P2Y₂ receptors and water transport in the kidney

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Abstract The kidneys play a critical role in the maintenance of water homeostasis. This is achieved by the inherent architecture of the nephron along with the expression of various membrane transporters and channels that are responsible for the vectorial transport of salt and water. The collecting duct has become a focus of attention by virtue of its ability to transport water independent of solutes (free-water transport), and its apparent involvement in various water balance disorders. It was originally

believed that the water transport capability of the collecting duct was solely under the influence of the circulating hormone, arginine vasopressin (AVP). However, during the past decade, locally produced autocrine and/or paracrine factors have emerged as potent modulators of transport of water by the collecting duct. Recently, much attention has been focused on the purinergic regulation of renal water transport. This review focuses on the role of the P2Y₂ receptor, the predominant purinergic receptor expressed in the collecting duct, in the modulation of water transport in physiological and pathophysiological conditions, and its therapeutic potential as a drug target to treat water balance disorders in the clinic. Studies carried out by us and other investigators are unravelling potent interactions among AVP, prostanoid and purinergic systems in the medullary collecting duct, and the perturbations of these interactions in water balance disorders such as acquired nephrogenic diabetes insipidus. Future studies should address the potential therapeutic benefits of modulators of P2Y₂ receptor signalling in water balance disorders, which are extremely prevalent in hospitalised patients irrespective of the underlying pathology.

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Molecular physiology of water handling by the mammalian kidney

Sixty percent of the human body by weight is water. The movement of water among the intracellular, extracellular and intravascular compartments and visceral cavities is very important for the proper function of the various organs. In

order to maintain water homeostasis, the human kidneys are equipped with the capacity to filter and reabsorb a large amount (~180 l) of water in a day. The reabsorption is achieved by aquaporin (AQP) water channels, which allow rapid movement of water across biological membranes, as well as by membrane transporters that are responsible for vectorial transport of solutes generating osmotic gradients. In addition, the inherent architecture of the nephrons, the functional units of the kidney, is critically important (Fig. 1). The ability of the mammalian kidney to absorb the bulk of the large amount of filtered water is due to coupling to the absorption of sodium and other solutes in the proximal nephron, which is very rich in AQP1 protein on both apical (brush border) and basolateral aspects of the cells. In this part of the nephron, 60–70% of the filtered solutes and water are reabsorbed into the blood. The part of the nephron from the tip of the loop of Henle to the

collecting duct is impermeable to water, but transports sodium out of the lumen (diluting segment). This creates the necessary osmotic gradients in the interstitium which are crucial for the osmotic reabsorption of water in the adjacent collecting duct.

Although the collecting duct system accounts for the reabsorption of only a small fraction of filtered water (~15%), this is very important for the maintenance of water homeostasis. First, unlike the proximal nephron, the reabsorption of water in the collecting duct is regulated independently of sodium reabsorption, by hormones and autocrine/ paracrine agents. Second, if the collecting duct system fails, there are no other tubular segments downstream which can compensate. Third, since the collecting duct system starts beyond the juxtaglomerular apparatus and macula densa, unlike failures in the more proximal part of the nephron, failure in the collecting duct system is exempt from sensing by the tubuloglomerular feedback mechanism. In addition, most forms of nephrogenic diabetes insipidus (NDI), whether acquired or hereditary, are due to defect(s) in the collecting duct system. In view of these facts, the collecting duct system has become the focus in recent years for intense research by renal physiologists and pathophysiologists, including our group.

Fig. 1 Architecture of rat nephron and collecting duct showing segmental localization of major transporters and channels that play critical roles in water and solute reabsorption (modified from [55]). *AQP1*, *AQP2*, *AQP3* and *AQP4* Aquaporin water channel isoforms 1 through 4, *NHE3* sodium–hydrogen exchanger isoform 3, *UT-A1* and *UT-A2* urea transporter isoforms A1 and A2, *BSC1* bumetanide-sensitive cotransporter-1, *ROMK* renal outer medullary potassium channel, *TSC1* thiazide-sensitive cotransporter-1, *ENaC* epithelial sodium channel

Cell biology of vasopressin action on collecting duct

The collecting duct system determines the concentration of the final voided urine. Arginine vasopressin (AVP), acting through the V_2 receptor, a G-protein-coupled receptor, in the collecting duct principal cell, activates membrane-bound adenylyl cyclase to produce cyclic AMP (cAMP) as a second messenger. The cellular effects of cAMP are connected to the activation of protein kinase A, which phosphorylates various key proteins and thus increases the water permeability of the principal cells of the collecting duct (Fig. 2) [1, 2].

AVP has both short- and long-term effects on collecting duct water permeability. The short-term effect involves the translocation of AQP2 water channels from a pool of subapical vesicles to the apical plasma membrane [3]. The apical plasma membrane is the rate-limiting barrier for the transepithelial water movement, as AQP3 and AQP4 water channels are constitutively expressed on the basolateral domain of the collecting duct principal cells under normal conditions (Fig. 2). The long-term effect involves an increase in the absolute amount of AQP2 mRNA and protein that result from increased transcription and translation of the AQP2 gene. Increased cyclic AMP generated by AVP action leads to protein-kinase-A-mediated phosphorylation and activation of CREB, which binds to CRE (cAMP response element) in the AQP2 promoter. AQP2 gene

Fig. 2 Schematic representation of the major G protein-coupled receptors and the channels involved in regulated reabsorption of water and sodium in the principal cell of the collecting duct. The scheme also depicts the major points of interaction between mutually opposing cyclic AMP and phosphoinositide signalling pathways through which these receptors act (modified from [16] and used with permission). For details refer to the text. *AVP* Arginine vasopressin; *ET* endothelin, *PGE2* prostaglandin E₂, *V2-R* vasopressin V2 receptor, *ET-R* endothelin receptor, *EP3-R* prostanoid receptor type 3, *AC* adenylyl

cyclase, *PLC* phospholipase C, *Gs* stimulatory G protein, *Gi* inhibitory G protein, *cAMP* cyclic AMP, *PKA* protein kinase A, *PKC* protein kinase C, *PDE* phosphodiesterase, *IP3* inositol triphosphate, *ER* endoplasmic reticulum, *CaM* calcium calmodulin, *DAG* diacyl glycerol, *cPLA2* cytosolic phospholipase A₂, *AQP2*, *AQP3* and *AQP4* aquaporin water channel isoforms 2, 3 and 4, *ENaC* epithelial sodium channel, α , β , γ subunits, *Aldo* aldosterone, *PIP2* phosphatidyl-inositol 4,5-bisphosphate, *PI3-K* phosphoinositide 3-kinase

transcription is ultimately activated via both CRE and AP1 (Activator Protein-1) sites in the AQP2 promoter [4–6].

Non-AVP regulators of collecting duct function

Apart from AVP, a variety of autocrine and paracrine agents, such as prostaglandin E₂ (PGE₂), endothelin and extracellular nucleotides (ATP/UTP), can regulate collecting duct water transport [7–14]. Acting through their respective receptors, and the associated phosphoinositide signalling pathway, these agents decrease AVP-stimulated osmotic water permeability in the collecting duct (Fig. 2). In the collecting duct, cAMP and phosphoinositide systems are mutually opposing signalling pathways (Fig. 2). There are specific points of interaction between these two pathways. Figure 3 illustrates the potential sites in the AVP signalling pathway that can be regulated. In general, AVP exerts a tonic effect on the collecting duct, while the non-AVP regulators, including PGE₂, endothelin or ATP, exert an opposing action, largely through a reduction of cAMP levels. In summary, cAMP levels and water permeability are tightly regulated by a balance between AVP and non-AVP regulators.

Physiology of the P2Y₂ receptor in the collecting duct

The intracellular concentrations of ATP are between 3 and 5 mM. Being a highly polar molecule, ATP cannot exit cells by diffusing passively through the lipid bilayer of the cell membrane. However, virtually all cells, including renal cells, release nucleotides into the extracellular milieu through specific membrane transporters in a regulated fashion [15, 16; and see article by Praetorius and Leipziger [17] in this Special Issue]. When extracellular ATP and other nucleotides reach even low micromolar concentrations locally, they stimulate a variety of P2 receptors, eliciting short- and long-term biological effects. In recent years, the potential roles of extracellular nucleotides in the regulation of renal tubular transport, especially salt and water, through P2 receptors are increasingly being recognised [15–21].

P2 receptor signal transduction is tightly controlled by a narrow range of extracellular concentrations of nucleotides, the latter being regulated by control of exocytosis or specific transporters, as well as by rapid enzymatic hydrolysis of released nucleotides [22]. Studies conducted by us and by others have documented that the collecting duct system is capable of releasing nucleotides [15, 16],

Fig. 3 Sequence of intracellular events leading from the binding of AVP to its V₂ receptor (*top*) to the insertion of AQP2 water channels into the apical membrane (*bottom*). The potential pre-cAMP formation sites that can be disrupted are (a) activation of inhibitory G protein (Gi) by the increased activity of PKC brought about by diacylglycerol (DAG) formed as a result of stimulation of the PI signalling pathway by agents such as PGE₂ and ATP, and (b) decreased activity of adenylyl cyclase (AC) isoforms 5 and 6 expressed in the medullary collecting duct. The potential post-cAMP formation sites which can be disrupted are (a) rapid hydrolysis of cAMP by phosphodiesterases (PDE; isoforms III and IV) by calcium-calmodulins activated through the PI signalling pathway by agents such as PGE₂ and ATP and (b) decreased activity of PKA, resulting in decreased protein phosphorylation and membrane insertion of AQP2

and the enzymes that hydrolyze the released nucleotides, such as NTPDases (nucleoside triphosphate diphosphohydrolases) and NPPs (nucleotide pyrophosphatases) are expressed in the kidney and/or in the vicinity of the collecting duct in the medulla [23, 24]. The expression and functional roles of ectonucleotidases in the kidney are dealt with elsewhere in this Special Issue (see article by Shirley et al. [25]); hence, we will not elaborate on ectonucleotidases here.

The P2Y₂ receptor (originally designated as P2u purinoceptor) is a G protein-coupled extracellular nucleotide receptor with an agonist potency order of UTP ≥ ATP > ATPγS >> 2-MeS-ATP. Pharmacological, functional and molecular methodologies localised the P2Y₂ receptor to the medullary collecting duct [26, 27]. Currently, the P2Y₂ subtype is the predominant P2Y receptor whose expression in native collecting duct of rat or mouse has been established by both molecular and functional approaches. However, the expression of other P2Y receptors has been reported in cultured cell lines of renal origin, using molecular and/or

functional methodologies [16, 28]. Recently, Unwin's group showed that collecting ducts of sodium-restricted rats have significant amounts of P2Y₄ and P2X₄ receptor mRNA, whereas the mRNA expression of these receptors in sodium-replete rats is insignificant. [29]. Hence, it appears that other subtypes of P2Y receptors, which may not be detectable in the collecting duct under normal conditions, may express significantly in pathophysiological states. In contrast to the murine collecting duct, functional studies in rabbit cortical collecting tubule (CCT) revealed the apparent expression of both P2Y₂ and P2Y₁ receptors [10]. Since pharmacological and/or functional characterization of the expression of multiple forms of P2Y receptors is a complex issue, additional molecular studies need to be performed to support these findings.

It is important to note that the activation of P2Y₂ receptors induces at least two signalling systems that affect collecting duct water transport. First, activation of the P2Y₂ receptor per se down regulates AVP-stimulated water transport in a protein kinase C-dependent and inhibitory G protein (Gi)-mediated manner [10, 11]. Secondly, activation of the P2Y₂ receptor causes the production and release of PGE₂ by the medullary collecting duct [30]. We have demonstrated that P2Y₂ receptor-mediated PGE₂ release is markedly enhanced in physiological polyuria induced by water loading, and blunted in oliguria caused by water deprivation or chronic dDAVP (V₂ receptor-specific analogue of AVP) infusion in rats [31, 32].

PGE₂ antagonises AVP-stimulated water permeability in the medullary collecting duct [7, 9], an effect that is partly due to activation of EP (E-prostanoid)₃ receptor-mediated retrieval of AQP2 from the apical membrane [13]. In addition, PGE₂ can chronically elevate phosphoinositides and thus potentially reduce the cAMP levels (Fig. 2).

Kishore, Knepper and Nielsen were the first group of investigators to generate a peptide-derived polyclonal antibody to the P2Y₂ receptor and to immunolocalise the receptor protein in rat kidney and lung [27]. The receptor protein is expressed on both apical and basolateral domains of rat medullary collecting duct [27]. While Kishore and Knepper, as well as others, have demonstrated that the basolateral P2Y₂ receptor is involved in the inhibition of AVP-induced water transport in medullary collecting duct [10, 11, 14], recent studies have demonstrated a role for the apical P2Y₂ receptor in the inhibition of amiloride-sensitive sodium transport via the epithelial sodium channel (ENaC) in the collecting duct [19, 33–35]. P2-receptor-mediated regulation of sodium transport in the collecting duct is dealt with elsewhere in this Special Issue (see articles by Bailey and Shirley [36] and Wildman et al. [37]), and so we will not elaborate this aspect here; instead we will focus on regulation of water transport by the P2Y₂ receptor. Thus, by

- E. Chronic effect of elevated circulating AVP levels on purinergic-mediated PGE₂ production: in normal rats chronically infused with high doses of dDAVP and in water-deprived rats (with raised circulating AVP levels), purinergic-mediated ex vivo PGE₂ production by medullary collecting ducts is significantly decreased [31, 32]. This effect is blunted in NDI, since purinergic-mediated ex vivo prostanoid production by medullary collecting ducts is actually increased, despite the fact that circulating AVP levels are either normal or elevated [43].

Potential role of the P2Y₂ receptor in acquired NDI

Diabetes insipidus (DI) causes considerable morbidity and even mortality, in addition to significant social inconvenience. Patients with DI have an elevated risk of dehydration, hypernatraemia, alterations in consciousness, and haemodynamic instability from hypovolaemia [44, 45]. Central diabetes insipidus is due to defects in AVP synthesis or release, whereas NDI is due to defects in the kidney collecting duct, or to reduced medullary osmolality, making the collecting duct non-responsive to the action of circulating AVP. Familial NDI, usually due to mutations in the genes coding for the vasopressin V₂ receptor or the AQP2 water channel, is relatively rare. It presents in children, with failure to thrive and hypernatraemic dehydration, and persists in adults resulting in lifelong disability due to only partially effective treatments. Acquired NDI, the more common form, can occur at any age. Patients with acquired NDI present with polyuria, polydipsia and a reduced ability to concentrate urine, and are unresponsive to AVP treatment [44, 45]. The most common cause of acquired NDI is chronic administration of lithium for the treatment of bipolar disorders [46]. In addition to its long-standing and proven beneficial effect in bipolar disorders, lithium is recently emerging as a potential treatment for acute brain injury as well as chronic neurodegenerative diseases [47–49]. Other drugs that are capable of inducing NDI are colchicine, methoxyflurane, amphotericin B, gentamicin, loop diuretics and demeclocycline. In addition to drugs, acquired NDI occurs as a result of certain diseases. These include, but are not limited to, chronic kidney diseases, hypokalaemia, hypercalcaemia, sickle cell disease, post-obstructive uropathy (due to benign prostatic hyperplasia or cancer), reflux nephropathy, renal dysplasia, cystic kidney disease and low protein diets. Despite these different aetiologies, the hallmark of all forms of acquired NDI is a marked decrease in the protein abundance of AQP2 even in the setting of normal or elevated circulating AVP levels [50]. Thus, in acquired NDI, the collecting duct is resistant to AVP action.

In view of the clinical importance of lithium as a potent drug for the treatment of bipolar disorders and chronic neurodegenerative diseases such as Alzheimer's, Parkinson and Huntington diseases, we have been studying the molecular physiology of the medullary collecting duct in lithium-induced NDI. Previous studies have attributed the AVP resistance of the collecting duct in lithium-induced NDI to increased production of renal PGE₂ [51, 52]. As described above, PGE₂ is a potent antagonist of AVP action on the collecting duct. Accordingly, administration of inhibitors of cyclooxygenases (COX) that decrease PGE₂ biosynthesis, such as indomethacin, ameliorates the polyuric condition of lithium-induced NDI (Fig. 5). Since the P2Y₂ receptor is known to antagonise the effect of AVP on the collecting duct, and can mediate increased production of PGE₂ by the collecting duct, we hypothesised that the P2Y₂ receptor may be involved in the genesis of polyuria in lithium-induced NDI. We found that in rats subjected to lithium-induced NDI, stimulation of medullary collecting duct by ATPγS results in markedly enhanced production of PGE₂, as compared with that seen in normal rats. Since previous studies in our laboratory showed that only ATPγS and UTP, but not ADP, are capable of inducing the production of PGE₂ by medullary collecting duct [30], it

Fig. 5 Potential utility of P2Y₂ receptor antagonists to block the production of PGE₂ in acquired NDI. The availability of free arachidonic acid is the rate-limiting step in the biosynthesis of PGE₂. Phospholipases, which release arachidonic acid from membrane phospholipids, are activated by calcium or protein kinase C (PKC) or mitogen-activated protein kinases (MAPK). Once arachidonic acid is released, either cyclooxygenase (COX)-1 or COX-2, or both, may be involved in the synthesis of prostaglandin E₂ (PGE₂)

is logical to presume that the observed effect is due to the P2Y receptor family, most probably the P2Y₂ subtype, although involvement of other P2Y receptors, such as the P2Y₄ subtype, in acquired NDI cannot be ruled out at this stage. This apparent increase in the sensitivity of P2Y₂ receptors in lithium-induced NDI is associated with upregulation of PGE₂ synthesizing machinery, exemplified by increased expression of mRNA for cytosolic phospholipase A₂, COX-1 and COX-2 [43]. At present, our data suggest a potential role for the P2Y₂ receptor in the genesis of polyuria in lithium-induced NDI. This notion has been substantiated by studies using P2Y₂ receptor knockout mice. When subjected to lithium feeding for 2 weeks, the P2Y₂ receptor null mice were markedly resistant to the development of lithium-induced polyuria, with about 50% lower urine volume and significantly higher urine osmolalities as compared with wild-type mice subjected to a similar regimen. Terminal serum osmolalities were the same in both groups, indicating that none of the animals were dehydrated under the experimental conditions [53]. If confirmed by more extensive and long-term studies, these novel findings provide a rationale to develop a new class of drugs for the treatment of lithium-induced NDI which specifically target the P2Y₂ receptor and desensitise it, thereby counteracting the AVP-resistant state in NDI. This approach may prove safer as compared to the current approach of directly inhibiting the activities of cyclooxygenases in lithium-induced NDI (Fig. 5).

Another commonly encountered acquired NDI condition among ageing men is post-obstructive uropathy due to benign prostatic hyperplasia (BPH) or cancer. About 300,000 surgical procedures, mostly transurethral resection of prostate, are performed each year in the USA for BPH. Release of the obstruction is often associated with diuresis, despite persistent decreases in renal cortical perfusion and glomerular filtration rate [54]. Although post-obstructive diuresis is a self-limiting condition, the transient loss of fluid can result in debilitating conditions in elderly patients, who often exhibit an impaired thirst mechanism [55, 56]. Increased production of renal PGE₂ is also implicated in the genesis of the polyuria of post-obstructive uropathy, which responds to treatment with inhibitors of PGE₂ biosynthesis [57]. In view of this, in parallel with our experiments with lithium-induced NDI, we also examined the potential involvement of P2Y₂ receptors in the genesis of polyuria in a rat model of post-obstructive uropathy. Our preliminary results indicate that in rats with post-obstructive uropathy, agonist-stimulation of P2Y₂ receptors in the medullary collecting duct results in markedly enhanced production of PGE₂ when compared with sham-operated control rats [43].

Based on the preliminary results from these two NDI models, as well as the published data, we have depicted in

Fig. 4, right panel, the changes in the interactions among AVP, prostanoid and purinergic systems in acquired NDI.

Future perspectives

The potential involvement of P2Y₂ receptors in water transport in the medullary collecting duct opens the possibility of exploring the utility of P2Y₂ receptor agonists and antagonists for the treatment of a variety of water balance disorders. These include water-losing disorders such as acquired NDI, as well as water-retaining conditions or disorders, such as pregnancy, hepatic cirrhosis, nephrosis and hypertension. For example, specific antagonists of P2Y₂ receptors could be used to overcome the AVP resistance in acquired NDI, as opposed to the current usage of a combination of a thiazide with a potassium-sparing diuretic or prostaglandin synthesis inhibitor (indomethacin or other COX-2 inhibitors). Thiazide diuretics should be used with caution in lithium-induced NDI, as they reduce the renal excretion of lithium, potentially resulting in lithium intoxication; while indomethacin, a non-steroidal anti-inflammatory drug (NSAID), increases the risk of gastrointestinal disorders and bleeding. In addition, recent reports indicate that the use of NSAIDs, especially COX-2-specific inhibitors (celecoxib and rofecoxib), in patients on lithium therapy is associated with increased serum lithium concentrations [58, 59]. Currently, the safety of long-term use of COX-2 inhibitors with their cardiovascular complications is in question and their future is uncertain. Replacement of the current side-effect-prone drugs with new ones based on improved understanding of molecular pathophysiology in NDI might result in improved efficacy and fewer side effects. In this context, targeting the P2Y₂ receptor with specific antagonists may prove to be a better and safer alternative (Fig. 5).

Specific agonists of P2Y₂ receptors may act on the collecting duct as diuretics or aquaretics in water-retaining conditions such as pregnancy, cirrhosis, nephrosis and cardiac failure, conditions which can potentially lead to hyponatraemia if not corrected promptly. Conditions such as pregnancy, cirrhosis and cardiac failure apparently cause water retention and dilutional hyponatraemia by a unified mechanism that involves arterial vasodilatation due to increased activity of nitric oxide (NO), haemoxygenases or prostaglandins, leading to arterial underfilling. The latter stimulates the non-osmotic release of AVP, resulting in increased expression and apical membrane targeting of AQP2 in the renal collecting duct, leading to water retention. To disrupt this pathway, recently introduced specific antagonists of vasopressin V₂ receptors, the so called “aquaretics”, are proving to be promising agents to increase “free-water” excretion in hyponatraemic states [60,

61]. In this context, the potential utility of P2Y₂ receptor agonists in water retention states that may result in hyponatraemia is worth exploring. Furthermore, because of the potential diuretic and natriuretic effects of these agents, the utility of P2Y₂ receptor agonists should also be explored in hypertension.

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