

Water transport controversies – an overview

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The last 20 years have seen major advances in the understanding of the mechanisms and molecular bases of water transport across cell membranes. Prominent among these advances was the discovery of a family of transmembrane proteins that permeate exclusively or dominantly water (aquaporins), followed by structural studies identifying the intramolecular permeation pathway, as well as by studies directed to a detailed understanding of these molecules in health and disease. Agre and colleagues (Agre *et al.* 2002) discuss the molecular structure of aquaporins and the physiology and pathophysiology of aquaporins in diverse organs and tissues. Another important advance was the development of methods for rapid measurements of changes in cell volume. This resulted in accurate estimates of cell-membrane water permeability, and in the prediction that very small osmotic gradients would suffice to drive transepithelial transport, without the need for the existence of compartments of much higher osmolality than that of the bathing solution. Around 1990, faced with the question of what pathways and driving forces underlie net water fluxes across cell membranes, most physiologists working on animal cells would have had direct and clear answers. Water moves across the phospholipid moiety of the plasma membrane (although this membrane can be extremely water-tight in certain cases), and through water pores, in cells that express these proteins. The driving force is the difference in effective osmolality across the cell membrane. Enlightened physiologists working on epithelia would add that transepithelial water absorption or secretion is always a passive phenomenon, secondary to net solute transport in the same direction. Further, complicated compartment models, such as the standing osmotic gradient hypothesis, are unnecessary to explain water transport, because very small osmotic gradients, perhaps too small to measure directly, are a sufficient driving force. The question of how water fluxes are partitioned between transcellular and paracellular pathways remained difficult to answer because of the lack of direct measurements.

The two central questions in the problem of water transport across simple or complex membranes are the pathway and the mechanism. Considering the cell membrane, one asks whether water permeates the lipid moiety and/or transmembrane proteins. These pathways are expected to have different properties, including the possibility that trans-

membrane water pores could also be permeable to other molecules. Concerning the driving force for water transport, in principle it could be primary active, secondary active or passive. At the time prior to the discoveries that provide the experimental bases for the Topical Reviews in this Special Issue, the virtually unanimous opinion of the experts would have been that water transport is passive. With respect to transepithelial water transport, the relative contributions of the transcellular and paracellular routes remain to be determined. There is no agreement on the molecular mechanism, i.e. whether there is secondary-active water transport at the cell membrane in addition to simple osmosis, or on the precise nature of osmotic water flow, i.e. is there truly isosmotic transport? This Special Issue highlights the current excitement in this area of physiology. Three current controversies in the field of water transport are discussed. In each case, the 'controversial' novel theory is presented (in the form of a Topical Review) and discussed critically in the form of a Perspective or a Research Paper. The three controversies presented in this Special Issue were debated at the XXXIV International Congress of Physiological Science in Christchurch, New Zealand.

1. Is aquaporin a gas channel?

The existence of proteinaceous water pores in some cell membranes is uncontroversial. Biophysical studies in red blood cells and in proximal renal epithelia predicted the existence of these pores and Agre and colleagues discuss the nature and function of aquaporins in this issue (Agre *et al.* 2002). The aquaporin family now includes several members, which have in common their high permeability to water, and differ in their permeability to other molecules, such as gases. Boron and his coworkers demonstrated CO₂ permeability of aquaporin-1 expressed in *Xenopus* oocytes, and argue that this pathway may be significant for transmembrane transport of this gas (Cooper *et al.* 2002). This view is controversial as discussed in the Perspective of Verkman (2002). In addition, Verkman and colleagues provide additional original data arguing against such a physiologically important function (Fang *et al.* 2002).

2. Water movements through the paracellular pathway: is transepithelial water transport truly isotonic?

Transepithelial water transport was implied to be an active transport process until it was demonstrated in mammalian

intestine that it is abolished in the absence of net salt absorption (Curran & Solomon, 1957). The first model proposed to explain this relationship was the three-compartment model of Curran & MacIntosh (1962). A refinement of this model was the standing osmotic gradient hypothesis of Diamond & Bossert (1967). In the Curran & MacIntosh (1962) model, the fluid exiting the middle compartment of the epithelium is always hypertonic to the *cis* solution, whereas in the model of Diamond & Bossert (1967) it can be near-isosmotic to a degree dependent on the permeabilities, transport rates and dimensions of the epithelium. The question of whether transepithelial fluid transport can be truly isosmotic has been a subject of discussion among epithelial physiologists. Recently, Larsen, Ussing and their associates proposed a transport model in which recycling of transported solute could account for exact isosmolality of the absorbate. Larsen *et al.* (2002) present the sodium recirculation theory of solute-coupled water transport, with a discussion in the Perspective of Spring (2002).

3. Is there active water transport?

The dominant view during the mid-1990s was that transepithelial water transport is a passive process driven by transepithelial salt transport. These two processes would be linked by the establishment of small osmolality gradients in regions adjacent to the two faces of the epithelium, the resulting osmotic gradient providing the energy for downhill water transport. In other words, the coupling between solute and water flux would be thermodynamic and not molecular, and these two fluxes would not necessarily occur across the same pathway. This view was challenged

by the work of Wright, Zeuthen and their associates. These authors provide experimental data that is interpreted as proof that the water flux can be directly coupled to solute transport via carriers expressed in *Xenopus* oocytes. That is, the water flux would be directly coupled to solute transport in the same direction, by a process that could be called solute–water cotransport (Loo *et al.* 2002). Lapointe and his colleagues, working on the same preparation, dispute this interpretation, claiming that the coupling between solute and water transport is osmotic, mediated by solute accumulation in restricted areas adjacent to the cell membrane (Lapointe *et al.* 2002).

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