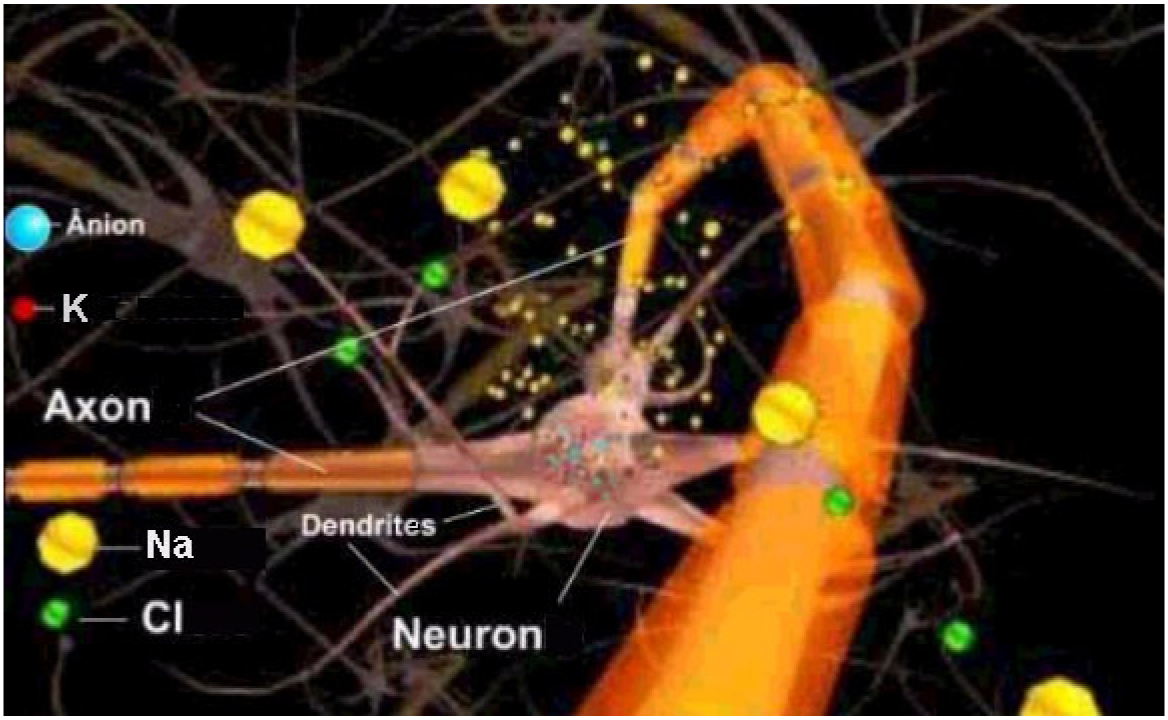
Clinical Summarization Report

**A Pain Management
Treatment Perspective**



How Nerve Cells Work

Silvia Helena Cardoso, PhD and Renato M. E. Sabbatini, PhD

The understanding of how the neuron (the basic functional cell of the nervous system) works is fundamental to all processes such as sensation, perception, memory, emotion, cognition, etc., in health and in disease.

In this article, the second of a series on the fundamentals of the neuron, you will learn how inorganic ions, the cell membrane and basic processes, such as diffusion and ion transport, generate one of its basic and most important characteristics, the resting membrane potential.

The resting membrane potential is a stable electrical charge of approximately -65 to -70 milivolts of the internal side (inside the cell) in relation to the external side. It is the basis of bioelectricity, that is, the generation and use of electrical energy by excitable cells such as the neuron to perform its functions of storage and transmission of information.

The last article of the series, in the next issue, will explain how neurons actively transmit information by means of the action potential. The action potential is a sudden and reversible depolarization (reversal of the membrane potential value) which propagates across the dendrites and axon of a neuron.

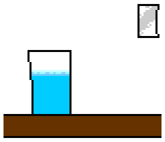
Our body is made mostly of water (around 60% of an adult's weight). Most of the solid substances are dissolved into this water and biochemical reactions can take place only in solution. All cells look like small closed bags of solution, with a wall made of a semi-permeable membrane. Inside the cell we have a complex chemical environment called the intracellular space. The internal structures of a neuron (called organelles) are embedded internally in a cytoplasm that is made up mostly of water, proteins and inorganic salts.

Cells are immersed into another big solution, which is called the extracellular space. The solutions inside and outside the cell have different compositions, and this fact is exceedingly important to cell function, as we will see, particularly excitable cells (cells, such as the neuron and the muscle cells, which can react to stimuli coming from the external environment).

In order to understand how nerve cells can be excited and transmit this excitation to other parts of the nervous system, muscles and glands, first we must understand the role of ions and water, because they are very important for so-called membrane processes, that is, functions which take place across the cell membrane.

When a substance like common salt, or NaCl (made of equal parts of elements sodium (Na) and chlorine (Cl), dissolve in water, the molecule ceases to exist as a solid crystal and becomes a set of particles called ions. Salt is soluble in water because the charged portions of water molecules have a stronger attraction to the salt atoms than to each other.

Ions are formed when sodium and chloride atoms lose or gain electrons in contact with water, thus becoming electrically polarized. In the case of common salt, sodium loses an electron and becomes positively charged (we denote this as Na+), while chloride gains an electron and becomes negatively charged (we denote this as Cl-).



Putting salt into water

H_2O

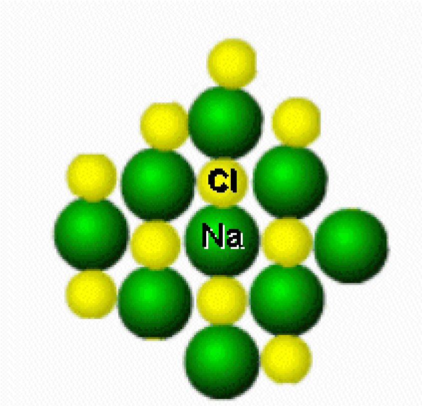
+

The two hydrogen atoms and the oxigen atom which make a water molecule (H_2O) are bounded together by covalent forces, sharing electrons betwen them.

H= Hydrogen
O= Oxigen

NaCl

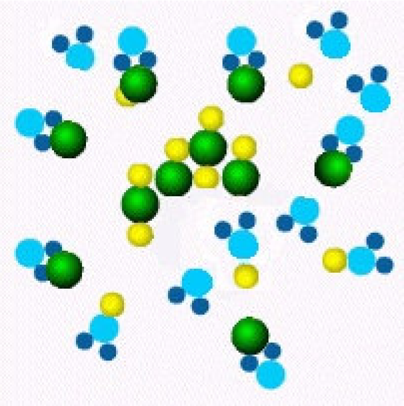
=



In crystals of common salt (NaCl), the sodium and chlorine atoms are covalently bonded by sharing one electron.

Na= Sodium
Cl= Chlorine

Na^+ Cl^-



In solution, crystals of salt separate and no longer exists as the usual atoms. Salt dissolves in water because the charged portions of the water molecule have stronger attraction for the ions than they have for each other. Sodium loses the electron to form positive ion, Na+; chlorine gains one to make a negative ion, Cl-.

The mean electrical charge of a salt solution is zero, because there is one Na+ ion for every Cl- ion. Thus, they balance each other out.

However, in living cells, an unequal distribution of ions of different charges is achieved. In this manner, the environment around the cell looses its electrical equilibrium and becomes electrically polarized around the membrane. This is the cause of bioelectricity, or the generation of electricity by cells, as we will see in the next section.

Therefore, the ability of nerve cells to process electrical information depends on the special properties of the cell membrane, which controls the flux of nutritive substances and ions from the internal to the external side of the cell and vice-versa. Special molecular channels, called pores, which are open in the membrane allows that a substance or ion traverses it in a given direction.

Ionic movements through channels are influenced by two processes:

- Passive transportation: ions move about following the laws of molecular diffusion, difference of concentration or chemical gradient and difference of electrical charge or electrical gradient. The cell membrane allows certain molecules to pass more easily than others, due to the size of channels and chemical conformation of molecules. Therefore, passive transport takes place across a semipermeable membrane.

- Active transportation: some ions and membranes can be transported actively across the cell membrane. This is done by small molecular "engines" called ionic pumps. The most important membrane pump for excitable cells is the Na+/K+ pump. For each sodium ion it transports across the membrane, it transports a potassium ion in the opposite direction.

Passive transport is important. However, unequal distribution of substances in the extracellular and intracellular spaces is maintained by the active pumps. Dead cells lose this capability, because active pumps require metabolic energy to work. This energy is extracted from foodstuffs by living cells, by means of complex chain reactions.

In a nervous cell, different ions (sodium, potassium, chloride, etc.) have different concentrations on each side of the cell membrane.

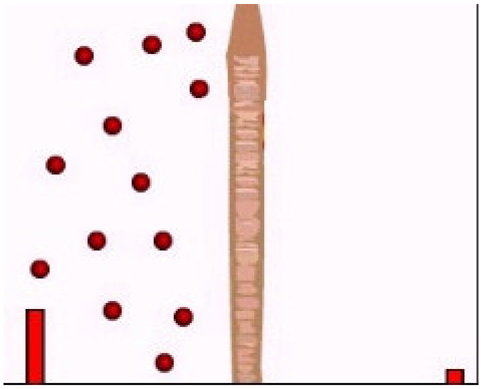
But, as we saw in the previous section, ions tend to diffuse rapidly around the solution which makes the inner and outer environments of cells, and gradually become balanced, that is, their concentration becomes the same in all parts of the solution.

How this phenomenon happens?

The first cause is temperature. When ions and molecules dissolve in a solution, they move randomly about (thermal agitation or Brownian movement), and thus travel to other parts of the compartment. The speed of this movement is dependent on the temperature, i.e.; the higher the temperature of the solution, the quicker it will reach equilibrium.

- The second cause is the the difference of concentration or chemical gradient: ions from regions of higher concentration move toward regions of lower concentration.
- The third cause is the difference of electrical charge or electrical gradient. Positive ions (cations) are electrically repelled away of parts of the solution which is positively charged and attracted to parts of the solution which are negatively charged. Negative ions (anions) are influenced in the same way: repelled by the same charge and attracted to the opposite charge.

Free Diffusion



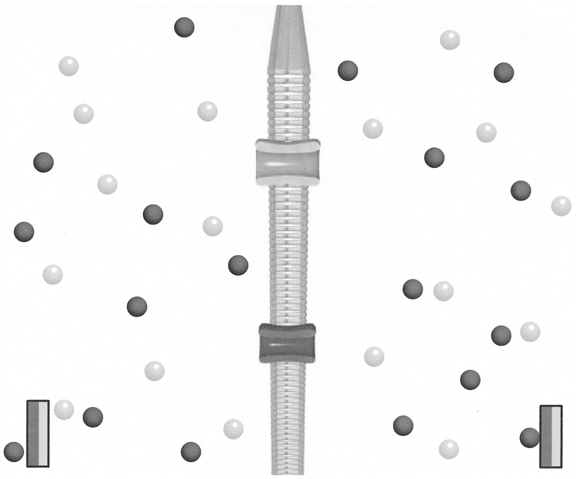
When the membrane is removed, it allows the water and molecules to move freely (diffusion) to the other side. The speed of diffusion is proportional to the temperature of the solution.

Molecules in solution move randomly about. In this beaker full of water, an impermeable membrane divides the beaker in half. On the left side there is a collection of molecules. The membrane prevents movement of the water and the molecules from crossing from one side of the beaker to the other

Now, biological membranes, such as the cell membrane. are permeable to many ions. This is so because of the existence of pores or passive transport channels bridging one side to the other, through which ions can pass freely.

For instance, if in the compartment on one side of the membrane there is a higher concentration of common salt (made of sodium and chloride ions) than in the other side, these ions will pass gradually to the other side, following the difference of concentration. Eventually, both compartments will have the same concentration of ions. The rate of passage is regulated by the number and size of pores (it is not an instant phenomenon, because it is a kind of slower diffusion).

Diffusion Across a Permeable Membrane



Small pores in the surface of the permeable membrane allow the selective passage of ions. There are specific channels for each ion (sodium, chloride, potassium, etc.). The rate of passage is regulated by the number and size of pores. After a while, the concentration of both ions (green and yellow bars) will be the same on both sides of the membrane.

All cells in the human body are characterized by having a net electrical charge across its membranes. We call this "membrane electrical polarization". There is a negative difference between the intracellular and the extracellular compartments, i.e., the interior of the membrane is electrically negative in relation to the exterior. This value, which is approximately -60 to -75 mV, depending on the type of cell, is called the "resting membrane potential".

How this potential appears?

Initially, we should know that there are different concentrations of ions (Na+, Cl- and K+) inside and outside the neuron.

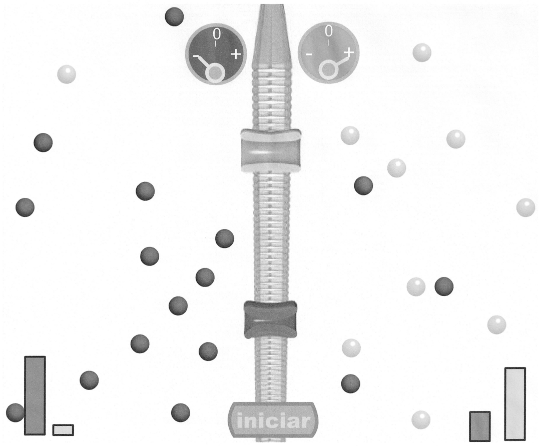
Under stable conditions (eletrochemical equilibrium), the Cl- and Na+ ions exist in a higher concentration outside the cell than inside. Potassim (K+) exists in higher concentration inside than outside the cell. Furthermore, there are some large organic anions (negative in charge), related to proteins, which exist in higher concentration inside the cell.

How these concentration differences arise?

One of the explanations is that the neuronal membrane doesn´t let ions traverse it all at the same speed. In other words, we say that the degree of permeability is different for each ion. Potassium has a higher permeability, around 25 times that of sodium. Chloride has an intermediate permeability and the organic anions have an almost zero permeability, i.e., in normal conditions they are not carried through the membrane, remaining in the cell´s interior.

In order to understant how different permeabilities generate different concentrations,It's repeat here the experiment we saw in the previous section: a beaker divided into two by a biological membrane, and a salt solution of two ions in equal concentrations on left compartment. In this example (see animation below), we will have sodium (Na+) represented as green balls, and potassium (K+) represented as yellow balls. Concentrations on both sides are indicated by vertical bars of the same color.

Now, instead of putting an impermeable membrane, where only osmosis can occur, or a permeable membrane, where eventually all ions will have the same concentration of both sides (diffusion), we put a selectively permeable membrane. This means that this membrane will have a higher permeability to one type of ion than to another.



When this happens, the ion with a higher permeability (K+) will flow more rapidly to the other side, following its chemical gradient. The other ion (Na+) will do the same, but it will flow slowlier. In this manner after some suitable short time there will be a higher concentration of K+ than Na+ in the right side of membrane, and a higher concentration of Na+ than of K+ in the left side.

As ions flow to one side to the other, a electrical charge builds up gradually between the two sides of the membrane (as shown by the voltmeter needles in the figure). For the potassium ion, the right side becomes more positive than the left side and a electrical gradient appears. Since K+ is positive, it is repelled by positive charges, which it contributes by moving swiftly to the right side. Therefore, diffusion slows down and eventually an electrochemical equilibrium is reached, i.e. for every difference of chemical concentration there is an electrical potential difference that opposes it..

Thus there will be an equilibrium between electrical and chemical forces driving the movements of ions across the selectively permeable membrane and the concentrations become stable. As a result, the polarization also stops to change and becomes steady.

A German scientist named Walther Nernst expressed this phenomenon as a law which was named in his honour. It states in mathematical terms that the chemical concentrations of ions and electrical charges are in equilibrium for any given ion, and that the steady potential is proportional to the logarithm of the ratio of concentrations on each side of the membrane.

There will be a Nernst potential for each ion. For the neuron membrane, the Nernst potential for K+ is -75 milivolts (mV). Since the neuronal membrane resting potential is around -60 mV, we conclude that other ions must be involved besides potassium. They are Cl-, with an equilibrium potential of -80 mV and Na+, with + 55 mV. These ions are called "the big three", because they are the most important ones to determine membrane resting potential.

The resting potential of the membrane is a composite (a sum) of all the Nernst potentials of all ions which are important. We name this as the Nernst-Goldman law. due to the scientist who helped to modify it. This law determines theoretically, with great precision, the expected value for the membrane potential, as determined experimentally. The ion with the higher speed of diffusion (in this case, K+) is the one that contributes most toward this value.

How the membrane potential is maintained?

Although Nernst law´s assures that there is an electrochemical equilibrium for each of the "big three" ions, in reality this should be understood as a dynamic, not static, equilibrium. Ions are always switching from one side to the other. On the long run, therefore, it would occur with neurons what always occurs with passive semipermeable membranes, that is, concentrations in the outside and inside the cell would be equal after a time, leading to a zero difference in membrane potencial.

Two things guarantee that the polarized state and the difference in ion concentration remain stable as long as the cell lives.

The first is comprised by those organic anions we have mentioned above, which have a higher preponderance inside the cells. They have a large chemical gradient from inside to the outside, but permeability is null. Therefore, according to Nernst law, they tend to generate an electrical polarity, and contribute toward attracting positive ions such as K+ to remain inside the cell. This special kind of equilibrium was discovered by a scientist named Donnan.

The second is comprised by the sodium-potassium pump we have mentioned in the previous sections, which grabs all K+ ions that go to the outside, and carry them to inside again, and grabs Na+ ions inside and carry them to the outside. For each pumping action, it spends an energy-carrying molecule of ATP.

Now, explaining in last detail what happens with the maintenance of resting membrane potential:

1) K+ is in higher concentration inside the cell. It diffuses out of the cell at a great speed, following its chemical gradient. Since the cell is more negative inside than outside, the electrical gradient is inverse, and this tends to stop diffusion. Organic anions inside the cell also contribute to limit this diffusion. With time, however, potassium would reach the same concentration inside and outside, but this is prevented by the action of the sodium-potassium pump;

2) Na+ is in higher concentration outside the cell. It diffuses into the cell at a slower speed, following its chemical gradient. Since the cell is more negative inside than outside, the electrical gradient is in the same direction. By the same token, with time sodium would reach the same concentrations inside and outside, but this is fixed up by the sodium-potassium pump;

3) Cl- is also in higher concentration outside the cell. It diffuses into the cell at a intermediate speed, following its chemical gradient. Since the cell is more negative inside than outside, then the electrical gradient is in the opposite direction, and limits this diffusion, reaching an equilibrium. There is no need for a Cl- pump!

Contributing to the membrane polarity, all potassium ions that come out of the cell form a fine positive layer on the outside, just by the membrane.

Things would stay the same in perpetual equilibrium except for two things: the sudden changes of action potentials (which inverts polarity for a brief one or two microseconds before the sodium-potassium pump arranges things nicely up again), and the continuous input of metabolic energy to the pump.

One interesting thing is that the quantity of ions which is required to pass from one side to the other in order to produce a potential difference is exceedingly small.

Silvia Helena Cardoso, PhD. Psychobiologist, master and doctor in Sciences. Editor-in-chief of Brain & Mind. State University of Campinas, Brazil.

Renato M.E. Sabbatini, PhD. director of the Center for Biomedical Informatics and Chairman of Medical Informatics of the Medical School of the State University of Campinas, Campinas, Brazil.

www.NeuroMedinc.com

For more information,
write to us at:

NeuroMed Consulting, Inc.
Medical Research and Science Department
647 Camino de Los Mares, Suite 108-81
San Clemente, CA 92673
Phone: (949) 369-7135