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REVIEW ARTICLE

Purinergic signalling in the kidney in health and disease

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Abstract The involvement of purinergic signalling in kidney physiology and pathophysiology is rapidly gaining recognition and this is a comprehensive review of early and recent publications in the field. Purinergic signalling involvement is described in several important intrarenal regulatory mechanisms, including tuboglomerular feedback, the autoregulatory response of the glomerular and extraglomerular microcirculation and the control of renin release. Furthermore, purinergic signalling influences water and electrolyte transport in all segments of the renal tubule. Reports about purine- and pyrimidine-mediated actions in diseases of the kidney, including polycystic kidney disease, nephritis, diabetes, hypertension and nephrotoxicant injury are covered and possible purinergic therapeutic strategies discussed.

Keywords Glomerulus · Tubules · Sodium transport · ATP release · Kidney failure · Diabetes

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Studies of the involvement of purinergic signalling in kidney physiology and pathophysiology are growing rapidly, so we believe it is timely to prepare a comprehensive review of the history and current views about the wide variety of events mediated by receptors for purines and pyrimidines. Reviews are available on various aspects of the field, including:

Adenosine and regulation of renin secretion [159,273];

Adenosine and kidney function [69,248,259,349,384];

Glomerulus and tuboglomerular feedback [148,200,255,320];

Nucleotide signalling along the renal tubules (sodium and water transport) [12,28,77,103,192,215,216,233,288,297,308,328,372,381,383,409,414];

Cilia in renal epithelium and paracrine purinergic signalling [298];

Nervous control (ATP as a cotransmitter) [306];

Ectonucleotidases in the kidney [333];

Purinergic regulation of renal blood flow [45,146,147,150,153,165,256,261,321];

P2X receptors and kidney function [17].

Pathophysiology [30,113,402,403];

Physiological and pathophysiological renal actions of purines [113,118,160,161,217,379,402,403];

Polycystic kidney disease (PKD) [133,139,267];

Role of dinucleotide polyphosphates in chronic kidney disease and uremia [171].

Renal microvascular function and hypertension [117].

Sympathetic hyperactivity in renal disease [6];

Mechanotransduction in the renal tubule [400].

Human embryonic kidney (HEK-293) cells are often used as a recombinant expression system for the study of a variety of receptors, including P2 receptors (see e.g. [7,68,334,374]), even though they express native $P2Y_1$, $P2Y_2$ and $P2Y_4$ receptors [88,89].

Glomerulus and the renal vasculature

The mammalian glomerulus is structurally complex, consisting of central glomerular tuft of endothelial (~20 % of total cells) and mesangial (~25 %) cells, encapsulated by a double layer of visceral (podocytes) and parietal epithelial (~55 %) cells ([266]; see Fig. 1). Most information concerning P2 receptor expression in the glomerulus comes from cell culture with very few studies on receptor distribution in the native mammalian glomerulus. Nevertheless, mRNA for $P2Y_1$ and $P2Y_2$ was identified in extracts from whole rat glomeruli [16]. $P2Y_2$ immunoreactivity colocalised with podocytes and cells of the parietal sheets; $P2Y_1$ immunoreactivity was limited to the mesangial cells. ATP evoked calcium transients in the intact glomerulus and in the isolated parietal sheet. These studies suggest that extracellular ATP may regulated glomerular ultrafiltration directly, independent of actions of the renal microvasculature. ATP can also relax glomeruli via P2Y receptors on endothelial cells resulting in release of nitric oxide (NO), supporting the notion that P2 receptors influence glomerular filtration rate (GFR) [166]. Uridine adenosine tetraphosphate may also act as an autocrine hormone affecting glomerular filtration rate [170]. Tubular sodium transport systems are more sensitive to diadenosine tetraphosphate (Ap_4A) than systems involved in glomerular filtration rates [167]. β-Blockers induce relaxation of the glomerular microvasculature by releasing ATP, which acts via P2Y receptors on endothelial cells to produce NO, resulting in vasodilation [180]. Connexin (Cx) 40 hemichannels and extracellular ATP are the key molecular elements of the glomerular endothelial calcium wave [371]. A review that discusses the roles of ATP and adenosine in tubuloglomerular feedback (TGF) regulation of glomerular filtration is available [46]. In addition to the effects of GFR, P2 receptors in the extraglomerular mesangium play an important role in TGF, as discussed below.

Mesangial cells

Functionally, ATP and uridine 5′-triphosphate (UTP), probably acting via $P2Y_2$ and/or $P2Y_4$ receptors, increased inositol 1,4,5-trisphosphate formation and activated the p38-stress-activated protein kinase cascade in rat renal mesangial cells [144,286,361]. Extracellular ATP increases $[Ca^{2+}]_i$ by release from intracellular stores, indicating mediation via P2Y receptors [121,282], although P2X receptor-mediated increase in $[Ca^{2+}]_i$ has also been claimed [311]. Cultured mouse mesangial cells expressed P2X2, P2X4, P2X7, $P2Y_2$ and $P2Y_4$ receptors; mRNA (but not protein) for P2X1 and P2X3 receptors was also found [311]. Using RT-PCR, P2X1 receptor mRNA was shown to be expressed by an immortalised mouse mesangial cell line (G3) [131]. ATP and UTP stimulate the mitogen-activated protein kinase (MAPK) cascade and the MAPK pathway to promote proliferation of rat renal mesangial cells [143,145,157,323,392]. Extracellular ATP causes apoptosis and necrosis of cultured mesangial cells via P2X7 receptors [326], although P2X4 receptors may also be involved in the apoptotic actions [347]. The generation of reactive oxygen species in rat mesangial cells may contribute to P2X7 receptor-induced apoptotic cell death [125]. ATP potentiates mesangial cell proliferation induced by growth factors [324] and growth hormones reverse desensitization of $P2Y_2$ receptors in rat mesangial cells [122].

Diadenosine polyphosphates, which influence renal perfusion pressure, activate Cl^- and non-selective cation conductance in rat mesangial cells as do ATP and angiotensin II (Ang II); Ap_4A was the most effective of the dinucleotides [194,318,325]. Diadenosine pentaphosphate (Ap_5A) and diadenosine hexaphosphate appear to play a regulatory role in mesangial cell proliferation [129]. Ap_4A and Ap_5A

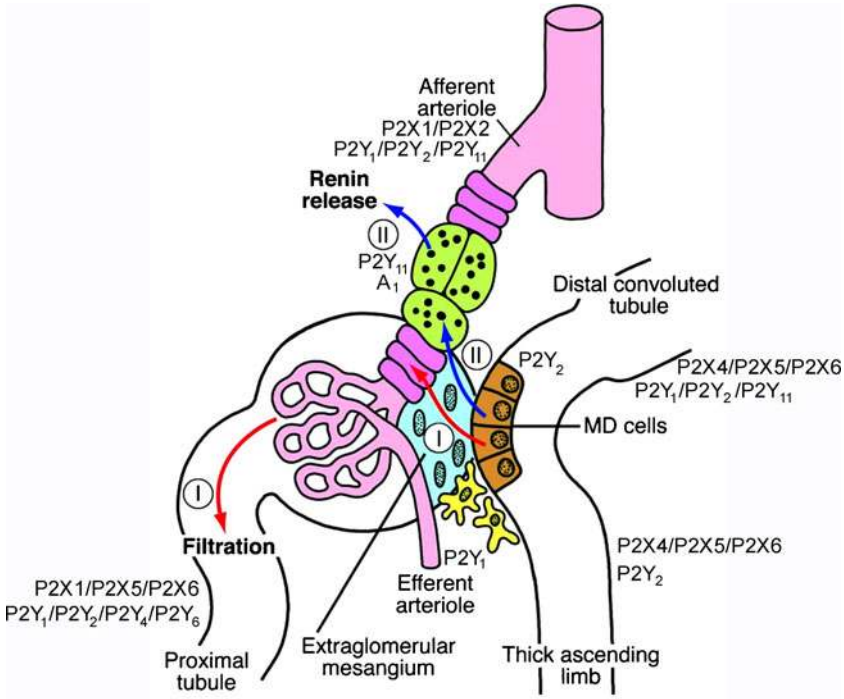

Fig. 1 Schematic showing the structural and functional relationships within the JGA. The macula densa (MD) cells are shown in *brown*, the extraglomerular mesangium in *blue*, the vascular smooth muscle cells (VSMCs) in *magenta*, the renin-producing cells in *green*, the fibroblasts of the adjacent interstitium in *yellow* and the blood vessels in *red*. Note that both signalling pathways from the MD pass the extraglomerular mesangium, either to reach the VSMCs (*I*) to regulate filtration or the renin-producing cells (*II*) to mediate renin secretion (reproduced from [200], with permission from the American Society for Clinical Investigation)

decrease, while diadenosine triphosphate appears to increase glomerular filtration rate [359].

The effect of sphingosine-1-phosphate, a potent mitogen of mesangial cells, is rapidly desensitized by activation of P2Y and P1 receptors [420]. ATP and UTP induce migration of mesangial cells by upregulating sphingosine kinase-1 expression and activity [193].

Adenosine inhibits platelet-derived growth factor in human glomerular mesangial cells via A_{2B} receptors [73]. A_1 and A_2 receptors appear to mediate opposite actions on intracellular levels of cyclic adenosine monophosphate (cAMP) in mesangial cells [265]. A_2 receptor-mediated hyperpolarisation of cultured rat mesangial cells has been described [283]. A_2 receptors have been identified on human glomerular mesangial cells [350]. Adenosine activates mesangial cell proliferation [235], but can also induce apoptosis of mesangial cells [437]. High concentrations of glucose increase extracellular levels of ATP in mesangial cells, which in turn activates ERK1/2. This effect is partially dependent on the generation of reactive oxygen species and subsequent upregulation of transforming growth factor-1β [300].

Podocytes

Podocytes maintain the permselectivity of the glomerular filtration barrier. Podocyte function is implicated in human health: proteinuria is a significant independent risk factor for cardiovascular mortality and an indicator of underlying chronic kidney disease. Cultured human podocytes produce superoxide in response to extracellular ATP [115]. Increase in $[Ca^{2+}]_i$ by purines and pyrimidines is mediated mainly by $P2Y_2$ and $P2Y_6$ receptors, but $P2Y_1$, $P2Y_{11}$ and P2X7 receptors are also expressed by podocytes [40,87,118,375]. ATP acting via P2 receptors stimulated AMP-activated protein kinase and suppressed superoxide generation in cultured mouse podocytes [287]. Functionally, activation of A_{2A} receptors reduces glomerular proteinuria at least in part by preserving the structure and function of podocytes [9].

Kidney blood vessels

P2X1 receptors have been identified in the vascular smooth muscle of the rat renal, arcuate and interlobular arteries and in the afferent arteriole: P2X1 is not expressed in the efferent arteriole [51,375]. A P2X1-like receptor has been confirmed functionally in the afferent arteriole [149]. In the smooth muscle of the larger renal arteries, P2X2 receptor subunits have been immunolocalised [146,375], and at a molecular level, P2X4 receptor subunits are found, at least in arcuate and interlobular arteries [127]. At a protein level, however, P2X4 expression is limited to the vascular endothelium [242]. P2X7 receptors are also expressed in the healthy kidney: expression in the vascular smooth muscle and outer-adventitium is very low [218], whereas functionally significant expression is observed in the endothelium [242]. Of the P2Y receptors, $P2Y_1$ is expressed in the endothelium of the large arteries and both afferent and efferent arterioles [375]. ATP released from renal tubular epithelial cells acts on pericytes to regulate the diameter of vasa recta capillaries that are in close proximity to renal tubules and are key to

regulating renal medullary blood flow [61]. P1 receptors are expressed on mouse afferent arterioles and it was concluded that activation of A_3 receptors blunted the vasoconstrictor effects mediated by A_1 receptors [231].

Physiological responses in the glomerulus and renal vasculature

Infusion of ATP into the renal artery alters renal vascular resistance, although the vasoactive response is dependent upon species and basal vascular tone and can be influenced by the experimental approach [147]. Functionally, the larger renal arteries serve principally as conductance vessels [428], and renal vascular resistance, which determines renal blood flow, is regulated primarily through pressure-dependent vasoactivity of the preglomerular arterioles [351]. The interlobular arteries also contribute, but to a lesser extent [130]. The responsiveness to ATP of the arcuate and interlobular arteries and the glomerular arterioles of the rat has been assessed in the isolated perfused kidney preparation [149]. The preglomerular arteries were relatively insensitive to ATP, with micromolar concentrations required to cause a short-lived vasoconstriction. In contrast, sub-micromolar concentrations of ATP caused sustained contraction of the afferent arteriole. The efferent arteriole was unresponsive to extracellular ATP, consistent with the reported absence of P2 receptors in this section. In the isolated perfused rat kidney, intrarenal administration of ATP is normally vasoconstrictive, an effect potentiated by inhibition of NO synthesis (NOS) [79]. In contrast, ATP causes *vasodilatation* when baseline renal vascular resistance is high. This reflects P2Y-mediated production of NO [86]. More recent data have shown vasoactive actions of P2X4 and/or P2X7 in the rat renal artery [242]. It would appear that P2 receptor 'tone' influences renal vascular resistance, with P2Y-mediated vasodilatation opposing P2X-mediated vasoconstriction.

Renal autoregulation

Autoregulation of blood flow is an intrinsic property of most vascular beds. In the kidney, autoregulation is highly efficient so that renal blood flow is effectively independent of blood pressure over the physiological range [64]. Whole kidney autoregulation is governed through the combined influence of TGF and the intrinsic myogenic response of the vascular smooth muscle. These regulatory systems have overlapping operational frequencies and may interact to a degree [394] so that afferent arteriolar constriction through TGF enhances the myogenic response in the upstream vasculature [135].

Myogenic responses to altered perfusion pressure

The intrinsic myogenic response to altered perfusion pressure is both necessary and sufficient for full whole kidney autoregulation [64]. The myogenic response operates along the preglomerular vascular tree, with increased transmural pressure causing channel-mediated calcium influx and promoting reflex vasoconstriction of the vascular smooth muscle. Mechanistically, the underlying signalling processes are not fully defined, but local release of ATP is implicated. In the afferent arteriole, for example, pressure-mediated vasoconstriction is markedly blunted by pyridoxalphosphate-6-azophenyl-2′,4′-disulfonic acid (PPADS) or suramin or by the saturation and subsequent desensitization of the P2 receptor system [151]. The central role of the P2 system is further suggested by the fact that pressure-induced reductions in afferent arteriole diameter are abolished in P2X1-deficient mice [152]. Pharmacological [272] or pathological [119] manoeuvres that impair P2X1 receptor signalling will also blunt whole kidney autoregulation of blood flow, both in vivo and in vitro. Finally, mice with a targeted deletion of the ectonucleotidase NTPDase1 exhibit enhanced pressure-induced vasoconstriction in the mesenteric artery [183]. This probably reflects the prolonged half-life of extracellular ATP and is consistent with a key role for local nucleotide signalling in the general myogenic response.

Tubuloglomerular feedback and the juxtaglomerular apparatus

TGF is a dynamic process whereby changes in the concentration of NaCl in the fluid emerging from the loop of Henle elicit inverse changes in the GFR of the nephron of origin. TGF is mediated by the juxtaglomerular apparatus (JGA), which includes a sensor, the macula densa and an effector (granulated cells in the afferent arteriole); other components of the JGA (e.g. mesangial cells) also play a role.

Changes in luminal NaCl concentration within the physiological range promote a directly correlated release of ATP from the basolateral membrane of macula densa cells [21,196]. Furthermore, the concentration of ATP in the cortical interstitium changes to reflect inhibition or activation of TGF [260]. These data suggest that ATP is the primary signalling molecule for TGF [22,258]. Gene targeting experiments, however, indicate that ATP is not the ultimate signal through which activation of TGF causes constriction of the afferent arteriole: hydrolysis of ATP to adenosine appears to be critical. A_1 receptors mediate TGF in both rats [91] and mice [34]. In vivo TGF responses are blunted in mice lacking either the adenosine A_1 receptor [222,356] or ecto-5′-nucleotidase, the enzyme catalysing the final stage of the degradation of ATP to adenosine [47]. This proposition is supported by a recent in vivo study in which the TGF response in mice (as assessed by changes in stop-flow pressure in the proximal tubule) was unaffected during intravenous infusion of PPADS or suramin [319]. Nevertheless, an anatomical consideration argues for involvement of the P2 receptor system in the TGF

response: the ATP released from macula densa cells cannot activate directly P2 receptors in the afferent arteriole, being physically separated in most species by the extraglomerular mesangium. An intact mesangium is required for TGF responses [307]. Intracellular Ca^{2+} wave propagation occurs between rat juxtaglomerular cells; this is mediated by ATP and is involved in the synchronisation of renin release [424]. It was later shown that both ATP and gap junctions were integral components of the TGF calcium wave and that TGF activation causes a wave of increased cytosolic calcium to pass through the mesangium, to the granulated cells of the afferent arteriole and into the glomerular podocytes [285]. Propagation of this calcium wave was abolished by suramin but not by adenosine receptor antagonism. The P2 receptor response requires gap junctional coupling and is inhibited by antagonists against Cx37 and Cx40 [364]. It has been claimed recently that TGF adapts and stabilizes early distal delivery at a new set-point, via an A_1 receptor-dependent mechanism [27].

Finally, the basolateral membrane of macula densa cells expresses a $P2Y_2$-like receptor. The function of this receptor is unknown but it may provide a mechanism through which ATP release can be coupled to production [22]. A schematic illustrating the underlying mechanism of TGF is shown in Fig. 2.

Glomerular and medullary microcirculation

Infusions of nucleotide analogues into the renal artery exert powerful effects on regional blood flow, and these can be measured by laser Doppler flow probes inserted into specific regions of the kidney. In the rabbit, ATP evokes a biphasic response, with vasoconstriction of the medullary blood flow being followed by hyperaemia [82]. On the basis of relative agonist potency, the vasoconstriction was attributed to P2X1 receptors; the secondary vasodilatation, which was independent of NO, to adenosine receptors. In the rat, the net effect of ATP is influenced by sodium status. In sodium-restricted rats,

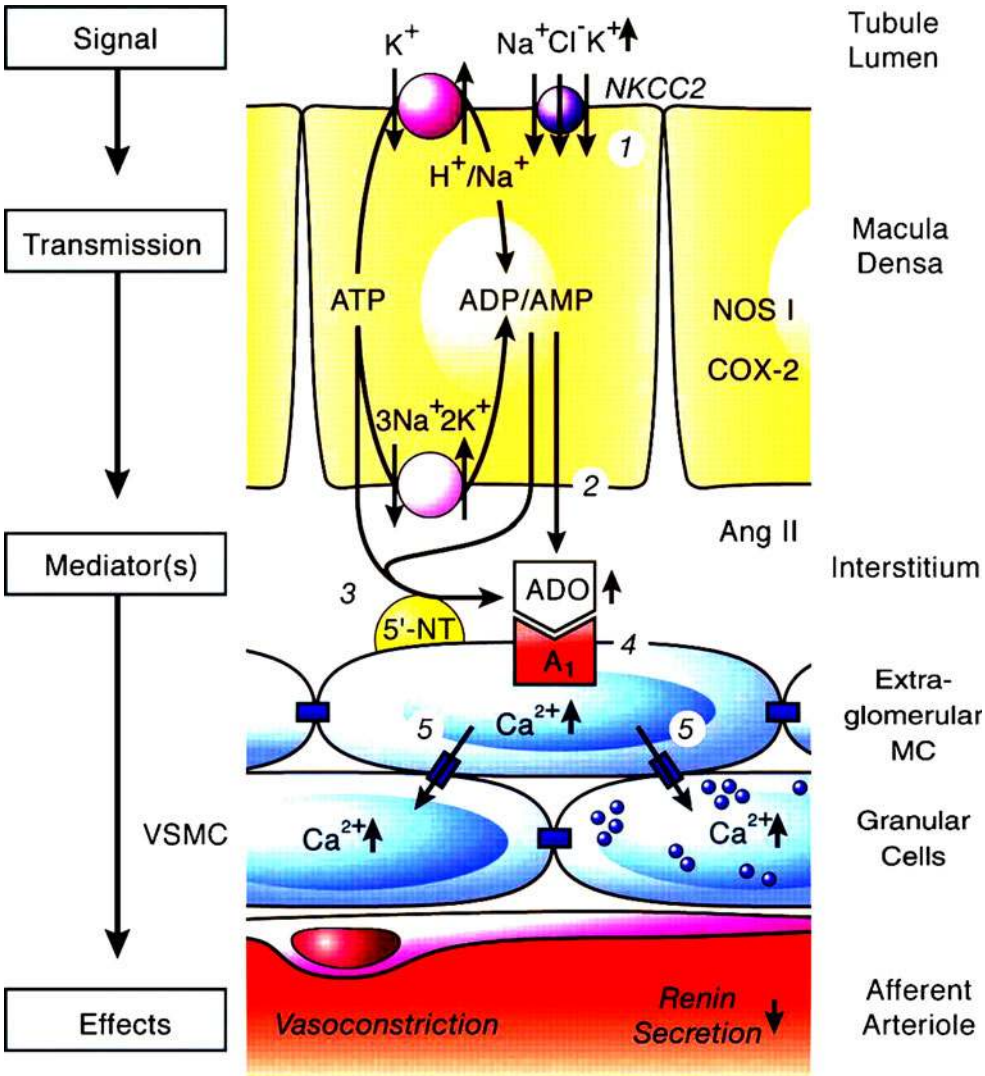

Fig. 2 Proposed mechanism of adenosine acting as a mediator of the tubuloglomerular feedback. *Numbers in circles* refer to the following sequence of events. *1*, Increase in concentration-dependent uptake of Na^+, K^+ and Cl^- via the furosemide-sensitive Na^+–K^+–$2Cl^-$ co-transporter (NKCC2); *2* and *3*, transport-dependent, intra- and/or extracellular generation of adenosine (ADO) and the extracellular generation involves ecto-5′-nucleotidase (5′-NT); *4*, extracellular ADO activates adenosine A_1receptors triggering an increase in cytosolic Ca^{2+} in extraglomerular mesangium cells (MC); *5*, the intensive coupling between extraglomerular MC, granular cells containing renin and smooth muscle cells of the afferent arteriole (VSMC) by gap junctions allows propagation of the increased Ca^{2+} signal resulting in afferent arteriolar vasoconstriction and inhibition of renin release. Factors such as nitric oxide, arachidonic acid breakdown products or angiotensin (ANG) II modulate the described cascade. *NOS I* neuronal nitric oxide synthase, *COX-2* cyclooxygenase-2 (reproduced from [384], with permission of the American Physiological Society)

ATP increased medullary blood flow in a NO-dependent manner [71]. In salt-loaded rats, ATP caused vasoconstriction in the outer medulla without affecting inner medullary flow. The authors speculated that the inner medullary vasodilatation reflected an effect of nucleotides on vasa recta pericytes. Consistent with this, purinergic cross-talk between the thick ascending limb and abutting vasa recta exerts a countervailing influence on Ang II vasoconstriction, an action lost during salt-sensitivity [263]. The integrated picture is far from clear, however, since data obtained in slices of rat kidney suggest that P2 receptor activation promotes vasoconstriction of the vasa recta due to contraction of pericytes [61].

Responses to adenosine, mediated by A_2 receptors, modulated TGF by counteracting the effects of A_1 receptor-mediated actions [44]. Both A_{2A} and A_{2B} receptors are functionally expressed in juxtamedullary afferent arterioles, and the dilator effects of adenosine are predominantly mediated by A_{2B} receptors, which counteract A_1 receptor-mediated vasoconstriction [84].

Renin release

The renin–angiotensin system is influenced by many factors, the final pathways of which converge at the level of altered intracellular calcium signalling in the granular cell; renin secretion is inversely related to $[Ca^{2+}]_i$ [424]. The renin-containing epithelioid juxtaglomerular cells are modified vascular smooth muscle cells and are localised in the media of the afferent arteriole close to its entry into the glomerulus and are innervated by sympathetic nerves. ATP was shown to increase renin release from juxtaglomerular cells in an early paper [97]. Both renal juxtaglomerular and microvascular endothelial cells express P2 purinoceptors and ATP inhibited cAMP-stimulated renin release from juxtaglomerular cells only in the absence of endothelial cells [203]. P2Y receptors mediate stimulation of renin secretion in rat renal cortical slices [59]. ATP can stimulate the renin gene promoter via $P2Y_{11}$ receptors [385]. Stimulation of sympathetic nerves released ATP as a cotransmitter with noradrenaline (NA) to elicit excitatory junction potentials in both smooth muscle and juxtaglomerular cells, to produce vasoconstriction and release of renin, respectively [38]. A recent paper reports that adenosine, formed during renal sympathetic nerve stimulation, enhances via A_1 receptors the postjunctional effects of released NA, thereby contributing to renal sympathetic neurotransmission [162]. Juxtaglomerular A_1 receptors are also involved in the control of the glomerular microcirculation [184]. Adenosine was shown to depress renin secretion in sodium-restricted rats, accompanied by a marked fall in GFR, while this effect was nearly abolished in sodium-loaded rats [274]. A_2 receptors mediate arteriolar dilation and stimulation of renin secretion, whereas activation of A_1 receptors mediates arteriolar constriction and inhibition of renin secretion [58,252]. Adenosine inhibits renin release by a mechanism that involves the juxtaglomerular cells located in the afferent arteriole at some distance from the glomerulus [343]. From other studies, it was concluded that adenosine decreases renin release via the activation of juxtaglomerular A_1 receptors and that adenosine may be an inhibitory signal from the macula densa to juxtaglomerular cells [158,271]. In A_1 receptor-deficient mice, TGF is abolished (see above) and there is increased plasma renin [34]. A_1 receptors are required for the inhibition of renin secretion produced by an increase in blood pressure, suggesting that adenosine is responsible for baroreceptor-mediated inhibition of renin release; in contrast, stimulation of the renin system by low blood pressure appears to follow a different pathway [327].

Renal tubules

The pattern and distribution of P1 [345,390] and P2 receptors [14,49,375] along the rat renal tubule have been reported (see Fig. 3), and the major transporters for sodium and water are illustrated in Fig. 4. In recent years, our understanding of the functional consequences of receptor activation has advanced considerably, in part due to physiological studies in gene-targeted mice (see Table 1).

Proximal convoluted tubules

P2Y receptors were identified in the renal cortex over 20 years ago [254], and since then, a variety of approaches has begun to catalogue the distribution of specific receptor subtypes. $P2Y_1$ and P2X5 receptors have been immunolocalised to the apical membrane in the S3 segment of the rat pars recta and $P2Y_4$ and P2X6 receptor protein is found basolaterally in the proximal convoluted tubule (PCT). Low level expression of P2X4 protein is also seen in the PCT but not ascribed to a specific membrane domain [375]. Western analysis has shown the $P2Y_1$ receptors in brush-border membrane vesicles from the S2 segment of rat PCT [12].

mRNA has been identified for $P2Y_{1,\ 2,\ 4\ and\ 6}$ receptors in the rat proximal tubule [14,15]. Measurements of Ca^{2+} transients following application of P2 receptor agonists of varying selectivity support expression of apical $P2Y_1$-like receptors in an immortalised cell line with a proximal phenotype [178] and for basolateral $P2Y_1$ receptors in native rat PCT [14,49]. Bailey and colleagues [15] also reported that basolateral uridine 5′-diphosphate (UDP) was effective in increasing $[Ca^{2+}]_i$, corroborating the presence of $P2Y_6$ receptors. Finally, ATP and UTP were equipotent when applied to rat or rabbit basolateral membranes [14,422], implying $P2Y_2$ or $P2Y_4$ receptors. Notably, the immunohistochemical evidence in rats favours $P2Y_4$ receptors [375].

In vivo, microperfusion studies show that adenosine nucleotides, applied from the luminal side, inhibited NHE3 activity in the rat PCT [11]. Adenosine diphosphate (ADP) was more effective than ATP, suggesting a $P2Y_1$ receptor effect. This

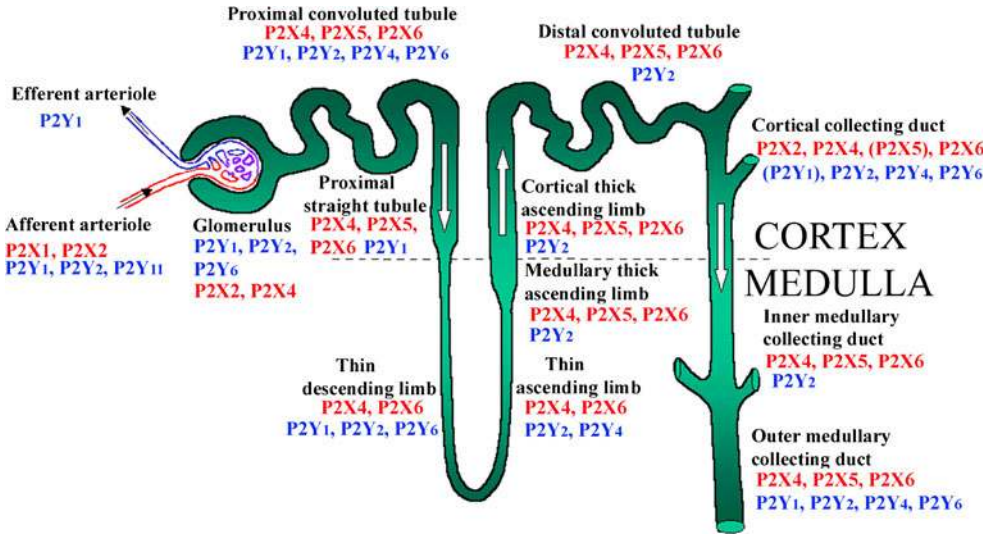

Fig. 3 The distribution of P2 receptors along the nephron: an amalgam of available functional, mRNA and protein (immuno-) detection studies showing how widespread and overlapping it is. To date, there has been no full report of their distribution in native renal tissue of any species. P2Y is shown in *blue* and P2X in *red*; presence of those in parentheses is still uncertain. (updated from [381], with permission from the American Physiological Society)

was supported by the observation that the $P2Y_1$-selective agonist 2-methylthio ADP also had a potent inhibitory effect, which was blocked by the $P2Y_1$-selective antagonist MRS2179. Addition of ATP to peritubular capillaries in vivo caused an increase in transepithelial bicarbonate reabsorption in rat PCT [70]. Increasing the viscosity of the peritubular perfusate also stimulated bicarbonate reabsorption, and this effect was blocked by peritubular suramin, suggesting P2 receptor mediation. (Shear stress was proposed as the activating factor.) Interestingly, the increase in bicarbonate reabsorption induced by ATP or by raised viscosity could be blocked by a NOS inhibitor. Thus, P2 receptors exert in distinct membrane domains opposing effects on sodium bicarbonate flux. This complexity of paracrine regulation is also observed for Ang II.

In the proximal tubules of $P2Y_2$ receptor knockout mice, the expression of NaPT2 protein is increased but NHE3 abundance is normal [225]. Consistent with this, ATP inhibits phosphate uptake (and mRNA for NaPT2) in primary cultures of rabbit PCTs [211]. In the same preparation, ATP stimulates sodium–glucose co-transport by increasing both SGLT1 and SGLT2 protein expression [210].

A study in rats, using lithium clearance as an index of end proximal tubular fluid delivery, reported that intravenous infusion of the diadenosine polyphosphate, Ap_4A, increased lithium clearance almost twofold. This occurred despite a fall in GFR and suggested that proximal tubular reabsorption was markedly reduced [353]. Ap_4A can stimulate a number of P2 receptor subtypes, including $P2Y_1$ and $P2Y_4$ receptors [331,410], which are both expressed in the rat proximal tubule ($P2Y_1$ apically, $P2Y_4$ basolaterally); intravenous delivery of the agonist does not allow differentiation between these possibilities.

Effects on transport have also been observed in the amphibian kidney. Cells of the frog proximal tubule contain at least two different K^+-selective conductances, both of which are regulated by extracellular ATP [312]. Extracellular ATP raises cytosolic Ca^{2+} and activates basolateral chloride conductance in *Necturus* proximal tubules [32]. A more recent paper presented evidence that P2X1 receptors played a role in the regulation of cell volume and K^+ channels in frog renal proximal tubule cells [66].

Adenine-based and uracil-based nucleotides can also regulate metabolic functions in the proximal tubule. Early papers showed that ATP inhibited citrate synthase activity in the kidney cortex [33] and stimulated tetraethylammonium transport by rabbit renal brush border membrane vessels [240]. Gluconeogenesis is also stimulated by P2 receptor activation [48,247] and by diadenosine polyphosphates [75]. ATP and UTP were equipotent in stimulating gluconeogenesis, implicating $P2Y_2$ or $P2Y_4$ receptors [247]. Although these authors suggested $P2Y_2$ mediation, these receptors have not been found in rat proximal tubules. $P2Y_4$ receptors are expressed here, making a basolateral $P2Y_4$-mediated effect more likely.

A long-term trophic role for purinergic signalling in the kidney has also been described, where ATP stimulates proliferation of proximal tubule cells via increase in $[Ca^{2+}]_i$ and activation of p38, p44/42, MAPKs and cyclin-dependent kinase [212]. It has been claimed that there is paracrine stimulation of vascular smooth muscle proliferation by diadenosine polyphosphates released from proximal tubule cells [169], probably via P2Y receptors [39]. Tubular remodelling is

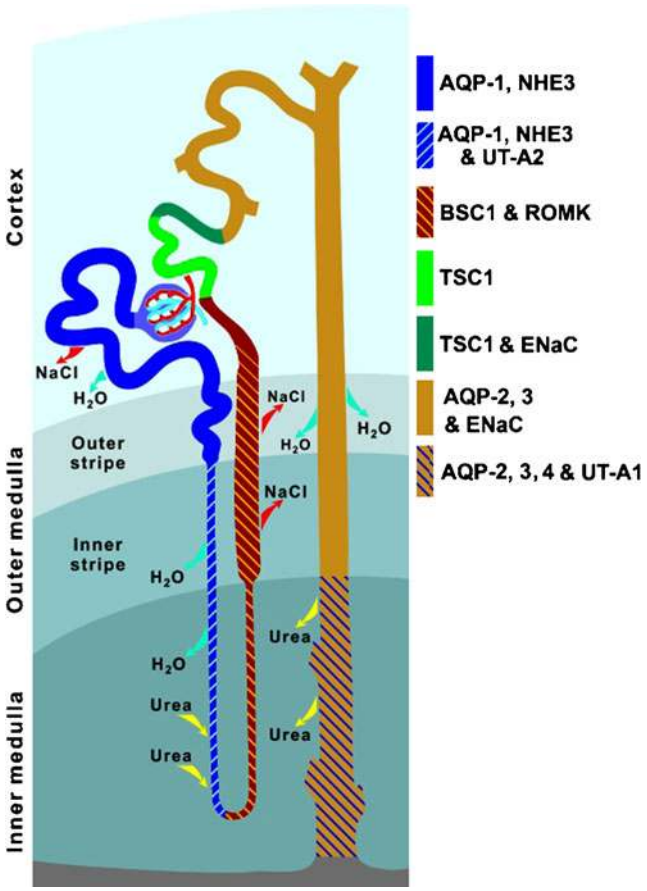

Fig. 4 Architecture of rat nephron and collecting duct showing segmental localisation of major transporters and channels that play critical roles in water and solute reabsorption. *AQP1*, *AQP2*, *AQP3*, *AQP4* Aquaporin water channel isoforms (reproduced from [189] with permission from Springer)

complex, and in cultured mouse, proximal cells subjected to ATP depletion below ~15 % of control died uniformly of necrosis, while cells subjected to ATP depletion by 25 % or more of controls all died by apoptosis [224]. Prior heat stress or Zn^{2+} inhibits apoptosis in ATP-depleted kidney proximal tubule cells [396,399]. Extracellular ATP protects cultured proximal tubule cells against oxidative stress [213].

Adenosine, acting via P1 receptors, also plays roles in the regulation of proximal tubule activity. Adenosine A_1 receptor mRNA was identified in rat nephron segments [423] and also A_{2A} receptor mRNA [398]. Regulation of Na^+-$3HCO_3^-$ co-transport in rabbit proximal tubules via A_1 receptors was claimed [360]. A_1 receptors were characterised in human proximal tubule epithelial (HK-2) cells [367]. In the pig proximal tubule, Na^+-ATPase activity is stimulated via adenosine A_{2A} receptors, thus regulating sodium reabsorption [406]. Transepithelial fluxes of adenosine across human proximal tubule cells involve specific nucleoside transporters [80]. Adenosine is deaminated to inosine in isolated basolateral membranes from proximal tubules, leading to modulation of protein kinase (PK) A activity [8]. Low salt intake increases A_1 receptor expression and function in rat proximal tubules [202]. Inhibition of A_1 receptors increases fluid uptake in the proximal tubule [278]. Adenosine-induced PKA activation reduced Ang II-induced stimulation of phosphoinositide specific phospholipase (PL) Cβ [109].

The loop of Henle

P2X4 and P2X6 receptors have been immunolocalised to the rat thin descending limb of Henle [375]. Measurements of agonist-induced $[Ca^{2+}]_i$ transients indicate a functional pyrimidine receptor in the basolateral membrane of this segment [14], but neither $P2Y_2$ nor $P2Y_4$ protein has been demonstrated. mRNA for $P2Y_1$ and $P2Y_6$ is expressed here [14,15], but again evidence of receptor protein is lacking. In the rat thin ascending limb, the functional evidence for a pyrimidine receptor in the basolateral membrane [14] is, in this case, supported by immunohistochemical confirmation of $P2Y_2$ receptor protein; P2X4 and P2X6 protein expression has also been reported [375]. The physiological role of P2 receptors in the thin limbs is unknown, but this reflects the general absence of information regarding transport in these segments.

The expression and function of P2 receptors in the thick ascending limb (TAL) is increasingly well-defined but there appear to be species differences between rat and mouse. In the rat TAL, basolateral binding sites for adenosine-5′-(γ-thio)-triphosphate (ATPγS) are found [13], but this agonist does not discriminate well between different receptor (both P2Y and P2X) subtypes. $P2Y_2$, P2X4 and P2X6 receptor proteins have been immunolocalised to the TAL [375] and mRNA is expressed here for $P2Y_{1,\ 2,\ 4\ \text{and}\ 6}$ subtypes [14,15,188].

Rat TAL segments appear poorly responsive to basolateral application of nucleotides, at least in terms of Ca^{2+} signalling [14,15]. In the mouse, however, basolateral ATP and UTP each causes large Ca^{2+} transients, consistent with $P2Y_2$ receptor activation [13,280]. This work is extended with luminal application of ATP or UTP causing calcium transients in mouse medullary TAL (mTAL) perfused in vitro, an effect absent in $P2Y_2$ knockout mice [174]. $P2Y_2$ knockout mice have proven a useful tool for defining the role of these receptors in the kidney. These animals have increased expression of the Na^+–K^+–$2Cl^-$ co-transporter and an augmented natriuretic response to furosemide [309]. These data imply that $P2Y_2$ receptors exert a tonic inhibitory effect on NaCl transport in mouse TAL. A recent study has further indicated that activation of basolateral P2X receptors triggers a marked reduction in NaCl absorption in mouse mTAL [237].

Further evidence directly supports a regulatory role for extracellular nucleotides on TAL function. In suspensions of rat mTAL, ATP increased intracellular NO production in a concentration-dependent manner, a response inhibited by suramin [340]. Flow-induced NO production is dependent on ATP release in TAL [41]. On the basis of agonist profiling,

Table 1 Effects of P2 receptor activation in kidney segments

Kidney segment	P2 receptor	Action
Aldosterone-sensitive distal nephron	P2	Decrease Na^+ absorption
	$P2Y_2$	Decrease aldosterone sensitivity and K^+ excretion (with high K^+ diet)
Proximal tubule	$P2Y_1$	Increase $[Ca^{2+}]_i$, decrease bicarbonate reabsorption
	$P2Y_2$	Increase $[Ca^{2+}]_i$ and gluconeogenesis
	$P2Y_6$	Increase $[Ca^{2+}]_i$ and inositol phosphates
Loop of Henle		
Thin descending limb	$P2Y_2$	Increase $[Ca^{2+}]_i$
Thin ascending limb	$P2Y_2$	Increase $[Ca^{2+}]_i$
Thick ascending limb	$P2Y_2$	Increase $[Ca^{2+}]_i$, decrease NKCC2 activity
Collecting ducts	P2	Decrease phosphatidylinositol bisphosphate
	P2X4	Decrease ENaC activity in high $[Na^+]$
	$P2Y_2$	Increase phospholipase C, decrease ENaC activity and H_2O reabsorption
Cortical collecting duct	$P2Y_2$	Increase $[Ca^{2+}]_i$ and phospholipase C, decrease ENaC activity and small conductance K^+ channel
Inner medullary collecting duct	$P2Y_2$	Increase $[Ca^{2+}]_i$, prostaglandin E_2 protein kinase C and phospholipase C, decrease endothelin-1 release, cAMP and vasopressin-stimulated osmotic water permeability

it was argued that the response was mediated primarily by P2X receptors. Further studies from the same group have defined NOS3 (eNOS) as the target for P2 receptor activation [338], in a process requiring activation of Akt1 (serine threonine kinase; aka PKB).

The physiological process coupling P2 receptor activation and NO production may be the flow rate of fluid thought the lumen of the TAL, which regulates nucleotide [174]. Increased flow within the physiological range has previously been shown to stimulate NO production [270] and promote translocation of NOS3 towards the apical membrane in TAL cells. Mechanistically, therefore, ATP is likely to reduce sodium flux in this segment via NO-mediated inhibition of apical transport processes and this has indeed been shown for both Na^+–K^+–$2Cl^-$ co-transporter [269] and Na^+/H^+ exchange activity [102]. Nevertheless, the primary effect of ATP may be reduction in basolateral Na^+–K^+–ATPase activity, since ATP reduces oxygen consumption in suspensions of TAL cells [339]. Pharmacological characterisation of this effect found it to be P2X-mediated and NOS-dependent. However, as with nucleotide-stimulated NO production, a weak inhibitory effect on oxygen consumption of UTP was found and there may be some additional P2Y involvement.

Distal tubules

The distal tubule is that segment of the nephron between the macula densa and the first confluence with another tubule in the collecting duct. It is a heterogeneous segment, incorporating the distal convoluted tubule, the connecting duct and the initial portion of the cortical collecting duct (CCD). The transport properties also vary: the distal convoluted tubule is the site of thiazide-sensitive sodium reabsorption and the epithelial sodium channel is expressed in the CCD. The connecting tubule, which is not well-defined in humans, has hybrid transport processes. P2 receptors have been identified in the native distal convoluted tubule and CCD ([13]; see [77]) and the collecting duct is discussed in detail below. However, many of the studies of distal tubule cells have been carried out on cell lines such as A6 (derived from *Xenopus* kidney) and Madin–Darby canine kidney (MDCK) cell. ATP activates both Cl^- and K^+ channels in distal nephron epithelial cells from the cell line A6 by a Ca^{2+}-dependent mechanism [243,257,315], probably via $P2Y_2$ receptors [19,250,251] and also in a rabbit distal convoluted tubule cell line [26]. The high-affinity Ca^{2+} channel of the distal tubule luminal membrane is regulated by ATP, and ATP plays a crucial role in the integrity of the cytoskeleton, which is also involved in the control of Ca^{2+} channels in this membrane [35,284]. Stretch-released ATP, acting through an autocrine PLC-dependent pathway, masks stretch activation of epithelial sodium channels (ENaC) in A6 distal tubule cells [232].

Connexin hemichannels have been shown to be localised in the luminal membrane of the distal nephron and may be the mechanism underlying ATP release from these cells and play a role in the regulation of salt reabsorption [239]. Multiple P2X receptors (P2X4, P2X5 and P2X6) have been

immunolocalised in the distal tubule cells [411]. In particular, P2X4 and P2X6 receptors are present on the basolateral membranes of the rat distal tubule epithelium [375], and it has been claimed that P2X4-like receptors regulate ATP-stimulated epithelial Na^{2+} channel activity in distal tubule A6 epithelium [432].

The intercalated cells of the distal nephron protrude 1–3 μm further into the lumen than the principal cells; they release ATP in response to mechanical stress [136]. Extracellular nucleotides regulate Na^+/H^+ exchanger isoform 3 activity in the A6-NHE3-transfected cell line; A6-NHE3 cells are A6 cells selected on the basis of high transepithelial responsiveness to aldosterone [10]. The $P2Y_1$ receptor in A6 cells can increase both cAMP/PKA and Ca^{2+}/PKC intracellular levels, and it is claimed that the PKC pathway is involved in cystic fibrosis transmembrane conductance regulator activation [120]. A6 cells were used to show that aldosterone stimulates ATP release from the basolateral side of distal tubular cells; ATP then acts via purinoceptors to produce contraction of small groups of adjacent epithelial cells, which results in apical swelling that disrupts the ENaC interaction with the F-actin cytoskeleton, opening the channel and hence increasing sodium transport [112]. 'Aldosterone escape' refers to the excretion of sodium during high sodium intake; local purinergic tone in the aldosterone-sensitive distal nephron downregulates ENaC activity. $P2Y_2^{-/-}$ mice had significantly less increased sodium excretion than wild-type mice [354]. It was concluded that control of ENaC by purinergic signalling is necessary for aldosterone escape and this was supported by another laboratory in a later paper, and in addition, it identified a potential role for NO and prostaglandins in response to aldosterone [434]. Mechanical stimulation of purinergic signalling leads to activation of transient receptor potential vanilloid (TRPV) 4 channels, an important component of the mechano-sensitive response of the aldosterone-sensitive distal nephron [236].

The MDCK cell line has been widely used for studies of distal tubule activities. An early paper showed that exogenous ATP stimulated ion transport in cultured MDCK cells [341]. Electrophysiological studies showed that ATP and UTP hyperpolarise MDCK cells by increasing the K^+ conductance [95,206]. A later paper from this group showed that ATP increased $[Ca^{2+}]_i$; calcium then activates K^+ channels and thus leads to hyperpolarisation of the cell membrane [281]. Regulation of transepithelial ion transport by two different receptors on the apical membrane of MDCK cells was claimed [430], the data implicating $P2Y_1$ and $P2Y_2$ (or $P2Y_4$) receptors. Lanthanum inhibits UTP-induced Ca^{2+} mobilization in MDCK cells [164]. $P2Y_1$, $P2Y_2$ and $P2Y_{11}$ receptor mRNA was shown to be expressed by MDCK cells, but the $P2Y_2$ receptor was dominant in mediating ATP activation of cAMP formation [155,295,373,427]. A later paper showed expression of $P2Y_6$ (as well as $P2Y_1$, $P2Y_2$ and $P2Y_{11}$) receptors in MDCK cells [142]. Functional P2X7 receptors are also expressed by MDCK cells [163].

Mechanical stimulation of ATP release from MDCK cells (as well as COS-7 and HEK-293 cells) occurs on changing the medium and other experimental protocols with cultured cells, leading to $P2Y_1$ and $P2Y_2$ receptor activation [275]. Activation of P2Y receptors caused strong and persistent shrinkage of MDCK renal epithelial cells [195]. The cloning and tissue expression of MDCK $P2Y_2$ receptors has been reported [426]. Cyclooxygenase (COX)-2 is constitutively expressed by MDCK cells, which participates in $P2Y_2$ receptor-mediated signalling [276]. Transcellular ion currents in ATP-treated MDCK cells are mainly caused by the coupled function of apical and basolateral anion transporters providing transient Cl^- secretion [31]. Adenosine induces ATP release via A_1 receptors in MDCK cells [244]. Cl^- secretion in MDCK monolayers treated with basolateral ATP is triggered by $P2Y_1$ receptors and is mediated by subsequent $[Ca^{2+}]_i$-independent activation of PLA and PKA [3]. Mitochondria play an important role in adenosine-induced ATP release from MDCK cells [245]. Activation of the Na^+–K^+–Cl^- co-transporter in MDCK cells is via Ca^{2+}-independent signalling triggered by apical $P2Y_2$ and basolateral $P2Y_1$ receptors [4]. Rapid pressure changes induce both apical and basolateral ATP release [299]. In a later paper, it was shown that subtle flow changes sensed by the primary cilium induced nucleotide release, which amplified the epithelial $[Ca^{2+}]_i$ response [296].

As reported earlier for proximal tubule cells, there is reversible tight junction disassembly during ATP depletion and repletion in MDCK cells [111]. MDCK epithelia spontaneously release ATP resulting in $[Ca^{2+}]_i$ oscillations leading to modifications of steady-state renal function [105]. In a later paper, it was shown that the frequency of oscillations was increased by extracellular nucleotides and was decreased if the nucleotides were removed by apyrase [380]. Betaine serves as an osmolyte that is accumulated by tubular cells to maintain osmotic balance. Acute inhibition of the betaine transport by ATP and adenosine in MDCK cells has been reported [185]. Endogenous ATP release inhibits electrogenic Na^+ absorption and stimulates Cl^- secretion in MDCK cells [419]. Activation of c-Jun and/or p38 contributes to Na^+–K^+–Cl^- co-transport suppression in MDCK cells by exposure to $P2Y_1$ agonists [5]. The proto-oncoprotein SYT(SS18) controls ATP release and regulates cyst formation by polarised MDCK cells, suggesting that SYT plays a vital role in controlling epithelial morphogenesis and might explain the lethality of its loss in the developing embryo [56]. P2 receptor-mediated inhibition of vasopressin (AVP)-stimulated fluid transport and cAMP response in AQP2-transfected MDCK cell has been reported [186].

Adenosine modulates Mg^{2+} uptake in distal convoluted tubule cells via A_1 and A_2 receptors [181] and a volume-sensitive-like chloride conductance in a rabbit distal convoluted tubule cell line (DC1) [316]. Both basolateral and apical

A_1 receptors were shown to mediate sodium transport in cultured A6 cells [234].

Collecting ducts

A large number of P2X and P2Y receptor subtypes have been localised to the rat collecting duct. Immunohistochemistry has identified the expression of P2X1 (intercalated cells only, sodium-restricted only) P2X2, 4, 5 and 6 subunits and $P2Y_{2, 4, 6, 11, 12 \text{ and } 13}$ subtypes [188,375,409]. These immunohistochemical data have largely been validated by mRNA expression profiles in the rat tubule. $P2Y_{1, 2, 4 \text{ and } 6}$ metabotropic and P2X4 ionotropic receptor mRNAs were identified in the cortical and outer medullary collecting duct [13,15,409], with P2X1 and 6 receptor mRNAs also reported following dietary sodium restriction [409]. mRNA for $P2Y_{1, 2, 4 \text{ and } 6}$ subtypes was identified in the inner medullary collecting duct (IMCD) [188,433]. P2X1, 4, 5, 6 and 7 mRNAs have been localised to the murine cortical and outer medullary collecting duct, indicative of species differences in expression profiles [219]. In humans, only P2X4 has been detected in significant amounts in the collecting duct [50]. Activation of P2X receptors increased both sodium and water excretion [168]. Hypotonic treatment evokes biphasic ATP release across the basolateral membrane of cultured A6 cells [106,172].

Although the functional role of P2 receptors in the collecting duct is complex, several studies, using a combination of approaches, have demonstrated that extracellular nucleotides modulate water and electrolyte handling in this region of the nephron. These effects are important for sodium and water homeostasis since it is in this section of the nephron that urinary excretion is fine-tuned to meet the body's overall requirements.

Water transport

The regulation of urine concentration and water homeostasis occurs in the collecting duct, under the control of AVP released from the brain. AVP increases the water permeability of the collecting duct by evoking the translocation to the apical membrane of the aquaporin 2 water channel (AQP2): this requires phosphorylation of AQP2 by PKA. In addition to these rapid, non-genomic effects, chronic AVP stimulation increases the water permeability of the collecting duct through the increased transcription of the AQP2 gene. Several studies have demonstrated that nucleotides have an inhibitory affect on the action of AVP in the collecting duct.

The ability of ATP to modulate AVP-induced water permeability in the collecting duct was first demonstrated in the mid-1990s. ATP was shown to reversibly inhibit AVPs' actions in isolated perfused rabbit CCD and rat IMCD [187,188,314]. Since UTP and ATP were equipotent, the inhibitory effects were attributed to the activation of $P2Y_2$ [188]. $P2Y_2$ couples to the G-protein G_q, and as such, its stimulation causes the activation of PLC, increased inositol trisphosphate production and consequently the mobilization of $[Ca^{2+}]_i$. Both ATP and UTP stimulated intracellular calcium release in rat IMCD [74], and inhibition of calcium mobilization attenuated ATP's effects in isolated rabbit CCD [314]. Notably, adenylate cyclase, stimulated by AVP and PLC, stimulated by ATP, are mutually inhibitory pathways. PLC activates PKC, which inhibits adenylate cyclase [369]. Indeed the inhibitory effects of $P2Y_2$ receptors have been shown to be associated with PKC-dependent reductions in cAMP [187]. More recently, COX-1-mediated prostaglandin (PG) E_2 synthesis has also been implicated in ATPs' inhibitory effects. ATPγS stimulation of IMCD fractions from hydrated rats resulted in increased PGE_2 synthesis [357,401], an effect that was blunted in IMCD fractions from dehydrated rats [357]. Furthermore, enhanced $P2Y_2$ abundance (mRNA and protein) was documented in hydrated rats and was associated with increased PGE_2 [191]. Since PGE_2 decreases the water permeability of the collecting duct, these data add support to the concept that cross-talk between AVP and ATP provides an additional level of hydrosmotic regulation. Indeed, chronic stimulation of V2R with ddAVP, as would occur during dehydration, reduced $P2Y_2$ abundance in rats [357]. However, the interaction between AVP and ATP may vary in the short and long term. In isolated perfused CCD, acute AVP exposure stimulated nucleotide secretion [264]. A recent paper has shown that ATP counteracts AVP-induced water permeability by increasing AQP2 degradation in lysosomes, preceded by ubiquitin internalization and by decreasing AQP2 gene transcription by reducing AVP-induced cAMP levels [29].

$P2Y_2$ is located on both the apical and basolateral membranes of the collecting duct [188]; however, the demonstration that luminal ATP did not alter AVP-stimulated water permeability in isolated rat IMCD suggested that its effects are mediated by activation of $P2Y_2$ receptors on the basolateral membrane [76]. Recent studies in immortalised mouse collecting duct cells (mpkCCDc14) have provided a possible mechanism for ATP's inhibitory effect on water transport. Whereas ddAVP application resulted in increased AQP2 immunofluorescence at the apical membrane, ATP and ATPγS resulted in AQP2 internalisation. In addition to basolateral $P2Y_2$ receptors, luminal P2X2 and $P2Y_4$ stimulation may also be involved in ATP's inhibitory effects. Co-expression of these receptors with AQP2 in *Xenopus* oocytes resulted in decreased membrane expression of AQP2 and, consequently, attenuated water permeability [415].

Gene deletion studies have substantiated the findings from the pharmacological manipulation. $P2Y_2^{-/-}$ mice have increased medullary AQP2 expression and greater basal collecting duct fluid reabsorption than wild-type controls. These data suggest that $P2Y_2$ stimulation provides a tonic inhibition of AVP actions at V_2 receptors [309,382,433].

Sodium transport

The effects of extracellular nucleotides on sodium reabsorption in the collecting duct have largely been discerned through the evaluation of amiloride or benzamil-sensitive sodium transport, taken to reflect the activity of the epithelial sodium channel. Koster et al. [197] made the first demonstration that activation of P2 receptors inhibited benzamil-sensitive sodium transport. Using cultured rabbit collecting duct cells, they showed that both apically and basolaterally applied ATP inhibited benzamil-sensitive short circuit currents (an indicator of sodium transport). The inhibition of Na^+ transport was dependent on PKC but not Ca^{2+} signalling. Since ATP and UTP were equipotent, and ADP had no effect, inhibition of ENaC-mediated sodium transport was attributed to activation of $P2Y_2$ [197]. Subsequently, studies in the M-1 mouse collecting duct cell line demonstrated that amiloride-sensitive sodium reabsorption was reduced by both the apical and basolateral application of ATP and UTP. Since ADP and UDP had no effect, these results were consistent with the activation of $P2Y_2$. Indeed, the presence of $P2Y_2$ receptors in the cell line was confirmed by RT-PCR [63]. However, in contrast to the data from cultured rabbit collecting duct cells, the effects of ATP were not dependent on PKC activation [370]. In a different model, mIMCD-K2 mouse collecting duct cells, apical (but not basolateral) nucleotides inhibited sodium reabsorption, an effect, which based on mRNA expression and pharmacological profiling, was attributed to activation of $P2Y_1$, $P2Y_2$, P2X3 and P2X4 receptors [238]. More recently, studies in the mouse IMCD cell line (mIMCD-3) provided a possible mechanism for nucleotide-mediated ENaC inhibition. Extracellular nucleotides caused a reduction in serum- and glucocorticoid-inducible kinase-1 (SGK1) expression and activity. Since SGK promotes the insertion of ENaC into the apical membrane, it was postulated that nucleotides modulate sodium reabsorption through the regulation of SGK1 and, consequently, ENaC activity [220]. In addition, local phosphoinositide levels may modulate basal and acute ENaC activity. In immortalised mouse CCD cells, (mpkCCDe14), phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2) concentrations correlated with ENaC activity. Given that the inhibition of both purinergic signalling and PLC rescued ENaC activity, it was postulated that purinergic regulation of PI(4,5)P2 concentrations, through the activation of P2Y receptors, modulates ENaC activity [288]. ENaC in the aldosterone-sensitive distal nephron is under tonic inhibition by local purinergic signalling responding to changes in dietary sodium intake [37]. Table 2 summarises P2 receptor actions on ECaC activity.

In addition to the inhibition of sodium reabsorption, ATP stimulation also increases Cl^- secretion. In mIMCD-3 cells, ATP stimulates Cl^- conductance by a calcium-dependent mechanism [352]. Extracellular ATP-induced calcium signalling requires both P2X and P2Y receptors in mIMCD-3 cells [417]. The TRPC3 is exclusively expressed in the apical membrane of principal cells of the collecting duct, both in vivo and in the mIMCD cell line. It has been shown that mIMCD-3 cells have two distinct calcium influx pathways: a store-operated channel activated by thapsigargin and basolateral ATP and TRPC3 channels activated by apical ATP [108]. Adenosine, acting on A_{2B} receptors, also enhances Cl^- secretion through cystic fibrosis transmembrane conductance regulator (CFTR) in IMCD-K2 cells [302]. The authors proposed that the adenosine receptor pathways might provide one mechanism for enhancing urine NaCl excretion in the setting of high dietary NaCl intake. It was later proposed that $P2Y_1$ and $P2Y_2$ receptors operate in tandem in IMCD cells to enhance urinary NaCl excretion in these conditions [303]. A recent whole kidney study showed that in rats on high sodium intake, adenosine had the potential to enhance renal excretion [201].

Table 2 A summary of the effects of P2 receptor activation on ENaC activity (reproduced from [414], with permission from Springer)

Epithelia	Species	P2 receptor involved (localisation)	Effect on $I_{am\text{-}s}$	Mechanism	Reference
CCD	Mouse	$P2Y_2$ (ap., baso.)	Inhibits	–	[214]
CD	Rat	P2X4-like (ap.)	Inhibits	–	[332]
CCD/OMCD	Rat	$P2Y_2$/$P2Y_4$ (ap.)	Inhibits	PKC	[413]
		P2X4/P2X4/6 (ap.)	Inhibits or potentiates	? or PI3K	[413]
M1 cell line	Mouse	$P2Y_2$ (ap., baso.)	Inhibits	$\uparrow [H^+]_{int}$	[63,370]
A6 cell line	*Xenopus*	$P2Y_2$ (ap.)	Inhibits	PLC, $\downarrow PIP_2$, ↓ open prob.	[232]
		P2X4-like (baso.)	Potentiates	PI3K, ↑ open prob.	[432]
CCD 1° cultures	Rabbit	$P2Y_2$-like (ap., baso.)	Inhibits	PLC, PKC	[197]
mIMCD-K2 cell line	Mouse	P2X3, P2X4, $P2Y_1$, $P2Y_2$ (ap.)	Inhibits	–	[238]

$I_{am\text{-}s}$ amiloride-sensitive current (i.e. ENaC-mediated current), *ap.* apical membrane, *baso.* basolateral membrane, ↑ increase, ↓ decrease, *PKC* protein kinase C, *PLC* phospholipase C, *PI3K* phosphoinositide 3-kinase, *PIP2* phosphatidylinositol bisphosphate, *MAPK* mitogen-activated protein kinase, *1°* primary cell cultures, *open prob.* single channel opening probability, *CCD* cortical collecting duct, *OMCD* outer medullary collecting duct

Further to the results from cell culture, nucleotide-induced inhibition of sodium transport has also been demonstrated in native collecting duct tissue. In isolated perfused mouse collecting ducts, the application of luminal ATP and UTP caused increased calcium release [67] and inhibition of amiloride-sensitive sodium transport [214], effects which were attributed to the stimulation of $P2Y_2$ receptors. Consistent with $P2Y_2$ receptors being the primary mediator of nucleotide-induced inhibition of ENaC, ATP's effects on sodium reabsorption were significantly reduced in collecting duct cells isolated from $P2Y_2^{-/-}$ receptor mice. However, residual ATP effects implicated the involvement of other P2 receptors [289]. Recently, $P2Y_2$ receptor activation has been shown to increase renal Na^+ excretion and decrease blood pressure [310].

Shirley et al. [332] provided the first in vivo evidence that P2 receptors on the apical membrane of the collecting duct inhibit sodium reabsorption. Rats were maintained on a low sodium diet to induce ENaC expression and urinary recovery of ^{22}Na during microperfusion of the late distal nephron used to assess sodium reabsorption. Notably, despite the firm evidence from in vitro studies in mice showing $P2Y_2$-mediated inhibition of sodium reabsorption in the collecting duct, $P2Y_2$/$P2Y_4$ 'selective' agonists had no effect in the rat preparation, and the involvement of a P2X heteromer was hypothesised [332]. More recently, patch-clamp studies in split open rat CCDs have demonstrated the involvement of both apical P2X and P2Y receptors in the modulation of ENaC activity. Activation of $P2Y_2$ and $P2Y_4$ receptors resulted in PLC-dependent inhibition of ENaC activity. Interestingly, activation of P2X4 and P2X4/6 receptors caused an inhibition of ENaC activity when luminal concentrations of sodium were high (145 mM); however, when sodium concentrations were reduced to more physiological levels (50 mM), activation of the receptors potentiated ENaC activity [412,413]. In accordance with a P2X4 component to purinergic regulation of sodium transport is the demonstration that in the 'distal-like' cell line, *Xenopus* A6 cells, activation of basolateral P2X4-like receptors resulted in increased apical membrane insertion of ENaC. These data suggest that there is reciprocal purinergic signalling for the control of sodium transport by both apical and basolateral purinoceptors ([432]; see Fig. 5). These data highlight the complex relationship between apical and basolateral P2 receptors in the modulation of sodium transport in the collecting duct.

An additional layer of complexity was unveiled with the demonstration that sympathetic nerve varicosities are in close apposition to basolateral membranes of collecting duct epithelial cells of the rat kidney [230]. It was suggested that while luminal responses to autocrine or paracrine release of ATP from epithelial cells may dominate in normal physiological conditions, in pathological states, such as stress and dehydration, ATP released as a cotransmitter from sympathetic nerves may be involved in modulating collecting duct fluid and electrolyte transport via basolateral purinoceptors. It is interesting that in a recent paper, it was shown that chronic renal sympathetic denervation increased the renal tubular natriuretic and diuretic actions of ATP mediated by P2X receptors [199].

Gene deletion studies have focused on sodium homeostasis in $P2Y_2$ null mice. Mice lacking $P2Y_2$ receptors have hypertension and facilitated sodium and water reabsorption of the aldosterone-

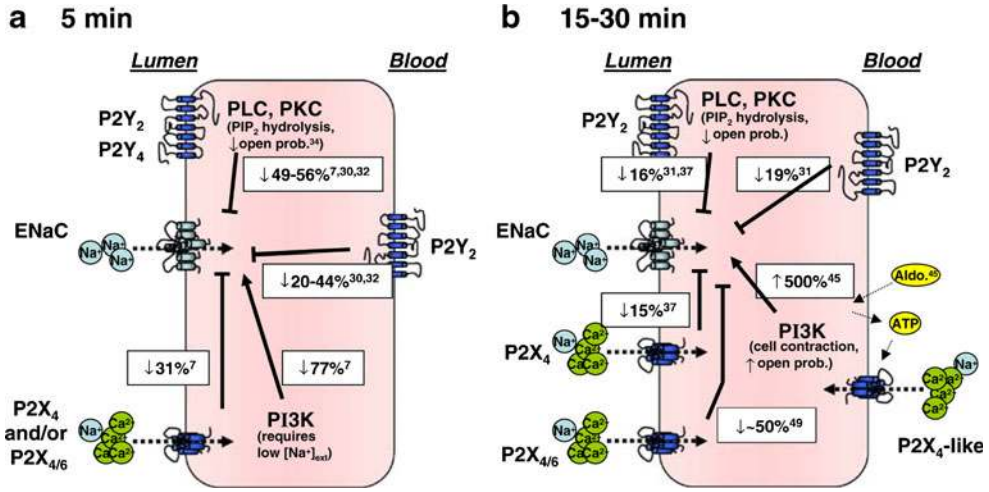

Fig. 5 A summary of known effects of P2 receptor (P2R) activation on ENaC activity taken from experiments using renal principal cells (PCs) or distal nephron-derived cell lines. Relevant references are superscripted. In **a**, effects where 5 min or less are left between P2R activation and measurements of ENaC activity. All but apical P2X4/6 activation decreases the activity of ENaC. Apical P2X4/6 has the ability to inhibit or potentiate ENaC activity depending on the concentration of luminal Na^+. Noteworthy is that basolaterally expressed P2X4 receptors have not been reported to affect ENaC activity. In **b**, effects where 15–30 min are left between P2R activation and measurement of ENaC activity. All apically expressed P2Rs inhibit ENaC, although the ability of P2Y receptors to inhibit ENaC is less than that in **a** (from 49–56 to 16 %). The potentiating effect of apical P2X4/6 receptors (when luminal Na^+ is low) has not been investigated over a 30-min period, but a potentiating effect of basolaterally expressed P2X4-like receptors has been reported (reproduced from [414], with permission from Springer)

sensitive distal nephron [309]. Resting ENaC activity was greater in $P2Y_2^{-/-}$ receptor mice than controls suggesting that local ATP may be involved in the regulation of basal ENaC activity in the murine collecting duct [289,290]. Additional studies from the same laboratory demonstrated that ENaC downregulation in response to sodium restriction was lost in the $P2Y_2$ null mice, suggesting a role for the receptor in the renal response to altered sodium intake [291]. Despite this, the hypertension was not salt-sensitive, suggesting that these renal changes are compensated for elsewhere.

Extracellular ATP in the CCD not only inhibits ENaC, but also stimulates calcium-activated chloride channels (CACC). It has been shown that ATP stimulates CACC-mediated Cl^- adsorption during aldosterone stimulation, and it was suggested that an interplay between purinergic signalling pathways and aldosterone may be involved in regulation of NaCl transport in CCD cells under different states of extracellular fluid volume [304].

Release and metabolism of nucleotides

Release of nucleotides from renal cells was originally suggested from studies of cell lines [328,329,387]; it is now clear that native renal tubules are also able to secrete ATP. Nucleotide release from renal epithelia is both constitutive (suggestive of a 'purinergic tone') and activated by mechanical or agonist-induced stimuli. Microelectrodes have measured steady-state ATP concentrations of ~400 nM in the rat kidney cortex and showed that infusion of Ang II caused a rapid and transient increase, consistent with regulated release of nucleotide [277].

In vivo micropuncture experiments indicate that luminal ATP in the PCT is 200–300 nmol/l, higher than concentrations in the glomerular filtrate [388], consistent of release into the urine from epithelial cells. In contrast, concentrations in distal tubule fluid were approximately 30 nmol/l.

In isolated perfused mouse TAL, spontaneous oscillations in $[Ca^{2+}]_i$ were dependent on tubular nucleotide release [105]. Furthermore, flow-induced elevations of Ca^{2+} transients were also dependent on nucleotide release, being blocked by application of an ATP scavenger or the P2 receptor blocker suramin [174]. Agonist-induced nucleotide release has also been demonstrated in the TAL, with intraluminal AVP causing intraluminal nucleotide concentrations to rise to 200–300 nmol/l [264]. This study also showed that AVP could trigger nucleotide secretion from the mouse CCD: intraluminal ATP/UTP concentrations again reached values approaching 300 nmol/l.

It is open to debate whether the nucleotide concentrations measured intraluminally in the above studies reflect those in

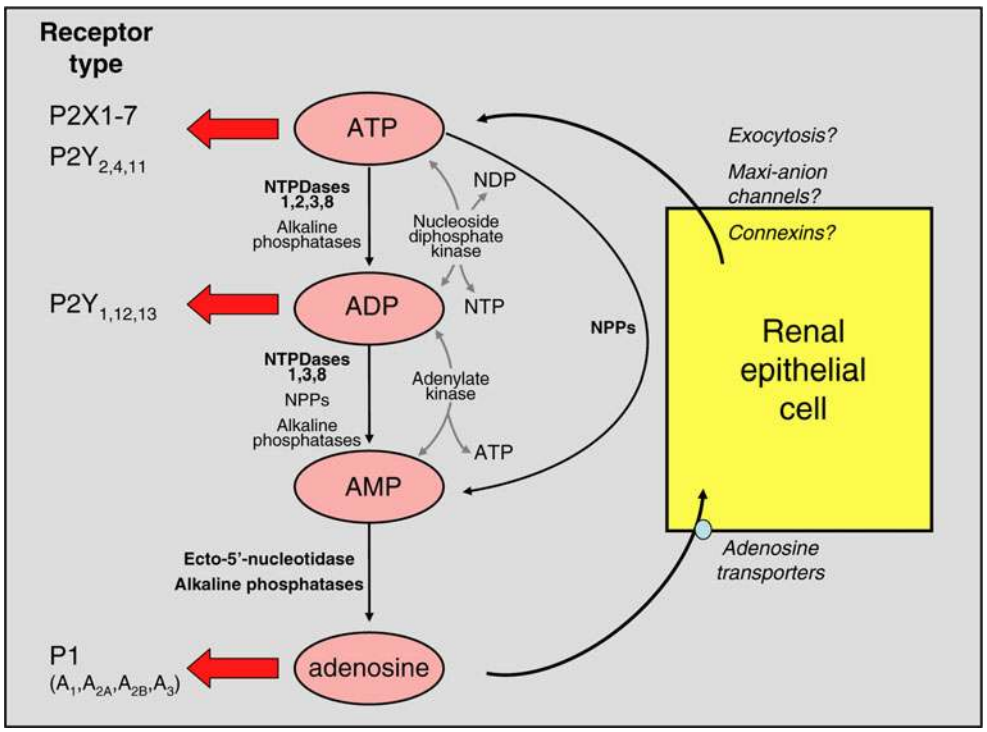

Fig. 6 Potential effects of renal ectonucleotidases and consequences for activation of purinoceptor subtypes. The major enzymes involved in each degradative pathway are shown in *bold print*; for more details, see text. The information given in the figure indicates the relative potencies of ATP and ADP with respect to P2X and P2Y receptor subtypes. At sufficiently high concentrations, ATP can activate all P2 receptors other than $P2Y_6$ and $P2Y_{14}$. It is important to note that nucleotides derived from other bases are also hydrolysed/synthesised by these enzymes, but have been omitted for clarity. Uracil-based nucleotides are particularly significant: UTP is a potent agonist of $P2Y_2$ and $P2Y_4$ subtypes, and its dinucleotide derivative UDP is the major naturally occurring agonist of the $P2Y_6$ subtype. The mechanism(s) of ATP exit from renal cells has/have not been defined. *NDP* nucleoside diphosphate, *NTP* nucleoside triphosphate (reproduced from [333], with permission from Springer)

the vicinity of the P2 receptors in the cell membrane. Membrane-bound and soluble ectonucleotidases (vide infra) will rapidly metabolize secreted nucleotides, and it has been estimated that bulk-phase measurements could underestimate concentrations at the cell membrane by more than 20-fold, at least in astrocytes [179]. Figure 6 summarises the distribution of ecto-nucleotidases along the nephron.

Flow-induced nucleotide release

In renal cells, a primary cilium protrudes into the tubule lumen and responds to changes in flow by bending and increasing $[Ca^{2+}]_i$ [299]. MDCK cells, which have properties of cells in the collecting duct, are ciliated and release ATP in response to increased flow [297]. Removal of the cilium or application of apyrase or suramin to the apical membrane prevented flow-induced nucleotide release.

TRPV4 channels are critical to flow-induced nucleotide release. In isolated thick ascending limbs, ATP secretion is substantially reduced following blockade or siRNA knock-down of TRPV4 [337]. Similar data were obtained in MDCK cells [198], and here TRPV4 colocalises in cilia with polycystin 2. Polycystin 2 is an ion channel devoid of intrinsic mechanosensitive properties but forms with TRPV4 in the cilium base a complex allowing Ca^{2+} influx when the cilium is bent. This triggers the release of nucleotides and autocrine/paracrine activation of P2 receptors [297].

Mechanism of nucleotide release

The exit route for secretion of nucleotide is not yet resolved: several pathways may contribute and this may differ from segment to segment. Exocytosis of vesicles containing ATP is well established in neurones, and a similar mechanism is observed in cell lines of proximal tubular origin [387]. A variety of channels/transporters may also contribute to nucleotide release. In the macula densa, for example, ATP transport across the basolateral membrane is mediated by maxi-anion channels [22] and contributes to tubuloglomerular feedback (see above). CFTR channels may also mediate ATP release in the kidney [348], but this has not received firm support [296].

More recently, connexin hemichannels have emerged as a route for ATP release from renal cells. Connexins are transmembrane proteins and several members of the family are expressed in the renal vasculature and tubules [123]. The homo- or heteromeric assembly of six connexins forms a connexon: two connexons from neighbouring cells can dock to form a gap junction. Undocked connexons may also function as transmembrane hemichannels and these contribute to cellular ATP secretion [60]. Evidence from Cx30 null mice suggests a similar role in the distal nephron [342]. In wild-type mice, increases in tubular flow or reductions in osmolarity of the bathing solution caused increases in ATP concentration to 10–50 μmol/l: these responses were almost absent in Cx30 knockout mice.

Although intriguing, these data must be assessed cautiously since connexin hemichannels appear to open only under non-physiological conditions [297]. In contrast, pannexins, structurally homologous to connexins [317], are permeable to ATP and can be activated by membrane depolarisations in the physiological range [229]. It now seems likely that pannexin-1 hemichannels mediate ATP release from epithelial cells involved in water and sodium reabsorption [124].

Metabolism by ectonucleotidases

Extracellular nucleotides are rapidly degraded to other nucleotides or nucleosides by surface-located and soluble enzymes (ectonucleotidases). Four families of ectonucleotidases exist: ectonucleoside triphosphate diphosphohydrolases (NTPDases), ectonucleotide pyrophosphatase phosphodiesterases (NPPs), ecto-5′-nucleotidase and alkaline phosphatises, and all are found in the kidney [333]. These enzymes play an important part in renal nucleotide signalling. They will control the availability of nucleotides agonists by hydrolysis and also dictate the signalling environment via generation of nucleotides or nucleosides that preferentially target different P2/P1 receptor subtypes.

The NTPDase family comprises eight members of which four (NTPDases 1, 2, 3 and 8) hydrolyse extracellular nucleotides. NTPDase1 hydrolyses ATP and ADP with almost equal preference, whereas NTPDase2 has a much greater preference for ATP, therefore causing accumulation of ADP; NTPDases 3 and 8 are intermediate in their preference [333]. These differential preferences for hydrolysis are functionally significant. For example, the presence of NTPDase1 will abruptly terminate all P2 receptor stimulation, whereas if NTPDase2 is expressed alone, the conversion of ATP to ADP would potentiate $P2Y_1$, $P2Y_{12}$ and $P2Y_{13}$ receptor activation [382].

NTPDase1 is prominent throughout most of the renal vasculature and evident in the thin ascending limb of Henle and medullary CD [190,389]. NTPDase2 has been immunolocalised to Bowman's capsules and to most nephron segments beyond the proximal tubule [190,389]. NTPDase3 has a similar distribution to NTPDase2 [389], whereas information on NTPDase8 is incomplete.

The NPP family comprises seven members, but only NPPs 1–3 are able to hydrolyse nucleotides. NPPs can hydrolyse ATP and ADP to AMP. Information on the intrarenal distribution of NPPs is limited. NPP1 protein is expressed in proximal tubules and in basolateral membranes of distal tubules [126]. NPP3 is localised to rat glomeruli and the proximal straight tubule but is absent in distal nephron segments [389].

Ecto-5′-nucleotidase catalyses the final stage of nucleotide hydrolysis to nucleoside and is highly expressed in the kidney;

it is found in apical membranes of rat PCT and in intercalated cells throughout the distal nephron, as well as the peritubular space [98,207,389].

The physiological role of these enzymes is not clear and experimental evidence is limited. Nevertheless, NTPDase1 in the vasculature prevents ADP-induced platelet aggregation [81] and may also terminate P2X1-mediated vasoconstriction in response to ATP. In the glomerulus, NTPDase1 and NPP3 could influence the ultrafiltration coefficient by controlling P2 signalling in mesangial cells [166].

Renal pathophysiology

Renal injury and failure

It has been proposed that adenosine mediates haemodynamic changes in adult renal failure [57,344]. In human renal cortex, sympathetic nerve stimulation releases ATP and NA, and NA acting on non-neuronal cells also releases ATP. The released ATP has mitogenic effects on glomerular epithelial cells, probably via $P2Y_1$ receptors, and ATP has the potential to contribute to remodelling of the kidney and progression to chronic renal failure, a condition that presents with sympathetic overactivity [391]. While P2X7 receptors are only weakly expressed in healthy glomerulus, following glomerular injury (for example, in diabetes and hypertension), it is significantly upregulated, mainly in podocytes, but also in endothelial and mesangial cells [393]. P2X7 receptors have been shown to participate in disturbed intracellular calcium homeostasis in peripheral blood mononuclear cells of patients with chronic kidney disease [205]. Cyclosporine has become a standard component of the immunosuppressive regime in both solid organ and bone marrow transplantation as well as for the treatment of autoimmune diseases. However, a limiting factor in its use has been the development of nephrotoxicity and hypertension in many patients. Using the adriamycin nephropathy mouse model of chronic renal injury, regulatory T cells were shown to participate in CD39-mediated protection from renal injury [397]. A K_{atp} channel opener, nicorandil, reduces chronic renal injury by targeting podocytes and macrophages [365].

Primary idiopathic nephrotic syndrome is a source of morbidity in children; in some cases, mutations in podocyte genes explain the proteinuria, although it has been proposed that the condition is linked to T cell immunity. It has been claimed that ATP plays a key role in the regulation of innate immunity in this disease, and the effects of adenosine are reduced by the decreased expression of ectonucleotidase in this syndrome [24].

A mechanism has been proposed linking renal tubular epithelial cell death and injury to renal interstitial peritubular fibroblasts, which suggests that P2X7 receptors mediate deleterious renal epithelial–fibroblast cross-talk [293]. In another paper from this group, it was shown that necrotic renal proximal epithelial cells stimulated the expression of P2X7 receptors in renal interstitial fibroblasts through activation of the ERK signalling pathway [294]. It has been suggested that P2X7 receptor antagonists could offer innovative preventive and therapeutic modalities for the treatment of morbidity and mortality associated with kidney injury [429]. ATP binding enhanced the activity of ClC-5, the transporter mutated in Dent disease, a disease affecting the renal proximal tubule [405]. Arterial calcification is prevalent in patients with chronic kidney disease and ATP signalling appears to be involved (see review by [90]).

It has been reported that A_{2B} receptor-mediated induction of interleukin (IL)-6 contributes to renal fibrogenesis, and the authors suggested that this receptor may have therapeutic potential for treatment of chronic kidney disease [65]. A_{2B} receptor activation protects against acute kidney injury via inhibition of neutrophil-dependent release of tumour necrosis factor-α [116]. Dendritic cells activated by A_{2A} receptor agonists attenuate acute renal injury [221]. A review describing adenosine generation and signalling during acute kidney injury is available [20].

Polycystic kidney disease

PKD is a genetic disorder associated with abnormal proliferation of tubular cells of the adult nephron [53]. This leads to progressive dilation of tubules, which eventually become encapsulated in fluid-filled cysts that compress and destroy neighbouring tissue. ATP is released and reaches high concentrations within cysts [329,416]. Autosomal dominant polycystic disease (ADPKD) is characterised by bilateral cyst formation in the kidneys. It is a genetic disease caused by the mutation of either PKD1 or PKD2, which encodes for polycystin. Polycystin-2 is localised to the cilia of mouse and human vascular endothelial cells, which sense fluid flow via purinergic receptor activation and NO release, but in ADPKD patients, it is absent [1]. The authors suggest that aberrant expression of polycistin-2 in cilia could promote high blood pressure because of inability to synthesise NO in response to shear stress produced by changes in blood flow. Expression of polycistin-1 enhances endoplasmic reticulum calcium uptake and decreases capacitative calcium entry in ATP-stimulated MDCK cells [137]. The nematode *Caenorhabditis elegans* has been used as an animal model for studying basic molecular mechanisms underlying human ADPKD; the *C. elegans* LOV-1 and PKD-2 proteins are homologues of human PC-1 and PC-2 proteins. Using this model, it was claimed that ciliary localised ATP synthase may play a role in polycystin signalling [141]. The involvement of nucleotide release in both fluid flow and pressure responses and its role in altered mechanosensory transduction in the aetiology of PKD is discussed in a recent review [279]. Using collecting duct principal cells derived from the Oak Ridge polycystic kidney

mouse model of ARPKD, it was shown that the loss of apical monocilia impairs flow-induced ATP secretion across the apical cell surface and ATP-induced calcium signals [140].

P2X7 receptors were shown to be expressed in collecting duct cysts in the *cpk/cpk* mouse model of congenital PKD [132], where it mediates cyst development [133]. In a later paper from this group $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, P2X5 and P2X7 receptors were detected on the epithelial cells lining renal cysts in the Han:SPRD cy/+ rat model of ADPKD [376]. The expression levels of mRNA and protein for $P2Y_2$, $P2Y_6$ and P2X7 receptors increased significantly as the disease developed, all mediating mechanisms potentially relevant to cyst growth and cell turnover. Blockade of the P2X7 receptor with oxidised ATP (or A-438079) reduced cyst formation via ERK-dependent pathways in a zebrafish model of PKD [52]. It was suggested that nucleotides present in the cyst lumen fluid could activate P2Y receptors to increase the growth of MDCK-derived cysts [377]. Attenuated flow-induced ATP release contributes to the absence of flow-sensitive, purinergic $[Ca^{2+}]_i$ signalling in human ADPKD cyst epithelial cells [421]. Monocilia of ductal epithelia are a major focus in PKD. It has been proposed that ATP is released from monocilia to act as an autocrine regulator via P2 receptors [138]. Deficiency of PKD-1 gene expression increases A_3 receptors in human renal cells [2]. The potential for cyst formation has been examined for two MDCK cell subclones, C7 cells that resemble principal cells and C11 cells that resemble α-intercalated cells [36]. It was concluded that principal rather than intercalated cells had the ability to form cysts, based on a synergism of cAMP and ATP signalling in enhancing apical fluid secretion.

Ischaemia

There is rapid early decline of proximal tubular ATP in ischaemic acute renal failure [336]. Over-expression of manganese superoxide dismutase protects against ATP depletion-mediated cell death of proximal tubule cells occurring with ischaemia/reperfusion injury during kidney transplantation [62].

Human antigen R (HuR) is a nucleocytoplasmic shuttling protein that binds and stabilizes mRNAs containing adenine- and uridine-rich elements. ATP depletion from proximal tubule cells during ischaemia results in heightened HuR protein translation and suggests a role for HuR in protecting kidney epithelia from injury during ischaemic stress [175]. STAT 3, a member of the family of signal transducers and activators of transcription, inhibits apoptosis of human proximal tubular epithelial cells induced by ATP depletion during ischaemia [395].

ATP depletion of MDCK cells has been used as an in vitro model of renal ischaemia and Rho GTPase signalling shown to regulate tight junction assembly and protect tight junctions during ATP depletion [110]. It has been claimed that in renal ischaemia, the ATP depletion-induced alteration in membrane transport function and cell viability are due to reactive oxygen species generation and cytosolic PLA_2 activation in proximal tubular cells [209]. Hepatocyte growth factor has been shown to enhance recovery from renal tubular ischaemia and to promote adhesion of the ATP-depleted renal collecting duct cell line, mIMCD-3, in a MAPK-dependent manner [228]. Restoration after ischaemia by perfusion of ATP-$MgCl_2$ was described early [104,335]. A_3 receptor knock-out mice are protected against ischaemic renal failure [208]. Ischaemia remodels filamentous actin leading to desquamation of proximal tubular epithelial cells via ATP depletion-induced p38 MAPK–HSP27 signalling [72]. These findings are of potential pathophysiological importance for understanding the overall involvement of the actin cytoskeleton in cell detachment during ischaemia. Deficiency or inhibition of the ectonucleotidase CD73 protected against kidney ischaemia–reperfusion injury and the authors suggested that AMP may play a direct protective role against this type of injury [305]. In a later study, it was claimed that CD73 protects the kidney from ischaemia–reperfusion injury through adenosine production and reduction of free radicals [177]. The role of adenosine in protection from acute kidney injury has been discussed [425].

Nephritis

Glomerulonephritis is a leading cause of end-stage renal disease and its treatment is non-specific immunosuppression, which has significant adverse side effects. Increased expression of the pro-apoptotic ATP-sensitive P2X7 receptors has been demonstrated in both experimental and human glomerulonephritis and opens up the possibility that P2X7 receptor antagonists may have therapeutic potential [378]. Indeed, a later paper from this group showed that P2X7 receptor deficiency attenuated renal injury in experimental glomerulonephritis [368]. In $P2Y_1$ receptor knock-out mice, there is protection against capillary loss, fibrosis and death by renal failure during experimental crescentic glomerulonephritis [134]. Treatment with an adenosine uptake inhibitor attenuates glomerulonephritis in mice [262]. Activation of A_{2A} receptors has been proposed as a treatment for macrophage-mediated experimental glomerulonephritis ([100]; see also [85]). In experimental mesangial proliferative glomerulonephritis in the rat (anti-Thy-1 model), there is a pronounced mesangial cell proliferative response leading to glomerular hypercellularity. In the anti-Thy-1 model, PPADS specifically and dose-dependently reduced early (day 3) but not late (day 8) mesangial cell proliferation [313]. The authors also reported that $P2Y_2$ and $P2Y_6$ receptors showed a transient marked increase in expression during anti-Thy-1 disease. There are significant pro-inflammatory activities of extracellular nucleotides during anti-Thy-1 nephritis, and an anti-inflammatory

role for glomerular ecto-nucleotidases suggested to convert ATP and ADP into anti-inflammatory adenosine [292]. Tuboglomerular feedback is diminished in Thy-1 nephritic rats, but this is improved by exogenous 5′-nucleotidase [363].

Lupus nephritis is a frequent and potentially fatal complication of systemic lupus erythematosus. A_{2A} receptor activation reduced inflammation in the kidneys of MRL/lpr mice and it was suggested that this could be considered as a novel therapeutic approach for human lupus nephritis [431]. In a recent paper, it has been reported that P2X7 receptor blockade attenuates lupus nephritis by inhibiting NLRP3/ASC/caspase-1 inflammasome activation [436].

Hypertension

Hypertension is a feature of chronic renal disease and it has been claimed that this is largely due to sympathetic overactivity triggered by afferent signals emanating from the kidney and resetting sympathetic tone by stimulation of hypothalamic centres [268]. Both essential hypertensive patients and patients with renal artery stenosis show a dose-dependent vasodilation following adenosine infusion [407,408]. Enhanced increase in $[Ca^{2+}]_i$ was found in mesangial cells in response to ATP in spontaneously hypertensive rats [226] and NO can increase P2Y receptor resensitization [227].

The kidney plays a dominant role in the development and maintenance of hypertension and the shift of renal autoregulation towards higher pressure underlying sodium-insensitive hypertension [362]. There is an enhanced P2 receptor-mediated vasoconstriction of afferent and efferent arterioles in chronic Ang II-induced hypertensive rats [94]. It was claimed that gap junction Cx37 and Cx40 transduce purinergic signals mediating renal autoregulation [364]. In a recent paper, it was shown that ATP release through Cx30 is part of a local regulatory system intrinsic to the aldosterone-sensitive distal nephron important for control of sodium excretion [246]. They showed that loss of paracrine ATP feedback regulation of ENaC to respond to changes in sodium levels contributed to salt-sensitive hypertension in $Cx30^{-/-}$ mice. Purinergic receptors contribute to early mesangial cell transformation and renal vessel hypertrophy during Ang II-induced hypertension [114]. Renal interstitial adenosine is increased in Ang II-induced hypertensive rats [93]. Mice lacking $P2Y_2$ receptors have salt-resistant hypertension [309]. There is an exaggerated response to adenosine in kidneys from high salt-fed rats [223]. While the P2X7 receptor is only weakly expressed in healthy kidney glomerulus, it is significantly upregulated in ren-2 transgenic hypertension [393]. In a recent paper, it was shown that P2X7 receptor antagonism prevented the development of salt-sensitive hypertension and renal injury in Dahl salt-sensitive rats [176]. ATP-induced hypotension is associated with alteration of sympathetic nerve activity mediated through vagal afferent pathways [366]. It has been reported that there is an increase in ATP hydrolysis resulting from an increase in ecto-5′-nucleotidase activity and accumulation of adenosine in the kidney of hypertensive animals [96]. A high salt diet given to Ang II hypertensive rats significantly impairs autoregulation of rat juxtamedullary afferent arterioles, which is associated with a decline in afferent arteriolar reactivity to ATP mediated by P2X1 receptors [154]. However, reactivity to UTP via $P2Y_2$ receptors or to adenosine via P1 receptors was unchanged. It was suggested that understanding this mechanism may lead to therapeutic interventions to prevent renal decline early in the hypertension progression. The hypertensive responses to L-N^G-nitroarginine methyl ester and Ang II were attenuated in A_1 receptor knockout mice [99]. Adenosine, acting via A_1 receptors in the proximal tubule, modulates deoxycorticosterone acetate–salt hypertension in mice [404].

Diabetic nephropathy

Diabetic nephropathy is the most common cause of end-stage renal disease. Lack of A_1 receptors augments diabetic hyperfiltration and glomerular injury [83]. Treatment with adenosine receptor agonists protected diabetic rats from nephropathy by exerting hypoglycaemic and antioxidant effects as well as reducing gene expression of proinflammatory cytokines [78]. A recent review is concerned with the targeting of adenosine signalling via A_{2B} antagonists for the treatment of diabetic nephropathy [301].

Increased ATP release induced by hyperglycaemia may contribute to mesangial extracellular matrix expansion that occurs in diabetes [346]. Increased expression of P2X7 receptors was shown in the streptozotocin diabetic rat model, mainly in podocytes but also in endothelial and mesangial cells [393]. Diabetic milieu, represented by high glucose concentrations, affects purinergic modulation of glucose transport into podocytes, which may play a role in the development of diabetic podocytopathy [182]. P2X4 receptors mediate high glucose-induced activation of the NOD-like receptor 3 inflammasome, regulate IL-1 family cytokine secretion and cause the development of tubulointerstitial inflammation in diabetic nephropathy [54].

A major limitation in chronic lithium treatment for bipolar patients is the development of nephrogenic diabetes insipidus, which manifests as polyuria, polydipsia and reduced ability to concentrate urine associated with a lack of response of the medullary collecting duct to AVP. Genetic deletion of the $P2Y_2$ receptor offers significant resistance to the development of lithium-induced nephrogenic diabetes insipidus polyuria [435].

Inflammation

ATP, via $P2Y_2$ receptors, inhibits inducible NOS (iNOS) in cultured mesangial cells and it has been suggested that it may play a critical role for iNOS expression and synthesis of NO during glomerular inflammatory disorders [249]. ATP has also

been claimed to produce long-term pro-inflammatory effects in rat mesangial cells via it degradation to adenosine and action on A_{2A} receptors, resulting in PLA_2 and cytokine induction [322]. The P2X7 receptor plays a major role in the inflammatory process, since activation leads to release of inflammatory cytokines [55,204]. Activation of A_{2A} receptors prevents progressive kidney fibrosis in a model of immune-associated chronic inflammation [101] and of obstructive nephropathy [418].

Hyper- and hypothyroidism

ATP-mediated vasoconstriction of perfused rat kidney was increased in hyperthyroid kidneys and severely attenuated in kidneys from hypothyroid rats and the vasodilator response abolished [386]. Experimental hyperthyroidism modifies binding of A_1 and A_{2A} agonists in rat kidney, and this might be responsible for the incapacity for urine concentration seen in the hypothyroid kidney [92].

Nephrotoxicant injury

Reduction of drug-induced nephrotoxicity by ATP-$MgCl_2$ was reported [355]. PKB activation increases intracellular ATP levels and decreases necrosis in proximal tubular cells injured by nephrotoxicants [330]. ATP levels in kidneys are decreased by ingestion of tullidora, a poisonous plant, which may partly explain its acute toxic effects and mortality [173]. Cisplatin is a potent anti-neoplastic drug whose clinical use is limited by its ability to induce nephrotoxicity. It has been suggested that adenosine may be involved in the haemodynamic changes in the kidney induced by cisplatin [128]. Cisplatin upregulates A_1 receptors in rat kidney [25] and A_1 receptor antagonists have a protective effect against cisplatin-induced acute kidney injury in rats [107]. Adenosine antagonists have protective effects against acute renal failure [156,253,358]. A_1 receptor antagonists are effective against the development of nephrotoxicity by cyclosporine, an immunosuppressive agent [18]. Cyclosporine increases plasma levels of adenosine in kidney transplant patients [43]. A_3 receptor antagonism is effective against acute tacrolimus toxicity [241].

Renal transplants

An ATP release assay has been used to help determine the risks of developing infection or rejection in renal transplant recipients [42]. The beneficial effects of adenosine and phosphate in kidney transplant preservation have been claimed [23].

Summary

Purines have been shown to control TGF, regulate renin release and regulate tubular ion and water transport. There is autocrine/paracrine release of ATP from epithelial and endothelial cells, as well as release as a cotransmitter from sympathetic nerves. Purinergic signalling is involved in kidney disorders, including PKD, nephritis, hypertension, diabetes and nephrotoxicant injury, and purinergic therapeutic strategies are being explored to treat these diseases.

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