

Water, water, everywhere?

Philip Ball

On Earth, no living organism can function without water. It is, in the words of Albert Szent-Györgyi, the matrix of life. But is it reasonable to assume that this maxim holds on other worlds too?

Is life possible without water? NASA has stated explicitly that its strategy in searching for extraterrestrial life is to “follow the water”. But is the space agency thereby overlooking other potentially fertile environments? A recent meeting* of physicists, chemists, biochemists and microbiologists grappled with the question of whether water-free life is feasible. No one can give a definitive negative answer, and neither can we expect the issue to be resolved by a show of hands. Rather, the task has to be that of reducing the basic question to smaller, tractable ones, in the hope that a framework might emerge for moving the discussion beyond mere speculation.

The naive response might be to suppose that the question is absurdly terracentric. If one allows — and it seems a reasonable, though not invulnerable, starting point — that a liquid of some kind is required simply for efficient mass transport in living systems, the cosmos could provide plenty of alternatives: ammonia, sulphuric acid, liquid carbon dioxide, even the putative hydrocarbon lakes of Saturn’s moon Titan.

But there is much more to water than that. It has long been recognized as a profoundly anomalous liquid, with properties that set it apart from all others. High heat capacity, expansion on freezing, maximum density at 4 °C, high dielectric constant — all of these so-called anomalies, and others, seem critical to its biological role. They are in fact relatively easy to rationalize on the grounds of water’s hydrogen-bonded structure, which joins the H₂O molecules into a fluctuating, three-dimensional network (J. Finney, University College London). Unlike ‘simple’ liquids, water’s molecular structure is dominated not by the hard core repulsions between molecules but by the directional, attractive interactions of hydrogen bonds.

Is this unusual character an essential, or just an incidental, factor in water’s life-giving agency? The mission of the meeting was to identify the molecular aspects of water’s role in life on Earth, and then to ask whether there was any reason to regard these properties as generic or optional. And if the former, could they be reproduced by any other liquid?

The apparent ‘specialness’ of water was pointed out in 1913 by the American biochemist Lawrence Henderson, who argued that the Universe seems remarkably ‘fit’ to



The meaning of life? Water molecules are involved in the biology of all life-forms on Earth. That might not be true on other planets.

foster life — a precursor to the anthropic principle. But there is an inherent danger of circularity here: because life is adaptive, who is to say that it has not simply found ways to exploit what water has to offer? For example, some proteins make use of the fast proton conduction that takes place in water, a consequence of bond-flipping along chains of hydrogen-bonded molecules. (The details are, however, more complicated than implied by the classical Grotthuss mechanism; see N. Agmon *Chem. Phys. Lett.* **244**, 456–462; 1995.) Some proteins use one-dimensional chains of water molecules to carry protons rapidly to active sites in their interior. The hydrogen-bonded network makes water particularly well suited to providing such ‘proton wires’. But if this trick were not available, is there any reason to suppose that life would be stymied?

One can postulate that life of any sort will require enzyme-like selectivity of molecular interactions for transmitting chemical information. Water does seem to play many subtle parts in enzyme function, but is it really irreplaceable? Solvation shells can be seen to be active components in protein function (J. Smith, Univ. Heidelberg; M. Nakasako, Keio Univ.; P. Rand, Brock Univ.). But it is not obvious that other small-molecule solvents could not substitute, in principle.

In fact, studies of enzymes in low-water environments give rather conflicting messages about the extent to which water is needed. The bacteriorhodopsin protein, embedded in its natural ‘purple membrane’, seems to switch on only when there is at least a monolayer of water hydrating the exposed protein surface (G. Zaccari, Inst. Biologie Structurale, Grenoble), whereas some enzymes work in the gas phase without any hydration layer at all (R. Daniel, Univ. Waikato). Although experience with non-aqueous solvents has given some researchers confidence that enzymes will ultimately be found that work efficiently entirely without water (D. Clark, Univ. California, Berkeley), part of the difficulty here is that ‘water-free’ means different things to different people. At present, all functional enzymes seem to retain ‘internal’ water bound strongly inside their protein structure (at concentrations as low as one to ten H₂O molecules per mole of protein) — can that, too, be removed? Whereas hydration-shell water seems mainly to promote flexibility (and may be fully replaceable by other solvents), internal water seems to preserve the protein’s conformation. It can, perhaps, be ‘designed out’ of the system, but not easily.

Yet how can molecules that have evolved in water tell us about what is possible without

*The Molecular Basis of Life: Is Life Possible Without Water? The Royal Society, London, UK, 3–4 December 2003.

it? They might at least help to narrow the question: if a wholly water-free enzyme were found, we could feel confident that at least this molecular aspect of life need not rely on water's uniqueness. Similar arguments apply to protein folding: that is, making the catalysts in the first place. Investigating water's role here reveals many subtleties. For example, a good solvent doesn't actually promote stability of the native fold — the conformation that a protein naturally assumes. Rather, it finds a remarkably delicate balance between strong, conflicting forces so as to promote only marginal stability (J. Goodfellow, BBSRC). If there is too much stability the structure 'freezes' and becomes inactive. The alternative protein conformations revealed in amyloid diseases may simply be the inevitable price that we pay for this.

There seems to be no simple molecule

that can mimic all of the useful biological functions of water. One school of thought asserts that it is therefore futile to look for replacements for any one, or even simultaneously for several, of its 'virtues': the biological importance of water lies in their synchronous operation in a single molecular system. But what we really need is a way of asking which, if any, of those functions is generic to life. Is there, for example, a temperature limit that rules out other tetrahedral liquids such as silica, because of the complications introduced by molecular excited states at high temperatures? At low temperatures, would slower diffusion rates prevent effective exploitation of thermodynamic equilibria? In other words, is there a habitable zone not just in physical space but in chemical and thermodynamic space too? ■

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Vision

The need for speed

Kendall J. Blumer

Neurons in the retina turn on and off rapidly in response to light. With the discovery of mutations in human genes that mediate this quick turn-off, we have the first picture of its importance in visual perception.

Imagine walking out of a dark theatre into a bright and sunny Sunday afternoon. You are momentarily blinded, but your eyes rapidly adjust to the change and you continue on your way. For some people with a rare visual defect, however, this momentary blindness can last for up to ten seconds. A similar, but potentially more dangerous, prolonged blindness occurs when these individuals drive from daylight into a darkened tunnel. Moreover, people with this problem also suffer from difficulties in seeing certain moving objects (such as balls thrown during

a sporting event). On page 75 of this issue, Nishiguchi *et al.*¹ describe a genetic cause of this condition. In so doing, they reveal that visual perception requires rapid deactivation of the light-stimulated responses shown by neurons in the eye.

Light streaming into the eye is detected by specialized neurons (photoreceptors) in the retina. In response to light, a coordinated series of molecular events — the so-called phototransduction cascade — is triggered in these cells² (Fig. 1). Photons excite pigment-containing proteins called rhodopsins, which

then switch on the protein transducin by loading it with the small molecule guanosine triphosphate (GTP). When bound to GTP, transducin turns on a phosphodiesterase, an enzyme that breaks down cyclic guanosine monophosphate (cGMP — another small molecule). High concentrations of cGMP open specialized ion channels in the outer cell membrane. Thus, by reducing the concentration of cGMP, light changes the flow of ions across the membrane of photoreceptive neurons, producing an electrical signal that is necessary for communicating with the brain.

Once this light-activated switch is on, how do cells turn it off? One mechanism is to limit the amount of time that GTP-bound transducin can keep the phosphodiesterase enzyme active. Transducin can accomplish this task itself by converting — hydrolysing — its bound GTP molecule into guanosine diphosphate, GDP. (This conversion from GTP to GDP is a commonly used molecular 'switch' in a variety of cellular signalling pathways.) Because transducin bound to GDP has a low affinity for phosphodiesterase, it releases the enzyme in an inactive form, allowing cGMP levels to rise again and return the flow of ions across the cell membrane to the 'dark' state. In this molecular cascade, then, the conversion of GTP to GDP by transducin is the rate-limiting step that defines the amount of time for which a photoreceptor responds to a light pulse.

But this presents a problem. Photoreceptor cells can turn off in less than a second in response to a brief flash of light². In contrast, the hydrolysis of GTP by transducin requires tens of seconds to complete, making it difficult to understand how such a mechanism could account for the rapid turn-off of photoreceptor cells. To get around this problem, photoreceptor cells possess a protein called regulator of G-protein signalling 9 (RGS9) that accelerates transducin's ability to hydrolyse GTP³. Indeed, mice that lack the RGS9 gene exhibit slow photoreceptor deactivation⁴.

Building on these studies of mice, Nishiguchi *et al.*¹ now show that disruption of this accelerator mechanism is the likely cause of a 'slow photoresponse recovery' condition previously described⁵ in several humans. The authors started by analysing the DNA of five unrelated people with the condition, and found that four of them had mutations in both copies of their RGS9 gene, producing a protein that is a poor accelerator of GTP hydrolysis. In the fifth patient, the RGS9 gene was normal. Instead, this person had a mutation that inactivates the R9AP gene, which encodes a retinal protein that anchors RGS9 to membranes⁶.

The identification of these mutations also provided an opportunity to study their effects on visual perception — something that, for obvious reasons, could not be studied in mice. The visual abnormalities of these patients

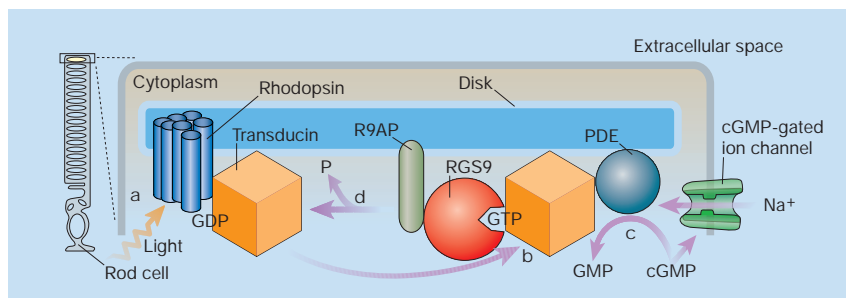


Figure 1 Phototransduction in photoreceptor cells. In the rod class of photoreceptors, the pigment-containing protein rhodopsin absorbs light (a) and activates transducin (b) by causing it to release GDP and bind GTP. GTP-bound transducin binds to and activates a phosphodiesterase (PDE), which converts cGMP to GMP (c). The concentration of cGMP decreases below what is required to open cGMP-gated ion channels, reducing the flow of ions across the cellular membrane. RGS9 bound to R9AP turns off the light-induced response by accelerating the rate of GTP hydrolysis by transducin, releasing phosphate, P (d). Other proteins that regulate the phototransduction cascade have been omitted for clarity. Nishiguchi *et al.*¹ have identified several people with mutations in RGS9 or R9AP. These patients show slow photoreceptor deactivation and have difficulty in adjusting to changes in light levels, as well as in seeing low-contrast, moving objects.