PROTEINES À LA >UNE<

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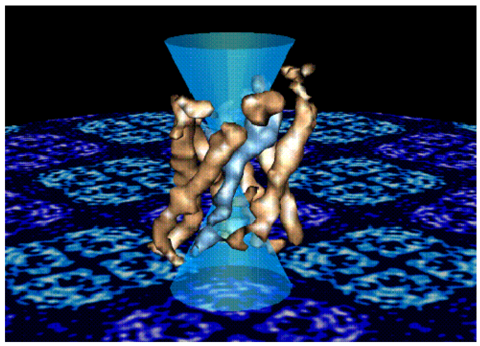
Aquaporins :
« A Nobel Prize for the water ferries »



To say that water is the source of life is not just a convenient catchword for the media. The first signs of life stirred in the depths of primitive oceans 3.5 billion years ago and as a result, water is the main constituent of all living creatures. Without water it would be impossible to digest food, think, walk, breathe, in short exist. With 2003 nominated Year for Water by the United Nations, it was only fitting to award the Nobel Prize to those who discovered the aquaporins – a family of proteins whose function is to ferry water.

All living things are essentially composed of water: be it a hippopotamus, a rhododendron, a human or bacteria. The human body for instance is made up of 65% of water, i.e. 45 liters for a person who weighs 70 kg! Of course, water concentration varies from one organ to another – tooth enamel represents only 1% whilst blood sports almost 90%! Yet the body cannot stock its water – it is constantly eliminated via excretions (in the urine mainly), breathing (when we exhale) and especially perspiration. So it is a good thing to make up for this daily loss by drinking large amounts of liquid since we experience physical fatigue after a fall of only 1% of our water content. This also applies for our intellectual capacities: short-term memory is affected after a water loss of 2%. It follows that it is possible to survive several weeks without food, but only a few days without water.

A large amount of this water is inside our cells but a certain quantity resides in the intercellular spaces as a reserve supply for the cells and blood vessels. The remainder is in the blood and the lymph and is thus continuously circulating in the body. To understand why we are composed of so much water, we must return to the origins of Life.

And the Lord said: "Let there be water…"

Scientists differ as to how Life originated on earth but they do agree on one point: it all started in water. When the Earth was formed 4.5 billion years ago, the conditions were not particularly welcoming for Life to develop. Indeed, the first traces only appeared one billion years later! During this lapse of time, in shallow pools along the ocean shores, molecules slowly organized themselves to form life. Then the first cells appeared. But as yet there was no ozone layer and the earth's surface was continuously subjected to an intense stream of ultra violet rays which would have destroyed any living organism that had dared stray out of the water. The protective screen afforded by the ozone layer was formed only 2 billion years later. Then only did the aquatic creatures emerge and venture onto dry land, finally overrunning the continents only 700 million years ago.

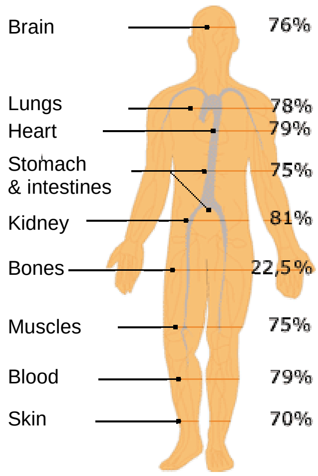


Fig.1 *Water content of different adult organs*

So, having developed for so long in water, cells are utterly dependent on it to function and survive. In fact, every one of our cells lives out its life immersed in water. Each cell is continuously engaged in supporting chemical exchanges via its membrane, between its outer environment (blood and interstitial liquids) and its own internal environment (various substances dissolved in water). Water is essential to cells for several reasons. First of all, it is needed for metabolic reactions to take place. To digest food, for example, besides the water ingested with food and drink, the body itself supplies liters to the stomach and small intestine not only to help the food circulate but also to assist in its digestion. Indeed, water is produced in the making of proteins but their digestion also demands water as a reagent. Water is also necessary to transfer various solutes from the cells' external environment to the interior and vice versa. Hence most of the digested nutrients are conveyed to the cells in an aqueous solution, whilst the waste matter of the metabolic process is evacuated from the cell in a water solution before being expelled from the body. Finally, water is used to transfer excess heat produced by cellular reactions. Indeed, water can "absorb" and discharge significant quantities of heat thus helping the body maintain an even temperature. Blood is mainly water and circulates either towards the surface of the body to lose heat or stay well inside to preserve it.

Animals and plants are provided with organs or physiological mechanisms especially adapted to get hold of water and trap it in case of extreme environmental fluctuations. Water has to penetrate into the organism, remain there for a while and then be discharged. Our kidneys, for instance, each deal with several hundreds of liters of water every day as they filter the blood to cleanse it of waste material. It has long been known that water is quite easily diffused through cell membranes but such a mechanism – although effective – is far too slow and insufficient to explain the flow of such large quantities of water. Another means must then exist. But which? The question arose as early as the 1950s but it was only due to an accidental observation, as is so often the case in science, that the mystery was actually solved in 1988 – over thirty years later.

The great Aquaporin family

The existence of canals that allowed the rapid flow of large quantities of water through certain tissues had long been suspected. This process had to be extremely selective to retain only tiny essential molecules within the cells. But since no one had, as yet, identified these canals most scientists purely and simply denied their existence.

In 1988, intent on their work on red blood cells, young scientists of Peter Agre's team in Baltimore came across a strange protein lodged in the cells' membrane, i.e. the envelope that surrounds each cell. A few more years' study revealed that this protein forms in effect a kind of pore through which water flows rapidly in and out of the red cells. The first water canal had finally been identified! It was named Aquaporin… number 1. 'Number 1' indeed, since laboratories all over the world have searched for these canals ever since and over 200 different aquaporins have been identified in all kinds of tissues, in mammals, invertebrates, plants and even microorganisms. In man, a dozen or so different aquaporins have been listed. Some 15 years later, Peter Agre was awarded the Nobel Prize for Chemistry for his discovery of Aquaporin 1 in *Xenopus* (a South African toad).

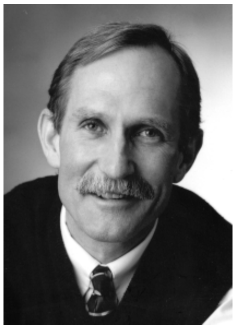


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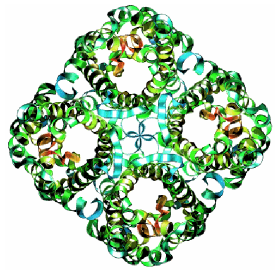
Fig.2 *Peter Agre, Nobel Laureate in Chemistry 2003*

A molecular ballet

With aquaporins, Nature has achieved what seemingly was impossible: it has developed a canal which can both filter a large volume of liquid and through which only water molecules can flow. There had to be an ingenious way of doing this.

An aquaporin pore is in fact a complex of four aquaporins linked relatively firmly together. Yet each protein acts as an independent canal. It is selective thanks to a narrowed region; a constriction in its middle allows no molecule larger than a water molecule to pass. But that is not all. A molecule of water comprises one oxygen atom and two hydrogen atoms. When water is in its liquid state, the molecules are "loosely" bound together by chemical links between the oxygen and hydrogen atoms[1]. When the water molecules reach a pore of aquaporins, they rush inside in a single file with the oxygen atom head first. Once they have reached the canal's center, they are literally snatched aside – via chemical attraction – by certain amino acids which line the canal. This attraction causes the molecules to perform a pirouette. As a result the single file is broken and the molecules proceed to the opposite end of the pore, but this time with the hydrogen atoms head first.

This molecular ballet is even more ingenious than it seems at first glance. Indeed, not only do the aquaporins usher the water through but they also prevent protons, the solitary hydrogen atoms, from passing through. Normally, protons use water molecules as a means to move from one place to another. A file of water molecules is known as a "proton path" where protons literally piggy-back from one molecule to another. If the path is discontinued, the protons cannot proceed and they return to where they came from. This is exactly what happens inside an aquaporin: the molecules' little pirouette disturbs the "proton path" and the protons are sent back while the water molecules carry on. Why such a stratagem? Simply because cells need protons to "charge", so to speak; if cells lose protons, they will also lose their energy. So they must not let them escape through their pores, at all costs. This method is devilishly clever: one second is sufficient for one billion water molecules to pass through a cell's membrane without a single proton escaping!



Courtesy of Richard J. Law

Fig.3 *Model of an aquaporin pore made up of 4 proteins which form a canal.*

For every novel protein a new disease…

It was inevitable that a great number of illnesses would involve aquaporins since their role is so essential in the development and dynamics of Life. And indeed, their discovery has turned out to be of capital importance in the understanding of many illnesses such as those affecting the kidneys, heart and muscles as well as some disorders of the nervous system. Defective aquaporins in the crystalline lens, for example, are responsible for cataracts. And yet other defective aquaporins can prevent the kidneys from reabsorbing water efficiently so that patients who have to pass water too frequently become dehydrated.

The list of pathologies related to aquaporins will no doubt lengthen over the years. This is why it is so important to improve our knowledge of their structure and function so that in the future new treatments may be developed. Hence, the world of aquaporins and their particular ballet will offer plenty scope for numerous researchers in the decades to come.

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[1] A molecule of water forms hydrogen links with its neighbors. Whilst there are 4 hydrogen links in ice, there are 3.4 in the liquid state.

For further information

- On Aquaporins : Structure, Dynamics and Function of Aquaporins (NIH resource for macromolecular modeling and bioinformatics) : ww.ks.uiuc.edu/Research/aquaporins/
- On water and its properties: CNRS: "Découvrir l'eau", www.cnrs.fr/cw/dossiers/doseau/decouv/rubrique.html

Illustrations :

- Heading illustration, Source: interactive model of a monomer AQP1, cover page, Journal of Structural Biology, volume 121, numéro 2, Heymann J.B., Agre P. and Engel A., copyright (1998), with the permission from Elsevier.
- Fig.1, Source: CNRS : « Découvrir l'eau » - www.cnrs.fr/cw/dossiers/doseau/decouv/rubrique.html
- Fig.3, Source: animation, Richard J. Law : http://mccammon.ucsd.edu/~rlaw/aquaporin.html

At UniProtKB/Swiss-Prot:

- Aquaporin-1, Homo sapiens (humain) : P29972

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