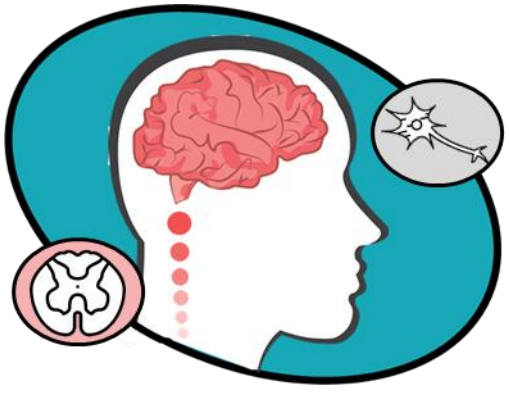

CNS

Physiology

Sheet Slide

Number

-2

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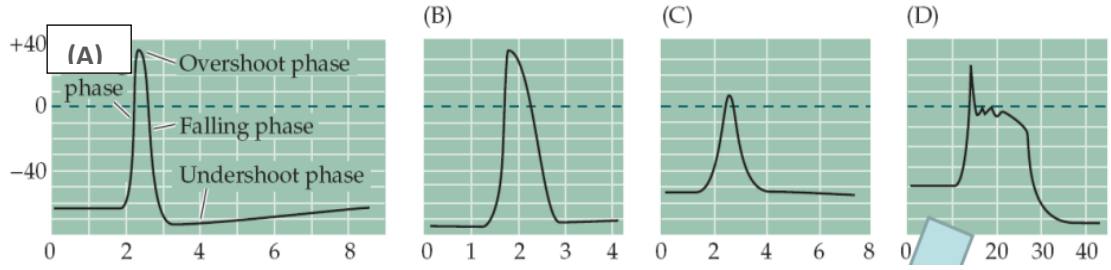
This lecture is divided into four main subjects:

1) Neuronal Action Potential
2) Channelopathies
3) Neuronal Circuits & Pools
4) Sensory Pathways and Receptors

- **Neuronal Action Potential:**00:00 – 08:35

As we have already said in the previous lecture, there are some characteristics of action potential (AP) such as threshold, peak, width, and presence of after hyperpolarization (relative refractory period). These properties are usually the same in **the same neuronal cell** upon receiving **a certain stimulus**.

-We've said that the cell will usually exhibit the same shape (properties) of AP, but this piece of information isn't really accurate. We are going to know why later.



In the figure above, we can notice the following:

- (A) & (B), to some extent, have the same threshold and peak. But they differ in their width (A is narrower) and the presence of after hyperpolarization (B does not have after hyperpolarization).
- (D) has a plateau phase due to the action of voltage-gated Ca++ channels.

*how can a neuron change the shape of its AP?

1) From (A) or (B) to (D)

-If it receives a stimulus that makes the cell synthesize new proteins (in this case, synthesis of new voltage-gated Ca++ channels) which will be attached to the membrane and enable Ca++ to enter the cell which produces the plateau phase.

2) From (A) to (B) or (B) to (A)

In this case, the difference is in the number of activated ion channels of **the same type** (there's no synthesis of new types of channels) since the difference between these two shapes is in their width.

*Width of AP indicates the velocity of ions conduction, which is mainly determined by the number of active ion channels. The more ion channels the cell has, the faster the AP and the narrower its shape becomes.

- This transformation of AP can be done very easily upon receiving a certain stimulus by changing the activation/deactivation ratio of the channels without synthesizing **NEW TYPES** of channels (be aware that the increased synthesis of already **existing types** of channels is a possible mechanism for this transformation).

-The stimulus is usually initiated by the attachment of a ligand (neurotransmitter/ hormone) to a second-messenger coupled-receptor like G-protein coupled receptors.

-Generally -as we all know- the targets of 2nd messenger receptors may involve:
Synthesis of new proteins, activation/deactivation of previously synthesized ones, or increase/decrease transcription of already found proteins.

** **So, a certain stimulus can change the response of the neuron by changing the shape of its action potential.** [This is considered as a type of processing of signals]

- According to the notes above, we can divide neurotransmitters into two types:

Neurotransmitters of excitation/inhibition effect. They carry out their action through **ion channels**, which produce graded potential (EPP/IPP)	Neuromodulators that change the function of the cell. They carry out their action through **2nd messenger receptors**. Serotonin, NE, and dopamine are examples.

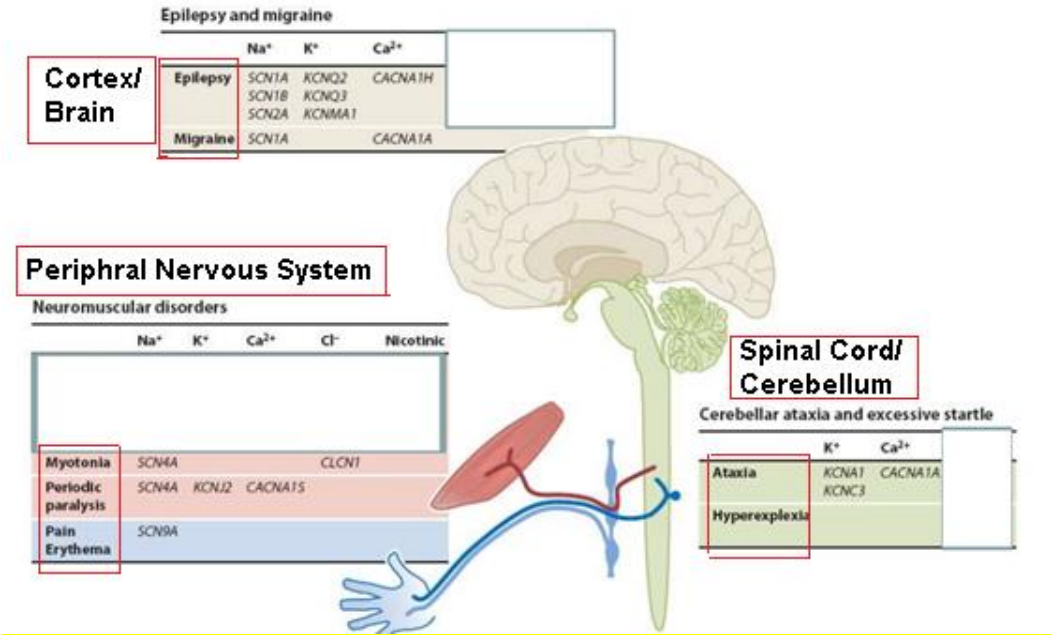
-For example, in some disorders in which dopamine levels drop this doesn't simply mean that the excitation of neurons is less, but it does mean that many **functions** of neurons are altered, and processing is abnormal and that is why we get behavioral changes. (Dopamine is a neuromodulator)

- **Channelopathies**08:34 – 12:50

-Several genetic diseases, collectively called channelopathies, result from small but critical alterations (mutations) in ion channel genes leading to changes in the ion channels.

These mutations will change AP → change the normal cell response to stimuli→ abnormal output/function → disorder.

-Each part of the nervous system expresses different subclasses of ion channels. So, a mutation in a certain subclass of an ion channel will affect the part of NS that expresses this subtype.



*Hyperekplexia: Exaggerated Startle reaction.
*Ataxia: the presence of abnormal, uncoordinated movements [No good coordination between sensation & motor activities].

** The following two pages are copied from pages 84 & 85 in Neuroscience 3rd edition by Dale Purves. [They're required]

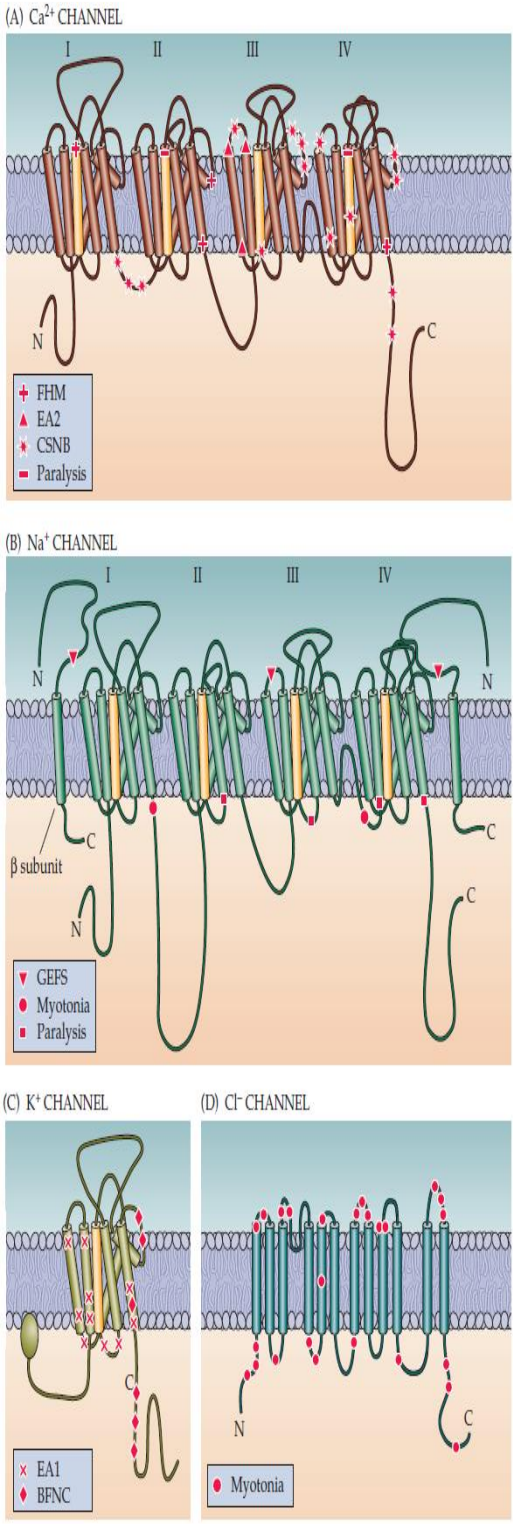
Diseases Caused by Altered Ion Channels

Several genetic diseases, collectively called *channelopathies*, result from small but critical alterations in ion channel genes. The best-characterized of these diseases are those that affect skeletal muscle cells. In these disorders, alterations in ion channel proteins produce either myotonia (muscle stiffness due to excessive electrical excitability) or paralysis (due to insufficient muscle excitability). Other disorders arise from ion channel defects in heart, kidney, and the inner ear.

Channelopathies associated with ion channels localized in brain are much more difficult to study. Nonetheless, voltage-gated Ca2+ channels have recently been implicated in a range of neurological diseases. These include episodic ataxia, spinocerebellar degeneration, night blindness, and migraine headaches.

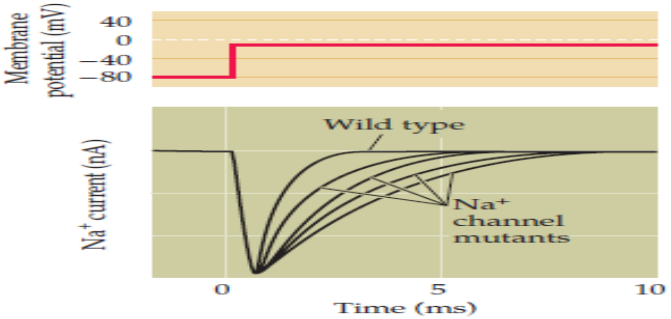
F*amilial hemiplegic migraine* (FHM) is characterized by migraine attacks that typically last one to three days. During such episodes, patients experience severe headaches and vomiting. Several mutations in a human Ca2+ channel have been identified in families with FHM, each having different clinical symptoms. For example, a mutation in the pore-forming region of the channel produces hemiplegic migraine with progressive cerebellar ataxia, whereas other mutations cause only the usual FHM symptoms. How these altered Ca2+ channel properties lead to migraine attacks is not known.

Episodic ataxia type 2 (EA2) is a neurological disorder in which affected individuals suffer recurrent attacks of abnormal limb movements and severe ataxia. These problems are sometimes accompanied by vertigo, nausea, and headache



Genetic mutations in (A) Ca2+ channels, (B) Na+ channels, (C) K+ channels, and (D) Cl– channels that result in diseases. Red regions indicate the sites of these mutations; the red circles indicate mutations.

Usually, attacks are precipitated by emotional stress, exercise, or alcohol and last for a few hours. The mutations in EA2 cause Ca2+ channels to be truncated at various sites, which may cause the clinical manifestations of the disease by preventing the normal assembly of Ca2+ channels in the membrane. X-linked *congenital stationary nightblindness* (CSNB) is a recessive retinal disorder that causes night blindness, decreased visual acuity, myopia, nystagmus, and strabismus. Complete CSNBcauses retinal rod photoreceptors to be nonfunctional. Incomplete CSNB causes subnormal (but measurable) functioningof both rod and cone photoreceptors. Like EA2, the incomplete type of CSNB is caused by mutations producing truncated Ca2+ channels. Abnormal retinal function may arise from decreased Ca2+currents and neurotransmitter release from photoreceptors (see Chapter 11). Adefect in brain Na+ channels causes *generalized epilepsy with febrile seizures*(GEFS) that begins in infancy and usually continues through early puberty. This defect has been mapped to two mutations: one on chromosome 2 that encodes an α subunit for a voltage-gated Na+ channel, and the other on chromosome 19 that encodes a Na+ channel β subunit. These mutations cause a slowing of Na+ channel inactivation(see figure above), which may explain the neuronal hyperexcitability underlying GEFS. Another type of seizure, *benign familial neonatal convulsion* (BFNC), is due to K+ channel mutations. This disease is characterized by frequent brief seizures commencing within the first week of life and disappearing spontaneously within a few months. The mutation has been mapped to at least two voltage-gated K+ channel genes. Areduction in K+ current flow through the mutated channels probably accounts for the hyperexcitability associated with this defect. Arelated disease, episodic ataxia type 1 (EA1), has been linked to a defect in another type of voltage-gated K+ channel. EA1 is characterized by brief episodes of ataxia. Mu
Mutant channels inhibit the function of other, non-mutant K+ channels and may produce clinical symptoms by impairing action potential repolarization. Mutations in the K+ channels of cardiac muscle are responsible for the irregular heartbeat of patients with long Q-T syndrome. Numerous genetic disorders affect the voltage-gated channels of skeletal muscle and are responsible for a host of muscle diseases that either cause muscle weakness (*paralysis*) or muscle contraction (*myotonia*).



Mutations in Na^+ channels slow the rate of inactivation of Na^+ currents. (After Barchi, 1995.)

In short, ion channels are integral membrane proteins with characteristic features that allow them to assemble into multimolecular aggregates. Collectively, these structures allow channels to conduct ions, sense the transmembrane potential, to inactivate, and to bind to various neurotoxins. A combination of physiological, molecular biological and crystallographic studies has begun to provide a detailed physical picture of K+ channels. This work has now provided considerable insight into how ions are conducted from one side of the plasma membrane to the other, how a channel can be selectively permeable to a single type of ion, how they are able to sense changes in membrane voltage, and how they gate the opening of their pores. It is likely that other types of ion channels will be similar in their functional architecture. Finally, this sort of work has illuminated how mutations in ion channel genes can lead to a variety of neurological disorders

- **Neuronal Circuits & Pools**13:00 – 29:50

*Neuronal responses and processing depend on:

-The type of neuron
-Properties of action potential
-Neuronal arrangements/ pathways

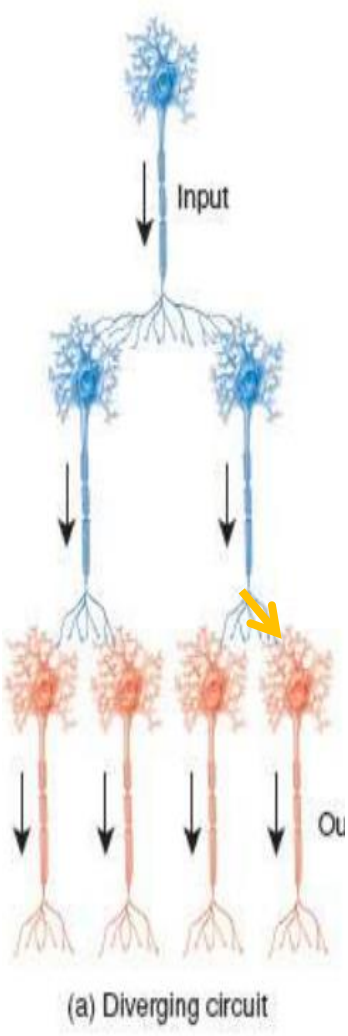
-Neuronal pathway: is the collection of neurons that initiate, conduct, and receive a signal.

-If the pathway is composed of three neurons, the first neuron is called the 1st order, the second is the 2nd order, and the third is the 3rd order neuron.

-At each synapse, a **processing** process takes place.

-This is an example of a linear pathway, but in reality, more complex pathways exist more in order to provide a higher processing power.

- **Transmission and Processing of Signals**:
  1) **Divergence**: an input signal spreads to an increasing number of neurons as it passes through a branching neuron of any order (1st / 2nd / …).
  -In the figure to the right, there are four different destinations for the same signal.
  -Collateral axons: is the branch of the axon that sends the signal to only one target. (Yellow arrow is an example)
  -Divergence is useful in sensory signals. The most important target of sensation is the cortex (to be aware and conscious about it), but there're some branches reaching the spinal cord (for reflexes if needed) and subcortex (to give the emotional part of that sensation). These branches are given off by means of divergence.
  -For example Pain sensation will be transmitted to the Central nervous system through sensory neurons, the sensation will go to the cortex as all sensations do, but along the way the neuron will give branches to the spinal cord in case reflexes are needed, it may also send branches

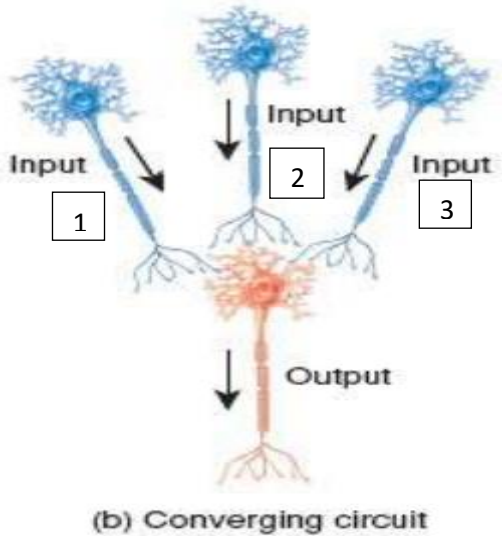


(a) Diverging circuit

to the subcortex to give the emotions.
- As we have already said all sensations main target is to reach the cortex (conscious part), but along the way they have check points in the spinal cord and subcortex to give the unconscious part of that sensation.
** And so we can conclude that sensations have targets other than the cortex.
* In Divergence the same pathway reaches the cortex, the spinal cord and the subcortex by giving collateral branches.

2) Convergence: Signals from multiple inputs uniting to excite a single neuron.

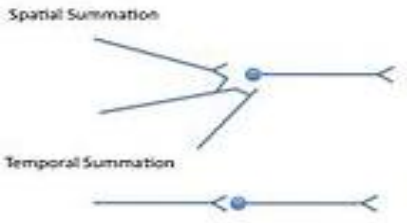
[More than one presynaptic neuron (1^{st} /2^{nd} order) synapse on the same postsynaptic neuron→processing↑**(spatial & temporal summation) * read the extra note below**].



(b) Converging circuit

–The importance of convergence is that neurons are almost never excited by a signal from a single input terminal. However, action potentials converging on the neuron from multiple terminals provide enough **spatial summation** to bring the neuron to the threshold required for discharge.
-This mode of arrangement increases probabilities. For example, a signal from 2 will give an output, from 1 → no output, from 2+3 → no output, and from 1+3 → output, and so on.
↑Probabilities→↑ Processing
*Convergence is found in most parts of CNS even the cortex and that is to increase the processing power.

Extra note:



Summation, which includes both **spatial and temporal summation***,it is the process that determines whether or not an action potential will be

generated by the combined effects of excitatory and inhibitory signals, both from multiple simultaneous inputs (spatial summation), and from repeated inputs (temporal summation). Depending on the sum total of many individual inputs, summation may or may not reach the threshold voltage to trigger an action potential.

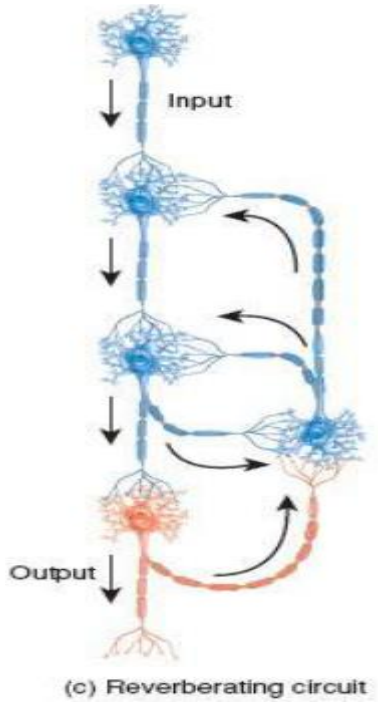
3) **Reverbrating:** Stimulation of a neuron from input and the transmission of this signal through **collateral axons**into 1) the final destination leading to an output 2) other neurons that will reactivate the same circuit from the beginning.

-One stimulus will give multiple outputs per a period of time.This period of time depends on the frequency of the stimuilus.

If the stimulus was big, the period of time between the multiple outputs will be short.

-This mode of signal transmission provides the following advantages:

- ✓ Increases the processing power: as it provides the application of **temporal summation** on the neuron that receives the multiple output.
- ✓ Automatic regeneration of a signal that will repeat itself in a certain frequency that could be maintained, increased, decreased, or stopped.



(c) Reverberating circuit

Examples:

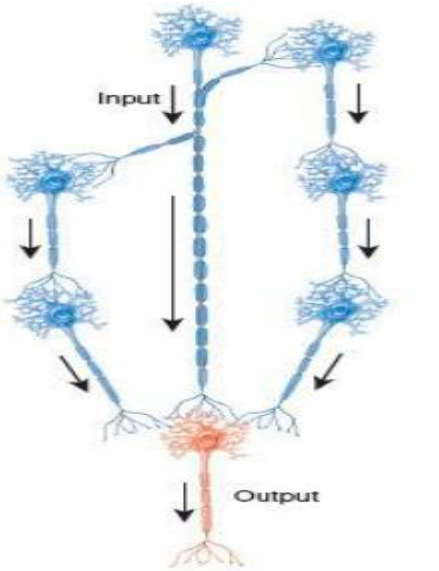
a- Breathing: is controlled by the respiratory center in the medulla (brain stem). There will be a rhythmic and automatic activity in this center (for example, an output of breathing for each 6 seconds) (since it is automatic there is no need for the brain to give orders every 6s) according to body's activity and its requirements of oxygen.

If O2 requirements increase, then the frequency of signal's regeneration will also increase therefore, increasing the respiratory rate (output).

b- Short-term memory: in the neocortex.
*Memory: is a facilitated circuit.[A group of neurons that are active or can be easily activated compared to other neurons in the background].

- ✓ Short-term memory: reverberating neurons that are active as long as the task exists and inhibited if the task is removed. For example, if you are given a random number (e.g. 7643) you will keep repeating the number and it will stay in your short memory once you stop repeating it, you will forget it.
- ✓ Long-term memory: anatomical and physiological changes of a certain group of neurons which make their activation easier. For example, your university number will stay in your memory even if you don't keep repeating it.

4) Parallel after discharge: An input neuron diverges to stimulate several chains of neurons. Chains eventually converge into the same output neuron. Each output neuron receives signals from multiple pathways, and may go on firing for some time after the input has ceased due to the delay that may occur in a particular pathways due to the number of synapses it has.



(d) Parallel after-discharge circuit

-Each pathway has a different number of neurons and synapses and so the time delay in each pathway will be different.Let's take the figure to the right as an example; the output neuron will receive three different action potentials at different points of time (each have a different # of neurons & synapses). This arrangement gives complex processing, because you start with one signal then diverge it into three parts through three pathways with different timing and processing, after that they are going to combine together into the output neuron.

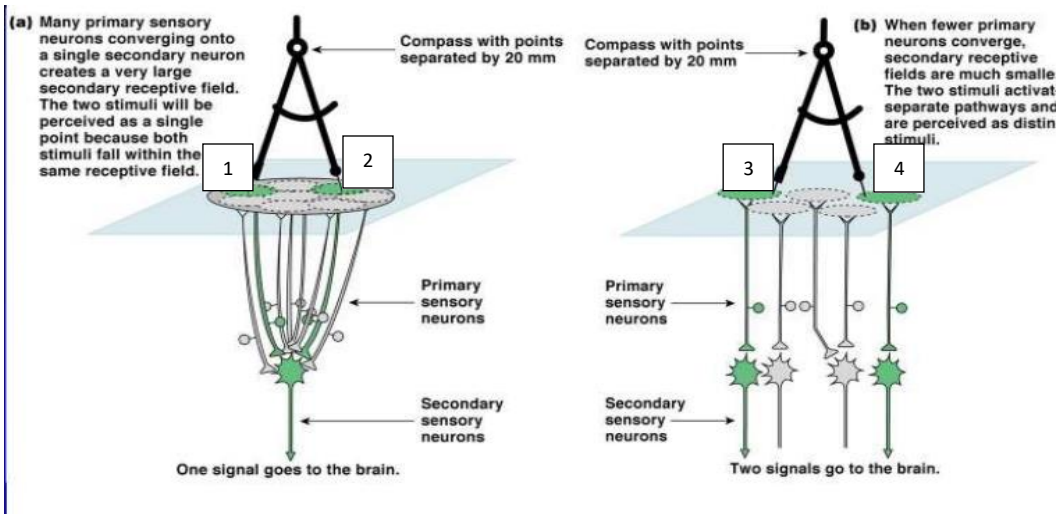
*As we have already said, each one of the three pathways will conduct the signal at a different velocity, process it in a different way, and the pathway could be excitatory or inhibitory. All these factors explain the

complexity of this type of neuronal pool, which is mostly found in neocortical areas which need higher processing power for higher thinking orders and activities.

- **Sensory Pathways** 29:50 – 39:00

We've previously discussed some features of sensory pathways; we've said that divergence pool is useful in the transmission of sensory signals as they have several destinations, the direct and most important is the pathway that goes to the cortex.

- Effects of neuronal arrangement in the sensory pathway:
  1) Modality of sensation: Let's discuss the following figure.



As you can see, in figure (B) each area of skin has a specific sensory neuron which will carry a specific sensory signal to the brain.
If area 3 is stimulated, the brain will receive a distinct signal that is different from the signal received from area 4. When both 3 & 4 are stimulated two signals will go to the brain. So, by using this type of neuronal arrangements the brain will be able to recognize the area that has been touched/ stimulated. [High resolution].

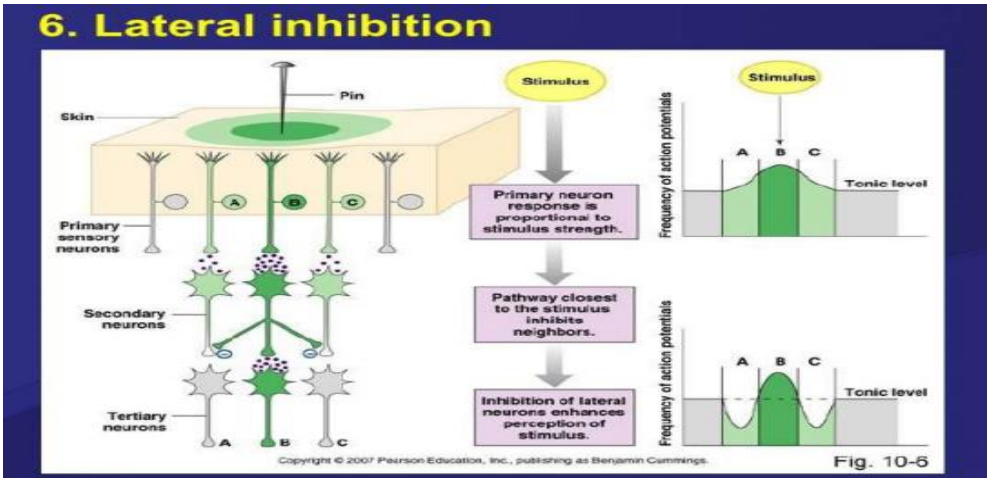
In figure (A) also each area of skin has a specific sensory neuron, but they will converge onto a single secondary neuron that will go to the brain, so the stimulation of area 1, 2 or both of them will have the same meaning and there's no real discrimination between them. [Low resolution].

*These differences in arrangements give different modalities*of sensation although the type and density of receptors are the same.
This is what happening in somatic sensation (skin) in which the same type of receptors (pressure receptors) give two different modalities of sensation due to different arrangements of neurons in the pathway.

a- Fine touch/ two-point discriminative touch. (as figure B)
b- Crude touch/ rubbing or itching. (as figure A)

*stimulus modality, also called sensory modality, it is what is perceived after a stimulus

2) Lateral inhibition:**lateral inhibition** is the capacity of an excited neuron to reduce the activity of its neighbours.
-One part of the sensory pathway will give off collateral branches that will inhibit other pathways (pathways of the same sensation, or other sensations of other modalities).



*It doesn't only occur in sensory pathways, but also in the processing carried out by the neocortex.

Examples on this phenomenon:

a- Somatic sensation: when you press on a certain area of skin other areas in the vicinity will be depressed which means that pressure receptors of the initial area of touch, as well as, other neighboring areas are activated. In this case, there's a difference in the activity of these receptors according to their location. The receptors in the exact area of touch will have the higher activity (let's say 100) and a gradual decay of receptor's activity will happen as we go far from the area of interest (90,80, 70, …). It will be hard for the brain to determine where the pressing exactly took place and thus a low resolution of sensation.

   With the application of lateral inhibition, neurons of the main pathway with the highest activity will inhibit signals from neighboring pathways

by decreasing their activities (for example from 90 to -10) which makes the main pathway have a relatively high activity in order to make it easier for the brain to focus on that specific area and enhance the resolution.

b- In the cortex, this allows it to focus on one piece of information not two.

c- In the processing of auditory information and helps the cortex to discriminate between very close sounds (مثل حرف الهاء والحاء).

d- In the processing of visual information, lateral inhibition increases the contrast and sharpness in visual response.

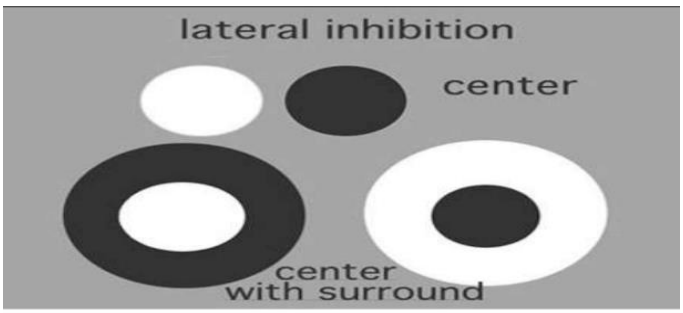
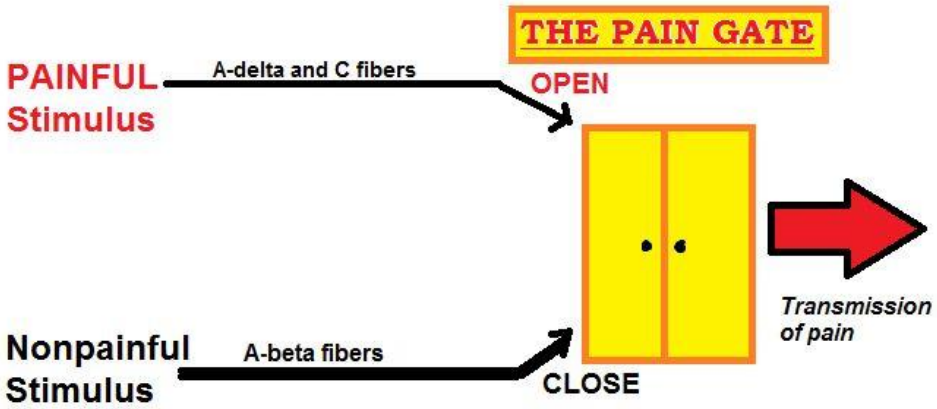


Fig. 10. Center-surround receptive fields can be ON center or OFF center with the opposite sign annular surround.

*Notice how the lower white circle is more obvious than the upper one due to the higher contrast in the black background.

e- Pain gate theory: The **gate control theory of pain** asserts that non-painful input closes the nerve "gates" to painful input, which prevents pain sensation from traveling to the central nervous system. Therefore, stimulation by non-noxious input is able to suppress pain.
We apply this frequently. When we injure our body, we spontaneously begin to press on or rub the injured area to relieve pain and now we know that lateral inhibition is responsible of that phenomenon.



- **Sensory Receptors** 39:00 – 44:00

-Sensory receptor: a cell that receives a certain type of stimuli and transforms it into neuronal signals. There are different types of receptors according to the different types of stimuli.

*Mechanical receptors, which receive mechanical information like touch& pressure.
*Chemical receptors, receive chemical information like olfaction and taste.
*Photoreceptors that receive optical information (vision).

-When the receptor receives a stimulus, a graded potential will be produced in that receptor (receptor potential).
-With stronger stimuli, the receptor will produce a higher graded potential and thus higher frequency and output.

-Baseline firing rate of neurons: frequency of action potentials produced by a neuron at rest (baseline). This feature of neurons makes the body able to apply a two-direction regulation on the receptor (increase or decrease the frequency of firing). If the receptor didn't have this baseline rate, it wouldn't be possible to control it by decreasing the frequency of firing below the zero! So this feature is extremely important especially in sensations as we'll learn in next lectures.

-Adaptation of Receptors:
"Another characteristic of sensory receptors is that they adapt either partially or completely to a constant stimulus after a period of time. That is, when a continuous sensory stimulusis applied, the receptor responds at a high impulse rate at first and then at a progressively slower rate until finally the rate of action potentials decreases to very few or often to none at all."
*From the definition above we can conclude the following:

- ✓ The exposure to the same stimulus for a relatively long period of time will make the receptor lower the graded potential and thus lowers the frequency of output.
- ✓ Receptors have different adaptabilities (some of them adapt quickly, some slowly, and others are non-adaptable).

-Central adaptation:
*Some sensory pathways of non-adaptable receptors may have adaptable neurons in their pathway which decreases the output. (it may also occur due to neuronal exhaustion)

*Orders from the neocortex (consciously) or the subcortex (unconsciously) can be sent to the sensory pathway and either [**sensitize**] increase its output by facilitating that pathway to focus on it well, or [**desensitize**] decrease its activity to stop receiving signals from that pathway.

In conclusion: Adaptation to sensory stimuli may involve:

1) changes in receptor sensitivity (peripheral/sensory adaptation)
2) Or inhibition along the sensory pathways (central adaptation).