Title:

Urinary concentration: different ways to open and close the tap

Running title: NDI review

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Abstract

Nephrogenic diabetes insipidus (NDI) provides an excellent model for the benefits and insights that can be gained from studying rare diseases. The discovery of underlying genes identified key molecules involved in urinary concentration, including the type 2 vasopressin receptor AVPR2 and the water channel AQP2, which constitute obvious pharmacologic targets. Subsequently developed drugs targeting AVPR2 not only provide potential benefit to some patients with NDI, but are now used for much more common clinical applications as diverse as nocturnal enuresis and heart failure. Yet, the story is still evolving: clinical observations and animal experiments continue to discover new ways to affect urinary concentration. These novel pathways can potentially be exploited for therapeutic gain. Here we review the (patho)physiology of water homoeostasis, the current status of clinical management and potential new treatments.

Introduction

Nephrogenic diabetes insipidus as an X-linked disease has been recognized for a long time. It was first described by McIlraith in 1892 as a familial form of polyuria affecting "chiefly males on the female side of the house" [1]. De Lange in 1935 reported a family with diabetes insipidus and no male-to-male transmission unresponsive to injections of posterior lobe extracts [2] and in 1947 Williams and Henry established the unresponsiveness to arginine-vasopressin (AVP) in these patients and coined the term nephrogenic diabetes insipidus (NDI) [3]. With the advent of molecular genetics our knowledge of this disease has much improved: In 1992 the *AVPR2* gene encoding the AVPR2 receptor was cloned and mutations identified in patients with X-linked NDI [4-7]. Approximately 90% of patients with inherited NDI are found to have mutations in this gene. Shortly after, the *AQP2* gene encoding the vasopressin-regulated water channel aquaporin-2 (AQP2) was cloned [8, 9] and in 1994 mutations in *AQP2* were found to underlie the rare autosomal forms of DI [10]. The discovery of these key molecules allowed the development of targeted drugs. Whilst these are of only limited and indirect use in the treatment of NDI, they are used in much more common disorders of water, such as heart failure or the syndrome of inappropriate antidiuretic hormone [11]. Thus, NDI provides an excellent example of how the study of a rare disease can benefit the treatment of common problems. Recently, new pathways to affect water handling in the collecting duct independent of AVPR2 have been described and these could potentially be exploited in the management of X-linked NDI. This review will focus on our current understanding of water homoeostasis and how new insights may provide new treatments.

Physiology of water homoeostasis

Vasopressin

Whilst the kidneys are tasked with water homoeostasis, they can only sense plasma volume via renal perfusion, but not abnormalities in plasma osmolality and sodium, which are the biochemical hallmarks of disorders of water [12]. Rather, osmolality is sensed by specialized neurons, so-called magnocellular neurosecretory cells, in the supraoptic and paraventricular nuclei of the hypothalamus [13]. These cells contain stretch-sensitive ion channels, TRPV1, which respond to osmolality-mediated changes in cell volume: hyperosmolality leads to cell shrinkage with subsequent depolarization and vasopressin secretion, whereas hyposomolality leads to hyperpolarisation with consequent inhibition of vasopressin release [13]. Interestingly, activity of these neurons can be modified by peptides involved in blood pressure regulation, such as angiotensin II (AngII) [13]. There is less suppression of vasopressin release at low plasma osmolarity in the presence of AngII (e.g. in hyponatremic dehydration) than in states with elevated blood pressure and low AngII (e.g. water overload), thus integrating homoeostasis of volume and osmolality.

Of note, AngII is also involved in thirst perception and there are some data suggesting that the use of angiotensin converting enzyme inhibitors may ameliorate thirst perception in dialysis patients [14].

Vasopressin receptor

There are different types of vasopressin receptors, the most common one being AVPR1a, present mostly in the vascular smooth muscle cell, where it mediates vasoconstriction. The AVPR2 receptor is primarily expressed in the connecting tubule and collecting duct, although observations in patients with X-linked NDI (i.e. loss-of-function mutations in AVPR2) demonstrate a role also in the vasculature, where it mediates vasodilatation and the release of factor VIIIc and von-Willebrand factor [15].

AVPR2 is a G-protein coupled receptor, which localizes to the basolateral membrane of principal cells in the collecting duct (Figure 1). Upon activation AVPR2 stimulates adenylyl cyclase and thus the production of cyclic adenosine monophosphate (cAMP). This, in turn, activates protein kinase A (PKA), which phosphorylates AQP2 molecules, leading to insertion of these molecules in the apical membrane of the principal cells [16]. The cAMP molecules are metabolized by phosphodiesterases in the cell to prevent ongoing activation.

Recently, it was shown that AVPR2 is also expressed on apical cilia, where it also colocalizes with adenylyl cyclase [17]. This ciliary localization could help explain the urinary concentrating defect often seen in patients with ciliopathies. Indeed, renal epithelial cells from patients with Bardet-Biedl syndrome were shown to not respond to luminal vasopressin administration [18]. However, the clinical relevance of this apical vasopressin pathway has yet to be clearly established.

The most obvious other important molecule for water permeability in the connecting tubule and collecting duct is AQP2, the final player in the signaling cascade. The importance of this water channel is clearly highlighted by the fact that loss-of-function mutations lead to the autosomal forms of NDI [10].

Aquaporines

Once AQP2 is inserted into the apical membrane, water can pass the epithelial cell layer from the tubular lumen into the interstitium following the osmotic gradient. On the basolateral side of the prinicipal cells the water channels AQP3 and AQP4 provide the exit pathway (figure 1). Whilst they are constitutively expressed, AQP3 appears to be more relevant, at least in mice, as genetic ablation of this channel leads to a severe NDI phenotype, whereas loss-of-function of AQP4 results only to mildly impaired urinary concentrating ability [19].

AVPR2-independent effects on water permeability

Whilst AVPR2 clearly is the most important pathway for insertion of AQP2 into the apical membrane, there are several other pathways that can influence this process and may be exploitable for therapeutic gain.

Calcium Sensing Receptor

AVPR2 is not the only receptor in the principal cell that can raise cAMP. On the apical side of principal cells is also expressed another G-protein-coupled receptor, the calcium-sensing receptor CaSR. Animal experiments demonstrate that raised luminal calcium concentrations blunt the antidiuretic response of AVP, i.e. that the CaSR inhibits movement of AQP2 into the membrane [20]. It has been speculated that this might be a protective mechanism against stone formation. Moreover, this pathway may be involved in some of the secondary forms of NDI, seen in disorders with hypercalciuria, such as Bartter syndrome [21, 22]. However, luminal calcium concentrations in concentrated urine are typically much higher than those seen in the dilute urine of patients with

secondary NDI, raising questions about the clinical relevance of this pathway [23, 24].

Secretin receptor

Another G-protein coupled receptor expressed in the collecting duct with the potential to increase cAMP is the secretin receptor [25, 26]. Indeed, mice deleted for the secretin receptor show an impaired urinary concentrating ability with decreased Aqp2 expression [26].

Secretin is a gastrointestinal signaling peptide and its role in the kidney is unclear. Nevertheless, there is emerging evidence that secretin and perhaps oxytocin are involved in the regulation of water permeability in the collecting duct [27].

Hypokalaemia

Another potential explanation for the presence of a secondary NDI in Bartter syndrome has been hypokalemia. Indeed, potassium deprivation in rats is associated with polyuria and decreased Aqp2 expression, through yet unidentified mechanisms [28]. But yet again, the clinical relevance in man is unclear, considering that patients with Gitelman syndrome have hypokalemia, but an apparent normal urinary concentrating ability [23].

Lithium

Lithium is probably the most common cause of NDI, although rarely seen in pediatrics. The molecular mechanisms of the Li+-related urinary concentration defect involve a dysregulation of the aquaporin system in principal cells of the collecting duct. ENaC is crucial as the luminal entry route for intracellular Li+ accumulation. The basolateral exit route is not clearly identified, but some evidence suggests Na+/H+ exchanger 1 (NHE1) as a potential candidate. Li+ promotes polyuria mainly by counteracting the intracellular vasopressin signaling, although the exact mechanisms remain to be elucidated [29]. Recent mouse data suggests that lithium mainly affects water permeability in the collecting duct, as mice with a segment specific knock-out in the connecting tubule are just as susceptible to lithium toxicity, as control mice [30].

Prostaglandins

The variety of prostaglandins and their receptors and the resultant divergent actions makes understanding their role in urinary concentration difficult. Prostaglandine E2 (PGE2) was noted early on to antagonize vasopressin in the collecting duct by inhibiting cAMP formation. Conversely, inhibition of prostaglandine synthesis by indomethacine enhances the effect of vasopressin [31, 32]. Recently, data for the role of PGE2 in urinary concentration were published that conflict with the earlier results of an antagonism between PGE2 and vasopressin [33]: these data show a vasopressin-independent direct increase in cAMP and consequent Aqp2 phosphorylation and membrane insertion after treatment with PGE2 or related agonists for the E-prostanoid receptors EP2 or EP4. Indeed, rats treated with a blocker of Avpr2 develop a pharmacologically induced NDI and the phenotype could be significantly

alleviated by treatment with an EP2 agonist [33]. Similarly, the NDI in mice deleted for the *Avpr2* gene could be ameliorated by selective EP4 agonists [34]. At this point it is unclear, whether these apparently conflicting results with regards to the benefits of prostaglandin synthesis inhibitors and prostaglandin receptor agonists can be explained by differential actions of the various prostaglandins on their receptors. Yet these animal data suggest that selective targeting of the EP2 and 4 receptors may provide a novel mode for the treatment of X-linked NDI.

Clinical aspects of NDI

So, how does this knowledge of the physiology of urinary concentration help us understand and manage NDI?

Clinical manifestations

Affected patients typically present in the first year of life with failure-to-thrive, vomiting and hypernatremic dehydration. Biochemistries obtained at the time show an inappropriately dilute urine (Uosm <Posm) in the context of elevated plasma sodium/osmolality, which establishes the diagnosis of DI. The nephrogenic aspect is proven, if there is no response to 1-Desamino-8-D-Arginine Vasopressin (DDAVP). However, some other disorders, such as Bartter syndrome can present similarly and should be considered if there are unusual features, such as a history of polyhydramnios or hypokalemia [23]. Molecular testing should establish a definitive diagnosis in the majority of cases, which is important, as treatment is different: patients with NDI typically receive thiazides,

which could be dangerous in Bartter syndrome, as it would compound the impaired tubular sodium reabsorption.

Diagnostic difficulties can also arise in those patients with milder mutations, that retain some functionality of AVPR2; so-called partial NDI [35]. Urine osmolality either spontaneously or after DDAVP can be above that of plasma, consistent with some urinary concentrating ability, but are below the normal response to DDAVP (Uosm>800 mosm/kg). Again, molecular diagnosis can be helpful, as several of these milder mutations are known [36]. The presence of some residual receptor function allows the use of DDAVP for treatment purposes, by stimulating AVPR2 with supraphysiologic doses of the agonist [35].

Clinical manifestations typically become easier to manage beyond infancy, when fluid and caloric intake can be separated and the patient can self-regulate fluid intake. Growth is usually within the normal range. However, life of these patients is clearly marked by the polyuria (10-12 l/d in adults) and some problems, such as nocturnal enuresis or urinary obstruction are amplified by it [37].

Previously reported mental impairment in patients with NDI has been attributed to recurrent episodes of hypernatremic dehydration and is fortunately rarely seen with early diagnosis and good management [38, 39].

Treatment

Diet

The mainstay of treatment is still diet modification. The total urine volume excreted depends on the osmotic load and this can be roughly estimated by the following formula: twice the millimolar amount of sodium and potassium (to account for the accompanying anions) plus protein (g) times 4 [40]. A reasonable

goal is a diet containing about 15 mosm/kg/d. A child with a urine osmolality of 100 mOsm will need a fluid intake of 150 ml/kg/d to be able to excrete that load, which is achievable. This demonstrates the importance of limiting salt intake, as 12 mosm/kg/d are already provided by the recommend daily protein intake of 3g per kg bodyweight.

Thiazides

The use of a diuretic in a polyuric disorder appears at first glance counterintuitive, but does make physiologic sense. The successful use of thiazides in NDI with a subsequent increase in urine osmolality and concomitant decrease in urine output was first reported in 1959 [41, 42]. Thiazides inhibit reabsorption of sodium and chloride in the DCT (part of the urinary dilution mechanism-see above) and thus increase the salt concentration and osmolality of the urine. The increased salt losses decrease intravascular volume with a subsequent up-regulation of proximal tubular reabsorption of salt and water. Consequently, less volume is delivered to the collecting duct and lost in the urine [43].

Indomethacine

The apparent antagonism between vasopressin and PGE2 [44] led to trials of indomethacine in NDI, which demonstrated a modest reduction in urine volume, which was additive to the effect of thiazides alone [45-47]. Since then, prostaglandine synthesis inhibitors (NSIAD) are commonly used in the treatment of NDI, yet it is unclear whether the therapeutic effect is actually mediated in the collecting duct or rather via the stimulatory effect of NSIAD on

proximal epithelial transport. Prostaglandins are saluretic by impairing proximal epithelial salt reabsorption [48]. Therefore, inhibition of prostaglandins enhances proximal sodium re-uptake and thus water reabsorption, as the proximal tubule is water permeable. In this way, the mechanism of NSIAD in urine volume reduction is actually very similar to thiazides.

New potential treatment options

The improved understanding of the molecular basis of renal water handling has opened up some intriguing new ways to potentially treat NDI. One of these has already demonstrated efficacy in a clinical trial [49].

Vaptans/Chaperones

The majority of patients with NDI have mutations on AVPR2 and these are overwhelmingly missense in nature leading to misfolding and consequent retention of the otherwise functional receptor in the endoplasmatic reticulum [50]. With advent of the AVPR2 blockers, it was recognized that these drugs, when membrane permeable, could bind to the mutant receptor and stabilize it sufficiently to allow proper routing to the cell surface [51]. The problem, of course, is that these drugs are blockers of the receptor and the higher the affinity to the receptor, the better the stabilization and membrane expression, but less likely the drug is to diffuse off and provide the binding site for vasopressin. Conversely, a drug with less affinity provides less stabilization and membrane expression, but will diffuse off more easily. In the end, those drugs with medium affinity seemed to work best and a clinical trial in patients with suitable mutations indeed showed a modest reduction in urine output [49].

PGE agonists

The recent data on AVPR2-independent activation by agonists for the EP2 and EP4 receptors raises the intriguing possibility of a new therapeutic pathway for patients with X-linked NDI [33]. However, at this point it is unclear how to resolve the contradiction between giving prostaglandins to reduce urine output, when the blockade of their synthesis by indomethacine has actually proven clinical efficacy. And unfortunately, Fenton et al do not address this apparent conundrum at all in their paper. Could it be that different pathways in the complex system of the various prostaglandins and their receptors mediate the beneficial effects of PGE2 and NSIADs, respectively? In that case a clever combination of specific agonists and blockers could combine the efficacy of these pathways. Yet, clearly, more research is needed to ensure that the PGE2 effect is not just observed in mice, but also in humans.

Secretin

Stimulation of the secretin receptor may be yet another possibility to increase cAMP in the principal cells of the collecting duct independent of AVPR2 and thus provide a potential treatment for X-linked NDI. Ideally, one would want to use a receptor agonist that is specific for the kidney to avoid the gastrointestinal and other extrarenal effects of this hormone. Moreover, as with the prostaglandins above, existing evidence is only from animal experiments and confirmation for the efficacy with respect to increasing water permeability in humans is missing.

Statins

Statins are well known and commonly used inhibitors of cholesterol biosynthesis. New evidence suggests that they also have off-target effects, including modulation of the actin cytoskeleton, which in turn affects AQP2 trafficking [52]. In a rat model of (central) DI, high-dose simvastatin increased membrane expression of Aqp2, associated with increased urine osmolality and decreased urine output [53]. Again, human data are missing, although it is quite possible that some patients with NDI may have been prescribed statins at some point.

Phosphodiesterase inhibitors

Inhibition of phosphodiesterases to prevent breakdown of cAMP has been another approach to try to ameliorate the polyuria. Specific inhibitors of the phosphodiesterase type 3 isoenzyme are available: rolipram and cilostamide. Indeed, in a mouse model of NDI, rolipram increased cAMP concentration in collecting duct cells [54]. Unfortunately, application in humans resulted in no change in urine osmolality [55]. Yet, recent data from a mouse model of autosomal dominant NDI suggests that rolipram may be effective in patients with heterozygous frame-shift mutations in the carboxy-terminus of AQP2 [56].

Conclusion

NDI provides an excellent example of how the study of a rare disease can provide important insight into human physiology and how in turn, this knowledge can be harnessed to develop new and specific treatments. For now, no “golden bullet” has been found to completely treat symptoms and complications, but there are

exciting new potential treatments that may improve management of these patients in the future.

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Figure 1: Schematic of a principle cell in the collecting duct

Shown are the key players involved in water reabsorption in the collecting duct. Whereas the water channels AQP3 and AQP4 are constitutively present in the basolateral side, the insertion of AQP2 into the apical membrane is regulated. Key signal for the insertion of AQP2 into the apical membrane is phosphorylation by protein kinase A (PKA), which, in turn, is activated by cyclic AMP (cAMP), produced by adenylyl cyclase, present on the basolateral side. Adenylyl cyclase is activated by the G-protein Gαs, released by AVPR2. Other G-protein coupled receptor, such as EP2, EP4 and the secretin receptor may also contribute.