

# PERSPECTIVES IN PHYSIOLOGY

## 'Active' water transport?

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Water transport across cell membranes, although less studied than ion transport, is a process of great physiological importance. In the steady state, cells maintain constant volume and water content, in spite of the risk of colloid osmotic swelling, and the maintenance and regulation of cell volume are essential for normal cell function. Furthermore, fluid exchanges between body fluid compartments and between the body and the outside world are essential for life of pluricellular organisms. Specialized layers of cells such as epithelia and endothelia perform the latter functions and thus regulate the volume and composition of fluids in intra- and extracellular compartments of the body.

In order to understand water transport, investigators must ascertain the pathway and the mechanism of water translocation across biological membranes. Currently accepted water transport pathways across cell membranes are the lipid bilayer itself (Finkelstein, 1987), and specialized, pore-like proteins, i.e. aquaporins (Agre *et al.* 1993). Net water transport occurs by osmosis and/or filtration, i.e. passive processes in which the flux is in the direction imposed by the water-chemical potential difference, and water transport can be related to, but not coupled – in a molecular sense – to the solute flux.

The article by Zeuthen *et al.* (1996) in this issue of *The Journal of Physiology* proposes an additional pathway for water transport, namely a solute transporter, and an additional mechanism that can be described as cotransport. If their observations and conclusions are correct, then we must expand our current notions on pathways and mechanisms of water transport across cell membranes and consider the three possibilities schematically shown in Fig. 1.

The idea of involvement of solute transporters in water transport is not new (see for example Solomon *et al.* 1983), but it has been

controversial. The current studies of Zeuthen *et al.* (1996) in retinal pigment epithelium of *Rana catesbeiana*, and previous experiments cited therein suggesting unusual coupling of  $K^+$ ,  $Cl^-$  and water transport in choroid plexus epithelium of *Necturus maculosus*, were based on rapid measurements of cell volume changes using an electrometric technique. The basic experimental approach of Zeuthen *et al.* (1996) was to measure changes in cell volume following modification of the composition of the solution bathing one (the retinal) side of the epithelium. Water fluxes were assessed from the changes in cell water volume, and transport of  $H^+$  and lactate were assessed from measurements of intracellular pH. The most compelling observation is that the presence of lactate in the external solution can elicit cell swelling even when the effective osmotic gradient across the membrane should elicit cell shrinkage. Other experiments and detailed analysis of the results allowed Zeuthen *et al.* (1996) to quantify both water transport pathways (one independent of and one dependent on the presence of lactate) and to assign parameters to the lactate-dependent pathway, which can be formally treated as a cotransporter.

The significance of this study (Zeuthen *et al.* 1996) is that it suggests the possibility of a rather direct coupling mechanism between transmembrane solute and water transport, i.e. independent of the development of solute concentration gradients which in turn would elicit osmotic water fluxes. Here, the 'coupling' would occur in the transport molecules themselves; it would have a defined stoichiometry, in this case 109 mmol lactic acid to 1 l of water, and it could formally occur against the water-chemical potential difference, using a favourable chemical gradient for solute transport. In other words, water transport would occur by a secondary active process, a mechanism conceptually different from previous proposals.

A definitive assessment of this work (Zeuthen *et al.* 1996) will have to await additional studies. First, it would be useful to confirm and extend these results in a non-polarized cell expressing the  $H^+$ -lactate cotransporter; this would eliminate the uncertainties imposed by the presence – in epithelial cells – of two membrane domains with different properties.

Second, to judge the physiological significance, it would be necessary to establish whether expression of this and/or other transporters confers additional plasma membrane water permeability in different cell types, and to determine the quantitative importance of this pathway *vis-à-vis* water permeation by other pathways, i.e. lipid bilayer and aquaporins. One would predict that some transporters are unlikely to carry out coupled water transport to a significant degree because the total water permeability of membranes in which they are expressed at high density is too low (e.g. the  $Na^+K^+2Cl^-$  cotransporter in the apical membrane of the thick ascending loop of Henle). Third, further work will be needed to ascertain the molecular mechanism of water transport. The stoichiometry of over 500:1 ( $H_2O$ :lactate) certainly does not suggest that water binds to the transporter. For speculations on how this coupling might occur, see Zeuthen & Stein (1994). Zeuthen *et al.* (1996) were careful to state that the transport mechanism can be treated as cotransport, not that it is cotransport. Their work provides a strong case for a novel pathway and mechanism of water transport across plasma membranes. Until this is definitively resolved, we should perhaps be less emphatic when stating that water transport across biological membranes is always passive.

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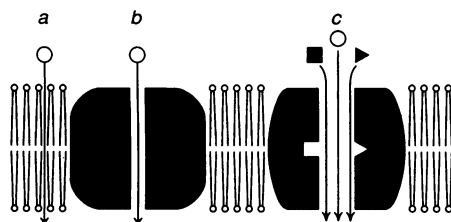


Figure 1. Diagram representing water transport pathways across plasma membranes

Water molecules (○), and relevant solutes,  $H^+$  (▴) and lactate (▣), are shown; no stoichiometries are implied. *a*, lipid bilayer (water transport by solubility-diffusion). *b*, specialized water pores (aquaporins). *c*, cotransporter (in this case  $H^+$ -lactate); in contrast to *a* and *b*, in this instance the water flux is energetically linked to solute translocation in the transporter itself, as if all three molecular species were cotransported.