Next slide

Ion Channels

- Ion Channels Ionotropic (fast).
- (also known as ligandgated ion channels).
- Whether a NT is excitatory or inhibitory depends on the receptor it binds to:

	Cation channels	Anion channels
Mechanism	Opening of Na^+ channels → Increase membrane potential in positive direction toward threshold level of excitation due to influx of (+)charges → (+) neuron.	Opening of Cl^- channels → Decrease membrane potential in negative direction away from threshold level due to influx of (-) charges → (-) neuron
Examples:	Na^+ (most common), K^+, Ca^{++}, …	Cl^- channels (mainly).

- The action of excitation and inhibition is depending on the charges.
- More positive = excitation.
- More negative = inhibition.

Extra

Functional differences between ionotropic & metabotropic receptors

IONOTROPIC	METABOTROPIC
Mediate rapid PSPs.	Mediate slower PSPs
Duration of PSPs is 10-30 ms or less	Duration from 100`s ms to minutes or longer.
PSPs (EPSP or IPSP) develop within 1-2 msec after an AP reaching the presynaptic terminal	This slowness is due to activation of second messengers leading to opening of ion channels

A NT may activate both ionotropic and metabotropic receptors to produce both fast & slow postsynaptic potentials at the same synapse

Electrical events in postsynaptic neurons

Electrical events in postsynaptic neuron

1. Resting membrane potential (RMP) of neuronal soma

- Soma of a neuron has a RMP of about -65 mv which is less negative than the (-70 to 90) mv found in skeletal muscles fibers.
- If the voltage is less negative → the neuron is excitable.

2. Excitatory postsynaptic potential (EPSPs)

- When excitatory neurotransmitter binds to its receptor on post synaptic membrane → partial depolarization (increase Na influx) of postsynaptic cell membrane Immediately under presynaptic ending, i.e. EPSPs.
- If this potential rises enough to threshold level → AP will develop and excite the neuron.
- This summation will cause the membrane potential to increase from -65 to -45 mV. (20 mV difference.)
- So the EPSPs = +20mV makes the membrane reach the firing level → AP develops at axon hillock.
- Synapse on the cell body is more effective than other parts of the neuron.

3. Inhibitory postsynaptic potentials (IPSPs)

How?

- When an inhibitory NT binds to its receptor on post synaptic membrane, it causes hyperpolarization of the postsynaptic membrane
- Increases membrane permeability to Cl^- of post synaptic membrane (produced by inhibitory neurotransmitter) →Decrease excitability and membrane potential(more negative). Where the membrane reaches -70 mV (5 mV difference of the RMP.)

How EPSPs differs from Action potential?

- Proportionate to the strength of the stimulus.
- Can be summated.
- If large enough to reach firing level à AP is produced.

EPSP & IPSP at Chemical Synapses

EPSP (excitatory postsynaptic potential):

1. Opening of Na channels to threshold level (Most Common).

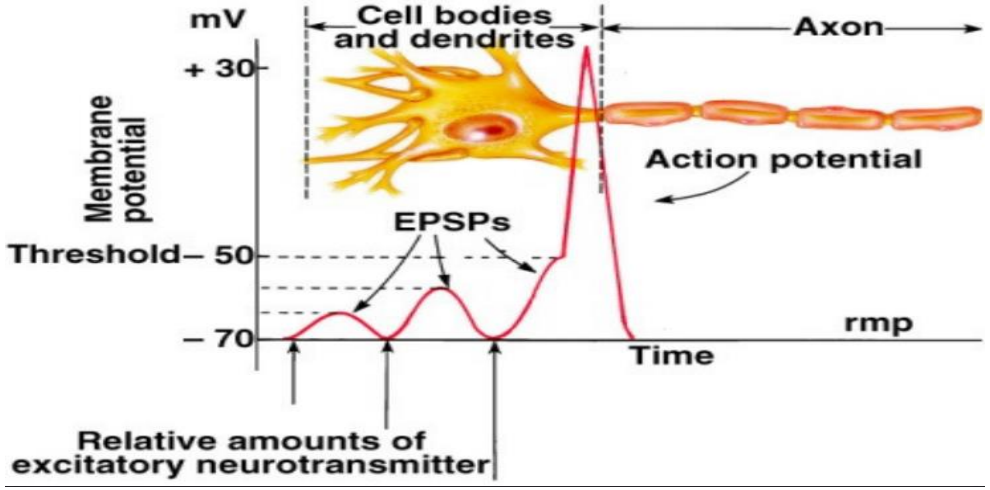
2. ↓ conduction through Cl^- or K channels, or both.

3. Various changes in the internal metabolism of the postsynaptic neuron to excite or, in some instances, to ↑ excitatory membrane receptors or ↓ inhibitory membrane receptors.

IPSP (inhibitory postsynaptic potential):

1. Opening of Cl^- ion channels through the postsynaptic neuronal membrane.

2. ↑ in conductance of K ions out of the Neuron.
3. Activation of receptor enzymes that inhibit cellular metabolic functions that ↑ inhibitory membrane receptors or ↓ excitatory membrane receptors.



Synaptic properties

Synaptic properties

1. One way conduction

Synapses generally permit conduction of impulses in one way
i.e. from presynaptic to postsynaptic neuron. "Bell- Magendie law".

2. Synaptic delay

- It is the minimum time required for transmission across the s ynapse.
- It is 0.5 ms for transmission across one synapse.

- This time is taken by:

1. Discharge of transmitter substance by presynaptic terminal.
2. Diffusion of transmitter to postsynaptic membrane.
3. Action of transmitter on its receptor.
4. Action of transmitter to increase membrane permeability
5. Increased diffusion of Na+ to increase postsynaptic potential.

- Clinical Importance: is that **ONLY IN MALES' SLIDES** we can know number of synapses involved in neuronal pathways by time lag.

3. Fatigue (synaptic depression)

It is due to exhaustion of neurotransmitter.

How?
If the presynaptic neurons are continuously Stimulated there may be an exhaustion of the neurotransmitter, (results in) → stoppage of Synaptic transmission.

In the pre synaptic membrane all of the neurotransmitters used from continuous stimulation will result in the arrival of ap but it won't propagate.

Synaptic fatigue is a protective phenomena.

Cont. Fatigue (synaptic depression)

- The cause of this sudden cessation of reverberation is fatigue of synaptic junctions in the circuit. Fatigue beyond a certain critical level lowers the stimulation of the next neuron in the circuit below threshold level so that the circuit feedback is suddenly broken.

- Synaptic fatigue short-term (synaptic depression), is an activity dependent form of short term synaptic plasticity that results in the temporary inability of neurons to fire and therefore transmit an input signal.

- Almost these exact patterns of output signals are recorded from the motor nerves exciting a muscle involved in a flexor reflex after pain stimulation of the foot.

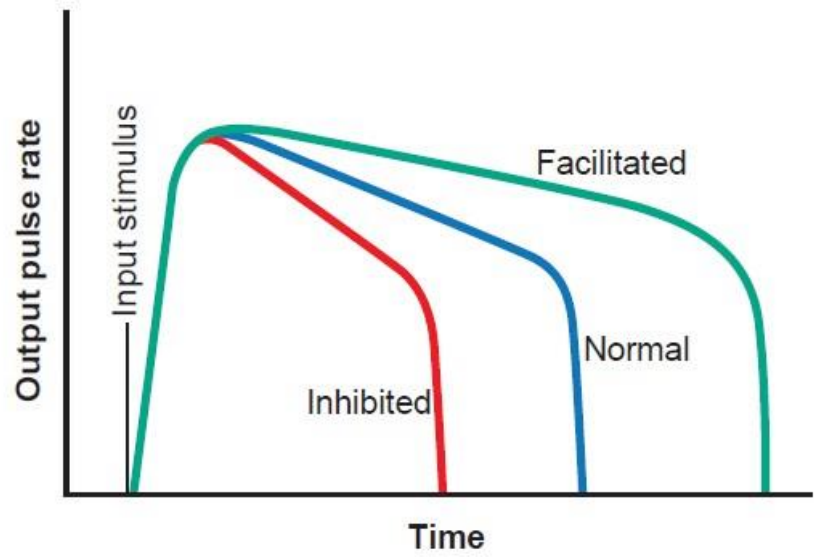
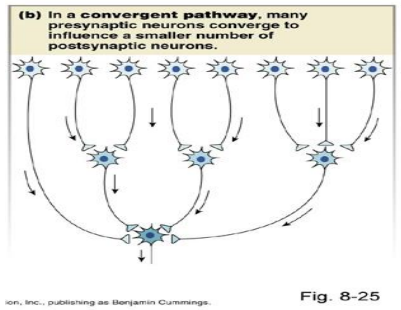


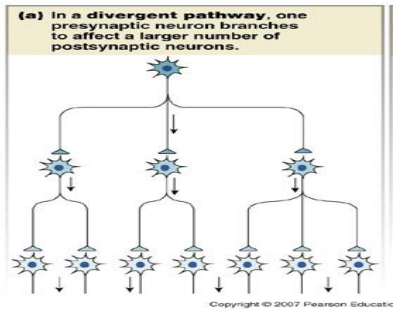
Figure 47-15. Typical pattern of the output signal from a reverberatory circuit after a single input stimulus, showing the effects of facilitation and inhibition.

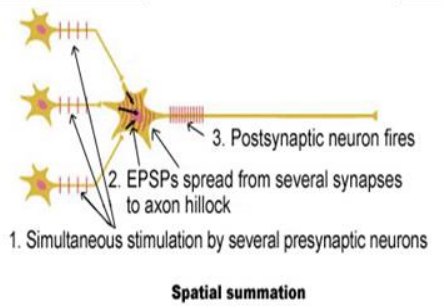
Cont.

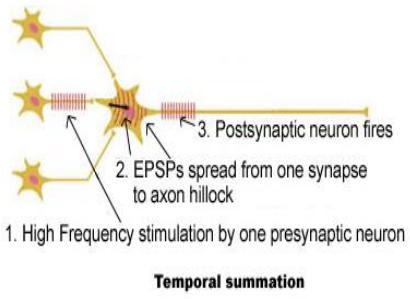
Synaptic properties

- **4. Convergence & Divergence**
  - **Convergence**
    - When many presynaptic neurons Converge on anysingle postsynaptic neuron
  - **Divergence**
    - Axons of presynaptic neurons devide into many branches that diverge to end on many postsynaptic neurons
- **5. SYNAPTIC INHIBITION**
  - Next slide.
- **6. Summation**
  - **Spatial**
    - Eliciting an action potential in a neuron with input from multiple presynaptic cells.
    - ONLY IN FEMALES' SLIDES
  - **Temporal**
    - When the frequency of stimulation increased from the same presynaptic fiver
    - ONLY IN FEMALES' SLIDES









Cont. (Summation)

Transmission of signals of different intensity in nerve tracts

Spatial	Temporal
Increasing signal strength is transmitted by using progressively greater numbers of fibers.	Transmitting signals of increasing strength is by increasing the frequency of nerve impulses in each fiber

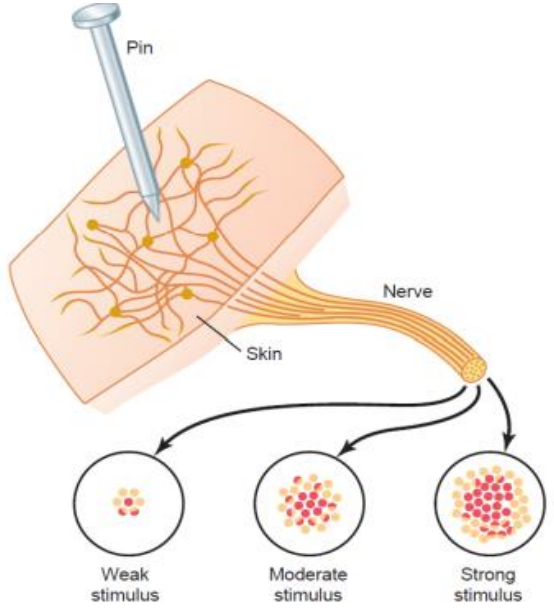


Figure 47-7. Pattern of stimulation of pain fibers in a nerve leading from an area of skin pricked by a pin. This pattern of stimulation is an example of *spatial summation*.

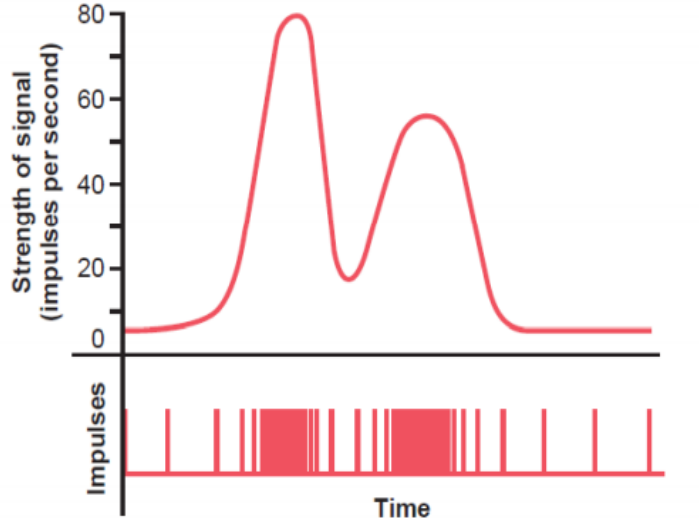


Figure 47-8. Translation of signal strength into a frequency-modulated series of nerve impulses, showing the strength of signal (*above*) and the separate nerve impulses (*below*). This illustration is an example of *temporal summation*.

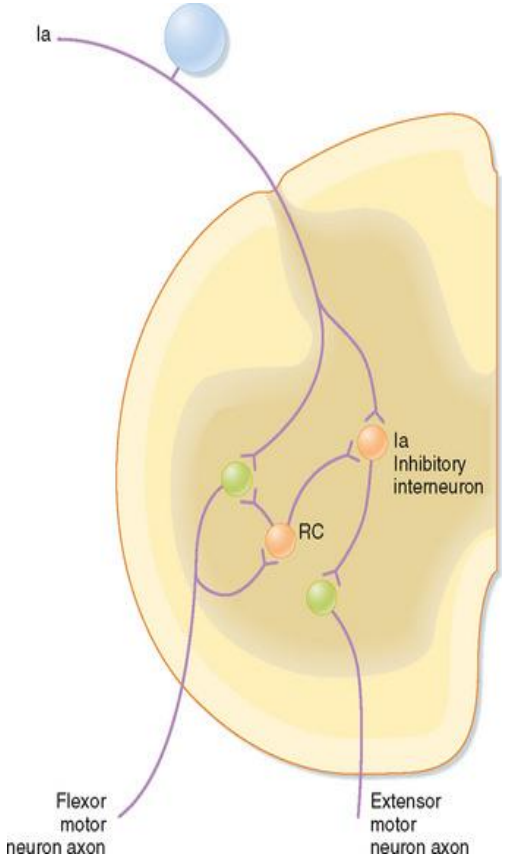
Synaptic Inhibition

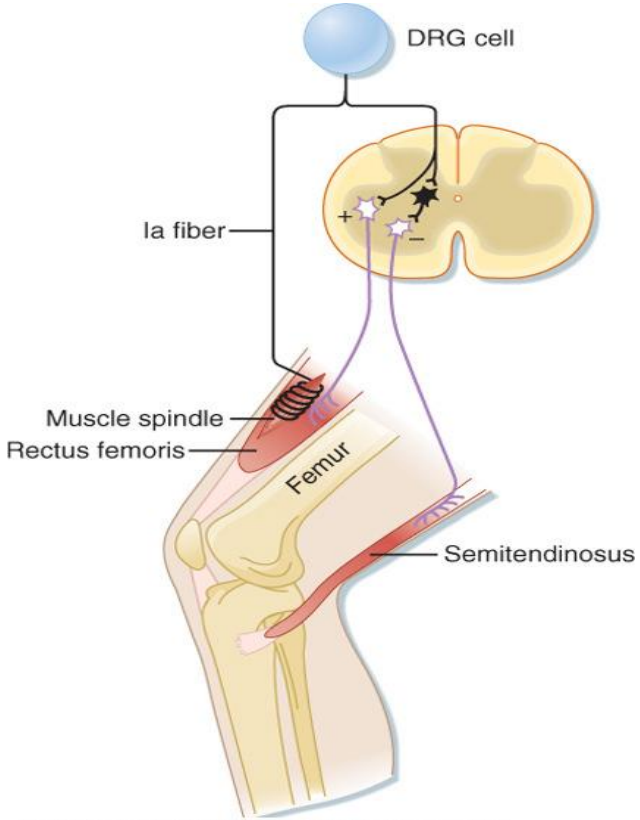
6. Synaptic inhibition	
Types	Definition
A. Direct Inhibition (postsynaptic inhibition) مباشر، لا يوجد وسيط أو تدخل.	Occurs when: An inhibitory neuron (releasing inhibitory substance) acts on a postsynaptic neuron leading to hyperpolarization due to opening of Cl^- [IPSPs] and/or K+ channels. Example: Glycine at the level of the spinal cord to block pain impulses.
B. Indirect Inhibition (Presynaptic inhibition) غير مباشر، تطلّب تدخل بري سينابتك وبوست سينابتيك.	Occurs when: An inhibitory synaptic knob lies directly on the termination of a presynaptic excitatory fiber. The inhibitory synaptic knob release a transmitter which inhibits the release of excitatory transmitter from the presynaptic fiber. Example: GABA (Pain modification)
C. Reciprocal Inhibition	Inhibition of antagonist activity is initiated in the agonist muscle when agonist is excited. ONLY IN FEMALES' SLIDES impulses pass directly to the motor neurons supplying the same muscle and via branches to inhibitory interneurons that end on motor neurons of antagonist muscle. When flexing the arm, flexors are activated while extensor muscles are inhibited.
D. Inhibitory Interneuron (Renshaw cells)	Negative feedback inhibitory interneuron of a spinal motor neuron. Control the strength of contraction. Renshaw cells have the same function as Reciprocal inhibition.

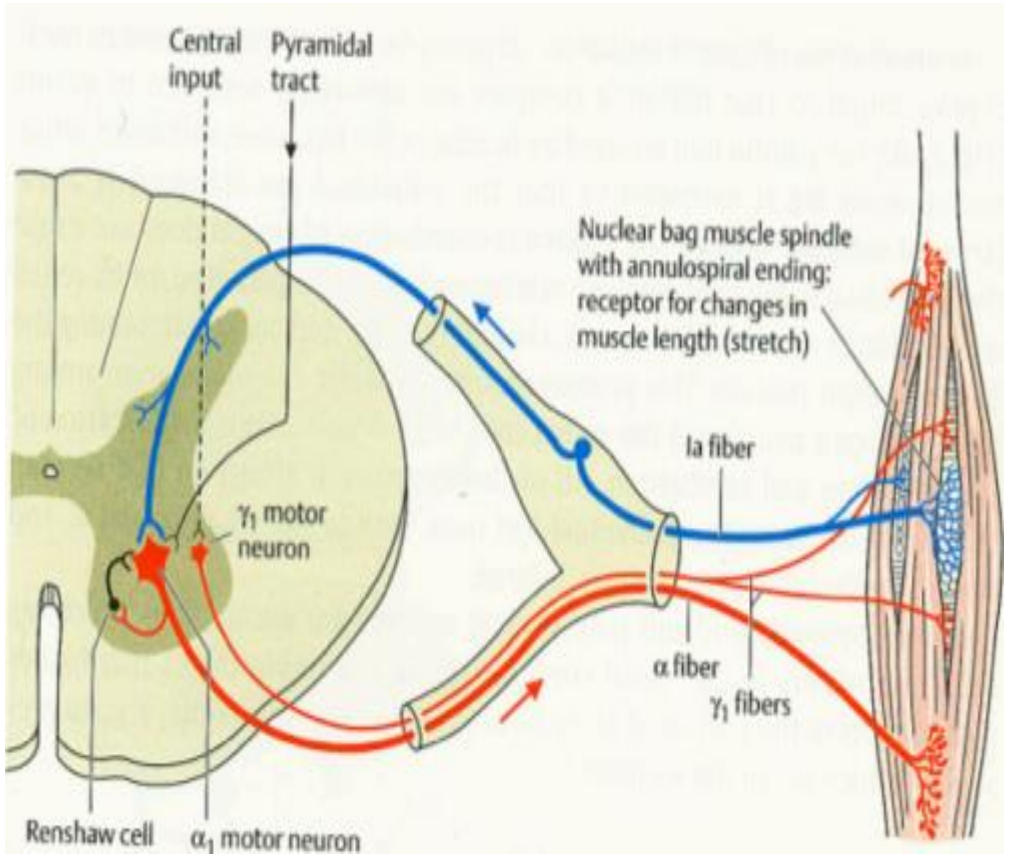
• Dopamine can be excitatory or inhibitory (depending on the receptor). However, glycine is always Inhibitory

Cont. Synaptic Inhibition: Inhibitory interneuron (Renshaw cells)

ONLY IN MALES' SLIDES | **ONLY IN FEMALES' SLIDES**

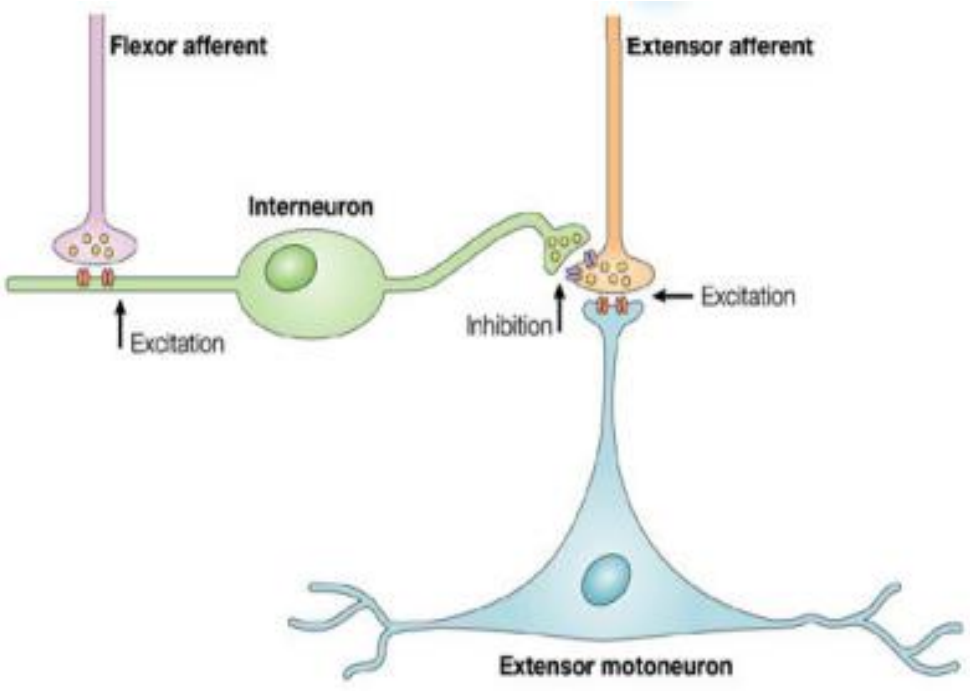






Cont. Synaptic Inhibition: Pre-synaptic inhibition

- Neuronal Circuit With Both Excitatory and Inhibitory Output Signals.
- This type of circuit is characteristic for controlling all antagonistic pairs of muscles, and it is called the reciprocal inhibition circuit.



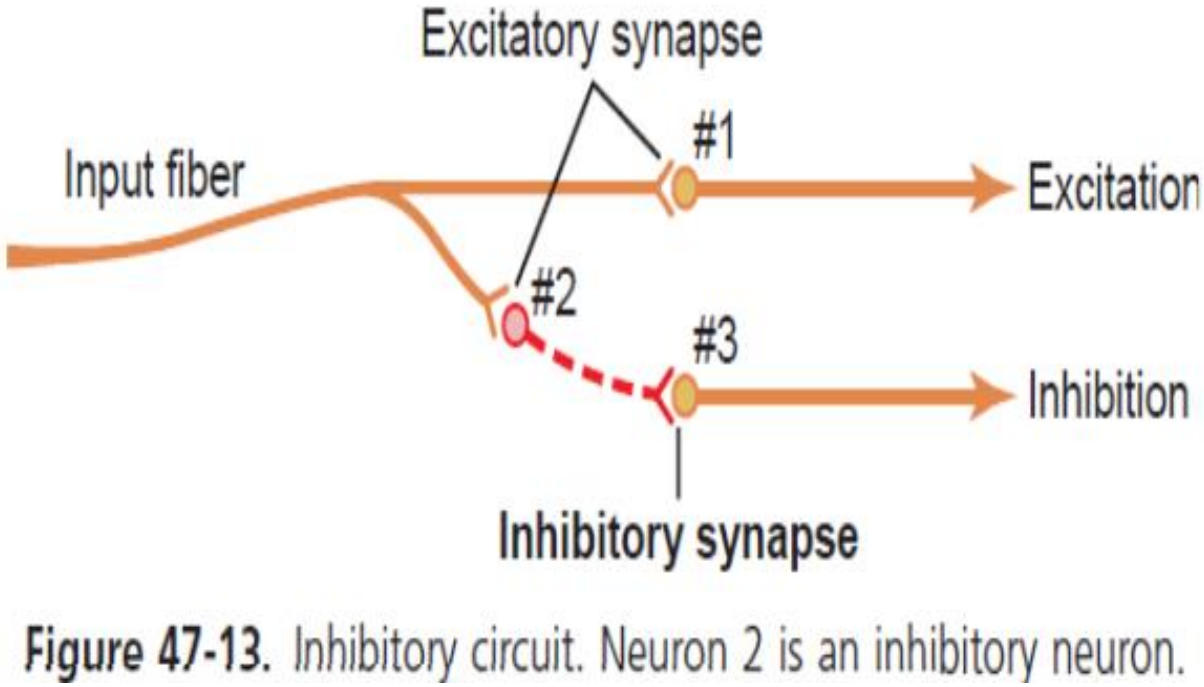


Figure 47-13. Inhibitory circuit. Neuron 2 is an inhibitory neuron.

Reverberatory (Oscillatory) Circuit

- Cause of Signal Prolongation. caused by positive feedback within the neuronal that re-excite the input of the same circuit. Once stimulated, the circuit may discharge repetitively for a long time called long term potentiation
- The simplest Fig A, involves single neuron.
- Fig B shows additional neurons in the feedback circuit, which causes a longer delay between initial discharge and the feedback signal.
- Fig C shows a more complex system in which both facilitatory and inhibitory fibers impinge on the reverberating circuit.
- Fig D shows reverberating pathways with parallel fibers.

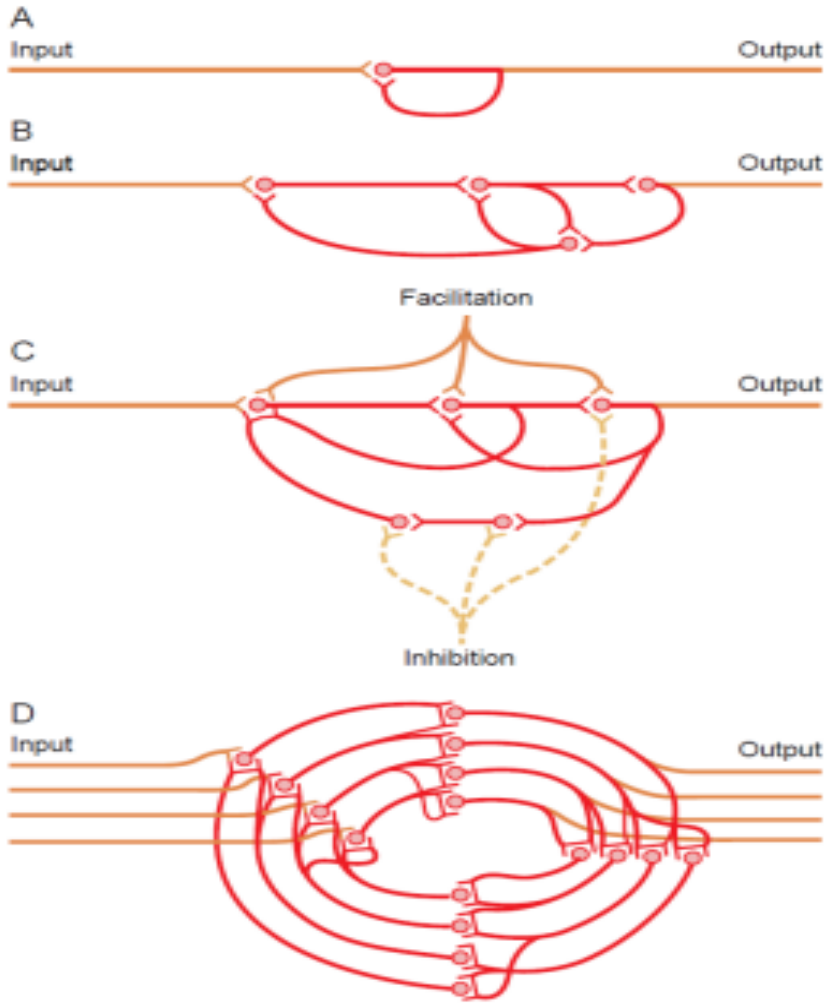


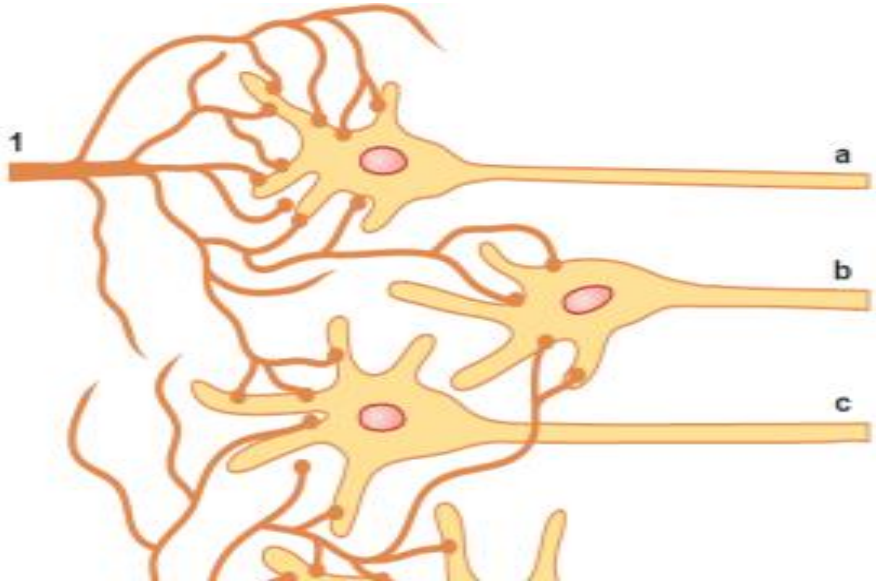
Figure 47-14. Reverberatory circuits of increasing complexity.

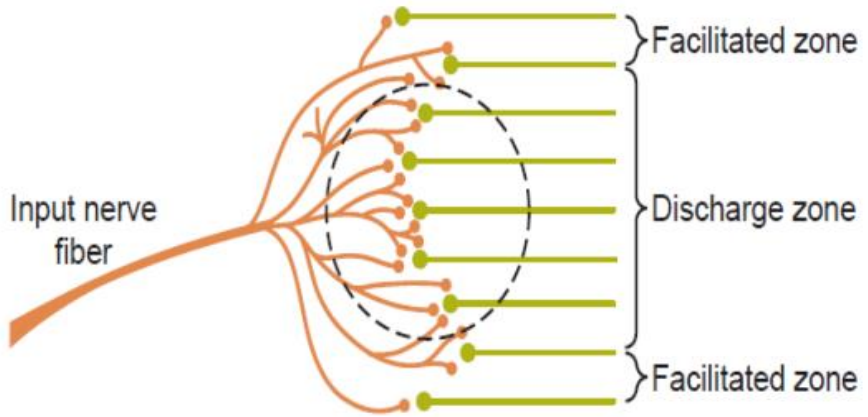
Zones of neuronal pool

- The neuronal area stimulated by each incoming nerve fiber is called its stimulatory field. Large numbers of the terminals from each input fiber lie on the nearest neuron in its "field," & fewer terminals lie on the neurons farther away.

- Discharge zone of the incoming fiber, also called the excited zone (a with suprathreshold stimulus).

- To each side, the neurons are facilitated but not excited, and these areas are called the facilitated zone, also •called the subthreshold zone or subliminal zone. (b & c not enough to cause excitation).





Divergence.

In divergence weak signals entering a neuronal pool are amplified. Two major types

Amplifying type	Divergence into multiple tracts
Eg: corticospinal pathway	Eg: dorsal columns: of the spinal cord takes two courses in the lower part of the brain: 1. into the cerebellum. 2. on through the lower regions of the brain to the thalamus and cerebral cortex.

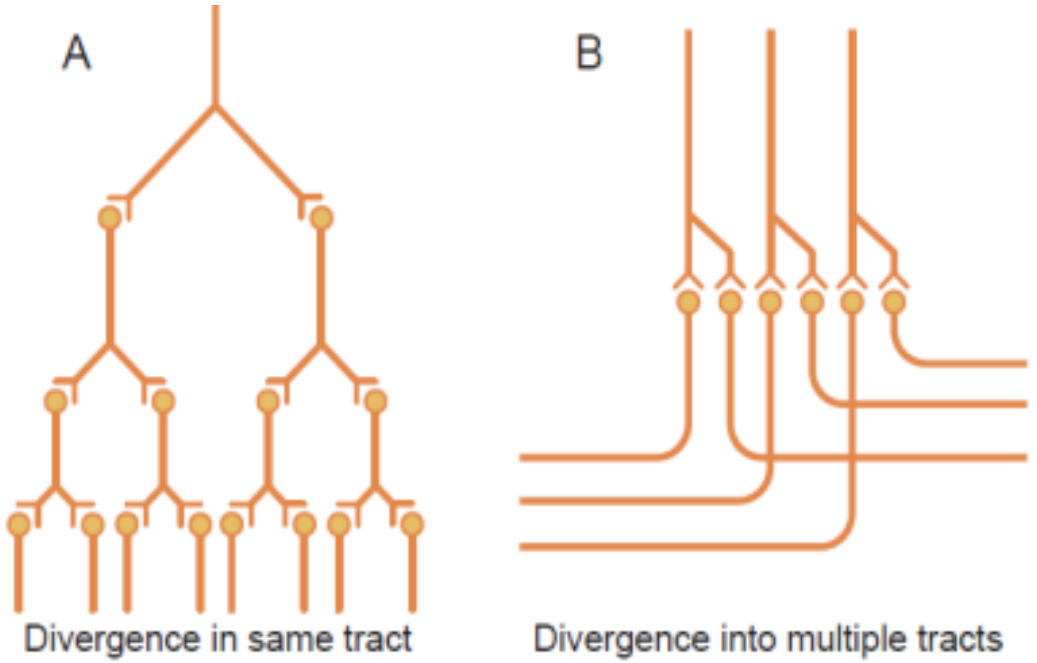


Figure 47-11. "Divergence" in neuronal pathways. *A*, Divergence within a pathway to cause "amplification" of the signal. *B*, Divergence into multiple tracts to transmit the signal to separate areas.

Convergence.

Convergence means signals from multiple inputs uniting to excite a single neuron

Action potentials converging on the neuron from multiple terminals provide enough spatial summation to bring the neuron to the threshold required for discharge.

Convergence can also result from input signals (excitatory or inhibitory) from multiple sources:

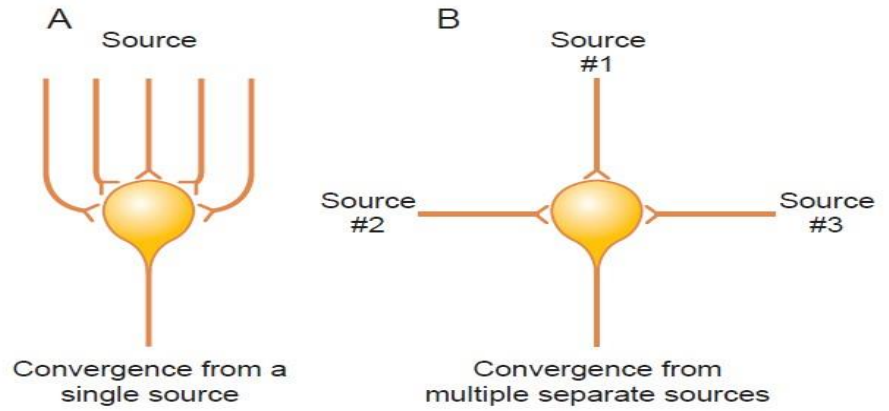


Figure 47-12. "Convergence" of multiple input fibers onto a single neuron. **A,** Multiple input fibers from a single source. **B,** Input fibers from multiple separate sources.

the interneurons of the spinal cord receive converging signals from:

1. peripheral nerve fibers entering the cord.
2. Propriospinal fibers passing from one segment of the cord to another.
3. corticospinal fibers from the cerebral cortex.
4. several other long pathways descending from the brain into the spinal cord.

From interneurons converge on the anterior motor neurons to control muscle function. By summation

Doctor's notes

Reciprocal Inhibition:

- Because the sensory will travel and at the level of the spinal cord, sensory information about the pain that we are experiencing will travel and give information to the motor component for the motor reaction and it will give responses to contract this muscle and to inhibit the antagonist and withdrawal will occur.
- Reciprocal antagonists are opposite each other. The type of action with inhibition of the opposite action
- It receives collateral information from the motor.
- That means when sensory information is received and the muscle gets contracted, the collateral and interneuron will receive the information from the motor through this collateral fibers to be informed about the muscle contraction because it will control the muscle contraction.

مثل لما ننجرح بالإبرة ما نجلس نقرر إذا هو يؤلمنا أو لا، من غير تفكير أو كنترول يصير مباشرة والشعور المؤلم يتوزع على الكثير من السيجمينتس من السباينل كورد عشان تعطينا الكثير من المسل كونتراكشين وانهيبيشن اكشنز.

Inhibitory Interneuron (Renshaw cells):

- It receives collateral information from the motor.
- That means when sensory information is received and the muscle gets contracted., the collateral and interneuron will receive the information from the motor through this collateral fibers to be informed about the muscle contraction because it will control the muscle contraction.

مثل لما يحدث عندنا ألم بسيط وظيفة النتيرنيورونز أنها تمنع زيادة الإنقباض في العضلات.

Factors affecting synaptic transmission

1. Alkalosis:

- Increases neuronal excitability.
- Causes cerebral epileptic seizures (due to Increased excitability of cerebral neurons).
- Example: over breathing in a person with epilepsy.
  The over breathing blows off carbon dioxide and therefore elevates the pH of the blood momentarily.

2. Acidosis:

- Depresses neuronal activity.
- pH around 7 "As in severe diabetic or uremic acidosis" usually causes a coma.

3. Hypoxia:

- Causes Depression of neurons.

4. Drugs:

- Caffeine found in coffee, tea, strychnine, theophylline and theobromine increases neuronal excitability, by reducing the threshold for excitation of neurons.

Thank you!

اعمل لترسم بسمة، اعمل لتمسح دمعة، اعمل و أنت تعلم أن الله لا يضيع أجر من أحسن عملا.

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QUIZ

اقتراحات وشكاوي

References:

- Females and Males slides.
- Guyton and Hall Textbook of Medical Physiology (Thirteenth Edition.)