# More than just water channels: unexpected cellular roles of aquaporins

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## Summary

**Aquaporins (AQPs) are membrane proteins that transport water and, in some cases, also small solutes such as glycerol. AQPs are expressed in many fluid-transporting tissues, such as kidney tubules and glandular epithelia, as well as in non-fluid-transporting tissues, such as epidermis, adipose tissue and astroglia. Their classical role in facilitating trans-epithelial fluid transport is well understood, as in the urinary concentrating mechanism and gland fluid secretion. AQPs are also involved in swelling of tissues under stress, as in the injured cornea and the brain in stroke, tumor and infection. Recent analysis of AQP-knockout mice has revealed unexpected cellular roles of AQPs. AQPs facilitate cell migration, as manifested by reduced tumor angiogenesis in AQP1-knockout mice, by a mechanism that might involve facilitated water transport in lamellipodia of migrating cells. AQPs that transport both glycerol and water regulate glycerol content in epidermis and fat, and consequently skin hydration/biosynthesis and fat metabolism. AQPs might also be involved in neural signal transduction, cell volume regulation and organellar physiology. The many roles of AQPs could be exploited for clinical benefit; for example, treatments that modulate AQP expression/function could be used as diuretics, and in the treatment of brain swelling, glaucoma, epilepsy, obesity and cancer.**

Key words: Aquaporin, Water channel, Epithelia, Cell migration, Adipocyte, Brain swelling, Epidermis, Gland, Angiogenesis

## Structure, function and cellular expression of aquaporins

The aquaporins (AQPs) are a family of small (~30 kDa/monomer), hydrophobic, integral membrane proteins that are expressed widely in the animal and plant kingdoms, 13 members having been identified so far in mammals. In mammals, they are expressed in many epithelia and endothelia involved in fluid transport, as well as in cell types that are thought not to carry out fluid transport, such as skin, fat and urinary bladder cells (Table 1). In most cell types, the AQPs reside constitutively at the plasma membrane. A notable exception is kidney AQP2, which undergoes vasopressin-regulated exo-/endocytosis similar to insulin-regulated GLUT-4 targeting. High-resolution X-ray crystal structures exist for AQP1 (Sui et al., 2001), the bacterial glycerol-transporting Glpf (Fu et al., 2000), and the major intrinsic protein of lens fiber, AQP0 (Harries et al., 2004). AQP1 monomers contain six tilted α-helical domains, forming a barrel-like structure in which the first and last 3 helices exhibit inverted symmetry (Fig. 1A) (reviewed by Fujiyoshi et al., 2002; Stroud et al., 2003). Two conserved Asn-Pro-Ala (NPA) motifs reside on opposite sides of the AQP monomer, which might allow water but not small solutes to pass across the pore. The monomeric AQP units contain independently functioning pores, although freeze-fracture electron microscopy of AQP1 (Verbavatz et al., 1993) reveals that monomers are stably assembled in membranes as tetramers (Fig. 1B). This technique has also indicated that AQP4 forms higher-order square arrays of particles (Yang et al., 1996; Verbavatz et al., 1997; Rash et al., 1998), whose functional significance is unclear.

AQP1, AQP2, AQP4, AQP5 and AQP8 are primarily water selective (Table 1), whereas AQP3, AQP7, AQP9 and AQP10 (called 'aquaglyceroporins') also transport glycerol and possibly other small solutes in the case of AQP9 (reviewed by Agre et al., 2002; Yasui, 2004). Molecular-dynamic simulations based on the AQP1 crystal structure suggest tortuous, single-file passage of water through a narrow <0.3 nm pore, in which steric and electrostatic factors prevent transport of protons and other small molecules (Tajkhorshid et al., 2002). There are reports that AQP1 transports cations (Anthony et al., 2000), AQP7 and AQP9 transport heavy metal salts such as arsenite (Liu et al., 2002), and AQP6 transports chloride at low pH (Yasui et al., 1999), although the significance of these observations is unclear and they await verification by other labs. Reports have suggested that AQP1 transports gases such as carbon dioxide (Cooper and Boron, 1998) and ammonia (Nakhoul et al., 2001), although data from others labs (reviewed by Verkman, 2002) lead to the conclusion that AQP1-dependent gas transport, if it occurs, is not biologically significant. With the exception of vasopressin-regulated AQP2, AQPs are subject primarily to transcriptional-level rather than short-term regulation. However, there is evidence, albeit controversial, for regulated targeting of AQPs in the liver (Marinelli et al., 1999) and salivary glands (Gresz et al., 2004) and for regulation of AQP4 function by protein kinase C (PKC)-dependent phosphorylation (Zelenina et al., 2002). The transport function of many AQPs can be inhibited by

**Table 1. Function and expression pattern of aquaporins**

| AQP | Permeability | Tissue expression |
|---|---|---|
| AQP0 | ? | Eye lens fiber cells |
| AQP1 | Water | Kidney tubules, endothelia, erythrocytes, choroid plexus, ciliary epithelium, intestinal lacteals, corneal endothelium |
| AQP2 | Water | Kidney collecting duct |
| AQP3 | Water, glycerol | Kidney collecting duct, epidermis, airway epithelium, conjunctiva, large airways, urinary bladder |
| AQP4 | Water | Astroglia in brain and spinal cord, kidney collecting duct, glandular epithelia, airways, skeletal muscle, stomach, retina |
| AQP5 | Water | Glandular epithelia, corneal epithelium, alveolar epithelium, gastrointestinal tract |
| AQP6 | Chloride? | Kidney collecting duct intercalated cells |
| AQP7 | Water, glycerol | Adipose tissue, testis, kidney proximal tubule |
| AQP8 | Water | Liver, pancreas, intestine, salivary gland, testis, heart |
| AQP9 | Water, small solutes | Liver, white blood cells, testis, brain |
| AQP10 | Water, glycerol | Small intestine |
| AQP11 | ? | Kidney, liver |
| AQP12 | ? | Pancreatic acinar cells |

nonspecific, mercurial sulfhydral-reactive compounds, such as $HgCl_2$; there is considerable interest in the identification of non-toxic, AQP-selective inhibitors (Castle, 2005; Verkman, 2001).

## Epithelial fluid transport

### The urinary concentrating mechanism

High water permeability, facilitated by AQPs, is crucial for kidney function. Several AQPs are expressed in the kidney. AQP1 is expressed in apical and basolateral plasma membranes in the proximal tubule and thin descending limb of Henle, and in microvascular endothelia of the outer medullary descending vasa recta; AQP2 is expressed in the apical membrane and intracellular vesicles in collecting duct principal cells; and AQP3 and AQP4 are expressed in the basolateral membrane of collecting duct epithelial cells. AQP1-null mice are polyuric and unable to concentrate their urine (Ma et al., 1998). Mechanistic studies indicate that the urinary concentrating defect in AQP1-null mice results from defective proximal tubule fluid absorption and defective countercurrent multiplication, which produces a relatively hypo-osmolar medullary interstitium (Chou et al., 1999; Pallone et al., 2000; Schnermann et al., 1998). Rare humans with AQP1 deficiency manifest a qualitatively similar urinary concentrating defect (King et al., 2001). Defective urinary concentrating ability is also caused by AQP2, AQP3 or AQP4 deficiency and results from reduced collecting duct water permeability and the consequent impaired osmotic equilibration of tubular fluid with the hypertonic medullary intestitium (Ma et al., 2000b; Ma et al., 1997; Yang et al., 2001). AQP2 mutations can cause an autosomal form of hereditary nephrogenic diabetes insipidus in humans (Deen et al., 1994).

The message from the kidney phenotype data is that AQPs can be important in rapid, osmotically driven water transport, as in the collecting duct, and in active, ‘near-isosmolar’ fluid transport, as in the proximal tubule. In the collecting duct, water is osmotically extracted from the tubule lumen into the hypertonic medullary interstitium of the kidney. If the water permeability of the collecting duct is low then the excreted urine is not concentrated, because of inadequate extraction of free water from the luminal fluid (Fig. 2A). In the proximal tubule, salt is pumped actively from the tubule lumen into a basal-lateral ‘third compartment’, which is mildly hypertonic compared with the luminal fluid. The mild hypertonicity drives water across the highly water permeable plasma membranes of proximal tubule cells. The reduced water permeability produced by AQP1 deficiency results in impaired fluid absorption.

Near-isosmolar fluid secretion works by a similar mechanism: active salt transport drives water across a highly water-permeable cell membrane, resulting in secretion of near-isosmolar fluid (Fig. 2B). Saliva secretion, for example, involves pumping of salt into the acinar lumen of the salivary gland, which drives water transport through AQP5. AQP5 deletion in mice reduces saliva secretion by ~50%, producing hypertonic saliva as a consequence of active salt secretion in the acinar lumen and impaired osmotic equilibration (Krane et al., 2001; Ma et al., 1999). Studies of AQP5 deficiency show that AQPs also function in near-isosmolar fluid secretion in airway submucosal glands (Song and Verkman, 2001). Likewise, AQP1-dependent secretion of cerebrospinal fluid (CSF) by the choroid plexus (Oshio et al., 2005) and aqueous fluid by the ciliary epithelium has revealed the role of AQP1 in these processes (Zhang et al., 2002). However, active fluid transport in many tissues is AQP independent, including alveolar fluid absorption (Bai et al., 1999; Ma et al., 2000a), sweat secretion (Song et al., 2002),

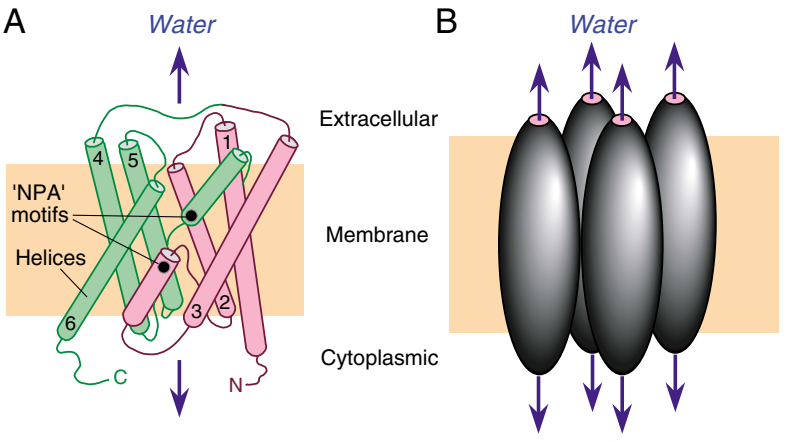


**Fig. 1.** Structure of AQP1 monomers and their tetrameric assembly in membranes. (A) Crystal structure of AQP1 monomer showing tilted transmembrane α-helical domains (numbered 1-6) surrounding a water pore. Conserved ‘NPA’ motifs are indicated. (B) Tetrameric assembly of AQP1 in a membrane in which individual monomers contain water pores.

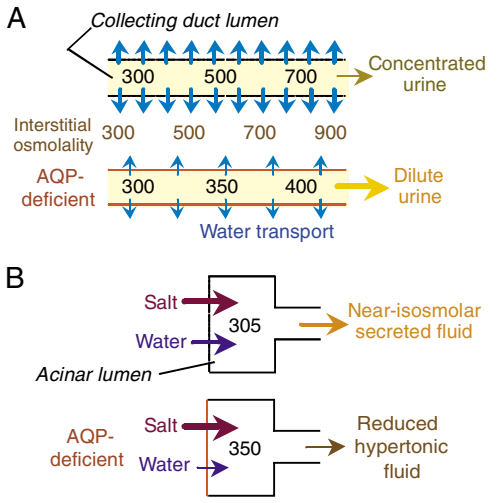


**Fig. 2.** Involvement of AQPs in epithelial fluid transport. (A) Reduced trans-epithelial water permeability in the kidney collecting duct impairs urinary concentrating ability by preventing osmotic equilibration of luminal fluid. (B) Reduced water permeability in glandular epithelium impairs active, near-isosmolar fluid transport by slowing osmotic water transport into the acinar lumen, producing hypertonic secretion.

and intestinal fluid secretion (Yang et al., 2005). Note that the rate of active fluid absorption/secretion per unit epithelial surface area in the alveolus, sweat gland and intestinal crypt is much lower than that in the kidney proximal tubule or salivary glands. A high, AQP-dependent water permeability is therefore required for relatively rapid near-isosmolar absorption/secretion.

## Brain and corneal swelling

Tissue hydration/swelling is another process that might involve AQPs. In the central nervous system (CNS), AQP4 is expressed in astroglial cells at the blood-brain barrier (BBB) and in ependyma and pial surfaces in contact with CSF (Fig. 3). Water moves into the brain across the BBB. It moves out of the brain by the same route or by transport into the CSF and subsequently into the venous circulation. Accumulation of excess brain water (brain edema) is a major cause of mortality and morbidity in stroke and in brain tumor, trauma and infection. 'Cytotoxic' or cellular brain edema results from excessive movement of water into the brain across an intact BBB, producing an expanded intracellular space. 'Vasogenic' or leaky-vessel brain edema results from leakage of fluid into the brain across a disrupted BBB, producing an expanded extracellular space.

Studies of AQP4-null mice provide compelling evidence for the involvement of AQP4 in both entry of water into and its exit from the brain. Although AQP4-null mice show no overt neurological abnormalities, they have remarkably reduced brain swelling after cytotoxic edema produced by acute water intoxication and ischemic stroke (Manley et al., 2000). Similarly, reduced brain swelling and intracranial pressure are found in AQP4-null mice in a meningitis model of cytotoxic edema (Papadopoulos and Verkman, 2005). However, brain swelling, intracranial pressure and clinical outcome are worse in AQP4-null mice (compared with wild-type mice) in models of vasogenic edema including intraparenchymal fluid infusion, cortical freeze injury, brain tumor and brain abscess (Papadopoulos et al., 2004; Bloch et al., 2005). The involvement of AQP4 in accumulation of excess brain water in cytotoxic brain edema is readily explicable, because AQP4 provides the principal water permeability pathway across the intact BBB (Solenov et al., 2004; Thiagarajah et al., 2005). However, the involvement of AQP4 in clearance of excess brain water was an unexpected observation, because extracellular fluid had been thought to move out of the brain by a bulk flow mechanism that does not involve cellular water channels. Exactly how salt and water move out of the brain in vasogenic edema will require further investigation, because AQP4 is a water-only channel.

AQP-dependent edema is also important in the cornea. Maintenance of corneal transparency requires precise regulation of stromal water content. This is believed to be controlled primarily by the transport of salt and water by the corneal endothelium (facing the aqueous fluid space), where AQP1 is expressed. Interestingly, corneal thickness is reduced ~20% in AQP1-null mice (Thiagarajah and Verkman, 2002). After exposure of the corneal endothelial surface to hypotonic saline, the rate of corneal swelling is reduced ~80% in the AQP1 knockouts. Although baseline corneal transparency is not abnormal in these mice, their recovery of corneal transparency and thickness after hypotonic swelling is remarkably delayed. This implicates AQP1 in active extrusion of fluid from the corneal stroma across the corneal

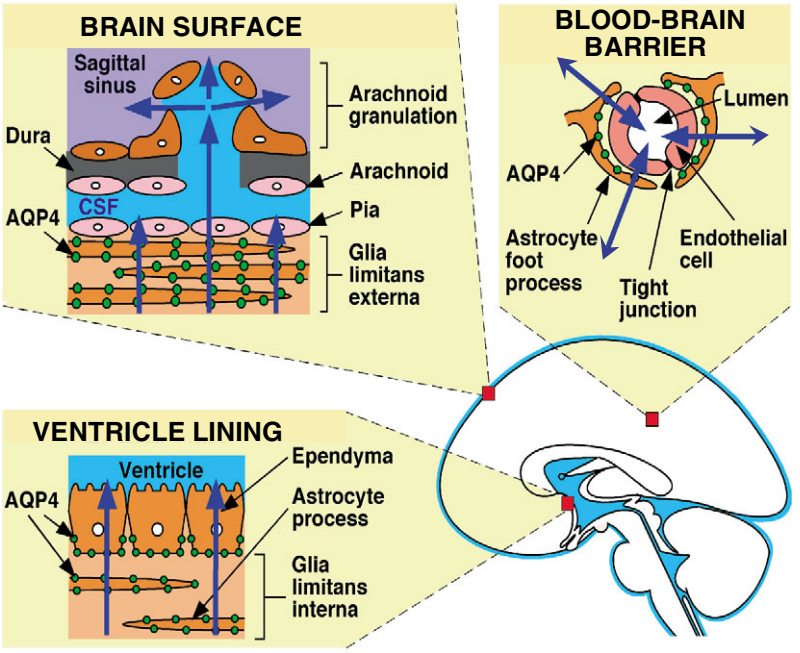


**Fig. 3.** Involvement of AQP4 in brain swelling. Pathways for water entry into and exit from brain, showing AQP4-dependent water movement across the blood-brain barrier, and through ependymal and arachnoid barriers.

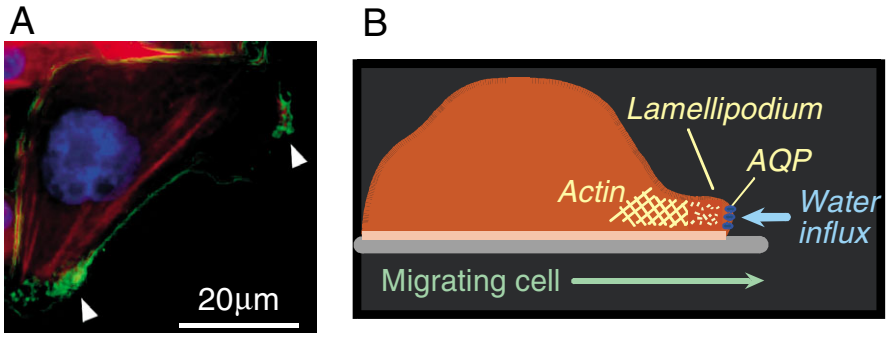


**Fig. 4.** AQP1 in migrating cells. (A) AQP1 (green, white arrows) localizes to lamellipodia in migrating AQP1-expressing CHO cells. Actin is stained red. (B) Proposed mechanism of AQP-dependent cell migration, showing water influx at the tip of a lamellipodium resulting in membrane protrusion.

endothelium. However, the precise dynamics of salt and water transport under stress remains to be established.

## Cell migration

Investigation of a possible role of AQP1 in tumor angiogenesis has revealed an unanticipated function of AQPs in cell migration (Saadoun et al., 2005). AQP1 is expressed in tumor microvessels (Endo et al., 1999; Vacca et al., 2001). AQP1-null mice exhibit greatly slowed tumor growth and improved survival (compared with wild-type mice) when implanted subcutaneously with tumor cells. The tumors in AQP1-null mice exhibit a much lower density of microvessels, and islands of viable tumor cells are surrounded by necrotic tissue. Furthermore, angiogenesis is impaired in these mice in an in vivo tumor-independent model involving vessel growth in implanted Matrigel pellets containing angiogenic factors.

Analysis of intrinsic endothelial cell functions in cultured endothelia indicates that cell migration towards a chemoattractant (fetal bovine serum) in Boyden chamber assays is significantly slowed in AQP1-deficient endothelial cells. Even larger differences are apparent in cell 'invasion' assays in which cells migrate through a Matrigel layer.

AQP-dependent water transport could account for the impaired migration in AQP1-deficient mice. Cell migration involves transient formation of membrane protrusions (lamellipodia and membrane ruffles) at the leading edge of the cell. This is thought to require rapid local changes in ion fluxes and cell volume, which are probably accompanied by rapid transmembrane water movement (Condeelis, 1993; Lauffenburger and Horwitz, 1996). Exogenously expressed AQP1 or AQP4 enhances migration of AQP-null CHO and FRT epithelial cells through a porous filter as well as wound closure. This indicates the effect is not AQP or cell-type specific. Interestingly in many cells, AQP1 localizes to the leading edge of the cell membrane (Fig. 4A), which has also been found for several transporters involved in migration, including the $Na^+/H^+$ and $Cl^-/HCO_3^-$ exchangers, and the $Na^+/HCO_3^-$ cotransporter (Schwab, 2001). Rapid time-lapse video microscopy shows that AQP1 expression produces more protrusions (lamellipodia) and a shorter mean residence time of protrusions. This suggests that AQPs accelerate cell migration by facilitating the rapid turnover of membrane protrusions at the leading edge.

Actin cleavage and ion uptake at the tip of a lamellipodium could create local osmotic gradients that drive the influx of water across the cell membrane (Fig. 4B). Water entry might then increase local hydrostatic pressure to cause cell membrane protrusion, which might create space for actin polymerization. AQPs in the region of membrane protrusions could enhance water entry and thus the dynamics of cell membrane protrusions and cell motility. Further biophysical studies are needed to test this proposed mechanism. Studies should also examine whether AQP-dependent cell migration is a general phenomenon in other biological processes besides angiogenesis, such as tumor spreading, wound healing, leukocyte chemotaxis and organ regeneration.

## Cellular roles of aquaporin-dependent glycerol transport

The roles of AQPs discussed above can probably be ascribed simply to their water-transporting function. But why do some AQPs, including AQP3 and AQP7 (the 'aquaglyceroporins'), transport glycerol as well as water, since glycerol is not generally thought to be a solute of major importance in mammals? Recent analyses of mice lacking AQP3 and AQP7 have provided interesting clues about the significance of AQP-facilitated glycerol transport.

### Epidermal hydration and biosynthesis

The most superficial layer of skin is the stratum corneum (SC), which consists of terminally differentiated corneocytes that originate from actively proliferating keratinocytes in the underlying epidermis (Fig. 5A). Hydration of the SC is an important determinant of the appearance and physical properties of the skin, and depends on several factors, including the external humidity, skin structure, lipid/protein composition, barrier properties, and the concentration of water-retaining 'humectants' such as free amino acids, ions and other small solutes. AQP3 is expressed strongly in the basal layer of keratinocytes in mammalian skin (Fig. 5B). Hairless mice (frequently used for functional analysis of skin) lacking AQP3 exhibit reduced SC hydration measured by high-frequency superficial skin conductance or by $^3H_2O$ partitioning (Ma et al., 2002). In addition, they have reduced skin elasticity, delayed biosynthesis of the SC after removal by tape-stripping, and delayed wound healing (Hara et al., 2002). Interestingly, exposure of mice to high humidity or occlusion increases SC hydration in wild-type mice, but not in AQP3-null mice, indicating that water transport through AQP3 is not a rate-limiting factor in trans-epidermal water loss. If reduced SC hydration were related to a balance between evaporative water loss from the SC and water replacement through AQP3-containing basal keratinocytes, then preventing water loss should have corrected the defect in SC hydration in the AQP3-null mice.

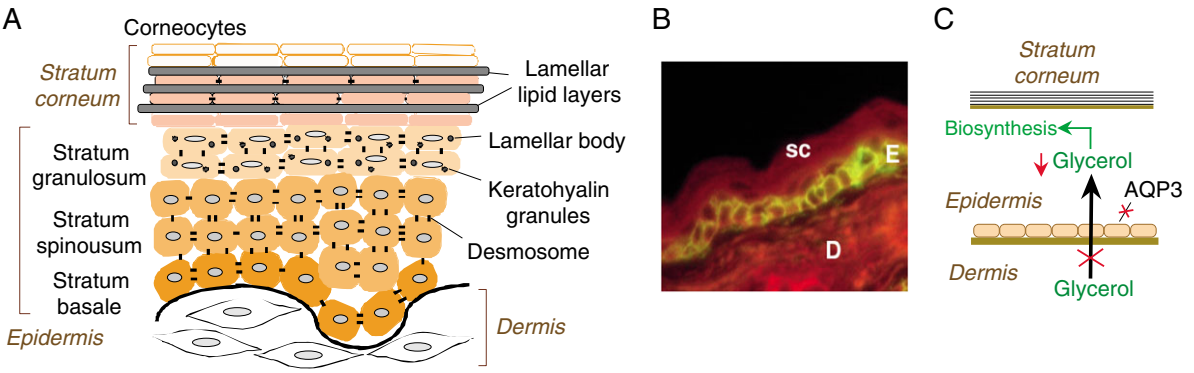


**Fig. 5.** Reduced skin hydration in AQP3 deficiency. (A) Schematic showing stratum corneum and epidermal layers. (B) Immunofluorescence showing AQP3 (in yellow) in the basal layer of epidermal cells in mice. E, epidermis; D, dermis; sc, stratum corneum. (C) Proposed mechanism of AQP3 function in skin, showing reduced steady-state glycerol content in epidermis and stratum corneum following AQP3 deletion.

Investigation of the mechanisms responsible for the skin phenotype in AQP3 deficiency showed reduced epidermal cell skin glycerol permeability, and reduced glycerol content in the SC and epidermis, with normal glycerol in dermis and serum. This suggests there is reduced glycerol transport from blood into the epidermis through the basal keratinocytes in the AQP3-null mice. Differences in SC structure, cell turnover, lipid profile, protein content, and the concentrations of amino acids, ions and other small solutes are not evident (Hara et al., 2002).

A reduced epidermal and SC glycerol content caused by lack of AQP3-facilitated glycerol transport is probably responsible for the abnormal skin phenotype in AQP3-null mice (Fig. 5C). Impaired glycerol transport into the epidermis and SC through the relatively glycerol-impermeable basal keratinocyte layer would reduce the steady-state epidermal and SC glycerol content. The reduced SC hydration and elasticity is likely to be related to the water-retaining property of glycerol, and the delayed barrier recovery and wound healing to the biosynthetic role of glycerol. Indeed, glycerol replacement by topical or systemic routes corrects each of the skin phenotype abnormalities in AQP3-null mice (Hara and Verkman, 2003). The data indicate the importance of glycerol in epidermal function and provide a rational scientific basis for the long-standing practice of including glycerol in cosmetic and medicinal skin-treatment preparations.

## Adipocyte fat accumulation

A principal site of expression of AQP7 is the plasma membrane of adipocytes. AQP7-null mice attain a much greater fat mass than wild-type mice as they age (Hara-Chikuma et al., 2005). Moreover, their adipocytes are much larger by 16 weeks (Fig. 6A) and accumulate approximately threefold more glycerol and approximately twofold more triglycerides than do wild-type adipocytes. Measurements in adipocytes of comparable size from younger mice showed ~65% reduction in glycerol permeability in AQP7-deficient adipocytes and slowed glycerol release from minced fat tissue. Lipolysis and lipogenesis rates are similar in wild-type and AQP7-deficient mice. The progressive triglyceride accumulation in AQP7-deficient adipocytes could be due to reduced plasma membrane glycerol permeability. This should increase the steady-state glycerol concentration in adipocytes, which would result in increased glycerol-3-phosphate and hence triglyceride biosynthesis (Fig. 6B). Adipocyte glycerol permeability may thus be a novel regulator of adipocyte size. Induction of adipocyte AQP7 expression and/or function might therefore reduce fat mass in some forms of obesity.

## Neural signal transduction

Several lines of indirect evidence suggest AQPs function in rapid neural signal transduction. If correct, this could be important for developing new therapies for epilepsy and pain. AQP4 is expressed in the CNS, inner ear and retina in non-

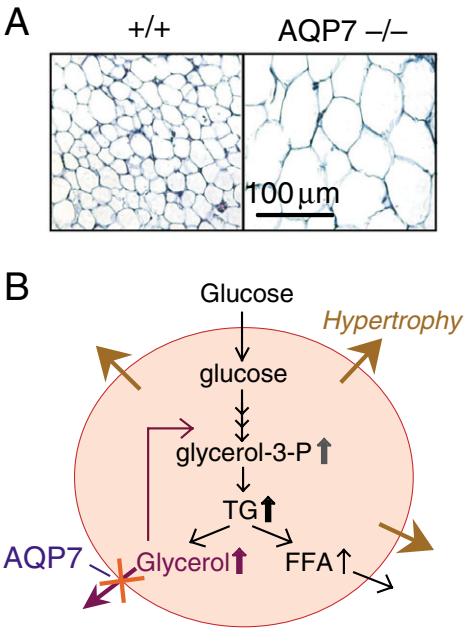


**Fig. 6.** Progressive fat accumulation and adipocyte hypertrophy in AQP7 deficiency. (A) Histology of gonadal white adipose tissue in AQP7-null mice at age 16 weeks, showing marked adipocyte hypertrophy. (B) Proposed mechanism for adipocyte hypertrophy in AQP7 deficiency, in which impaired AQP7-dependent glycerol escape results in intracellular glycerol accumulation and increased triglyceride (TG) content. FFA, free fatty acid.

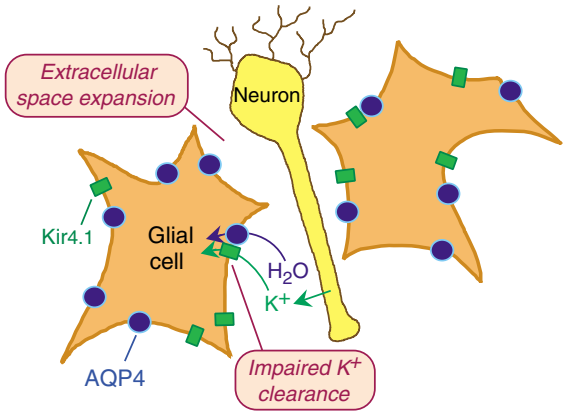


**Fig. 7.** Possible mechanisms for involvement of AQPs in rapid neural signal transduction. AQP4 expression on astroglia may alter the volume of the extracellular space and its composition by interactions with Kir4.1 $K^+$ channels or by impairing water re-uptake into astroglia during neural signaling.

electrically-excitable cells that are close to excitable cells (which do not express AQPs): in astroglia supporting neurons, in retinal Muller cells supporting bipolar cells, and in cochlear Clausius and Hensen's cells supporting hair cells. AQP4 in these cells might alter the properties of the extracellular space, such as its volume or ionic composition, modulating the function of the nearby electrically excitable cells. Mice lacking AQP4 have reduced seizure susceptibility (Binder et al., 2004a), and reduced evoked potential responses to light (Da and Verkman, 2004; Li et al., 2002) and acoustic (Li and Verkman, 2001; Mhatre et al., 2002) stimuli. Mice lacking α-syntrophin, which exhibit altered AQP4 localization, show reduced extracellular $K^+$ clearance following evoked neuronal activity and a greater severity of hyperthermia-induced seizures (Amiry-Moghaddam et al., 2003). Mice lacking AQP1, which is expressed in C-fibers in the dorsal horn of spinal cord (Solenov et al., 2002), have reduced nociception in response to thermal stimuli and capsaisin (our unpublished data).

Given the membrane colocalization of AQP4 and the inwardly rectifying $K^+$ channel Kir4.1, AQP4 might augment rapid $K^+$ transport by a 'siphoning' mechanism (Nagelhus et al., 1999; Nagelhus et al., 2004), and thus modulate the rapid changes in extracellular $K^+$ that occur during neural signaling (Fig. 7). Alternatively, the chronically expanded extracellular space volume evident in AQP4 deficiency (Binder et al., 2004b) might impair water re-uptake into astroglia. Quantitative studies relating extracellular space volume and ionic concentration to neural stimuli will be needed to establish the mechanism underlying the apparent alteration in neural signal transduction in AQP4 deficiency.

## Other proposed cellular roles of aquaporins

A few studies have raised the possibility that AQPs function in cell volume regulation (Krane et al., 2001; Kuang et al., 2004). Since volume regulation involves active solute movements that drive osmotic water transport, it is not unreasonable to speculate about a role for cell membrane water permeability. However, since osmotic equilibration in nearly all cells occurs in under one minute, often in seconds or less, and since volume regulation occurs over many minutes, water permeability should not be rate limiting in volume regulation. If AQPs are involved in volume regulation, then other mechanisms would need to be involved, such as interactions between AQPs and solute transporters involved in the primary volume regulatory response. Involvement of AQPs in organellar physiology in vesicular swelling (Cho et al., 2002) and mitochondrial metabolism (Calamita et al., 2005) has also been suggested. However, these observation will require independent corroboration and evaluation of the mechanisms, since osmotic equilibration times in organelles, which have high surface-to-volume ratios, should be in the order of milliseconds and so are unlikely to be rate limiting for much slower cellular processes.

## Conclusions and perspective

There is now compelling evidence, largely from analysis of AQP-deficient mice, for the involvement of AQPs in a variety of physiological and cellular functions. The anticipated roles of AQPs in trans-epithelial fluid transport and tissue swelling have been confirmed, and a diverse set of unanticipated cellular roles of AQPs has been discovered. Their involvement in cell migration, fat metabolism, epidermal biology and neural signal transduction may be important in the pathophysiology of cancer, obesity, immune cell dysfunction and epilepsy. Consequently, research in this area could lead to the development of new therapeutic strategies. Further work is now needed to test the proposed mechanisms for the roles of AQPs in these processes, as well as to examine their recently proposed roles in cell volume regulation and organellar physiology. Specific, non-toxic AQP inhibitors, when available, will be useful to complement knockout and knock-down approaches. Discovery of additional roles of AQPs is likely. These could be based on the water/solute-transporting functions of AQPs, or possibly non-transporting functions such as interactions with other membrane or cytoplasmic proteins.

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