Physiology 435 team

SYNAPSES AND SYNAPTIC TRANSMISSION

Objectives:

- **Definition** and **Functions** of synapses.
- **Structure and Types** of synapses: anatomical & functional.
- Synaptic **transmission** & neurotransmitters. what neurotransmitters are, and how they are released and act on their receptors.
- **Fate** of neurotransmitters.
- Differentiate between neurotransmitter receptors **(ionotropic and metabotropic)**
- **Electrical events** at synapses (EPSPs & IPSPs) and the differentiation between **post**synaptic and **pres**ynaptic inhibition.
- **Properties** of synaptic transmission and the nature of temporal and spatial summation.
- **Factors** affecting synaptic transmission.
- Appreciate that effectiveness of neurotransmitters can be modified by **drugs and diseases.**

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Color index: Important - Further explanation - Doctors Notes - Numbers.

*Please check out this link before viewing the file to know if there are any additions or changes.

SYNAPSE - General Info

- It is a **junction** where the axon or some other portion of one cell (**pre**synaptic cell) terminates on the dendrites, soma, or axon of another neuron (**Post**synaptic cell).
- The CNS contains **more** than 100 billion neurons. 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 the neuron.

Note: Synapse is the connection between a neuron and another neuron (inside the CNS). Junction is a connection between a neuron and any other structure, e.g. muscle (outside the CNS).

يعني الجنكشن هي الإلتقاء بين أي حاجتين، ولما نتكلم عن الإلتقاء داخل الجهاز العصبي نقول سينابس، كل سينابس هو جنكشن لكن العكس غير صحيح.

Structure of chemical synapses (Guyton 12th edition Page 547)

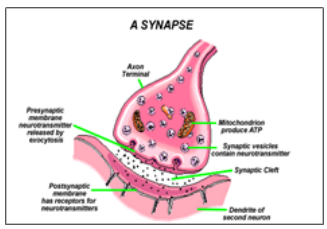
1) **Synaptic knob (presynaptic terminal):**

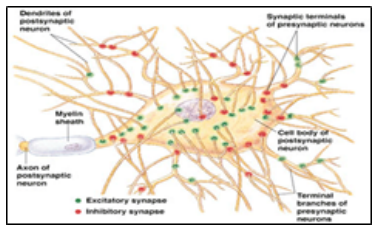
   It has synaptic vesicles (neurotransmitter vesicles).

2) **Synaptic cleft (gap):** الفجوة مابينهم
   - The space between the axon terminal and sarcolemma where neurotransmitters release into.
   - It has a width of 200-300 angstroms.

3) **Postsynaptic membrane:**

   It has receptors for neurotransmitters or ion channels.





Functional anatomy: Types of synapses (Guyton 12th edition Page 546)

❖ Anatomical types:

لا تطول بحفظها أمسك الأكسون ومرره على كل الستركتشرز، بعدها الديندرايت ومررها على الستركتشرز عدا الأكسون وبكذا حفظتهم!

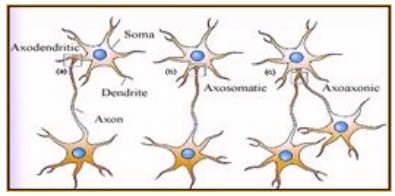
1. **Axodendritic:**

   synapses between the **axon** of one neuron and the **dendrite** of another neuron.

2. **Axosomatic:**

Synapses between the **axon** of one neuron and the **soma** of another neuron.

3. **Other types:**



- **Axo**axonic: **axon** to **axon.**
- **Dendro**dendritic: **dendrite** to **dendrite.**
- **Dendro**somatic: **dendrites** to **soma**.

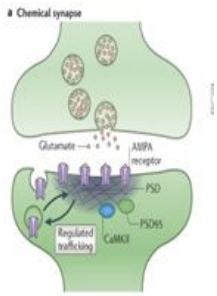
❖ Junctions outside the CNS:

- When the presynaptic terminal is in contact with other tissue other than neurons.
- **Examples:**
  - ★ **Neuromuscular junction.**
  - ★ **Contact between: Autonomic** neurons and smooth, cardiac muscles and any other effectors cell.

❖ Functional types:

Chemical synapses	Electrical synapses	Conjoint Synapse
Via **Neurotransmitters** 20-30 nm	Ion exchange via **Gap Junctions** 2-4 nm	Both electrical and chemical.
one-direction transmission. " Because NTs affect receptors and they're always present on the postsynaptic neuron."	**Bi**-direction transmission. "Because they don't need receptors. They work on the principle of exchanging ions through the junctions."	
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** which is responsible for balance & equilibrium.

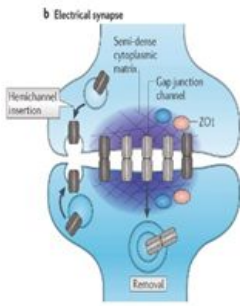
A neuron secretes a chemical substance called **neurotransmitter** at the synapse to act on the next neuron (by binding to a specific receptor enabling an electrical signal "postsynaptic potential or action potential") to excite it, inhibit or modify its sensitivity.



- membrane of the pre- and postsynaptic neurons come close together. Direct contact between the 2 membranes.
- Gap junctions form. Electrical synapses are faster than the chemical because of these gap junctions.
- No membrane borders, which allows **direct** passage of ions and **small** molecules.

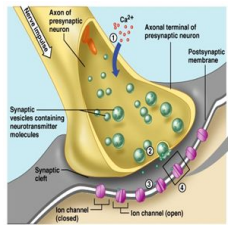
- If present, they are Important in the CNS in:

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

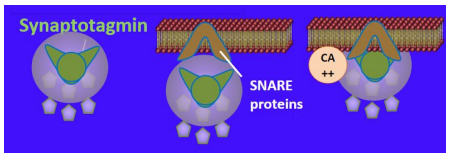


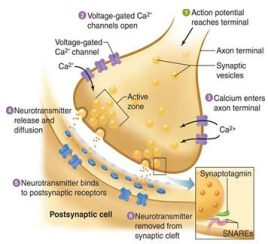
-lateral vestibular nucleus is one of the four vestibular nuclei on each side of the medulla oblongata.
-The other three vestibular nuclei:
1-Medial vestibular nucleus .
2- Cranial vestibular nucleus.
3-Caudal vestibular nucleus.

Synaptic Vesicle



- An abundant organelle with a diameter of 40 nm.
- Can accommodate only a **limited** number of neurotransmitters.
- 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.





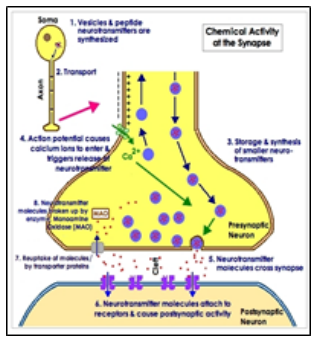
❖ Synaptic vesicular membrane:

- **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 membrane.

❖ Classes of Neurotransmitters: (present in the boys slides but NOT in the objectives of the guide so we deleted the table (we will study a whole lecture about them.)

Mechanism of a synaptic transmission (Guyton 12th edition Page 548)

1) **Action potential** arrive to the axon terminal of the presynaptic neuron opening the **Ca-gated channel** that allows the Ca ions to enter Synaptic knob.
2) Ca **binds** to synaptic vesicle.
3) Vesicles move toward **pre**synaptic membrane and neurotransmitters are released to **synaptic cleft** by **exocytosis**. "Ca is **essential** for NT releasing!"
4) Neurotransmitters attach to **post**synaptic receptors and cause postsynaptic activity " **inhibition or excitation"** according to the type of receptor and the type of the NT." "Glutamate is excitatory, GABA is inhibitory."



Synaptic Transmission (Duration: 1:51)

❖ What will happen to the neurotransmitters (Fate of the NT) ?

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

- **Diffusion out** of the synaptic cleft into the surrounding fluid.
- **Enzymatic destruction: e.g. Ach esterase for Ach.**
- **Active transport (reuptake)** back into pre-synaptic terminal itself **: e.g. Norepinephrine** that will be broken down inside the neuron by MAO "Monoamine Oxidase". Why is it "active"? Because the amount of NT inside is higher so it will move in low-high concentration gradient.

Components of postsynaptic receptors (Guyton 12th edition Page 548)

Types of receptors and EPSPS (Duration: 9:53) "VERY SIMPLE LIKE THE GREATEST EXPLANATION EVERRR"

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

2. Ionophore: It passes all the way through the membrane to interior.

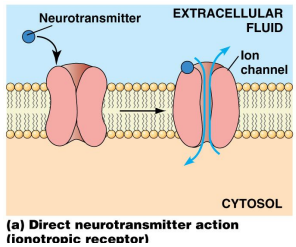
- **It is of 2 types either ion channels or 2nd messenger system.**

a) 2nd messenger system in the postsynaptic membrane -Metabotropic[1] (slow) receptors.

- **This mechanism is important where prolonged** postsynaptic changes are needed to stays for days, months, years **(memory).** "Recall: electrical synapse is important in memory, also the chemical synapse that has the 2nd messenger system."
- **Effects:** Intracellular enzymes activation, gene transcription, etc.

Explanation from the **boys lecture:**

Metabotropic (slow) receptors are linked to G-proteins, as soon as the ligand binds the receptor, G-protein will get activated. Once activated, the G-protein itself goes on and activates another molecule, This new molecule is called a "secondary messenger[2]".



B) Ion Channels - Ionotropic (fast)

Receptors that are linked directly to ion channels (also known as **ligand-gated ion channels**), so it is a receptor and channel at the same time .

- Whether a NT is excitatory or inhibitory depends on the receptor it binds to.

	Cation channels (For +ve charge ions):	Anion channels (for -ve charge ions):
Mechanism	Opening of Na+ channels → **Increase** membrane potential in positive direction toward threshold level of excitation due to **in**flux of (+)charges → (+) neuron. الشخص المتحمس دايم إيجابي، إذا بتثير نورون تبي تسويله ديبولارايزيشن excitation is towards positivity	Opening of cl- channels → **Decrease** membrane potential in negative direction away from threshold level due to **in**flux of (-) charges → (-) neuron

[1] the Greek **tropos** means to move in response to a stimulus.
[2] Intracellular signaling molecules released by the cell to trigger physiological changes.

Examples:	**Na++ (most common)**, K+, Ca++, ..	**Cl-** channels (mainly).

Functional Differences Between Ionotropic & Metabotropic Receptors

(From the **boys'** slides)

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 (Guyton 12th edition pg 552 – 553 - 554)

1. Resting membrane potential (RMP) of neuronal soma:

- Soma of a spinal motor neuron has a RMP of about -65 millivolts, Which is less negative than the (-70 to -90) millivolts found in skeletal muscles fibers.

- If the voltage is less negative ⟶ the neuron is excitable.
  - Extra Explanation:

الخلية تثار كلما اتجهت نحو الأعداد الموجبة، كونها أقل سالبية معناها أقرب للأرقام الموجبة، وكلما كانت أقرب للموجبة كلما كانت احتاجت أيونات موجبة أقل للوصول لحالة الـ depolarization.

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2. Excitatory postsynaptic potential (EPSPs): (Guyton 12th edition page 553)

- **What is it?**

  It is a postsynaptic potential that makes the postsynaptic neuron more likely to fire an action potential.

- **How?**
  - When **excitatory** neurotransmitter binds to its receptor on postsynaptic membrane ⟶ **partial depolarization** (increase **Na influx**) of post-synaptic cell membrane immediately under presynaptic ending, i.e. EPSPs.
  - This summation will cause the membrane potential to **increase** from -65mV to -45mV. (20 mV difference.)
  - So the **EPSPs = +20mV** makes the membrane reach the firing level ⟶ AP develops at **axon hillock**.

- If this potential rises enough to threshold level → AP will develop and excite the neuron.
- Synapse on the cell **body** is more effective than other parts of the neuron.
- **From the boys slides:**
  - Postsynaptic potentials (PSPs) decline within 15 ms (not long enough). This is the time needed for excess **positive** charges to leak **out** of the excited cell. هذا الوقت اللي الأيونات الموجبة اللي دخلت الخلية وقت الديبولارايزيشن تحتاجه عشان تطلع من الخلية وترجع طبيعية للرستنق ميمبرين بوتنشل.
  - Firing of only few synapses (4 or 8) will cause PSPs, but these are not large enough to reach threshold. To reach firing you will need at least 16 synapses on the neuron.

★ Extra Explanation:

- Presynaptic terminal secrets excitatory transmitters → increase Na permeability → rapid influx of Na to the interior → RMP will increase in the positive direction from -65mC to -45mV.

- The positive increase in voltage to a less negative value is called EPSP, which values +20mV (20mV more positive than the resting value "-65+20 = -45").

- It is called "Excitatory postsynaptic potential" because it will elicit an AP in the postsynaptic neuron if it rises enough in the positive direction.

- The increase of the neuronal potential from -65mV to -45mV requires simultaneous discharge of many terminals (not a single one) at the same time or in rapid succession which occurs by a process called summation.

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3. Inhibitory postsynaptic potentials (IPSPs):

- ### What is it?

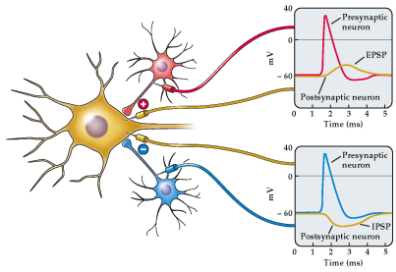
  A kind of synaptic potential that makes a postsynaptic neuron less likely to generate an action potential.

- ### How?

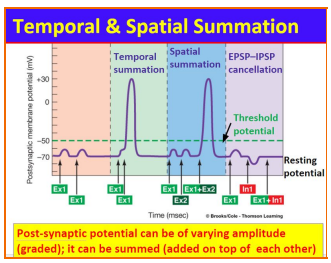
  - An **inhibitory** neurotransmitter binds to its receptor on postsynaptic membrane.
  - **Increases** membrane permeability to **Cl-** of post-synaptic membrane.
  - **hyper**polarization of the postsynaptic membrane.
  - **Decrease** excitability and membrane potential(more negative). Where the membrane reaches **-70 mV** (5 mV difference of the RMP.)
  - From the boys slides: A single presynaptic terminal can never cause a large voltage change that reaches threshold. That's why **summation is needed (either spatial or temporal.)**

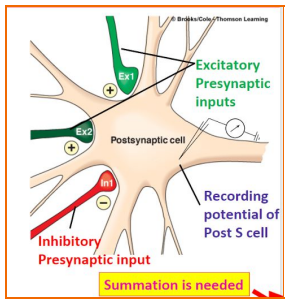
★ Extra Explanation:

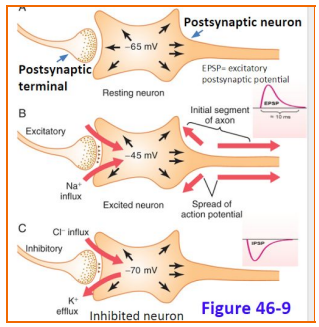
- The inhibitory synapses open mainly chloride channels, allowing Cl- influx which will make the interior membrane more negative than normal
- Opening K channels will allow K+ efflux which will make the interior membrane potential more negative!
- Thus, both Cl- influx and K+ efflux which will cause HYPERPOLARIZATION.
- This inhibits the neuron because the MP is more negative than the normal (from -65mV to -70mV).
- Therefore, an increase in negativity beyond the normal resting membrane potential level is called "inhibitory postsynaptic potential" and it values -5mV (5mV more negative than normal).



Pictures from the boys slides







Synaptic properties (Guyton 12th edition Pages 557).

1. ONE-WAY CONDUCTION:

- Synapses generally permit conduction of impulses in **one-way** i.e. from presynaptic to postsynaptic neuron.
- It means this process is always from pre-synaptic neuron → cleft → postsynaptic neuron

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2. SYNAPTIC DELAY:

- It 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:** (all these processes take 0.5 ms to complete) باختصار من يوم مايطلع الناقل العصبي لين ما تدخل الأيونات بياخذ وقت 0.5 ملي سكند
  - **Discharge** of transmitter substance by presynaptic terminal.
  - **Diffusion** of transmitter to postsynaptic membrane.
  - Action of transmitter on its **receptor**.

- Action of transmitter to increase membrane **permeability**.
- **Increased diffusion of Na+** to increase postsynaptic potential.

3. Fatigue:

- It is due to **exhaustion** of neurotransmitter, **(How?)** → If the pre synaptic neurons are continuously stimulated, **(Results in)** → **stoppage of synaptic transmission.**

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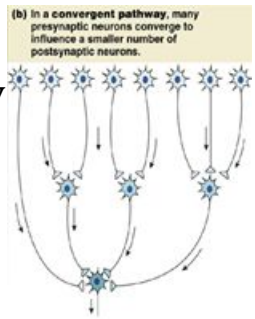
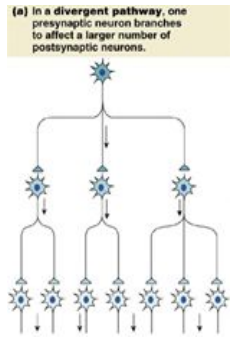
4. CONVERGENCE & DIVERGENCE:

CONVERGENCE (تجميع)	DIVERGENCE(تفريق)
When many presynaptic neurons **Converge**[3] on any single postsynaptic neuron. 	Axons of pre-synaptic neurons **divide** into many branches that **diverge**[4] to end on many postsynaptic neurons. 

طيب يمكن يسأل واحد ذكي (وش الفرق بين الكونفيرجنس وبين السبيشل سميشن اللي تحت؟) عاد اللي ما سأل عليهم العوض p:
التجميع هي إمكانية الخلايا العصبية إنها تتراكب على بعضها أو تتجمع وتنتهي بنقطة واحدة يعني نوعا ما خاصية حسية، السبيشل سميشن هي إمكانية إن السيالات العصبية إنها تنتقل عبر هذي الطريقة وتنتهي لنفس المكان بالتالي تزيد قوتها (مثل الفرق لما أقول لك فيه 5 طرق تؤدي لطريق تيم الفزيو هذي خاصية، وبين أن السيارات اللي جاية من كل طريق بالنهاية سببت زحمة فظيعة على طريق الفزيو واللي هي تمثل السيالات اللي تجمعت من كل مكان) > اجتهاد شخصي بالفهم.

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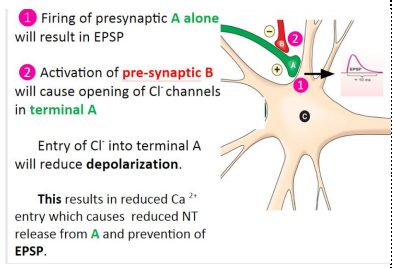
5. SUMMATION (The action potentials are added together)

SUMMATION	Spatial سبيشل	When EPSP occurs in more than one synaptic knob at **the same time.** خمس طرق نهايتها طريق واحد بيعطيك زحمة فظيعة، تذكرها سبيشل يعني سبيس وزحمة سيارات one neuron receives signals from more than one neuron.
	Temporal	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. مثل النطيطة بعد كل نطة تزيد الارتفاع .. نفس السيالة العصبية إذا تكررت بفارق زمني قصير

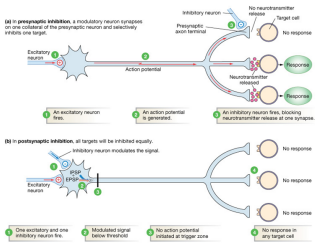
[3] To tend to meet in a point or line.
[4] Extend in different directions from a common point.

6. SYNAPTIC INHIBITION

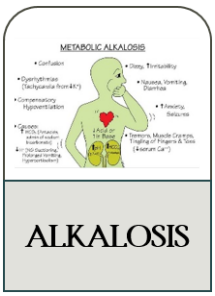
Types (all are fast responses, ionotropic receptors)		Definition
A	**Direct Inhibition (postsynaptic inhibition)** "No AP is generated" (2 neurons are involved pre- and post)	**-Occurs when:** An inhibitory neuron (releasing inhibitory substance) acts on a postsynaptic neuron leading to **hyper**polarization due to opening of Cl^- [IPSPs] and/or K+ channels. The goal is to make the inside of the cell **negative** which keeps the membrane potential away from threshold. This can be done by either the 1- **In**flux of negative ions by opening of **Cl** channels or by 2- **E**fflux of **K** ions making the inside of the cell less positive → moving towards negativeness. **- Example: Glycine** at the level of the spinal cord to **block pain** impulses.
B	***In*direct Inhibition (Presynaptic inhibition)** (3 neurons are involved)	**- 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** will be discussed later :) "Spinal cord reflexes lecture"	- Inhibition of antagonist activity is initiated in the agonist muscle. - 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. مثال: لما رجلي تدعس دبوس او شي حاد بيشتغل الرسبروكل إنهبشن مؤديًا إلى تثبيط الـ إكستنسرز مسل

		When the impulses pass to motor neuron that supply muscle, at the level of ganglia it has other branch which goes to inhibitory interneuron that will end as motor neuron to the agonist muscle
D	**Inhibitory Interneuron (Renshaw cells)** Renshaw = Inhibitory.. Don't even think!	**Negative feedback** inhibitory interneuron of a spinal **motor** neuron. (lateral inhibition) The inhibition here is via inhibitory interneuron. Impulses generated in the motor neuron activate the inhibitory interneuron to secrete inhibitory mediators, and this slows or stops the discharge of the motor neuron. This inhibitory interneurons also called Renshaw Cells.

GREAT PICTURE "EXTRA"



Factors affecting synaptic transmission (Guyton 12th edition Pages 557).



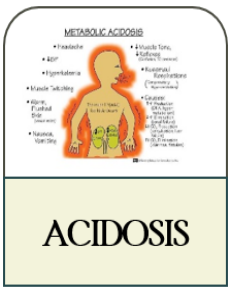
1-Alkalosis:

- **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 (removes) carbon dioxide and therefore elevates the pH (causing alkalosis) of the blood momentarily (gradually).

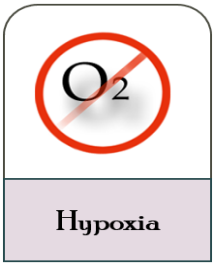


2-Acidosis:[5]

- **Depresses** neuronal activity.

[5] It is the increase in acidity in blood and other tissue (increased H+ concentration).

- pH around 7 "As in severe diabetic or uremic acidosis" usually causes a **coma** (Normal pH is around 7.35 – 7.45).



3-Hypoxia:[6]

- **Causes Depression** of neurons.

4-Drugs (important): Drugs could influence the effectiveness of synaptic transmission by:

- Altering synthesis, storage, or release of neurotransmitter.
- Or Modifying interaction of neurotransmitter with postsynaptic receptor.
- Influence **reuptake or destruction** of neurotransmitter.

- **Caffeine reduces** the threshold for excitation of neurons → **increases** neuronal excitability.

➔ **Other drugs mentioned in the boys slides:**

- **Cocaine**: **blocks the reuptake of Dopamine** by binding competitively with dopamine reuptake transporters. This causes prolonged activation of pleasure pathway (euphoria).
- **Strychnine** **competes with glycine**; it combines with the glycine receptor & blocks it (no IPSPs).
- **Prozac**, an example of a Selective S**erotonin Reuptake Inhibitor** (SSRIs). Serotonin is involved in neural pathways regulating mood & behavior so **Prozac is used for treating depression**, which is characterized by deficiency of serotonin.

[6] It is condition in which the body or a region of the body is deprived of adequate oxygen supply. It may be classified as either generalized, affecting the whole body, or local, affecting a region of the body. Mostly pathological but can also be physiological due change in arterial O2 concentration as in exercise for example.

This topic is present in the guide's objectives and the boys slides but not in the girls'.

Diseases that Affect NTs or their Receptors

Disease	Parkinson's disease	Myasthenia Gravis
Cause	due to A **deficiency of Dopamine** in a brain region (substantia nigra) controlling complex movements.	**Autoimmune** disease that targets **nicotinic ACh receptors** on **skeletal** muscle fibers (antibodies directed against these receptors).
Features	- Involuntary tremor (shaking of hands). - Muscle rigidity.	Muscle weakness (hallmark).
Treatment	**Levodopa** (L-dopa). Which is a **precursor** of dopamine, which crosses the blood-brain barrier (unlike dopamine), Once inside the brain, it is converted to dopamine & relieves the symptoms of disease.	**-Inhibitors of Acetylcholinesterase.** (like pyridostigmine) "Ach esterase is the enzyme that normally degrades Ach at the neuromuscular junction".

★ **References:**

- 435 girls and boys slides and notes.
- Guyton and hall textbook of medical physiology 12th edition. (Chapter **46**)
- Ganong's review of physiology.