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> ONE MONTH, ONE PROTEIN <

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thirst

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Water is one of the major molecules of life. Which is why the greater part of us is made of it. As a child, I found this hard to fathom. Should we not then be relatively liquid? I don't think I ever found a satisfying answer, nor did I really seek one, until I gained knowledge on the underlying physiology of organisms. Water is harboured within cells or flows in the fluids outside our cells, while our organs and tissues are held together in a semi-rigid mass thanks to our skeleton. Water is always moving around inside us too, and continuously leaves our body as we transpire, breathe or excrete – so it needs to be replaced. This is why we drink, and why we it is so important to feel the sensation of thirst. Quenching our thirst is not just deeply satisfying to our senses, it keeps us alive. But where does the sensation arise from? There's a thought. Is it just the result of a dry palate? No. The appetite for water is shaped by something far more intricate. We have a thirst centre in our brain where protein sensors measure the levels of molecules such as salt or glucose in our blood. When our organs are hungry for water, it shows in our blood and chemical messages are sent to our brain to nurture the feeling of thirst. In animals, this sensor is known as TMEM63B.

Summer Rain – Version 1

by Susan Noble
courtesy of the artist

Living beings are made, roughly, of 70% water. In humans, the level is estimated at 60%. If we need it so much, it is because life depends on it. When we drink water, it goes straight into our blood which distributes it throughout our body – to help cells perform their daily tasks, to transport nutrients or dissolve them or to carry waste products through our body, for example. Specialised pores let water molecules in and out of cells. These are called aquaporins* and are found across all kingdoms of life, and even in viruses. But aquaporins are merely channels for letting water molecules pass from one side of a membrane to another. They are vital in regulating water homeostasis within cells, but they have no role in producing the sensation of thirst.

What is it that gives us an appetite for water? It is one of these intangible things in the realm of biology. We all know what it means and what it feels like, but it is very difficult to describe – apart from when using the adjective 'thirsty'. Animals know instinctively that they must find a source of water when they feel thirst, and they will make their way towards a drop of dew, a freshwater lake or the kitchen tap. It all has to do with an organism's capacity to perceive its inner state – such as the level of water. It is the fascinating field of interoception, when our body tells us what it needs by providing us with sensations – such as thirst – that make us react.

For a long time, now, scientists have known that a part of our brain called the lamina terminalis is responsible for the perception of thirst, so much so that it is also called the thirst centre. Within the lamina terminalis resides the subfornical organ, or SFO. By way of the (thirst) neurons that compose it, the SFO senses changes in blood osmolarity – i.e. when levels of solvents in the bloodstream, such as salt or glucose, are too high. This occurs when the blood's water has been lapped up by the organs that

need it. What scientists could not understand was how the lack of water was measured by the SFO, and how the message was understood and sent on to the brain.

The answer turned out to be mechanosensitive ion channels, or mechanosensors. Mechanosensors perceive changes in mechanical forces, such as pressure or solvent concentration, and will open to let pass a flow of ions. This ionic flow ultimately changes an initial mechanical stimulus into an electric or chemical signal that is transmitted to the brain. The existence of mechanosensors was put forward in the 1950s by the German-British biophysicist Bernard Katz. 25 years later, the Hungarian-American biophysicist Georg Békésy postulated that some kind of mechanical receptor must know how to perceive different tones in the ear. Finally, in the late 1980s, the existence of mechanosensitive ion channels in bacteria was firmly established.

Mechanosensors are found in all domains of life, in a variety of tissues, and respond to an array of mechanical forces. Those present in the SFO were only recently identified, even though they constitute the largest family of mechanosensors: transmembrane protein 63, or TMEM63. The TMEM63 family of mechanosensitive ion channels is conserved from plants (where they are known as OSCAs) to animals and is composed of three members: TMEM63A, B & C. TMEM63B is highly expressed in SFO neurons where it senses blood hyperosmorality. In other words, TMEM63B measures an abnormally high concentration of particles such as salt or glucose due to a lack of water. This is transformed into a chemical signal which is relayed to the brain and translated into "thirst".

TMEM63B acts as a monomer with eleven transmembrane helices that form the actual ion pore, an N-terminal domain which folds into a hairpin on the external side of the channel, and a structure called IL2 which runs parallel to the internal side of the channel. A hook forms on one end of IL2 and protrudes into the membrane – which hints that it could sense membrane tension. Though it has not been demonstrated, a cavity formed by the transmembrane portion of TMEM63B may be for lodging lipids. Lipids are known to be critical in regulating mechanosensitive ion channels, so this would make sense. Strangely enough, OSCA, the plant equivalent of TMEM63, happens to function as a dimer, although each monomer forms a pore. Scientists have suggested that IL2 could be involved in forming a monomer or a dimer, especially as switching from one form to the other seems to affect mechanosensitivity – not in pore conductance but in the length of time a pore remains open.

I was listening to someone on the radio recently who wondered why everyone feels the need to walk around with a bottle of water these days. People were not less hydrated in the past, but it does show that we have recognised the fact that water is essential to our well-being, and for good reason. TMEM63 deficiency dysregulates body water homeostasis which brings about hypertension and kidney diseases but also brain function impairments such as intellectual disability and motor or visual impairment. Whichever way we look at it, life is a question of balance – or homeostasis to put it in biological terms. Homeostasis is vital to life, which is why, like tight-rope walkers, we, like all organisms, spend a lot of time and energy doing our best to keep it stable.

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* *LIQUID STATES, Protein Spotlight issue 36*

Cross-references to UniProt

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