Physiology Team 439

MED439
KING SAUD UNIVERSITY

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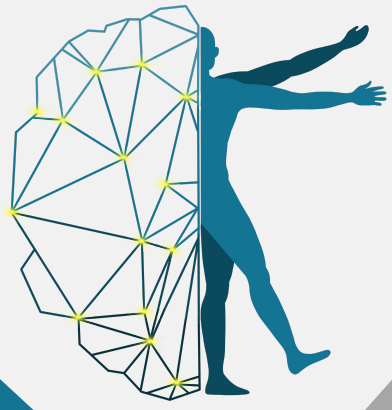


Synapse and receptors

Objectives:

- Define synapse
- Functions of synapses
- draw and label Structure of synapses Dr Shahid said "We usually give labelings in SAQs"
- Types of synapses:anatomical & functional
- Synaptic transmission & neurotransmitters
- Fate of neurotransmitters
- Electrical events at synapse (EPSPs & IPSPs)
- Properties of synaptic transmission
- Factors affecting synaptic transmission .

Color index:

- Important.
- Girls slide only.
- Boys slide only.
- Dr's note.
- Extra information.

Editing File

The Synapse

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

Synapse :Communication between neurons within the CNS

Junction: communication between neuron and other structure outside the CNS

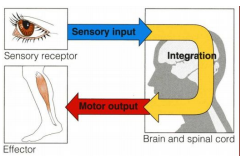
In the PNS, it communicates between two neurons or neuromuscular and neuroglandular junctions

General Facts abouts Synapses:

- A connection between a neuron and a second cell, within the CNS this other cell is also a neuron, while in PNS this other cell maybe either a neuron or an effector cell eg;- gland or muscle.
- The CNS contains more than 100 billion neurons.
- "Synaptein", from the Greek "syn-" ("togather") and "haptein" ("to clasp").

How Brain Function?

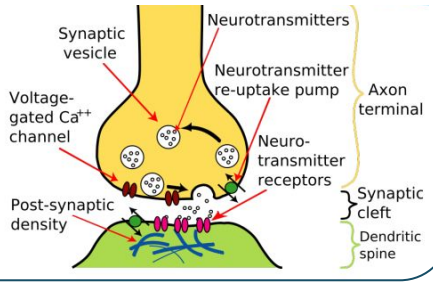
- Collection of sensory input
- Central Integration
- Motor output



Synaptic Structure

(girls only slides)

1. **Synaptic knobs (presynaptic terminal):** : It has synaptic vesicles (neurotransmitters).
2. **Synaptic cleft:** It is the space between the axon terminal and sarcolemma. It has a width of 200-300 angstroms.
   angstroms: Equivalent of 10−10 m, not an SI unit.
3. **Postsynaptic membrane:** It has receptors for neurotransmitters



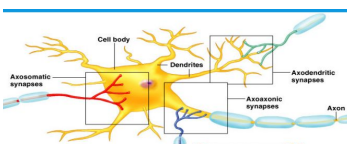
Synaptic Function

- The synapse is where the Information is transmitted in the central nervous system in the form of nerve action potential, called **nerve impulses**, though a succession of neurons, one after another.
- The synapses determine the directions that the nervous signals will spread through the nervous system.
- The synapses perform a selective action, often blocking weak signals while allowing strong signals to pass.

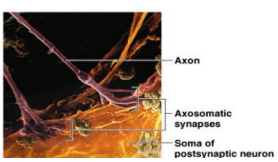
Synaptic Types

Anatomical

- **Axosomatic**
  Synapses between the axon of one neuron and the soma of another.
- **Dendrosomatic** (dendrites to soma)
- **Axoaxonic** (axon to axon)
- **Dendrodendritic** (dendrite to dendrite)
- **Axodendritic**
  Synapses between the axon of one neuron and the dendrite of another.

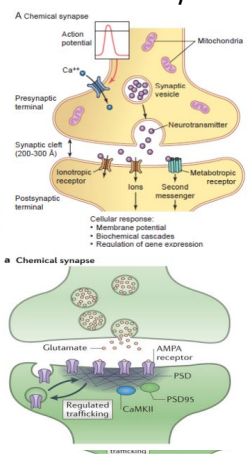
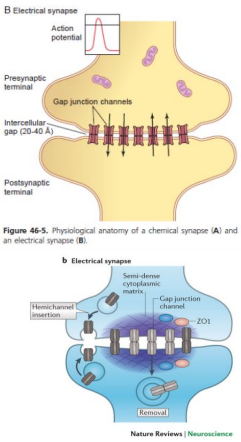


1- axodendritic is the most common
2- depending on the needs the signal is modified



Functional

- **Chemical**
- **Electrical**
- **Conjoin**
  Both electrical and chemical. Example: **Neurons in lateral vestibular nucleus.**

1. CHEMICAL SYNAPSE	2. ELECTRICAL SYNAPSE مو موجودة بكثرة لكن مهمة it acts as one unit
there is cleft **NTs** Definition: chemical substances secreted by the presynaptic neuron at the synapse to act on receptor on the next neuron to excite it, inhibit or modify its sensitivity. Amount of NTs released depends upon frequency of AP → Vesicles fuse with axon membrane and NT released by exocytosis  	**Gap Junction** Definition: Adjacent cells electrically coupled through a channel. Membranes of the pre- and postsynaptic neurons come close together and gap junctions form → low membrane borders which allow passage of ions. Each gap junction is composed of 12 connexion proteins. 
→ Two separate cells that do not touch → Terminal button is separated from postsynaptic cell by synaptic cleft 20-40 nanometer → Exhibits synaptic delay → Slower	→ Gap junctions are intercellular connection that directly connect the cytoplasm of cells → Cells approach within about 3.8 nm of each other so the impulses can be regenerated without interruption in adjacent cells. → Almost no delay in transmission. → Faster, many neurons fire synchronously
Act on receptors which are specific → complex behaviors	Without the need for receptors to recognize chemical messengers → simple behavior
"One-Way" conduction at chemical synapses.	The **bidirectional** transmission of electrical synapses permits them to help coordinate the activities of large group of interconnected neurons. Promotes synchronous firing of a group of interconnected neurons **For example, in mental attention, emotion and Memory, arousal from sleep.**
The response may not be the same as the source.	The response is always the same sign as the source.
The response in the postsynaptic neuron is variable.	Lack Gain the signal in the postsynaptic neuron is the same or smaller than that of the originating neuron
More common than electrical synapses Almost all synapses in the CNS	**Examples: Smooth and cardiac muscles, brain, and global cells, present throughout the central nervous system.**

Mechanism Of Synaptic Transmission

L1

1. Action potential leading to opening of voltage-gated calcium channels
2. Ca2+ enters bouton down concentration gradient.
3. Ca2+ activates calmodulin, which activates protein kinase. Protein kinase aid in the fusion of synaptic vesicles.
4. Inward diffusion triggers rapid fusion of synaptic vesicles with the presynaptic terminal membrane and release of NTs
5. Neurotransmitter release at docking site and diffuse across synaptic cleft.
6. Binding to postsynaptic receptors (inhibition or excitation) of the postsynaptic membrane (Depending on the type of the neurotransmitter, i.e. excitatory or inhibitory).
7. 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.

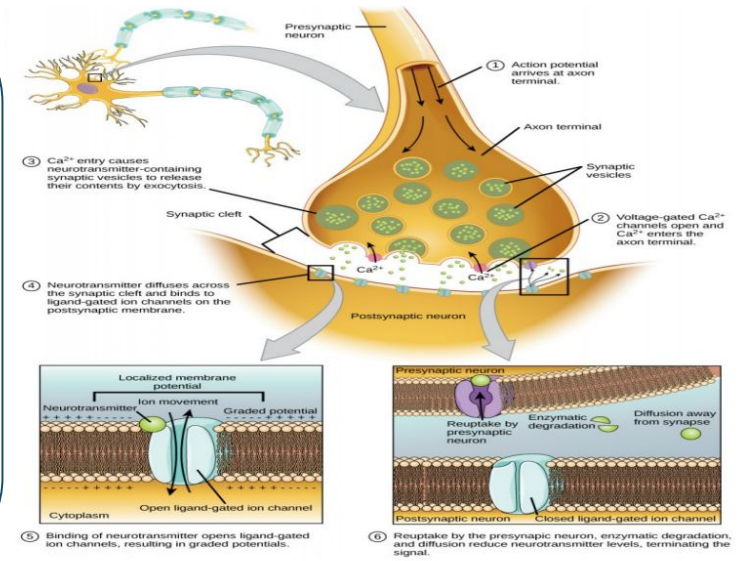
- NT release is rapid because many vesicles form fusion-complexes at "docking site."

Fate of Neurotransmitter

SAQs

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

1. Diffusion out of synaptic cleft into surrounding fluid.
2. Enzymatic destruction e.g Ach esterase for Ach.
3. Active transport back into presynaptic terminal itself e.g norepinephrine



there are two proteins, one is called syntaxin and the other is called synaptobrevin
Syntaxin lines the synaptic vesicles while synaptobrevin lines the docking site, when synapsin is activated it links the two proteins together and only then the vesicles are moved to the docking site and released by exocytosis

Interactions And Physiological Effects of Neurotransmitter

Transmitter Substance acts on the Postsynaptic Neuron via "Receptor Proteins", these receptors have two components.

COMPONENTS OF RECEPTOR PROTEINS

BINDING SITE

that faces the synaptic cleft to bind the neurotransmitter.

binding will trigger changes in ionophore which cause the entry of ions or it will trigger the activation of other protein

IONOPHORE

It passes all the way through the membrane to the interior.

ION CHANNELS (IONOTROPIC RECEPTORS)

Neurotransmitter receptors that directly gate ion channels allowing passage of (specified) types of ions

Anion channels

- Cl- mainly.
- Opening of Cl channels → diffusion of negative charges into the membrane → decreased membrane potential making it more negative away from threshold level (-) neuron.

Cation channels

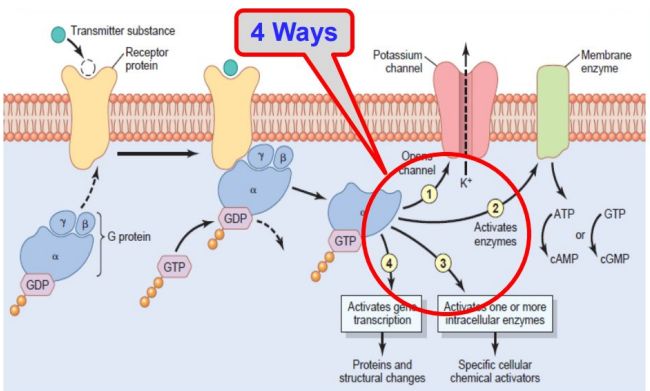
- Na+ (most common), K+, Ca++.
- Opening of Na+ channels → an increased membrane potential in positive direction toward threshold level of excitation (+) neuron.

The action of excitation or inhibition depend on the charge :
More (+) = excitation
More (-) = inhibition

2nd MESSENGER SYSTEM (METABOTROPIC RECEPTORS)

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

- Not an ion channel but a molecule that protrudes into the cell cytoplasm and activates one or more substances inside the postsynaptic neuron.
- In the postsynaptic neuron, this mechanism is important where prolonged postsynaptic changes are needed to stay for days, months.. years (memory).
- Effects : intracellular Enzymes activation, gene transcription, etc…
- acts in….



Electrical Events In Postsynaptic Neurons

L1

RESTING MEMBRANE POTENTIAL OF NEURONAL SOMA

- -65 mV i.e. less negative than skeletal muscles (-70 to -90 mV).
- If the voltage is less negative the neuron is excitable.

EXCITATORY POSTSYNAPTIC POTENTIALS (EPSPs)

- When excitatory neurotransmitters binds to its receptor on postsynaptic membrane a **partial depolarization** occurs **(increase Na influx)** of postsynaptic cell membrane
- immediately under presynaptic ending, i.e. EPSPs.
- If this potential rises enough to threshold level an AP will develop and excite the neuron.
- This summation will cause the membrane potential to increase from -65 mV to -45mV.
- EPSPs = +20mV (an increase strong enough to open enough voltage-gated sodium channels) which makes the membrane reach the firing level and an AP develops at axon hillock.

- How EPSPs differ from Action Potential ?

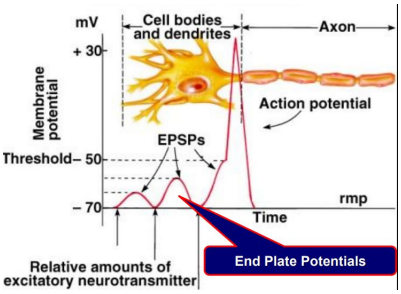
Proportionate to the strength of the stimulus,
can be summated
and if large enough to reach firing level an AP is produced.

Action potential is:
1- not graded (above threshold)
2- propagate (not localized)
3- all or none

While end plate potential is:
1- graded (below threshold)
2-localized

INHIBITORY POSTSYNAPTIC POTENTIALS (IPSPs)

When an inhibitory NT binds to its receptor on postsynaptic membrane, it causes **hyperpolarization** of the postsynaptic membrane.
- Increase membrane permeability to Cl- of post-synaptic membrane (produced by inhibitory neurotransmitter) leads to decreased excitability and membrane potential (more negative).



(Male slides)

EPSPs	IPSPs
1- Opening of Na channels to threshold level (Most Common).	Opening of Cl ion channels through the postsynaptic neuronal membrane.
2. Decrease conduction through Cl or K channels, or both.	2. Increase in conductance of K ions out of the Neuron
3. Various changes in the internal metabolism of the postsynaptic neuron to excite or, in some instances, to Increase excitatory membrane receptors or decrease inhibitory membrane receptors	3. Activation of receptor enzymes that inhibit cellular metabolic functions that increase inhibitory membrane receptors or decrease excitatory membrane receptors.

Dr shahid: "We usually give MCQs and SAQs about the properties"

Synaptic properties

Chemical Synapse

L1

1-One-way conduction:

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

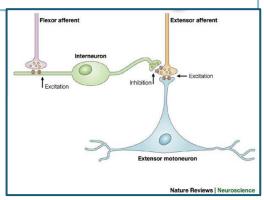
2-Synaptic Delay

Is the minimum time required for transmission across the synapse. the interval between the arrival of a nerve impulse at the ending of a presynaptic fiber and the start of the postsynaptic potential.
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
Clinical Importance is that we can know **number of synapse** involved in neuronal pathways by time lag

3-Synaptic inhibition

Direct inhibition

Occurs when an inhibitory neuron (releasing inhibitory substance) acts on a post-synaptic 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.
Block the impulse From peripheral to spinal cord



Indirect Inhibition

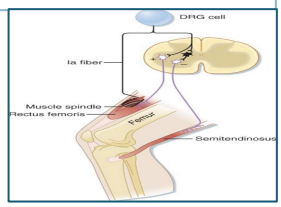
Not directly through another neuron
(Pre-synaptic inhibition): This happens when an inhibitory synaptic knob lie directly on the termination of a pre-synaptic excitatory fiber.

The inhibitory synaptic knob inhibits the release of excitatory transmitter from the pre-synaptic fiber. e. g. GABA (Pain modification).

Reciprocal inhibition

Inhibition of antagonist muscle when agonist is excited.Impulses pass **directly** to the motor neurons supplying the same muscle and via branches to inhibitory interneurons that end on motor neurones of antagonist muscle.

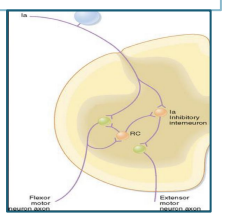
إذا دخل دبوس بيدنا نسحب يدنا بسرعة بسبب وجود الخطر
flexor (agonist) muscles will contract and extensor (antagonist) muscle will relax automatically



Inhibitory interneuron (Renshaw cells)Control the strength of contraction

control the flow of signals between sensory and motor neuron and determine the extent of motor neuron contraction

Negative feedback inhibitory interneuron of a spinal motor neuron .
Send inhibitory cells that transmit inhibitory signals to the surrounding motor neurons -> lateral inhibition -> Sharpens Signals



4-Summation

transmission of signals of different intensity in nerve tracts by summation (increase intensity of signals)

Spatial Summation: Increasing signal strength is transmitted by using progressively greater numbers of fibers.Eliciting an action potential in a neuron with input from multiple presynaptic cells.

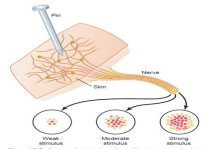
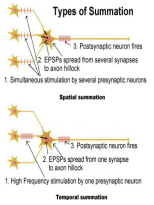
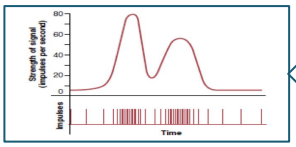


Figure 47-7. Pattern of stimulation of pain fibers in a nerve leading from an area of skin pricked by a pin. This pattern of stimulation is an example of spatial summation.



Temporal Summation: Transmitting signals of increasing strength is by increasing the frequency of nerve impulses in each fiber.When the frequency of stimulation increased from the same presynaptic fiber



If EPSPs in a pre-synaptic knob are successively repeated without significant delay so the effect of the previous stimulus is summated to the next.

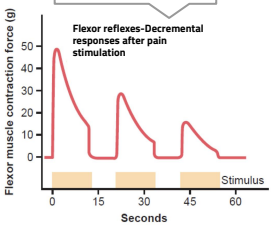
5-Fatigue (synaptic depression)

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 means simply that synaptic transmission becomes progressively weaker the more prolonged and more intense the period of excitation. It is a short-term 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 (synaptic depression).
It is due to exhaustion of neurotransmitter. If the presynaptic neurons are continuously stimulated there may be an exhaustion of the neurotransmitter. Resulting in stoppage of synaptic transmission.

Mechanism(may come in SAQ):

- Exhaustion of the stores of transmitter
- inactivation of many of the postsynaptic membrane receptors
- Abnormal ion concentrations in postsynaptic neuron

Fatigue is a protective mechanism against excess neuronal activity. **Epilepsy !!**



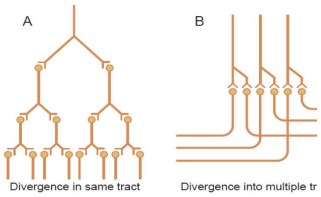


Figure 47-11. "Divergence" in neuronal pathways. *A*, Diver

6-Difference:

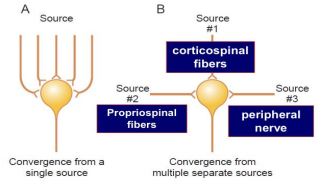


Figure 47-12. "Convergence" of multiple input fibers onto a single neuron. **A,** Multiple input fibers from a single source. **B,** Input fibers from multiple separate sources.

Divergence: Divide

Axons of presynaptic neurons divide into many branches that diverge to end on many post-synaptic neurons.
In divergence weak signals entering a neuronal pool are **amplified**. Two major types: -Amplifying type.
Eg; corticospinal pathway.
-Divergence into multiple tracts. Eg; dorsal columns: of the spinal cord takes two courses in the lower part of the brain:(1)into the cerebellum and (2) on through the lower regions of the brain to the thalamus and cerebral cortex.

Convergence: Collect

When many presynaptic neurons converge on any single postsynaptic neuron.
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.
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, and
(4) several other long pathways descending from the brain into the spinal cord.

Patterns of synaptic transmission in neuronal pools

- Convergence
- Divergence
- Reverberatory(Oscillatory) Circuit
- After-Discharge
- Irradiation
- Reciprocal Inhibition
- Local Sign

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, if the net result is facilitatory activation will occur and vice versa

Fig D shows reverberating pathways with parallel fibers, like basal Ganglia and cerebellu…

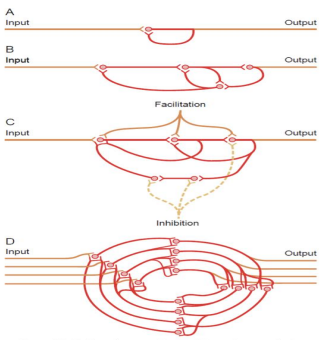


Figure 47-14. Reverberatory circuits of increasing complexity.

After-Discharge

A prolonged maintained output discharge of AHCs (anterior horn cells) called **after-discharge**, lasting a few milliseconds or many minutes after the incoming signal is over. Due to:

1- EPSP can continue to excite the neuron to transmit (a series of continuous repetitive discharges) .

2- Reverberating circuits: Presence of reverberating circuit restimulate AHCs

Irradiation

Spread of impulses up & down to different segments and motor neurons in the spinal cord Ex; A strong stim in sensory afferent irradiate to many segments of S.C due to **divergence**.

Reciprocal 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**.

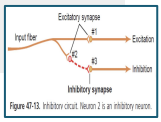


Figure 47-13. Inhibitory circuit. Neuron 2 is an inhibitory neuron.

Local Sign

The response to the stimulus by the body will be determined by the location of the stimulus on the body – i.e., a noxious stimulus to the hind limb does not result in withdrawal of a forelimb.

Factors affecting synaptic transmission:

Changes in internal environment:

- **Alkalosis**: ↑ neuronal excitability ; e.g. overbreathing in epilepsy The overbreathing blows off carbon dioxide and therefore elevates the pH of the blood momentarily Over breathing will cause faint in people with abnormal brain cells
- **Acidosis**: ↓ neuronal activity; e. g. diabetic or uremic acidosis coma
- **Hypoglycemia**: ↓ neuronal activity
- **Hypocalcemia**: ↑ neuronal excitability (tetany) Ca competes with Na to enter the cell, if Ca is low it's easier for Na to enter therefore hypocalcemia increases neuronal activity
- **Hypoxia**: Depression of neurons

Drugs:

- **Caffeine** found in coffee, tea, increases neuronal excitability, by reducing the threshold for excitation of neurons.depolarizes postsynaptic membrane
- **Strychnine**: competes with inhibitory transmitters
- **Theophylline** and **theobromine** increases neuronal excitability, by reducing the threshold for excitation of neurons.
- **Sedatives**, **hypnotics** & **anesthetics**: hyperpolarize (↑threshold) postsynaptic membrane.

Diseases:

- **Tetanus**: Inhibits release of GABA (spastic)
- **Botulism**: Inhibits release of Ach (Flaccid)

Chemical Synapse	Electrical Synapse
Exhibits synaptic delay eg at NMJ reveal a delay of 0.5 to 4.0 mili sec	Almost no delay in transmission.
20- to 40-nanometer distance that separates cells	Cells approach within about 3.8 nm of each other
Two separate cells that do not touch	Gap junctions are intercellular connection that directly connect the cytoplasm of cells
Slower than Electrical	Faster: many neurons fire synchronously
Mostly unidirectional	Mostly bidirectional
More complex behaviors	Are fast, but can produce only simple behaviors
Act on receptors which are specific	Without the need for receptors to recognize chemical messengers
The response may not be the same as the source.	The response is always the same sign as the source.
The response in the postsynaptic neuron is variable.	Lack Gain the signal in the postsynaptic neuron is the same or smaller than that of the originating neuron

MCQ & SAQ:

Q1: If a neurotransmitter substance resulted in formation of new proteins after excitation of a postsynaptic terminal, what type of receptor does the postsynaptic terminal possess?

A. Metabotropic receptor
B. Ionotropic receptor
C. Ligand-gated ion channel
D. No receptor needed

Q2: An anatomical type of synapse:

A. Axodendritic
B. Electrical synapse
C. Chemical synapse
D. Conjoint synapse

Q3: Axons of pre-synaptic neurons divide into many branches called:

A. Convergence
B. Divergence
C. None
D. Both

Q4: A prolonged maintained output discharge of AHCs called

A. Irradiation
B. Local sign
C. After discharge
D. Reverberatory circuit

Q5: Characteristic for controlling all antagonistic pairs of muscles, and it is called

A. Irradiation
B. Reciprocal inhibition
C. After discharge
D. Reverberatory circuit

Q6: Which of the following is mostly bidirectional

A. Chemical synapse
B. Electrical synapse
C. Conjoint synapse
D. Both A and C

answer key:
1: A
2: A
3: B
4: C
5: B
6: B

1- Describe the fate of Neurotransmitters?

2- what are the two types of channel activities/affect produced in the postsynaptic membrane?

3- Mention 3 conditions that cause synaptic fatigue:

4- What is the difference between spatial summation and temporal summation?

A1: Diffusion out of synaptic cleft into surrounding fluid.
- Enzymatic destruction e.g Ach esterase for Ach.
- Active transport back into presynaptic terminal itself e.g norepinephrine

A2: Excitatory postsynaptic potentials EPSP.
- Inhibitory postsynaptic potentials IPSP

A3: Exhaustion of the stores of transmitter
- inactivation of many of the postsynaptic membrane receptors
- Abnormal ion concentrations in postsynaptic neuron

A4: Spatial Summation: Increasing signal strength is transmitted by using progressively greater numbers of fibers. Temporal Summation: Transmitting signals of increasing strength is by increasing the frequency of nerve impulses in each fiber.

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- Homoud Algadheb.
- Raghad Albarrak.
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- Abdulrahman Almegbel.
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- Bader Alrayes.
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- Bushra Alotaibi.
- Faisal Jazzar.
- Feras Alqaidi.
- Ghaida Alassiry.
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