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Review: Membrane physiology and the basis of excitability

Ref: Guyton, 14th ed. 63-76, Jordan and 13th ed. pp: 61-71. 12th ed. pp: **57-69**,

MEMBRANE POTENTIALS AND ACTION POTENTIALS:

MEMBRANE POTENTIAL:

Excitable tissues: muscles and nerves.

Impulses are used to transmit signals along the nerve or muscle membranes.

The function of excitable tissue is related to the conductance of ions.

What governs the conductance of ions is the difference in concentrations for these ions.

Membranes potentials caused by diffusion.

"Diffusion potential" caused by an ion concentration difference on the two sides of the membrane.

If we assume that a cellular membrane is permeable **only** to K+, which is found in a very high concentration inside the cell. K+ will diffuse to the extracellular fluid because of the concentration gradient. The diffusion of K+ will result in a movement of positive charges outside the cell and leaving behind negative charges inside the cell (thus creating electropositivity outside the membrane and electronegativity inside the membrane because of negative anions that remain behind and do not diffuse outward with the potassium, and the potential difference between inside and outside is called the diffusion potential). This will create an electrical potential difference across membrane (positive outside and negative inside). Creation of this potential difference will oppose diffusion of K+ to the outside at a certain concentration difference (the diffusion potential becomes great enough to block further net potassium diffusion to the exterior despite the high potassium ion concentration gradient).

- In the normal mammalian nerve fiber, the potential difference that required to block further net potassium diffusion OR WE CAN SAY ACCORDING TO DOCTOR'S SLIDES oppose diffusion

of K+ to the outside يعني بيعكس انتشارهم إلى الخارج فبيصير إلى الدّاخل فالمحصّلة بتصير صفر the potential difference required is about 94 millivolts with negativity inside the fiber membrane (-94 millivolts))

When you reach a point at which diffusion of K+ is completely opposed by the potential difference created across membrane and the net diffusion for K+ is zero even though you still have a concentration gradient, you have reached the equilibrium potential for K+ (E_K). The equilibrium potential for any univalent ion at normal body temperature 37C can be calculated by Nernest equation:

$$E\ (mV) = -\ 61.\log\ (Ci/Co)$$

-This equation shows the relation of the diffusion potential to the concentration difference.
-The diffusion potential here (we mean for one ion) is called the Nernst potential, and its magnitude is determined by the ratio of the concentration of that specific ion on the two sides of the membrane.
-The greater this ratio, the greater the tendency for the ion to diffuse in one direction, يعني كل مازاد اختلاف التركيز على الجانبين and therefore the greater the Nernst potential required to prevent additional net diffusion.

E = equilibrium potential for a univalent ion Ci = concentration inside the cell.
Co = concentration outside the cell.

When more ions are involved in creating the potential, we can calculate the potential according to Goldman-Hodgkin-Katz equation.

$$E_m = \frac{RT}{F} \ln \left(\frac{P_{Na^+}[Na^+]_o + P_{K^+}[K^+]_o + P_{Cl^-}[Cl^-]_i}{P_{Na^+}[Na^+]_i + P_{K^+}[K^+]_i + P_{Cl^-}[Cl^-]_o} \right)$$

P = permeability of the membrane to that ion.

In this equation, Goldman and his colleagues considered that these ions are mostly involved in the development of membrane potential.

- According to this formula the diffusion potential that develops depends on three factors: (1) the polarity of the electrical charge of each ion(polarity=separation, the polarity of the membrane قصدهم انّه الغشاء بيقدر يفصل بين الشحنات الموجبة والسالبة كل وحدة على جهة,
(2) the permeability of the membrane (P) to each ion, and (3) the concentrations (C) of the respective ions on the inside (i) and outside (o) of the membrane.

According to this equation the permeability of the membrane to an ion is very important in determining the membrane potential. If the membrane is permeable only to K+ and not permeable to Cl- and Na+, the membrane potential will be equal to E_{K+}.

*الّي مكتوب تحت مبيّن كثير بس كلّه شرح وفهم، قراءة سريعة بتكفي مع التركيز على الّي تحته خطّ بيكفي...

Several key points become evident from the Goldman equation:

- First, sodium, potassium, and chloride ions are the most important ions involved in the development of membrane potentials in nerve and muscle fibers, as well as in the neuronal cells in the nervous system. The concentration gradient of each of these ions across the membrane helps determine the voltage of the membrane potential.

- Second, the quantitative importance of each of the ions in determining the voltage (كم مساهمة الأيون في تحديد قيمة فولتيّة الغشاء) is proportional to the membrane permeability for that particular ion.

- Third, a positive ion concentration gradient from inside the membrane to the outside causes electronegativity inside the membrane. The reason for this phenomenon is that excess positive ions diffuse to the outside when their concentration is higher inside than outside. This diffusion carries positive charges to the outside but leaves the nondiffusible negative anions on the inside, thus creating electronegativity on the inside. The opposite effect occurs when there is a gradient for a negative ion. That is, a chloride ion gradient from the outside to the inside causes negativity inside the cell because excess negatively charged chloride ions diffuse to the inside, while leaving the nondiffusible positive ions on the outside.

- Fourth, as explained later, the permeability of the sodium and potassium channels undergoes rapid changes during transmission of a nerve impulse, whereas the permeability of the chloride channels does not change greatly during this process. Therefore, rapid changes in sodium and potassium permeability are primarily responsible for signal transmission in neurons, which is the subject of most of the remainder of this chapter.

Resting membrane potential:

In excitable cells the membrane potential is not constant. When the cell is stimulated, the membrane potential changes. These changes in membrane potential are due to changes in permeability of plasma membrane to different ions. For example, when neuron is stimulated, this will result in increased permeability to Na+. This will bring the membrane potential closely to E_{Na}. The recorded membrane potential for a cell under resting conditions when no stimulus is involved is known as **resting membrane potential**. For neurons the recorded resting membrane potential is about (– 90 mV). This represents a potential difference between the inside to the outside when

neuron is not active. the potential inside the fiber is 90 millivolts more negative than the potential in the extracellular fluid on the outside of the fiber.

Origin of resting membrane potential:

Contribution of K+ diffusion:

As mentioned earlier, if the membrane is permeable only for K+ the calculated E_{K+} is about (-94mV).

Co_{K+} = 4meq/l , Ci_{K+} = 140meq/l

E_{K+} = -61. log 140/4 = -94mV

Which is not far from the recorded membrane potential but not exactly.

The contribution of Na+ diffusion:

Membrane is also permeable to Na+. The permeability of the plasma membrane for Na+ is much less than that of K+. If the membrane is permeable only to Na+, the calculated E_{Na+} = + 61mV.

…….. (Co_{Na+} = 142meq/l , Ci_{Na+} = 14meq/l).

Because of the permeability of the membrane for the two ions, the E would be between (-94mV and +61mV) (the calculated E for each ion using Nernst equation). The calculated E for the two ions is –86mV (calculated using Goldman-Hodgkin-Katz equation), which is not far from the E_{K+} because of the higher permeability of membrane for K+ than for Na+ (100 times more). So, it is logical that the diffusion of potassium contributes far more to the membrane potential than does the diffusion of sodium.

So the Na+ contribution in resting potential is by bringing the membrane potential to a lower value than the calculated E_{K+}.

Contribution of Na+ - K+ pump:

As mentioned earlier, this pump is electrogenic. It moves more positive charges outside the cell (3 for 2). This will induce loss of positive charges from the cell and bring the membrane potential to a higher negativity (about –4mV additional negativity).

Therefore all these factors, during **rest**, will give a net membrane potential of –90mV (called **Resting Membrane Potential**).

ACTION POTENTIAL:

- Nerve signals are transmitted by *action potentials*, which are rapid changes in the membrane potential that spread rapidly along the nerve fiber membrane.

As we have seen, the plasma membrane is **polarized** (has ability to separate opposite charges) during resting state. When the membrane potential decreases (becomes less negative), the membrane is in **depolarization** stage. While the change in membrane potential in opposite direction (becomes more negative than resting potential) is known as **hyperpolarization**.

When a cell is depolarizing, it reaches a maximum according to stimulus, then the membrane potential returns to its resting state. The phase of returning from depolarized state to resting state is known as **repolarization**. These changes in membrane potential can be recorded by placing one electrode inside the cell and the other out side the cell. By recording of whole action potential in this way, we will obtain a **monophasic action potential**.

The successive stages of the action potential are as follows:

- **Resting Stage**: The resting stage is the resting membrane potential before the action potential begins. The membrane is said to be "polarized" during this stage
- **Depolarization Stag:** At this time, the membrane suddenly becomes permeable to sodium ions, allowing tremendous numbers of positively charged sodium ions to diffuse to the interior of the axon.
- **Repolarization Stage**: after the membrane becomes highly permeable to sodium ions, the sodium channels begin to close and the potassium channels open to a greater degree than normal.

Let us consider the changes in membrane potential of an excitable cell to understand the events that appear during changes of membrane potential. To induce a change, a stimulus must be applied to change activity of channels at the membrane. Any increase in permeability of membrane to Na+ will result in diffusion of (+) charges inward. This event will decrease the membrane potential (becomes less negative). And conversely any increase in K+ diffusion (movement outward) will result in an increase in membrane potential (becomes more negative). The diffusion of these ions depends on the activity of Na+ and K+ channels that are found on the membrane. Activation of Na+ channels will induce depolarization, while activation of K+ channels will increase the potential difference across membrane inducing repolarization or hyperpolarization.

Action potential and the role of Na+ channels:

- *The voltage-gated sodium channel* is the necessary actor in causing both depolarization and repolarization of the nerve membrane during the action potential.
- This channel has two gates—one near the outside of the channel called the activation gate, and another near the inside called the inactivation gate. (it's more clear in the figures in the book).

On the membrane, most Na+ channels during resting state are inactive (closed). According to channel type, these channels can be activated by a chemical stimulus (in case of chemical gated channels), electrical stimulus (in case of voltage gated channels), or mechanical stimulus. In the case of chemical gated channels, binding of ligand to its receptor will induce activation of chemical gated Na+ channels. Once activated, the membrane potential will decrease (becomes less negative). Which means that the membrane depolarizes (in the depolarization Stage, the membrane **suddenly** becomes permeable to sodium ions). The voltage changes in the membrane will cause the other type of channels (Na+ voltage gated channels) to be activated. Activation of these channels will cause more changes in membrane potential (more depolarization). More and more depolarization will occur in the membrane by a positive feed back mechanism (*activated state*). If we reach a point at which most voltage gated Na+ channels are activated, this will cause a sudden increase in Na+ permeability. This increase in Na+ permeability will even reverse the membrane potential (In large nerve fibers, the great excess of positive sodium ions moving to the inside causes the membrane potential to actually "overshoot" beyond the zero level and to become somewhat positive.) (becomes positive inside and negative outside) (this is known as the **overshot** in the action potential), because Na+ is trying to approach its equilibrium potential (E_{Na}). At this point membrane has reached maximal changes in membrane potential (a peak of an action potential).

- In some smaller fibers, as well as in many central nervous system neurons, the potential merely approaches the zero level and does not overshoot to the positive state.

As we have seen, during depolarization there is a point at which a sudden increase in Na+ influx which induces rapid and maximal change in membrane potential. This point is known as **threshold** of an action potential. The rapid change in membrane potential during the raising phase of an action potential is known as **firing stage**. When a stimulus causes a depolarization that brings the membrane potential to the threshold, the membrane will respond by the firing stage of an action potential. If depolarization in the membrane has not reached threshold, the membrane will not enter firing stage, and instead, the potential returns to its resting level. Therefore the response in the membrane will be either by an action potential when threshold is achieved or no appearance of an action potential when the membrane potential has not reached threshold. For that reason induction of an action potential in excitable cells follows the **NONE OR ALL PRINCIPLE**.

The voltage changes in membrane potential not only activate voltage dependent Na+ channels, but also inactivate these channels at certain potential difference (The same increase in voltage that opens the activation gate also closes the inactivation gate getting the channels in *closed state*). This inactivation appears because channels have changed their state from opened channels to closed channels due to voltage changes. The closing event of Na+ channels does not make these channels as the only responsible for bringing membrane potential to its resting level. But also, activation of voltage dependent K+ channels is the main player in returning the membrane potential to its resting level.

- Another important characteristic of the sodium channel inactivation process is that the inactivation gate will not reopen until the membrane potential returns to or near the original resting membrane potential level. Therefore, it is usually not possible for the sodium channels to open again without first repolarizing the nerve fiber.

Action potential and K+ channels:

- *The voltage gated potassium channel* plays an important role in increasing the rapidity of repolarization of the membrane.

Although there is some leakage of K+ during resting state, which maintains the resting membrane potential close to $E_{K+,}$ depolarization causes activation of voltage gated K+ channels. The activation of these channels is much slower than activation of Na+ channels. This results in a delay in the maximal activation of K+ channels.

- When the membrane potential rises from −90 millivolts toward zero, this voltage change causes a conformational opening of the gate and allows increased potassium diffusion outward through the channel. However, because of the slight delay in opening of the potassium channels, for the most part, they open just at the same time that the sodium channels are beginning to close because of inactivation.

-يعني بيفتحوا مع بعض بس يبلش يتغير الجهد، بس الصوديوم بتفتح بشكل مفاجئ، والبوتاسيوم بتتأخّر لتوصل الشغل ال max تاعها، فلما نعتبرها احنا انها بلشت تشتغل عنجد بتكون الصوديوم صارت inactive .

The delayed activation of K+ channels combined with inactivation of Na+ channels will result in a rapid returning of the membrane potential to its resting level causing the **falling phase** in the action potential. The membrane potential may go for a while to more negative potential than during resting potential, which is known as **positive after potential** (**after hyperpolarization**). Followed by a full recovery in membrane potential (returns completely to its resting level). The positive after potential is probably due to an excess in K+ efflux, which causes more deficit of positive ions inside the cell.

Action potential and Ca++:

- The membranes of almost all cells of the body have a calcium pump similar to the sodium pump, and calcium serves along with (or instead of) sodium in some cells to cause most of the action potential.
- The gating of calcium channels, however, is slow, requiring 10 to 20 times as long for activation as for the sodium channels. For this reason they are often called *slow channels*, in contrast to the sodium channels, which are called *fast channels*.
- the opening of **calcium channels** provides a more sustained depolarization, whereas the **sodium channels** play a key role in initiating action potentials.

As discussed before, the raising phase of an action potential results by fast activation of Na+ channels. These are called *fast channels*. In some excitable cells, like cardiac muscle and uterine muscle, cells are equipped with another type of channels known as *slow* Na+ – Ca++ *channels* (voltage-activated calcium-sodium channels (*L-type calcium channels*)). These channels are

activated at slower rate than Na+ channels. The slow and prolonged opening of slow channels will cause mainly Ca++ to enter the cell (these cells (cardiac and smooth muscles like uterine muscule) have a calcium pump serves along with (or instead of) sodium pump in some cells to cause most of the action potential. Like the sodium pump, the calcium pump transports calcium ions from the interior to the exterior of the cell membrane) After entering the cell the Ca++ prevents the rapid fall induced by activation of K+ (which is going outward leaving negative charges inside the cell) channels, and the membrane potential is maintained for a while then the potential falls to its resting level. This is known as **plateau** in action potential (In some instances, the excited membrane does not repolarize immediately after depolarization; instead, the potential remains on a plateau near the peak of the spike potential for many milliseconds, and only then does repolarization begin). The presence of plateau in this type of cells is important in prolonging the time of an action potential, giving more time for the cell to be able to respond to another stimulus, because the cell remains longer time in **refractory period**.

- This type of action potential occurs in heart muscle fibers, where the plateau lasts for as long as 0.2 to 0.3 second and causes contraction of heart muscle to last for this same long period.

- إعادة ترتيب للفكرة السّابقة بطريقة الكتاب بس لتأكيد انّك فاهم الموضوع فهم مش حافظه:

- The cause of the plateau is a combination of several factors:

1) First, in heart muscle, two types of channels contribute to the depolarization process: (1) the usual voltageactivated sodium channels, called fast channels, and (2) voltage-activated calcium-sodium channels (L-type calcium channels), which are slow to open and therefore are called slow channels. Opening of fast channels causes the spike portion of the action potential, whereas the prolonged opening of the slow calcium-sodium channels mainly allows calcium ions to enter the fiber, which is largely responsible for the plateau portion of the action potential.

2) A second factor that may be partly responsible for the plateau is that the voltage-gated potassium channels are slower to open than usual, often not opening much until the end of the plateau. This factor delays the return of the membrane potential toward its normal negative value of −80 to −90 millivolts. The plateau ends when the calciumsodium channels close and permeability to potassium ions increases.

Refractory periods of an action potential:

During action potential the cell is not able to respond to another stimulus. From the firing stage to the end of first third of falling phase the cell will not respond at all even by a stronger stimulus. In this stage the cell is said to be in **absolute refractory period**. From the beginning of the second phase until the resting membrane potential is achieved the cell cannot respond the usual stimulus, but a stronger stimulus can change the membrane potential. In this period the cell is in **relative refractory period**.

The periods depend on the activity of Na+ channels. These channels pass three states during action potential. During resting potential, Na+ channels are **closed but capable for opening** when stimulated. During the raising phase (firing), almost all Na+ channels are **opened**. And any other stimulus (even stronger one) will not cause activation of more Na+ channels. During this period the membrane is in absolute refractory period.

In the third state, when voltage dependent Na+ channels become closed after the membrane potential has reached positive values. At this state Na+ channels are not capable for opening. During

all the falling phase of an action potential, these channels remain **closed and not capable for opening**. They can pass to the first state (closed and capable for opening) when the membrane potential returns to its normal level or to a more negative potential than resting potential. During this period, the membrane is in relative refractory period. This means that a stronger (suprathreshold) stimulus may activate the closed channels that are not capable for opening by normal stimulation. In addition to the role of voltage gated Na+ channels in establishing the relative refractory period, the presence of widely opened K+ channels during falling phase, which cause excess flow of positive charges to the outside, may also play a role by opposing stimulating signals.

Na+ -K+ pump and action potential:

This pump has **no** role in the electrical activity that are taking place during action potential. But it plays an important role in restoring ionic composition that has been altered during action potential. This role is important in maintaining the ionic composition of the intra-and the extracellular fluids.

- The transmission of each action potential along a nerve fiber reduces slightly the concentration differences of sodium and potassium inside and outside the membrane because sodium ions diffuse to the inside during depolarization and potassium ions diffuse to the outside during repolarization. For a single action potential, this effect is so minute that it cannot be measured. with time, it becomes necessary to re-establish the sodium and potassium membrane concentration differences, which is achieved by action of the Na+ -K+ pump.
- RE-ESTABLISHING SODIUM AND POTASSIUM IONIC GRADIENTS AFTER ACTION POTENTIALS ARE COMPLETED—IMPORTANCE OF ENERGY METABOLISM

Nerve Cells (Neurons)

The nervous system is formed of neurons and supportive cells. A neuron, typically consists of 3 basics parts: **cell body, dendrites, and axon** (or nerve fiber). Dendrites are short projections from the cell body, which receive inputs from neighboring neurons. Axon is a long tubular like structure which projects from cone-shaped elevation in the cell body known as **axon hillock** (means small hill). The impulse begins at the junction between axon hillock and the initial segment of axon. Axon ends into fine processes called axon terminals. Some of these terminals end with a bulb-shape structure called **synaptic end bulb (synaptic knob)**, where neurotransmitter is stored in vesicles and ready for the release.

Many classifications for neurons are known, according to shape, function, neurotransmitter they release, myelination, location…etc.

Supportive cells and function (NEUROGLIA):

Many types of supportive cells around neurons have been described (at least 6). Microglia, Astrtocytes, oligodendrogliocytes have been shown around neurons from the CNS. And glial cells

which are similar to astrocytes from the CNS have been described in the neural network of the GI tract.

These cells perform the following functions:
*Maintenance of neural environment.
-uptake of K+ and neurotransmitters from the interstitial fluid around the neurons.

*Synthesize and release neurotrophic factors → maintain the survival and protection of neurons

* Other specialized supportive cells are responsible for myelination of axons. In the CNS these cells are oligodendrogliocytes. In the peripheral nervous system, these cells are known as **Schwan cells**. These cells wrap around axon segments and secrete myelin sheath (a protein lipid complex that insulates nerve fiber). There are gaps in myelin sheaths known as **nodes of Ranvier**, which appear at intervals along axon. These gaps are used for transmission of impulse along myelinated nerve fiber.

TANSMISSION OF ACTION POTENTIAL ALONG NERVE FIBERS:

Once action potential is generated at the axon hillock, no more triggering events are needed to activate the whole nerve fiber (axon). The generated impulse is conducted along the nerve fiber by one of the followings 2 methods of propagation:

1. Continuous conduction (conduction by local current flow): occurs in unmyelinated fibers. Local currents flow between the active area, which is at the peak of action potential and inactive area, which is still in resting potential. This flow will cause activation of Na+ channels in inactive area and reduce the membrane potential to the threshold, which triggers an action potential in this area (that was previously inactive).

This process is repeated all along the nerve fiber until the impulse has reached nerve terminals.

2. Saltatory conduction: In myelinated fibers the impulse skips the myelinated regions in the axon and jumps from one node of Ranvier to the adjacent node. This process ensures faster propagation of an action potential along the myelinated axons (50 times faster than in unmyelinated fibers of the same size) (the first value of saltatory conduction). The conduction also involves current flow between two adjacent nodes of Ranvier, which results in activation of Na+ channels in the adjacent node, which is still in resting potential. The process is repeated until the impulse activates the axon terminals.

- action potentials occur only at the nodes… saltatory conduction conserves energy for the axon because only the nodes depolarize, allowing perhaps 100 times less loss of ions than would otherwise be necessary, and therefore requiring little energy expenditure for re-establishing the

sodium and potassium concentration differences across the membrane after a series of nerve impulses (the second value of salutatory conduction).

NOTE: current flow in both types of conduction is from the **positively charged to the negatively charged regions at both sides of the membrane**, and the membrane high resistance to the passage of current flow across it (no current flow can pass through the membrane).

Not only myelination can influence the velocity of conduction, but also the diameter of nerve fibers. Larger fibers conduct impulse with higher velocity.

Nerve fibers have been classified in (A, which includes as subtypes (alpha, beta, gamma, sigma) fibers, B, C). The diameter and the velocity of conduction is the highest in Aalpha, and is the lowest in C fibers.

The importance of refractory periods in conduction:

The presence of refractory periods during action potential is very important in the conduction of impulse. The refractory periods ensure the **one-way (unidirectional)** propagation of action potential. Once an area has developed an action potential, the previous region is still under refractory period (unresponsive area). This area will not develop another action potential. But the following area that is at resting potential is capable to initiate an action potential.

SYNAPSES AND INTEGRATION OF RESPONSES:

Synapses:

Neuron may terminate at one of three structures: a neuron, a muscle, or a gland. The junction between 2 neurons is known as synapse. The first neuron ends with end bulb (**synaptic knob**), where neurotransmitters are stored in vesicles and ready for the release. The membrane of the synaptic knob is known as **presynaptic membrane**. When secretory vesicles fuse with presynaptic membrane, they release their content into a small space between two membranes known as **synaptic cleft**. The released transmitters act on the second neurons by binding to their receptors at the second membrane, which is called **postsynaptic membrane** (**subsynaptic membrane**).

Synapses operate in one direction. Transmit signals from one neuron to adjacent neuron. When the impulse from the presynaptic neuron reaches the synaptic knob, this will cause activation of voltage dependent Ca++ channels. This will result in Ca++ diffusion into the synaptic knob. The

increase in Ca++ concentration inside axon terminal will trigger the release of neurotransmitter from vesicles into synaptic cleft by a process of exocytosis. Inactivation of synaptic knob by inhibitory inputs that may synapse with the membrane at the nerve terminal may induce inhibition of the release of transmitter. This inhibition that appears at this site reduces the effectiveness of transmission in the synapse. This type of inhibition is known as presynaptic inhibition.

Once released, neurotransmitter binds to its receptor at the postsynaptic membrane. According to transmitter – receptor combination, this will induce either a decrease in membrane potential (depolarization) or increase in membrane potential (hyperpolarization). When there is a decrease in membrane potential, the developed postsynaptic potential is called **EPSPs** (**E**xcitatory **P**ost **S**ynaptic **P**otentials), while the increase in membrane potential is called **IPSPs** (**I**nhibitory **P**ost **S**ynaptic **P**otentials).

After inducing the appropriate response at the postsynaptic membrane, the transmitter is inactivated or removed leaving the postsynaptic membrane ready to receive additional messages from the same presynaptic membrane. The inactivation of transmitter takes place by postsynaptic membrane bound enzymes. An example of these enzymes is *acetylcholine esterase*, which destroys acetylcholine (Ach) into acetyl and choline molecules, which then transported back to the synaptic knob, where they combine again to form new Ach molecules. Some types of transmitters are transported back, without inactivation, into synaptic knob. Conditions that alter the activity of destroying enzyme, uptake of transmitter by nerve terminal, or induce release of high concentration of transmitter (presynaptic facilitation) alter the activity of synapse by prolonging the activation of receptors at the postsynaptic (subsynaptic) membrane. In addition to that, some drugs may combine with receptor and prevents binding of transmitter to its receptor. These drugs are known as **blockers**. An example of these is hexamethonium, which can bind to acetylcholine (Ach) receptor at postsynaptic membrane and prevents Ach from binding. This will inhibit transmission induced by Ach neurons.

The EPSPs are not action potentials. They are small depolarization (subthreshold potential) that can be induced by activation of few Na+ channels.

The IPSPs are usually induced by activation of K+ channels. Which result in efflux of K+ and change in the membrane potential to more negative p[otential. Some transmitters activates Cl- channels, the activation of these channels will not induce hyperpolarization (during rest, neural cell is near the E_{cl}, and the opening of Cl- channels will not induce inward diffusion of Cl-). But this activation is inhibitory on neural activity. This inhibition is achieved by holding the membrane at its resting potential and preventing depolarization.

The time it takes for a signal from the first neuron to induce changes in membrane potential in the second neuron is known as **synaptic delay**.

Integration of responses at postsynaptic membrane:

Usually, the complexity of neural network connections permit synapsing of many axonal terminals from different neurons to one neural cell body (called **convergence**), and branching of one nerve fiber to many terminals that synapse to different neurons (**divergence**). This complexity results in converting the signal from one neuron to many postsynaptic neurons in the case of divergence, and many inputs from presynaptic neurons can be received by single postsynaptic neuron in the case of convergence.

As mentioned before, one stimulus may induce depolarization or hyperpolarization at the postsynaptic membrane. The induced depolarization is not an action potential, but it is a subthreshold potential. The action potential will develop only when threshold is achieved. In neural network, to have subthreshold potentials eliciting an action potential, **summation** (two depolarizations can sum to elicit a higher depolarization) must take place between responses at the postsynaptic membrane.

Two types of summation are known at the postsynaptic membrane. **Spatial summation** appears when 2 or more responses from 2 or more different neurons have appeared simultaneously (at the same time) at the same site of postsynaptic membrane, which result in summing of these responses into a final response. This summation can take place between 2 or more IPSPs to elicit more hyperpolarization, two or more EPSPs to elicit more depolarization in the membrane, or between excitatory and inhibitory potentials which results in cancellation of potentials and induce postsynaptic inhibition.

The second type of summation is called **temporal summation**. Appears when 2 or more postsynaptic potentials, which were elicited by **one** presynaptic neuron at different times, sum to induce more depolarization in the membrane potential. In this case, the repetitive excitation of postsynaptic membrane from a single input induces a higher depolarization that may elicit an action potential at the postsynaptic membrane.

Recordings of action potential:

Recording of **monophasic action potential** is by placing one electrode inside the cell and the other electrode outside the cell. While a different configuration of an action potential can be obtained by placing the two electrodes outside the cell membrane. The later recording is known as **biphasic action potential**. Two waves are obtained in the recording of biphasic action potential, the first represents depolarization, and the second is in the reverse direction of the first and represents repolarization.

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