ION CHANNELS

Trafficking of small charged molecules (ions) thru the cell membrane of neurons determine their ability to signal and respond to each other. The electric charges of ions are in fact responsible for the membrane potential and action potential. But since the cell membrane is almost totally impermeable to ions, there is a need to use specialized cellular devices that can transport ions in and out of the cell thru the membrane. These devices are called ion channels. The ions that are mostly carried in physiological conditions are free atoms in solution, typically sodium, potassium, calcium and chlorine. Since the physiological function of neurons is to carry information in the form of electrical impulses (action potential), ion channel function is determinant of brain function. But once an ion has entered or exited the cell, it not only changes its electrical membrane potential, but also several ions, particularly calcium, are used as messengers within the cell, and can regulate many complicated and long lasting effects of the cell's metabolism.

Although there are probably tens of different types of ion channels, they all share some distinctive characteristics:

-ion channels are formed of glycoproteins (proteins with sugar molecules attached) that tranverse the cell membrane.

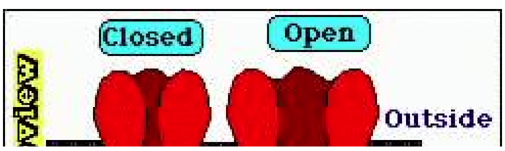
-they are formed by aggregation of subunits, each a protein by itself, into a cylindrical configuration that allows a pore, thus forming a kind of tube. The subunits can be copies of the same protein or be a combination of quite different proteins. In some cases the subunits are formed by the folding of some very large, but single, protein.

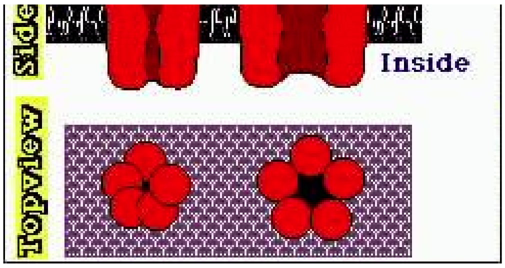
-ions cross thru their channels by electrical potential or concentration differences across the cell membrane, the passage itself does not require metabolic energy expenditure. The energy derives from the chemical forces of diffusion, osmosis, and electrochemical equilibrium. There are other types of membrane spanning proteins that move ions against these forces, of course with great energy expenditure, but are not considered channels and are called ion pumps.

- these channels are selective of the types of ions it allows to cross. In this sense, ion channels are not only open holes of different diameter, since channels that allow the passage of a certain ion do not allow passage of larger or even smaller ones. The type of ion that is allowed to cross depends on the electrochemical configuration of the protein subunits, especially of the side that faces inside the pore. It is common that a type of ion channel will allow several kinds of ions to cross, specially if they all share the same charge (positive or negative).

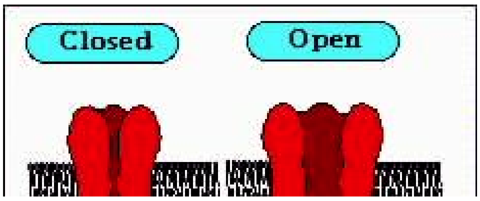
- the variety and number of ion channels that a cell has will be determined by its type. In fact this distribution can be used to determine the type of neuron or other cell that is being measured. Additionally the distribution within the same cell can have great variability; for instance, the axon of neurons have larger density of sodium and potassium channels than the rest of the cell body.

Very few ion channels are open all the time (called leak channels), and most have very complex ways of opening and closing. In all cases where the channels open or close, the conformation of the channel is changed, sometimes passively, and sometimes with





energy expenditure. What is changed exactly depends on the type of channel, but in all cases it must involve the blockade of the pore. Sometimes channels change some physical aspect inside the pore, thus leaving no space for ion flux, and sometimes the change involves a different distribution of charges inside the pore that constrain passage of charged particles. The open or closed state in which a channel can be (gating) depends on signals coming from either inside or outside the cell. It is very common for a channel's gating to be controlled by the membrane potential (the difference between the total outer and inner charges), opening or closing when changes occur and a certain threshold is crossed. Another common type of gating is by a ligand binding to a receptor in the channel. Receptors are mentioned in another document, but basically consist of sections of a protein that allow very specific molecules to bind, and causing it to change conformation. The ligand can come from outside of the cell or from an inner message, and it is not uncommon that a single ion channel has several receptors for the same type of ligand or even for very different types, thus allowing very complex cellular signaling resulting in either the opening or closure of the channel. These types of receptor-ion channel complexes are usually classified not as types of channels but as receptors having an associated ion channel (ionotropic receptors), but it is just a nomenclature discrepancy. Another signal that can control gating takes advantage of the fact that most protein metabolism depends on the phosphorylation by enzymes. A phosphorylated protein has more energy and can therefore withstand some configurations in shape and charge that cannot exist when not phosphorylated. Gating can happen whenever the proteins that conform the subunits of the channel are phosphorylated or not. n



Different mechanisms for the opening or closing of ion channels

1.- By phosphorylation and desphosphorylation or the protein, structural changes can be achieved.

2.- The coupling of a messenger (typically a neurotransmitter), causes it to open. These are called direct gated receptors, or ionotropic receptors.

3.- The change in membrane potential can cause a conformational change. These are the voltage sensitive channels.

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