Long-term regulation of aquaporins in the kidney

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Marples, David, Jørgen Frøkiaer, and Søren Nielsen. Long-term regulation of aquaporins in the kidney. Am. J. Physiol. 276 (Renal Physiol. 45): F331–F339, 1999.—The discovery of the aquaporin family of water channels has greatly improved our understanding of how water crosses epithelial cells, particularly in the kidney. The study of the mechanisms involved in the regulation of collecting duct water permeability, in particular, has advanced very rapidly since the identification and characterization of aquaporin-2 (AQP2) in 1993. One of the more surprising findings has been the dramatic long-term changes that are seen in the abundance of this protein, as well as the recognition that these changes represent a way of modulating the acute antidiuretic effects of vasopressin. Furthermore, such changes seem to be of etiological and pathological significance in a number of clinical disorders of water balance. This review focuses on the various conditions in which AQP2 expression is altered (either increased or decreased) and on what this can tell us about the signals and mechanisms controlling these changes. Ultimately, this may be of great value in the clinical management of water balance disorders. Evidence is also now beginning to emerge that there are similar changes in the expression of other renal aquaporins, which had previously been thought to provide an essentially constitutive water permeability pathway, suggesting that they too should be considered as regulatory factors in the control of body water balance.

collecting duct; water permeability; nephrogenic diabetes insipidus; water balance disorders; aquaporin-2

WATER REABSORPTION in different regions of the kidney depends on several members of the aquaporin family of water channels (1), as shown in Fig. 1. Most reabsorption in the proximal tubule occurs constitutively, with water movement being facilitated by aquaporin-1 (AQP1) (39) and possibly AQP7 (24). AQP1 also plays an important role in the thin descending limb of the loop of Henle (38, 39). The main site at which urine output, and hence body water balance, is regulated is the collecting duct, where AQP2, AQP3, and AQP4 are all involved (47). The water permeability of the collecting duct can change rapidly (within a few minutes) in response to vasopressin (recently reviewed in Refs. 5 and 28). This acute response is mediated by V2 receptors in the basolateral membrane of the cells, with cAMP acting as the second messenger. This induces the transfer of AQP2 water channels from a store in intracellular vesicles to the apical plasma membrane of the collecting duct principal cells. When vasopressin levels decline, AQP2 is retrieved endocytically, returning the membrane to its resting state of low water permeability. AQP3 and AQP4 are present in the basolateral membrane and provide an exit pathway for water movement out of the cells.

In addition to this acute regulation of collecting duct water permeability, it is now clear that there is a longer-term modulation of the permeability, brought about by changes in the total amount of AQP2 present in the cells. It is these changes in expression that will form the focus of the present review. As well as its role in normal physiology, these long-term changes may be important in a wide range of pathological conditions, including a number of forms of acquired nephrogenic diabetes insipidus (NDI), and it was studies of these conditions which first brought the importance of long-term changes in AQP2 levels into focus; although in retrospect, it can now be seen that earlier evidence pointed in this direction. Table 1 sets out the conditions in which AQP2 levels have been shown to be altered. In addition, evidence is beginning to accumulate that there are also changes in the expression of other renal aquaporins in these conditions, and that such changes may be functionally important. This will also be covered briefly at the end of the review (see Changes in Expression of Other Aquaporins).
Table 1. Conditions and water balanced disorders associated with changes in aquaporin expression and/or targeting

<table>
<thead>
<tr>
<th>Polyuric Conditions</th>
<th>Conditions with Water Retention and/or Edema</th>
<th>Conditions with Urinary Concentrating Defects</th>
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<tbody>
<tr>
<td>Hereditary DI</td>
<td>Congestive heart failure</td>
<td>Low-protein diet</td>
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<td>Central PDA</td>
<td>Hepatic cirrhosis</td>
<td>UUO</td>
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<td>AQP2 defects</td>
<td>CCl₄</td>
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<td>V₂ R defects?</td>
<td>Bile duct ligation</td>
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<td>Acquired NDI</td>
<td>Nephrotic syndrome</td>
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<td>Lithium</td>
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<td>Electrolyte distur-</td>
<td>Adriamycin</td>
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<td>bances</td>
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<td>Hypokalemia</td>
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<td>UTO</td>
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<td>Polydipsia</td>
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<td>Renal failure</td>
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<td>Acute, ischemic</td>
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<td>Chronic, 5/6 nephrectomy</td>
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These results come in most cases from work with experimental rat models. In conditions listed as having a urinary concentrating defect, there is no overt polyuria, but the animals are unable to concentrate the urine normally in response to dehydration. DI, diabetes insipidus; NDI, nephrogenic DI; AQP2, aquaporin-2; SIADH, syndrome of inappropriate antidiuretic hormone production; PDA, phosphodiesterase overactivity; V₂, V₂ receptor; UTO, urinary tract obstruction; PAN, puromycin aminoglycoside; UUO, unilateral ureteral obstruction.

Although collecting duct water permeability is the principal determinant of the degree of urinary concentration, many other factors also play a role. Chief among these is the osmotic gradient produced by the loop of Henle. This is itself a regulated process, with salt uptake in the thick ascending limb being modified by vasopressin action, as well as other factors, in both the short and the long term. Tubular flow rate is also important and, hence, renal blood flow, glomerular function, and proximal tubule reabsorption will all have an influence. As discussed in the last section of the review (see Changes in Expression of Other Aquaporins), AQP1 is important in water handling by both the proximal tubule and the loop of Henle. The other factors lie outside the scope of this review, but it is important to remember that changes in aquaporins are not occurring in isolation and will interact with other changes in kidney physiology.

Downregulation of AQP2 Is a Common Feature in Multiple Forms of NDI/Concentrating Defects

The most common drug-induced form of NDI is due to lithium treatment. About one American in 1,000 is on lithium treatment (42), and as many as 50% of these patients will have a significant urinary concentrating defect (4). In a rat model of this condition, plasma lithium levels in the therapeutic range are associated with a profound polyuria. Previously, it had been assumed that this reflected an impaired ability of vasopressin to stimulate adenylate cyclase (8). Direct studies demonstrated that a smaller fraction of the AQP2 was found in the plasma membrane in lithium-treated animals than in controls, despite their polyuria and presumed dehydration, but the most striking finding was that there was a 95% decrease in total AQP2 levels in the cells (34). Clearly, such a decrease in AQP2 would have had a profound effect on the ability of the cells to mount an antidiuretic response, and in conjunction with the decrease in delivery, this explained the polyuria seen in these animals.

It was of interest to know whether such a decrease in AQP2 was a specific feature of lithium treatment, or whether it was characteristic of many forms of NDI. A number of water balance disorders have now been investigated, and the results are summarized in Fig. 2. Two other clinically important causes of NDI are electrolyte disturbances: hypokalemia and hypercalcemia. These commonly arise in association with diuretic therapy and cancer, respectively. In neither case is the degree of polyuria as marked as with lithium treatment, but both were also associated with decreased levels of AQP2 in rat models (10, 35, 45). Interestingly, in hypercalcemia, as with lithium, targeting of the remaining AQP2 appeared to be impaired, whereas in hypokalemia the remaining AQP2 appeared to be delivered to the apical plasma membrane normally. This suggested that changes in AQP2 expression were not necessarily linked to blockade of the acute response to vasopressin and indicated that signals other than vasopressin acting at V₂ receptors might be involved in regulating AQP2 levels.

A major cause of morbidity among older men is urinary retention, usually as a consequence of prostatic hypertrophy. This obstruction is often compounded by an impaired concentrating ability, which increases the amount of urine produced. Because of this concentrat-
ing defect, we looked at a rat model of bilateral ureteric obstruction (20). These animals had both ureters tied using a reversible ligature for 24 h, and AQP2 levels were assessed either at the end of this period or 1, 2, or 7 days after release of the obstruction, during which time the urine output was monitored. The animals showed a marked osmotic diuresis during the first 24 h after release, as they cleared all the urea and excess salt that had built up during the obstruction, but they then had a persistent polyuria that was not a consequence of solute excretion. AQP2 levels were already decreased to 25% of control levels even at the end of the obstructed period, and remained low for several days afterward. As in the hypokalemic animals, AQP2 appeared to be very efficiently delivered to the apical plasma membrane, and therefore it seems likely that it was the reduction in total AQP2 available, perhaps combined with changes in the osmotic gradient driving the water reabsorption, that was responsible for the concentrating defect seen in these animals.

A variety of other situations not generally thought of as forms of acquired NDI are also associated with vasopressin-resistant urinary concentrating defects. Among these is a protein-deficient diet, which has been shown to cause changes in both urea and water reabsorption (46). Interestingly, there appears to be an impairment of vasopressin-induced water transport only in the terminal inner medullary collecting ducts, and there is also a specific decrease in AQP2 expression in this part of the tubule (46). This is an interesting observation, because in several other conditions where AQP2 levels are reduced, the effect seems to be present along the whole length of the collecting duct (34, 35). It is also consistent with previous evidence that some local factors, rather than circulating vasopressin, may be involved in the decreased expression under certain conditions (18, 34).

Renal failure, both acute and chronic, is associated with polyuria and a concentrating defect, although in both cases there are a wide range of tubular abnormalities that contribute to the overall dysfunction. However, recent studies have shown decreased AQP2 levels in both an ischemic acute renal failure model (16) and a five-sixths nephrectomy chronic renal failure model (29), suggesting that this may be one factor involved in impaired collecting duct function and vasopressin responsiveness during renal failure.

Defects in AQP2 Expression Often Persist After Correction of the Primary Defect

One feature of a number of forms of acquired NDI is the length of time taken for a normal concentrating capacity to be reestablished once the underlying condition has been corrected. This is also the case in animal models, such as the lithium treatment model (34). In this study, return to a lithium-free diet for 7 days was associated with only a moderate increase in urine osmolality. Interestingly, this was correlated with a persisting deficit in AQP2 expression. Similar results were obtained in the ureteric obstruction study (20), where after 7 days the animals still had AQP2 levels only one-half of that seen in the controls. Although
their urine output was apparently normal, water deprivation tests revealed a significant persisting urinary concentrating defect (20). Indeed, such defects were observable at periods up to 1 mo after obstruction (19). In contrast, in hypokalemic animals both AQP2 levels and concentrating ability returned to normal levels within a week. Thus chronically decreased AQP2 levels appear to correlate with urinary concentrating defects in animal models and may also be of clinical significance in patients with similar problems.

Upregulation and Water Retention

In contrast to the situation in NDI, some conditions result in the inappropriate retention of water. Ultimately, this can lead to extravascular fluid accumulation, with the risk of ascites and edema, including pulmonary edema. In the light of the reports of decreased AQP2 in NDI, it was of interest to see whether there were changes in AQP2 levels in water-retaining states.

Two studies have looked at AQP2 expression in rats with congestive heart failure (CHF) induced by coronary artery ligation (40, 49). These studies showed a clear increase in AQP2, both at the mRNA and protein levels, in association with the development of hyponatremia. These changes were seen only in rats with CHF, whereas rats that had undergone the same procedure but had compensated heart failure (i.e., which were not hyponatremic) showed no changes in AQP2 expression (40). Furthermore, immunocytochemistry showed that the AQP2 was predominantly in the apical plasma membrane, where it would be active in facilitating water reabsorption (40). Thus both increased expression of AQP2 and enhanced delivery to the plasma membrane seem to be important in the water retention associated with CHF. Both of these effects could be explained by the observed raised circulating vasopressin levels. Consistent with this, treatment of CHF rats with a vasopressin V2 receptor antagonist, OPC-31260, for 24 h reversed the increase in AQP2 levels and increased urine output (49). This drug also has similar effects in normal animals (7, 33), as discussed below.

Similar results were obtained in a rat model of hepatic cirrhosis with ascites induced by CCl4 treatment (3, 22). Again, AQP2 protein and mRNA levels were increased, and the increase correlated with the amount of ascites. As with the CHF rats, the vasopressin V2 receptor antagonist OPC-31260 reversed the increase in AQP2 mRNA levels (22). In this model, however, the rats had normal serum sodium levels or osmolality, indicating that inappropriate renal retention of water was not a major factor in the generation of ascites. However, there was a correlation between ascites volume and AQP2 mRNA levels (3). In another model (using ligation of the common bile duct) leading to cirrhosis without ascites, and with normal circulating vasopressin levels, AQP2 expression in the cortex was reduced, whereas inner medullary AQP2 was unchanged (25). The authors suggested that the down-regulation of AQP2 may be an appropriate response to the water retention, which is overcome when cirrhosis becomes decompensated, as vasopressin levels rise (25). In yet a third model, using CCl4 inhalation, there was cirrhosis with ascites and hyponatremia (evidence of excess water retention). No change in AQP2 expression was observed, but AQP1 expression in the cortex was increased (17). The authors concluded that water retention is likely to be due to increased reabsorption in the proximal tubule, combined with a failure of the normal “vasopressin escape” phenomenon, discussed below. It is clear that cirrhosis is a complex situation in which there are multiple disturbances of normal physiology and that additional studies will be needed to clarify the role of aquaporins in compensated and decompensated cirrhosis fully.

In marked contrast are the results of studies on three models of nephrotic syndrome (2, 14, 15). In this condition, protein is lost into the urine as a consequence of glomerular damage, and there is salt and water retention and ascites. As with CHF and cirrhosis, circulating vasopressin levels are high in at least one of the rat models (2), although the situation in human patients seems to be very variable. Nevertheless, AQP2 levels were dramatically reduced in the kidneys from animals with nephrotic syndrome. This may represent an “escape” phenomenon, in which alternative pathways provide a way for water to be lost from the body in the face of an inappropriately high vasopressin level and water retention. Certainly, it indicates that there is a signal other than vasopressin that can cause changes of AQP2 expression.

The most dramatic demonstration of an escape phenomenon has been provided by Ecelbarger et al. (12), who used a rat model of the syndrome of inappropriate antidiuretic hormone (ADH) production (SIADH). In this model, rats were infused with ADH via micropumps for 7 days, and then, while ADH continued to be administered, the rats were given a liquid diet so that they became water loaded. After 3 days of water loading, AQP2 levels in the inner medulla fell to 17% of those seen in non-water-loaded animals treated with ADH, indicating that the animals were able to reduce both AQP2 protein and mRNA despite high circulating levels of ADH. A subsequent study has shown that the tubules become resistant to vasopressin, producing less cAMP in response to a given level of vasopressin, which may be important in the reduction of AQP2 production (11). These studies not only demonstrate that a reduction of AQP2 levels plays a major part in the vasopressin escape phenomenon but also confirm previous evidence that factors other than vasopressin are important in the control of AQP2 expression.

Hereditary Disorders of Water Balance

If AQP2 levels are reduced in acquired forms of diabetes insipidus, then is the same true in the genetically determined forms? This has not yet been determined for hereditary NDI, but Brattleboro rats provide evidence about the situation in central DI. This strain has a defect in the neurophysin gene and as a conse-
quence is unable to produce any vasopressin and is extremely polyuric. Inner medullas from Brattleboro rats expressed only about one-third of the AQP2 seen in the parent strain (Long-Evans). Infusion of vasopressin for 5 days increased AQP2 expression to levels closely comparable with those in the parent strain, as well as correcting the urinary concentrating defect (9). This demonstrated that vasopressin activity is an important regulator of AQP2 expression and that patients lacking such activity are likely to have reduced levels of AQP2. This may contribute to their polyuria, although the lack of regulated delivery of AQP2 to the apical plasma membrane is probably a more important factor. Current studies are consistent with this view (43). Such studies are hard to perform in humans, but tentative support for this view comes from studies looking at AQP2 excretion in the urine (26, 44). It appears that AQP2 is lost into the urine as a function of vasopressin action on the principal cells, rather than providing a direct measure of AQP2 levels in the kidney, since urinary AQP2 drops very rapidly with diuresis induced by water loading and recovers again once the water load has been excreted (26). In patients with central DI, baseline AQP2 loss in the urine is very low, and rises with injection of vasopressin (26). However, it never reaches the levels seen in normal patients, consistent with such patients having reduced cellular levels of AQP2. In patients with nephrogenic DI, urinary AQP2 levels remain low, as expected (26), but it is impossible to draw useful conclusions about kidney AQP2 expression from this. The development of more sophisticated tests may make such urinary testing useful both diagnostically and as a research tool, but results to date remain intriguing but inconclusive. Results with central DI suggest that AQP2 levels may also be reduced in hereditary nephrogenic DI, since the lack of V2 receptors underlying the disease in most cases may also prevent vasopressin-stimulated AQP2 production.

A mouse strain with nephrogenic diabetes insipidus (DI +/+ Severe) exists that gives indirect support for the hypothesis that AQP2 levels may be reduced and also provides information about the mechanism by which vasopressin probably induces AQP2 expression. These animals have a defect in the gene for cAMP phosphodiesterase, resulting in exaggerated activity. As a consequence, cytosolic cAMP levels remain low, so vasopressin cannot provoke a normal diuresis, and the animals have severe NDI (21). In such animals AQP2 levels are greatly reduced, to less than 25% of control levels in many cases, and the AQP2 expression correlated with the degree of polyuria from mouse to mouse (21). Thus it seems that cAMP acts as a signal controlling AQP2 expression, consistent with the identification of a cAMP-responsive element in the promoter region of the AQP2 gene (48). It is interesting that the reduction of AQP2 seen in these animals is greater than that seen in the Brattleboro rats, raising the possibility that cAMP provides a common pathway for a number of modifiers of AQP2, of which vasopressin is only one.

Evidence for Regulation of AQP2 by Signals Other Than Vasopressin

A number of experimental approaches have been taken to provide information on the factors controlling AQP2 expression. It has been known for many years that long-term changes in body hydration status could alter maximal urinary concentrating capacity (13, 30), and experiments in which rats were water deprived or water loaded confirmed that dehydration caused an increase in AQP2 expression, whereas water loading reduced it (37). Initially, it seemed likely that these results reflected changes in endogenous vasopressin production, since vasopressin infusion also caused increased AQP2 expression, both in Brattleboro rats and in normal rats (9, 12). Furthermore, prolonged treatment with OPC-31260, a relatively specific vasopressin V2 receptor antagonist, also caused a decrease in AQP2 expression (23, 33), albeit only to about one-half of control levels (33). However, it was striking that lithium treatment caused a decrease in AQP2 expression of much greater magnitude than the changes seen with vasopressin infusion in either Brattleboro or normal rats. Furthermore, attempts to reverse the downregulation caused by lithium with either infusion of 1-deamino-8-D-arginine vasopressin (DDAVP) (a stable V2-specific vasopressin analog) or water deprivation showed that doses of DDAVP sufficient to cause efficient targeting of AQP2 to the plasma membrane had only a very modest effect on AQP2 expression, whereas dehydration caused a much greater increase in AQP2 levels, despite failing to induce the delivery process (34). Thus it seemed that downregulation of AQP2 caused by lithium treatment was unlikely to be solely a consequence of vasopressin resistance of the collecting ducts and that dehydration could stimulate AQP2 expression via a non-vasopressin-mediated pathway. This was confirmed by experiments in which animals pretreated with OPC-31260 were subsequently water deprived (33). Under these conditions, AQP2 expression returned to normal levels despite continued blockade of the V2 receptors. The vasopressin-escape model (12) described above showed that water loading could also decrease AQP2 expression despite ongoing V2 receptor stimulation, directly demonstrating the existence of vasopressin-independent signaling pathways controlling AQP2 expression.

Possible Mechanisms for AQP2 Regulation

A number of possible signals other than vasopressin could be involved in the control of AQP2. One candidate would be the rate of diuresis itself. However, severe glycosuria in streptozotocin-treated rats with diabetes mellitus caused either no change or a modest increase in AQP2 expression (possibly due to mild dehydration and/or increased vasopressin levels), rather than a decrease (27, 36). Furthermore, furosemide treatment for 1 or 5 days had no significant effect on AQP2 expression (33), although another study found a modest increase (47) following furosemide treatment. Thus diuresis in itself does not appear to cause a decrease in AQP2 expression. Because furosemide causes a wash-
out of the medullary interstitial hypertonicity, these results also demonstrate that loss of this hypertonicity is also not an important signal modulating AQP2 expression. Further evidence that hypertonicity is not a major signal came from the observation that the down-regulation of AQP2 expression caused by lithium and hypokalemia is identical in the inner medulla and in the cortex (35), where interstitial tonicity is much more stable (and lower). However, as discussed above, some studies have revealed regional differences in the changes in AQP2 expression, suggesting that local factors may be important in some conditions. This is clearly the case in experiments with unilateral ureteric obstruction, where there is a profound downregulation of AQP2 in the obstructed kidney, with only a modest decrease in the nonobstructed kidney, indicating that local factors play the major role, whereas systemic and/or neural factors induce a change in the nonobstructed kidney (18). Such local factors might include pressure effects specific to this model and/or metabolite accumulation within the tissue. As a possible example of the latter, it is known that prostaglandin production in the inner medulla is increased in a number of the NDI models in which decreased AQP2 expression has been found (20, 34, 35). However, recent preliminary studies have suggested that inhibition of prostaglandin production results in a decrease in AQP2 levels, rather than the increase expected from the above hypothesis. It is possible that prostaglandins increase AQP2 synthesis and that their production in NDI is an attempt to compensate for some other factor which is causing decreased expression, but much more work needs to be done before these signals will be fully understood.

Changes in Expression of Other Aquaporins

Although AQP2 controls water movement across the apical plasma membrane of the collecting duct principal cells, AQP3 and AQP4 appear to provide the exit pathway across the basolateral membrane. Although this membrane has a constitutively high water permeability, changes in expression of both AQP3 and AQP4 have been reported (2, 15, 29, 47). The expression of AQP3 appears to alter in response to changes in vasopressin activity, as well as being altered in a number of pathological states (2, 15, 29), but does not always change when there are changes in AQP2 (40, 46), indicating that the signals controlling expression of AQP2 are not the same as those controlling AQP3 and AQP4.

Fig. 3. Regulation of water permeability in collecting duct principal cells. In absence of vasopressin (AVP), there is little AQP2 in the apical plasma membrane, which therefore has a very low water permeability and prevents water being reabsorbed from the urine. AQP3 and AQP4 are constitutively present in the basolateral membrane, so the water permeability is always high. Vasopressin binds to V2 receptors in the basolateral membrane and activates adenylyl cyclase (A.C.), hence causing a rise in cAMP levels in the cell. This activates protein kinase A (PKA), which phosphorylates AQP2 as well as other targets. Following phosphorylation of AQP2, it is translocated to the apical plasma membrane, increasing the water permeability of the membrane. When vasopressin levels fall, AQP2 is retrieved endocytically from the apical plasma membrane. Long-term changes in AQP2 expression depend on multiple signaling cascades. The best established involves cAMP via cAMP-response element binding protein (CREB) phosphorylation (CREB-P) and a cAMP-responsive element (CRE) and an AP1 transcriptional factor consensus site in the 5′-untranslated region of the AQP2 gene. However, other signals, including prostaglandins, also appear to be important, although much work remains to be done to characterize these.
of the two channels are not identical. In contrast, AQP4 appears to change little in most conditions, although it was greatly reduced in the adriamycin-induced nephrotic syndrome model (15). In mice with a knockout of the AQP4 gene (31), vasopressin-induced collecting duct water permeability was reduced by 80% (6), indicating that AQP4 provides an important exit pathway for water out of the cells, at least in the inner medullary collecting ducts. More recently, it has become clear that AQP1 also plays an important part in the generation of a concentrated urine, since an AQP1 knockout mouse is unable to concentrate its urine in response to dehydration, although its urine output in the state of normal hydration is not obviously different from that of wild-type mice (32). This probably reflects the greatly reduced water permeability of the thin descending limb of the loop of Henle, and consequent impairment of the countercurrent multiplication mechanism required for the generation of the medullary osmotic gradient. Furthermore, changes in AQP1 have also been described in a number of conditions in which concentrating ability is impaired, including ureteric obstruction (19), nephrotic syndrome models (2, 15), and chronic renal failure (29) (see Table I). The signals involved in such changes remain to be discovered but may also represent a means by which long-term modulation of urinary concentrating ability can be controlled.

Summary

Regulation of urine output, and hence control of body water balance, occurs mainly in the renal collecting duct, where water permeability is controlled acutely by shutting of AQP2 from a store in intracellular vesicles to the apical plasma membrane in response to vasopressin. This acute response is modulated by changes in the total level of AQP2 in the tissue, and these changes appear to be important in both normal physiological adaptation to changes in hydration status and in pathological disorders of water balance. One of the signals for such changes in AQP2 expression is vasopressin itself, acting via cAMP, but it is now clear that other signals are also important, although their identity and mode of action remain to be elucidated (see Fig. 3). The role of changes in the expression of other aquaporins and the signals that regulate such changes remain even less well defined and will provide a rich avenue for future research.

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