ATP and adenosine in the local regulation of water transport and homeostasis by the kidney

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Rieg T, Vallon V. ATP and adenosine in the local regulation of water transport and homeostasis by the kidney. Am J Physiol Regul Integr Comp Physiol 296: R419–R427, 2009. First published November 19, 2008; doi:10.1152/ajpregu.90784.2008.—Regulation of body water homeostasis is critically dependent on the kidney and under the control of AVP, which is released from the neurohypophysis. In the collecting duct (CD) of the kidney, AVP activates adenyl cyclase via vasopressin V₂ receptors. cAMP-dependent activation of protein kinase A phosphorylates the water channel aquaporin-2 and increases water permeability by insertion of aquaporin-2 into the apical cell membrane. However, local factors modulate the effects of AVP to fine tune its effects, accelerate responses, and potentially protect the integrity of CD cells. Nucleotides like ATP belong to these local factors and act in an autocrine and paracrine way to activate P₂Y₂ receptors on CD cells. Extracellular breakdown of ATP and cAMP forms adenosine, the latter also induces specific effects on the CD by activation of adenosine A₁ receptors. Activation of both receptor types can inhibit the cAMP-triggered activation of protein kinase A and reduce water permeability and transport. This review focuses on the role and potential interactions of the ATP and adenosine system with regard to the regulation of water transport in the CD. We address the potential stimuli and mechanisms involved in nucleotide release and adenosine formation, and discuss the corresponding signaling cascades that are activated. Potential interactions between the ATP and adenosine system, as well as other factors involved in the regulation of CD function, are outlined. Data from pharmacological studies and gene-targeted mouse models are presented to demonstrate the in vivo relevance to water transport and homeostasis.

aquaporin-2; cAMP; collecting duct; vasopressin; cell volume

WATER IS THE MOST ABUNDANT molecule in the human body. The maintenance of water balance is dependent on water intake, initiated by the sensation of thirst, and the regulation of water excretion by the kidneys. Whereas all nephron segments contribute to various extents to water homeostasis, it is primarily the collecting duct (CD) system in which the reabsorption of 5–10% of the filtered water is regulated and adjusted to meet bodily needs. The antidiuretic hormone AVP is the primary regulator of water reabsorption in the CD system and critically involved in the regulation of water balance and stabilization of plasma osmolality (52). AVP is released from the neurohypophysis in response to small increases in plasma osmolality or greater reductions in circulating volume (52). As illustrated in Fig. 1, AVP acts on the CD via the G₂ protein-coupled vasopressin V₂ receptor (V₂R) to stimulate adenyl cyclase (AC) and thus the synthesis of cAMP. Increases in cAMP activate PKA, which phosphorylates the water channel aquaporin-2 (AQP2), with subsequent insertion of the channel into the apical plasma membrane. This allows water to be reabsorbed from the CD lumen into the cell and via basolateral AQP3 and AQP4 into the interstitium down its osmotic gradients. In addition, PKA-mediated phosphorylation of a cAMP response element binding protein (CREB protein) promotes its binding to DNA and increases the transcription of the AQP2 gene in the longer term (for a review, see Ref. 50).

Importantly, the AVP-mediated effects on water reabsorption are modulated by local factors. The functional importance of local factors may, in part, relate to the relatively long AVP half-life of 10–35 min (15). Since AVP-mediated free water reabsorption in the kidney is an important determinant of plasma osmolality, and thus the water distribution between extracellular and intracellular spaces, rapid adjustments in renal free water handling in response to changes in plasma osmolality are necessary. Local mechanisms may thus serve to tune CD water transport to bodily needs until responses in AVP levels can take over, as well as to fine adjust the effects induced by AVP. In addition, local factors may modulate AVP actions to protect CD cells from excessive perturbations in cell volume as a consequence of rapid changes in extracellular osmolality in the inner renal medulla. Increases in CD cell volume may release local factors and thus serve as a sensor of changes in plasma osmolality to accelerate AVP responses as well to maintain cell volume and integrity (see below).
Effects of P2Y and adenosine A1 receptor activation in native renal tissue

<table>
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<tr>
<th>Receptor</th>
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<tr>
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<td>CD, diverse</td>
<td>PLC ↑, [Ca&lt;sup&gt;2+&lt;/sup&gt;] ↑, PKC ↑, cAMP ↓, AVP-stimulated P&lt;sub&gt;i&lt;/sub&gt; ↓</td>
<td>Isolated, perfused CCD, OMCD, or IMCD of rabbit or rat (B) agonist profile (13, 19, 21, 42, 64)</td>
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<td>CCD</td>
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<td>Isolated, perfused rat or rabbit CCD, principal and intercalated cells (A and B) agonist profile (17, 64, 84)</td>
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<td>A&lt;sub&gt;1&lt;/sub&gt;R</td>
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<td>AVP-induced increases in P&lt;sub&gt;i&lt;/sub&gt; and cAMP formation ↓</td>
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A<sub>,</sub> apical; AVP, arginine-vasopressin; B, basolateral; [Ca<sup>2+</sup>], intracellular Ca<sup>2+</sup>; IP<sub>3</sub>, inositol phosphates; P<sub>i</sub>, osmotic water permeability; PLC, phospholipase C; PKC, protein kinase C; COX-1, cyclooxygenase 1; CD, collecting duct; CCD, cortical collecting duct; IMCD, inner medullary collecting duct; OMCD, outer medullary collecting duct.

Rouse et al. (64) (Table 1) were the first to report that ATP can modulate the AVP-stimulated P<sub>i</sub> in rabbit CCD by activation of the PLC/Ca<sup>2+</sup> signaling pathway, consistent with the expression of a functional purinergic receptor. Ecelbarger et al. (19) provided evidence for the existence of a P2Y<sub>2</sub>-like receptor in rat terminal IMCD using ATP, UTP, and ATPyS (a stable analog of ATP), which all increased [Ca<sup>2+</sup>], Cha et al.
Ecelbarger et al. (19) demonstrated that prior exposure of rat IMCD to indomethacin, an unselective COX inhibitor, attenuates [Ca\(^{2+}\)], responses to ATP, suggesting that PGE2 is facilitating or mediating the response in [Ca\(^{2+}\)]. Moreover, ATP-PS stimulated PGE2 release in freshly isolated IMCD preparations of hydrated rats, whereas the response was blunted in dehydrated rats (67). Finally, hypervolemic conditions are associated with greater P2Y2 receptor abundance in the renal medulla than hypovolemia (68). The purinergic-prostanoid system was speculated to represent a vasopressin-independent regulatory mechanism of IMCD function (68).

To further substantiate the above pharmacological evidence, we studied aspects of renal water transport in mice lacking P2Y2 receptors (P2Y2\(^{-/-}\)) (59). Studies in freshly isolated IMCD showed that ATP-PS enhanced the EC\(_{50}\) for the stimulation of cAMP formation by the V2R agonist, 1-desamino-8-D-arginine vasopressin (dDAVP) in wild-type (WT) mice, but not in P2Y2\(^{-/-}\) mice (59). To determine the ambient contribution of V2R activation on water transport in WT and P2Y2\(^{-/-}\) mice, acute responses to the V2R antagonist SR121463 were assessed. In WT animals, SR121463 increased urinary flow rate and electrolyte free water clearance (Cl\(_{\text{e-H2O}}\)) (Fig. 2, A and C). These changes in WT were associated with an increase in urinary PGE2 (Fig. 2B) but a reduction in urinary ATP (Fig. 3A), implying a tonic inhibition of PGE2 formation but stimulation of ATP release by V2R activation (the regulation of ATP release in CD is discussed in more detail below). In P2Y2\(^{-/-}\), SR121463 elicited a significantly greater diuresis and Cl\(_{\text{e-H2O}}\) compared with WT (Fig. 2, A and C), indicating greater basal reabsorption of fluid in the CD of P2Y2\(^{-/-}\), which was associated with greater renal AQP2 expression in the latter animals. SR121463 induced similar increases in urinary PGE2 in P2Y2\(^{-/-}\) and WT (Fig. 3A). Basal urinary excretion of fluid and Cl\(_{\text{e-H2O}}\) were not different between P2Y2\(^{-/-}\) and WT mice. This is proposed to be the consequence of a greater delivery of a more hypotonic fluid to the distal nephron segments in P2Y2\(^{-/-}\), which is the consequence of the integrated renal and blood pressure phenotype of these mice (59, 75). Under basal conditions, the hyperactivity of the V2R-AQP2 system reabsorbs the excess water resulting in urinary PGE2 in P2Y2\(^{-/-}\) and WT (Fig. 3A). Basal urinary excretion of fluid and Cl\(_{\text{e-H2O}}\) were not different between P2Y2\(^{-/-}\) and WT mice. This is proposed to be the consequence of a greater delivery of a more hypotonic fluid to the distal nephron segments in P2Y2\(^{-/-}\), which is the consequence of the integrated renal and blood pressure phenotype of these mice (59, 75). Under basal conditions, the hyperactivity of the V2R-AQP2 system reabsorbs the excess water resulting in
may relate to the delivery of greater amounts of hypotonic fluid to the distal nephron in these mice, they also presented greater urinary excretion of both PGE2 (Fig. 2A) and ATP in response to acute water loading (Fig. 3A).

Our unpublished work showed that treatment of WT mice with indomethacin (5 mg/kg ip) 30 min before an acute oral water load (3% of body weight) almost completely inhibited urinary PGE2 excretion and blunted the urine flow response in the 2-h experimental period (Fig. 2, A and B). Remarkably, urinary PGE2 excretion in P2Y2−/− was reduced to levels observed in WT mice without indomethacin treatment, and the responses in urinary flow rate and CF2-H2O were unaffected compared with untreated P2Y2−/− mice (Fig. 2, A and C). Whether this is due to incomplete COX inhibition in P2Y2−/− or involves indomethacin-insensitive PGE2 formation, needs to be determined, but it stresses potential differences in the quantitative or qualitative role of PGE2 in P2Y2−/−.

**P2X Receptors and CD Water Transport**

P2X receptors are ligand-activated ion channels with permeability to Na+, K+, Ca2+ and in a few cases Cl−, and in a cases P2X1, P2X2, P2X3, P2X4, P2X5, P2X6, and P2X7 channels have been described (40, 53). Studies in native rat tissue have immuno-localized P2X4, P2X5, and P2X6 in CD principal cells (74) and protein expression of P2X1, P2X4, and P2X6 was confirmed by mRNA expression of these receptors in microdissected CD (72). Preliminary studies in the *Xenopus* oocyte expression system proposed a functional interaction between AQP2 and P2X2 (82, 83), but the in vivo relevance remains to be determined. In conclusion, very little is known about the physiological relevance of P2X receptors for water transport in the kidney. The use of knockout mouse models should be helpful to unravel their functions.

**Nucleotide Release in CD**

Cellular ATP release is an essential and physiological relevant part of purinergic signaling in the kidney with the released ATP acting on P2 receptors in an autocrine/paracrine way (47, 59). Possible sources of extracellular ATP in the kidney include perivascular and peritubular nerve terminals, circulating erythrocytes, aggregating platelets, and renal endothelial and epithelial cells (8, 14). In human renal cortex, adrenergic stimulation was shown to release ATP from neuronal and nonneuronal sources (79). Under basal conditions, intracellular ATP concentrations are in the range of 3–5 mM (27). Thus, there is a big pool of intracellular ATP and just a fraction (resulting in values 100-fold lower than those inside the cell) needs to be released to mediate purinergic autocrine/paracrine signaling (1, 58). Once outside the cell, ATP has a half-life of minutes due to ecto-nucleotidases and other hydrolytic activities (23).

With regard to ATP release mechanisms in the kidney, evidence has been provided for a role of a maxi-anion channel (57) and in a few cases Cl−. In contrast to P2Y2 receptor inhibition (V2-R) but increased by acute WL. Increasing urinary flow rate alone is not a good predictor of ATP excretion. For further details, see text. B: a proposed positive relationship between the cell volume, manipulated by different maneuvers in WT and P2Y2−/− mice and urinary ATP excretion. We propose that feedback regulation of cell volume via cell volume-regulated ATP release is absent/reduced in P2Y2−/− mice resulting in greater ATP release. The influence is minimized by reducing water uptake by V2-R and maximized by water loading-induced cell swelling. All data are from Ref. 59.

Normal net fluid excretion in P2Y2−/−. Together, the data are consistent with the concept that P2Y3 receptor activation inhibits the cAMP-mediated effects of AVP on water transport in the CD (Fig. 1) (59).

How does the absence of P2Y2 receptors affect the response to acute water loading? Acute water loading induced similar increases in urine flow rate and CF2-H2O in WT mice as observed in response to V2-R blockade (Fig. 2, A and C). Likewise, water loading increased urinary PGE2 excretion (Fig. 2B). In contrast to V2-R blockade, however, water loading enhanced urinary ATP excretion (Fig. 3A). In P2Y2−/−, the water load-induced increase in CF2-H2O was similar to that in WT. However, a lesser suppression of the vasopressin cAMP and PGE2 system was sufficient in P2Y2−/− to increase CF2-H2O to the same extent as in WT, indicating that free water excretion was actually facilitated in the P2Y2−/− (59). Whereas this
are also largely unknown. Connexin (Cx) hemichannels have been proposed to contribute to ATP release, and recent studies by McCulloch et al. (49) identified continuous Cx30 hemichannel expression from the medullary thick ascending limb to the CD system. In the mouse CCD, the expression of Cx30.3 appeared to be restricted to the cytosol and the apical membrane of intercalated cells (29). A physiological role in ATP release remains to be established.

The presence of ATP in tubular fluid and its release by epithelial cells in the rat was described by means of micropuncture (77). In this study, the half-life of ATP in proximal tubular fluid was ~3.4 min with concentrations between 100 and 300 nM. Concentrations closer to the plasma membrane are expected to be significantly greater. Measurement of ATP in distal tubules showed 3.5-fold lower ATP values compared with the proximal tubule. However, ATP concentrations in the distal tubule may have been underestimated because of the need for longer collection times and the presence of soluble nucleotidase. ATP in tubular fluid of CD has not been measured yet.

ATP release in the CD is triggered by changes in tubular flow rate, as well as cell volume (31, 39). In the kidney, flow-induced ATP release was shown to be at least partially dependent on the presence of the primary cilium (57). Cilia have important roles in sensory physiology in response to flow and osmotic stimuli (reviewed in Refs. 57 and 66). Supporting this concept, Hovater et al. (31) showed that ATP release is impaired when the cilium is malformed. This conclusion was drawn from studies in CD principal cells derived from an Oak Ridge polycystic kidney (Tg737orpk) mouse model of autosomal recessive polycystic kidney disease, which lack a well-formed apical cilium: principal cell monolayers with normally formed apical cilia responded with 3- to 5-fold greater ATP release to hypotonicity than mutant monolayers lacking cilia. The observed cilia-derived Ca\(^{2+}\) transient required an underlying paracrine/autocrine ATP signal that is likely transduced by P2X and P2Y on or near the cilium (31). Notably, Woda et al. (84) showed that a flow-induced rise in [Ca\(^{2+}\)]\(_i\) can also be triggered in intercalated cells from perfused rabbit CD, which do not have cilia.

IMCD were shown to respond to AVP-stimulation with an increase in cell volume (25). Cells of various organs respond to changes in cell volume with a release of ATP (23, 80). Measuring urinary ATP excretion, our studies in P2Y\(_2\)\(^{-/-}\) mice provided indirect evidence for a volume-dependent ATP release in CD in vivo (59). Urinary ATP excretion was similar in P2Y\(_2\)\(^{-/-}\) compared with WT during inhibition of water transport by V\(_2\)R blockade but modestly greater under basal conditions and much greater in response to acute water loading in P2Y\(_2\)\(^{-/-}\) compared with WT. A summary of these findings is illustrated in Fig. 3A. V\(_2\)R blockade and acute water loading both increased urinary flow rate but had opposite effects on ATP excretion. We propose that 1) urinary flow rate alone is not a good predictor of urinary ATP excretion, 2) acute water loading increases ATP release, which may reflect increases in CD cell volume due to a reduction in extracellular tonicity, 3) acute pharmacological blockade of V\(_2\)R reduces cell volume by blocking the apical water entry, thus offsetting the basal, AVP- and cell volume-induced ATP release, and 4) urothelial cells of the lower urinary tract, which were exposed to similar increases in flow rate and therefore similar distension, and hypotonicity may not play a dominant role for urinary ATP excretion. A graph illustrating the proposed relationship between CD cell volume and ATP release and thus urinary ATP excretion is shown in Fig. 3B.

**Adenosine Receptors and CD Water Transport**

Consistent with a prominent role of adenosine A\(_1\) receptor (A\(_1\)R) in the regulation of CD function, studies in rats and mice revealed a strong corticomedullary gradient for the A\(_1\)R expression, with the highest density in CD and, in particular, IMCD (56, 73, 76, 78, 87, 90). In fact, stimulation of A\(_1\)R by adenosine and other agonists inhibits AVP-induced cAMP formation in cultured rabbit CCD cells (2, 3), as well as rat medullary and IMCD cells (85, 86). Basal, nonstimulated, cAMP formation is reduced in rabbits, rats, and mice by selective A\(_1\)R activation (3, 60, 85). Activation of A\(_1\)R inhibits AC activity through activation of pertussis toxin-sensitive Gi proteins, as well as through activation of PLC via G\(_{\beta}\), subunits (55) (Fig. 1). The selective A\(_1\)R agonist, N\(^{-}\)-2-phenylethyladenosine (NPEA), mobilized [Ca\(^{2+}\)]\(_i\) in IMCD, a response that was significantly inhibited by the selective A\(_1\)R antagonist, 8-phenylthephylline (8-PT) (19). This would suggest that A\(_1\)R, like P2Y\(_2\) receptors, are linked to a signaling pathway capable of mobilizing [Ca\(^{2+}\)]\(_i\) in the IMCD (Fig. 1).

Studies by Yagil (85, 86) showed the dose dependence of AVP-stimulated cAMP in primary cultures of rat IMCD. Interestingly, AVP applied from either side increased cAMP formation, although lower concentrations (100 pM and 1 nM) were more effective when applied from the basolateral side. When adenosine was applied from the basolateral side, 1 \(\mu\)M was sufficient to inhibit AVP-stimulated cAMP formation, whereas 100 \(\mu\)M was necessary to inhibit AVP-stimulated cAMP formation from the apical side. In this regard, it may be relevant that concentrative nucleotide transporters (CNT) expressed in the apical membrane (16, 28) could reduce adenosine availability on the apical surface and increase basolateral adenosine because of passive adenosine efflux via equilibrative nucleoside transporters (ENT1 and ENT2) expressed in the basolateral membrane (16, 28, 63) (Fig. 4).

Using freshly isolated IMCD, we showed that the A\(_1\)R agonist N\(^{-}\)-cyclohexyladenosine (CHA, 1 \(\mu\)M) reduced basal, as well as forskolin-stimulated cAMP formation in WT, but was without effect in A\(_1\)R\(^{-/-}\) (60). dDAVP-induced increases in cAMP formation were about twofold greater in A\(_1\)R\(^{-/-}\) compared with WT mice, and, in contrast to WT mice, A\(_1\)R\(^{-/-}\) mice were not inhibited by CHA. Thus, A\(_1\)R\(^{-/-}\) mice show an absence of CHA-mediated inhibition of cAMP formation in IMCD cells, as well as an enhanced response to dDAVP, consistent with the loss of a A\(_1\)R-mediated inhibition of this response.

With regard to functional consequences, Dillingham and Anderson (18) showed, using an in vitro CCD perfusion system, a stimulatory effect of high concentrations of adenosine on hydraulic conductivity and net volume flux. In rat IMCD, Edwards and Spielman (20) found that adenosine, acting from the basolateral side, inhibits AVP-induced increases in cAMP formation and P_{\text{f}}.

Little has been known about the net in vivo role of A\(_1\)R for water transport in the intact organism. We observed that A\(_1\)R\(^{-/-}\) mice have higher urinary flow rates and greater fluid
Adenosine Generation in CD

In the CD, extracellular adenosine can be generated by different mechanisms. Some are more closely linked to ATP metabolism and, therefore, discussed below in the section on ATP-adenosine interactions. Another mechanism relates to the metabolism and, therefore, discussed below in the section on different mechanisms. Some are more closely linked to ATP.

Integrative contribution of extracellular adenosine

In the CD, extracellular adenosine can derive from extracellular breakdown of ATP, AMP, or cAMP. Vekaria et al. (77) provided evidence for the breakdown of exogenous and endogenous ATP in tubular fluid by soluble nucleotidases. In addition, various ecto-ATPases and ecto-5'-nucleotidase are differentially expressed along the tubular and collecting duct epithelia (for a review, see Ref. 75). As a consequence, the cellular release of ATP can inhibit water transport by activation of P2Y<sub>2</sub> receptors and via A<sub>1</sub>R after ATP breakdown to adenosine (Figs. 1 and 4). Both pathways converge and suppress AVP-induced cAMP formation and, thus, reduce water transport and potentially cell volume.

Intracellular breakdown of cAMP and ATP can also generate adenosine. Adenosine itself can exit the cell by ENT1 and ENT2 primarily localized to basolateral membranes, where they mediate bidirectional facilitated diffusion of adenosine (16, 28, 63). In comparison, CNT1-CNT3 are mainly localized to the apical membrane, where they mediate unilateral, cellular uptake of nucleosides (Fig. 4) (36). The role of ecto-nucleotidases and of the asymmetric expression of these transport pathways for basolateral vs. luminal effects of ATP and adenosine remain to be determined.

The fact that A<sub>1</sub>R<sup>-/-</sup> presented no in vivo phenotype after V<sub>2</sub>R activation or blockade prompted us to assess under basal conditions and after acute water loading the expression level of several local factors that may compensate. Acute water loading upregulated inner medullary mRNA expression of ET-1 in WT (60), confirming previous studies (26). Notably, CD-specific ET-1 knockout mice have a reduced ability to excrete an acute water load (26). Moreover, acute water loading also increased inner medullary expression of A<sub>1</sub>R mRNA in WT (60). Although the mechanism(s) that contribute(s) to the upregulation of A<sub>1</sub>R in WT under these conditions remain to be determined, this response can help to facilitate water excretion. Under basal conditions A<sub>1</sub>R<sup>-/-</sup> had greater inner medullary expression of COX-1, and acute water loading increased P2Y<sub>2</sub> and EP<sub>3</sub> receptor expression more in A<sub>1</sub>R<sup>-/-</sup> than in WT mice (60), responses that may have compensated for the absence of A<sub>1</sub>R and support the functional interaction between these systems. Unpublished observations showed that urinary nitric oxide metabolite excretion (NO<sub>x</sub>) was not significantly different between genotypes in response to acute water loading (WT: 8.3 ± 3 vs. A<sub>1</sub>R<sup>-/-</sup>: 9.2 ± 2 nmol·min<sup>-1</sup>·g body weight<sup>-1</sup>),
consistent with similar endothelial nitric oxide synthase expression between genotypes under basal conditions or after acute water loading (60). The up-regulation of ET-1 on the mRNA level by water loading was not altered in A\textsubscript{1}R\textsuperscript{−/−}.

Why, with regard to AVP-induced cAMP formation and antiureasis, do A\textsubscript{1}R\textsuperscript{−/−} mice have a phenotype in isolated IMCD, but not in vivo, whereas P2Y\textsubscript{2}−/− mice show a phenotype in vivo, but not in freshly isolated inner medulla. In experiments in isolated IMCD, application of the V\textsubscript{2}R agonist is expected to trigger cAMP formation, perhaps followed by extracellular adenosine formation, activation of A\textsubscript{1}R, and inhibition of AC activity, an effect that is blunted in mice lacking A\textsubscript{1}R. In the absence of osmotic gradients, however, the in vitro application of the V\textsubscript{2}R agonist may not alter cell volume and thus may not generate a stimulus for ATP release. To unmask a defect in isolated IMCD of mice lacking P2Y\textsubscript{2} receptors, we had to apply ATP\textsubscript{γ}S. In vivo, lesser compensation in the absence of P2Y\textsubscript{2} receptors than of A\textsubscript{1}R may indicate that the feedback inhibition via cell volume-regulated ATP release and activation of P2Y\textsubscript{2} receptors is a more potent system than the extracellular formation of adenosine (from cellular release of cAMP and extracellular breakdown of ATP) and the subsequent activation of A\textsubscript{1}R.

**Perspectives and Significance**

Multiple P2X, P2Y, and adenosine receptors are expressed in renal epithelial cells, often in the same membrane domain. There is accumulating evidence for an important role for both ATP, via P2Y\textsubscript{2} receptors, and adenosine, via A\textsubscript{1}R, to inhibit AVP-stimulated water transport in the CD. Interactions between ATP and the adenosine system support the concept of sequentially organized feedback loops. The complexity of the ATP-adenosine interaction is further enhanced by the existence of receptor heterodimers (1, 24, 40). Heterodimeric associations between P2Y\textsubscript{2} and A\textsubscript{1}R were described in transfected cells (88, 89), but their relevance in the kidney is unknown. Important issues to be clarified in future studies also include the identification and regulation of transport pathways involved in ATP release, as well as the variation of ATP and adenosine concentrations close to the receptor under physiological conditions. The role of apical basolateral signaling deserves further consideration, including the conversion of ATP to adenosine, and transport of the latter by asymmetrically expressed concentrative and equilibrative nucleoside transporters. The use of gene knockout mice will be helpful, but compensatory changes have to be considered, as shown in our studies using the A\textsubscript{1}R\textsuperscript{−/−}. Finally, a potential role of the ATP and adenosine system in the pathophysiology of CD water transport needs to be explored.

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Review

P2 AND ADENOSINE RECEPTORS IN WATER HOMEOSTASIS


