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The $P2X_7$ ATP Receptor in the Kidney: A Matter of Life or Death?

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Abstract
$P2X_7$ is an intriguing membrane receptor for the extracellular nucleotide ATP, which functions as a ligand-gated ion channel; it can activate cell membrane permeabilization and also has a wide range of downstream signaling pathways, including mediation of inflammatory responses and modulation of cell turnover. Despite recent identification of $P2X_7$ receptor protein in the renal tract, the biological and potential pathological functions of this receptor and its signaling cascades in the kidney are not yet fully understood. $P2X_7$ receptor protein is expressed in normal kidney development, predominantly in the condensing mesenchyme, and later in the maturing and adult derivatives of the ureteric bud. Glomerular expression of the molecule is scarce in normal kidney, but is upregulated in chronic and inflammatory conditions, suggesting a role in the inflammatory response or in repair and remodeling in these settings. $P2X_7$ receptor expression in the adult collecting ducts of murine kidney, as well as the collecting duct cysts in autosomal recessive polycystic kidney disease, has been described and agonists of the receptor can modulate the development of renal cysts in an in vitro model of cyst formation derived from the *cpk/cpk* mouse. Further investigation of the function of the $P2X_7$ receptor in normal and abnormal kidneys might lead to novel therapeutic targets in a wide range of renal diseases.

P2X Receptor Signaling

The history of extracellular nucleotides as signaling molecules, from the pioneering demonstration of their cardiovascular actions by Drury and Szent-Gyorgi in 1929, to the initial suggestion of a 'purinergic' autonomic signaling system [1] and subsequent classification of the two groups of receptors (P2X and P2Y) for extracellular nucleotides [2, 3], has been extensively reviewed [4]. The P2X family of purinergic receptors includes seven ligand-gated ion channels, with two membrane-spanning domains, intracellular N- and C-termini, and a large cysteine-rich extracellular loop, similar in structure to the DEG/ENaC superfamily of membrane receptors. The latter include the mechanosensitive receptors of *Escherichia coli*, degenerins in *Caenorhabditis elegans* and the vertebrate epithelial sodium channel (ENaC) [5], which display a wide variety of biological functions, including mechanosensation, proprioception, epithelial sodium

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transport and, importantly, cell loss. Following cloning and production of specific antibodies to P2X receptor proteins, it has been demonstrated that they have a remarkably wide pattern of expression; the potential significance of this receptor family in the renal tract has already been reviewed [6].

The $P2X_7$ receptor, first characterized in immune cells [7] and subsequently cloned from a rat brain cDNA library [8], has now been shown to have a wide expression pattern, particularly in epithelial cells of the gastrointestinal tract, skin, salivary gland and urinary tract. The receptor has unique properties, which appear to relate to its structural differences from the other P2X members, namely a longer intracellular C-terminus encoded by exons 12 and 13. The resulting 200 amino acid tail confers the ability of the molecule to form a large permeabilizing 'pore' [8], enabling the receptor to function not only as a non-selective cation channel, but also to mediate cell membrane permeabilization. In addition to its membrane properties, $P2X_7$ receptor mediates many other cellular sequelae: some are related to immune responses, including cytokine release, phospholipase D activation and L-selectin shedding, as well as structural responses like microvesiculation and surface blebbing seen in fibroblasts [9]. $P2X_7$ receptor stimulation also has significant effects on cell survival, inducing release of interleukin-1β, activation of NFκB and NFAT and the induction of both apoptotic and necrotic cell death. Apoptosis occurs in cells endogenously expressing $P2X_7$ receptors, such as dendritic cells [10], lymphocytes [11], macrophages [12], microglial cells [13] and renal mesangial cells [14], as well as transfected cell lines [15]; it has also been suggested that $P2X_7$ activation can cause proliferation of lymphocytes [16].

However, the functional importance of the $P2X_7$ receptor in either normal or disease states is still unknown. The ability of $P2X_7$ receptors to mediate modulation of inflammatory responses and the dual role in cell turnover, potentially effecting both apoptosis *and* proliferation, suggest they may be important in situations in which these processes are prominent, including normal and abnormal renal function. The recent discovery of a polymorphism in the C-terminus of human $P2X_7$ causing loss of receptor function [17], may support a role for this receptor in control of cell turnover in the hematopoietic system, although its significance remains unclear. Initial reports of increased frequency of the loss of function polymorphism in subgroups of leukemic patients [18] suggested a tumor-suppressor role for $P2X_7$, but there is now a growing consensus that $P2X_7$ may be overexpressed in hematopoietic tumors, expression relating to poorer prognosis and lower remission rates [19, 20]. Thus, the importance of $P2X_7$ in the control of cell survival remains controversial.

$P2X_7$ Receptor Expression in the Kidney and Urinary Tract

Early studies of $P2X_7$ receptor expression demonstrated only low levels of mRNA in normal kidney [21], but now there is increasing evidence for changes in its expression in the kidney and renal tract (table 1). Two groups have shown that despite low levels being found in normal rat kidney, rat mesangial cells in culture show upregulation of expression when exposed to inflammatory mediators such as LPS, interferon-γ or TNF-α [14, 22]. $P2X_7$ mRNA has also been detected in differentiated podocytes in culture [23]. The presence of receptor protein in these in vitro cell lines has still to be confirmed, and immunohistochemical evidence for $P2X_7$ receptor protein expression in the intact urinary tract has been largely restricted to rodent models: $P2X_7$ receptors were first documented in the urothelium of normal adult rat bladders [24] and have now been localized to specific cell types of the developing mouse kidney, normal adult tubular epithelium and cystic epithelia of a mouse model of polycystic kidney disease [25], as well as in human autosomal recessive polycystic kidney disease (ARPKD) [26].

Sources of Extracellular ATP

Recent data reveals functionally significant levels of ATP, the endogenous P2X receptor ligand, within the renal tract. In addition to release of intracellular ATP by stressed or dying cells, it is also well established that nerve cells (including neurotransmitter release), endothelia, platelets, red cells and epithelia can release nucleotides in a non-lytic (independent of cell damage) and physiological manner [27]. In the kidney, ATP has been shown to be released from normal tubular epithelium: micromolar concentrations are released from proximal tubule epithelial primary cultures or cell lines; nanomolar concentrations from thick ascending limb and collecting duct cell lines [28] and, interestingly, higher concentrations from abnormal cystic epithelial cells derived from both human and mouse polycystic kidneys [29]. ATP can also be measured in tubular fluid, with significantly higher concentration in the proximal tubule [30] and virtually undetect-

Table 1. $P2X_7$ receptor expression in the urinary tract: expression of $P2X_7$ receptor mRNA or protein in cell lineages of mouse, rat and human renal and lower urinary tract

Distribution	Protein	mRNA	Species	Reference (first author)
Whole kidney		+	Human	Rassendren, 1997 [21]
Metanephric mesenchyme	+		Mouse	Hillman, 2002 [25]
Podocytes		+	Mouse	Fischer, 2001 [23]
		+	Human	Vonend, 2002 [39]
	+		Rat	Vonend, 2004 [35]
Mesangial cells		+	Rat	Schulze-Lohoff, 1998 [14]
		+		Harada, 2000 [22]
Collecting duct epithelium	+		Mouse	Hillman, 2002 [25]
cpk/cpk mouse cysts	+	+	Mouse	Hillman, 2002 [25]
ARPKD cysts	+		Human	Hillman, 2004 [26]
Bladder/ureter urothelium	+		Rat	Lee, 2000 [24]
	+		Mouse	Hillman, 2002 [25]

able amounts in Bowman's space [D.G. Shirley, pers. commun.]. It is released predominantly from the apical surface of lining cells and in response to cell swelling, suggesting a role in the regulation of cell volume [31]. In addition, recent demonstration of ATP release from the *macula densa* cells of the thick ascending limb suggests a role in tubulo-glomerular feedback regulation of glomerular filtration rate [32]. The augmentation of ATP levels by downregulation of ectoATPases in conditions like inflammation and hypoxia could also enhance the functional contribution of this P2X receptor in the diseased kidney.

$P2X_7$ Function in the Renal Tract

The demonstration of both the presence of $P2X_7$ receptors and the release of ATP in the renal tract are consistent with a functional role for nucleotide signaling. Attempts to define the functional importance of this potential signaling system, however, have been impeded by the limitations of available agonists and antagonists. There are to date no specific agonists of the P2X receptors: the nucleotide potency profile of $P2X_7$ differs from the other P2X molecules, the more potent agonists being shown first: BzATP >> ATP >2-MeSATP > ATPγS >> ADP [8], which can aid investigation of receptor function in vivo. A blocking monoclonal antibody to human $P2X_7$ is available for in vitro studies, but available antagonists of the rodent receptor tend to be species-specific, non-selective and may be associated with toxicity on prolonged use. This review describes the results of investigations using currently available pharmacological tools, but the development of more selective agents is anticipated.

$P2X_7$ Receptors in Nephrogenesis

In developing mouse kidneys, $P2X_7$ receptor immunoreactivity exhibits an interesting pattern, both spatially and temporally. During the early stages of nephrogenesis, between embryonic days 13 and 15 (E13 and E15) after conception, at which time mesenchymal cells form aggregates around the arborizing ureteric bud, $P2X_7$ receptor protein is expressed by cells of the condensing mesenchyme. These aggregates mature into glomeruli and associated proximal tubules; however, from E16 on, $P2X_7$ receptor immunoreactivity is found only in derivatives of the ureteric bud, such as collecting duct and ureteric epithelium, and is no longer found in the derivatives of the aggregating mesenchyme [25]. $P2X_7$ receptor protein is therefore expressed in two distinct cell lineages in a time-dependent manner during nephrogenesis. This study also confirmed previous findings of $P2X_7$ receptor protein in the urothelium of rodent bladder and ureter [24].

The specific expression pattern of $P2X_7$ receptors in the condensing mesenchyme in early nephrogenesis correlates spatially and temporally with marked cell proliferation and apoptosis, consistent with the concept that the receptor may have an important role in cell turnover in the developing kidney: $P2X_7$ receptors are expressed

by mesenchymal cells condensing around the ureteric bud at a time when they are undergoing rapid turnover as modeling of the maturing organ takes place. Although $P2X_7$ receptors can be shown to be present in cells positive for proliferating cell nuclear antigen (PCNA), a marker of cell proliferation, as well as those with morphological features of apoptosis, functional studies are required to determine if there is any direct relationship between $P2X_7$ receptor expression, cell survival and subsequent renal histomorphology. It is also noteworthy that the $P2X_7$ receptor is expressed at a time, and location, of cell aggregation and early lumen initiation. It could be surmised that $P2X_7$ receptor-mediated alteration of cell survival, or other function, at this crucial stage might affect the renal architecture. However, the apparent lack of any gross renal anomaly in a recently produced knockout mouse suggests that if this is the case, it is subtle, for example, a change in nephron number. To address this issue, culture of mouse kidneys with varying exposure to both agonists and antagonists of the $P2X_7$ receptor, as well as closer examination of nephrogenesis and adult histology of the $P2X_7$ knockout mouse will be necessary.

$P2X_7$ Receptors in Tubular Epithelium

$P2X_7$ receptor protein has been localized to the epithelium of the collecting ducts of normal mice from development to 4 weeks postnatally, or early adulthood [25], although its functional importance in this site is unclear. There is little in the way of cell turnover in the adult collecting duct, so it may be that $P2X_7$ has an alternative role in this situation. $P2X_7$ has been found in various epithelial tissues, such as rat submandibular salivary gland, where apical receptors respond to apical BzATP, a potent ligand for the $P2X_7$ receptor [33]. It has been proposed that $P2X_7$, by means of its ability to act as a cation channel, can cause fluxes of solute and water across the luminal surface, and that ATP signaling may mediate regulation of cell volume. However, there are currently no data to support the role of the receptor in the normal collecting duct: a study of potential P2Y activity in isolated mouse collecting ducts found no response in terms of calcium influx to apically or basolaterally applied BzATP [34]. This suggests that the protein may be nonfunctional in this segment, that it is expressed in an age-dependent manner, or that its stimulation is not coupled to a change in intracellular calcium. $P2X_7$ has been immunolocalized only to 4 weeks postnatally in the mouse, while adult mice were used in this functional study [34].

$P2X_7$ Receptor in the Glomerulus

Although expression of $P2X_7$ receptors by mesangial cells has been clearly documented in terms of mRNA localization in cultured cells, attempts to demonstrate protein expression in vivo yielded very low levels of expression in the normal rat kidney [22]. However, in vitro investigation did find that upregulating expression of the receptor mRNA using inflammatory cytokines resulted in functionally significant receptor protein: exposure of mesangial cells under these conditions to external ATP induced apoptotic cell death [14]. This is the only direct evidence for function of the protein in glomerular cells and it is important in that as well as showing that $P2X_7$ receptors can influence cell survival, it supports a potential role for this molecule in glomerular function in disease. Recent demonstration of the upregulation of $P2X_7$ receptor mRNA and protein in two models of chronic renal injury also support a role for this receptor in the glomerulus. In both the streptozotocin-induced diabetic and ren-2 transgenic (TGR) hypertensive rat models, $P2X_7$ receptors were upregulated in the glomerulus and localized to podocytes, but also to mesangial and endothelial cells [35].

To investigate further the role of $P2X_7$ receptor-mediated cell death, and in inflammatory pathways in the glomerulus, it will be important to examine inflammatory models of renal disease, such as the anti-Thy-1 model in the mouse, an inflammatory state in which apoptosis has been shown to be an important mechanism of clearance of excess cells, and an important correlate of recovery of normal renal histology and function [36]. A more definitive approach to determine the importance of the $P2X_7$ receptor in this setting would be to assess the severity and recovery from renal inflammatory injury in a $P2X_7$ knockout mouse.

$P2X_7$ Receptors in Polycystic Kidney Disease

In addition to the expression of $P2X_7$ receptor protein in normal developing collecting ducts, receptor expression has also been documented in the abnormal, dilating collecting duct cysts of the *cpk/cpk* mouse [25], a model with significant phenotypic similarity to human ARPKD. Receptor expression is identified from prenatal stages through to 4 weeks postnatally and at the stage of severe uremia, that is, throughout the period of development and expansion of renal cysts. Expression of $P2X_7$ receptors has also been shown in fetal ARPKD renal cyst epi-

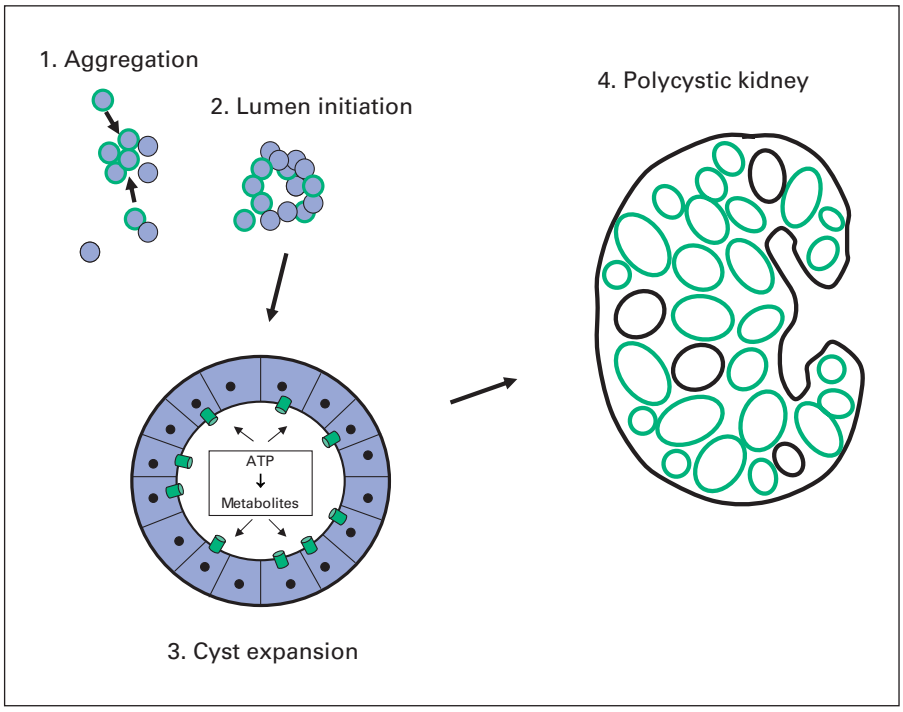

Fig. 1. Potential role of $P2X_7$ receptors in renal tubule and cyst formation. Schematic representation of potential $P2X_7$ receptor activity during the three stages of initiation and formation of lumen, tubes and cysts. (1) Cells initially aggregate and (2) a lumen is initiated. Cells of (a) the condensing metanephric mesenchyme and (b) aggregates in 3-dimensional *cpk/cpk* cyst culture preceding cyst formation, express $P2X_7$ receptor protein (shown in green). Aggregating cells receive polarizing signals to set apico-basal polarity and vesicles carrying apical membrane antigens are targeted to the prospective apical region and fuse with existing membrane or each other to form a lumen. Apoptosis of interior cells that fail to receive the polarizing signal, along with continued vesicle fusion and apical secretion expand the lumen. $P2X_7$ receptors may be important in aggregation or apoptosis at this stage. (3) Subsequent lumen expansion is a regulated process dependent on the balance of proliferation and apoptosis of epithelial cells and the net flux of fluid into the lumen. In tube formation, expansion occurs until inhibited by a size sensor, failure of which may result in abnormal tube and cyst expansion. In the kidney, $P2X_7$ receptors expressed in normal and cystic collecting ducts are well placed to modulate tubule or cyst expansion via changes in cell turnover within the epithelium, or transduction of solute and water flux into the lumen. (4) $P2X_7$ receptor protein is expressed in the majority of cysts at all stages of progression of *cpk/cpk* mouse polycystic kidney disease, and in established human ARPKD and ADPKD.

thelium [26] and also in human autosomal dominant polycystic kidney disease (ADPKD) kidneys. Prior to this finding, a role for nucleotides and purinergic receptors in the expansion of renal cysts had already been proposed. Nucleotides and their metabolites have been found in detectable amounts inside cysts of human polycystic kidneys, as well as significant and greater ATP secretion from cyst lining cells in culture when compared with normal human cultured proximal tubule cells [29].

ATP and other 'trapped' nucleotides are thought to act on (undefined) P2 receptors to induce solute and water influx and cause cyst expansion [29]. The recent description of $P2X_7$ receptor protein in the epithelia of the *cpk/cpk* mouse [25] lends some support to this hypothesis, the receptor being well placed to transduce solute and water fluxes into the lumen. An alternative role for the receptor in this setting is the induction of cell death. Apoptosis is known to occur in polycystic kidney diseases, predominantly in the interstitium between the cysts [37], where loss of tissue correlates closely with the decline in renal function [38]. However, in the *cpk/cpk* mouse, $P2X_7$ receptor expression is restricted to the cystic epithelium, known to undergo proliferation rather than apoptosis, suggesting $P2X_7$ receptors may have a very different role in this context, perhaps transducing solute and water fluxes or affecting cell turnover. An alternative function might involve modulation of initial cell aggregation and/or apoptosis at an earlier stage in lumen initiation (fig. 1).

Experiments to assess the functional role of $P2X_7$ receptors in cyst development have been performed in vitro using a 3-dimensional suspension model of cyst development derived from the *cpk/cpk* mouse, in which cysts form from an initial suspension of cell aggregates over a period of hours [26]. Intriguingly, exposure of dissociated 3-week-old *cpk/cpk* kidneys to agonists of the $P2X_7$ receptor results in a significant reduction in the numbers of cysts after 24 h, which can be markedly diminished by pre-incubation of tissue with the $P2X_7$ receptor antagonist oxidized ATP. Additional supportive evidence that this is $P2X_7$-mediated, rather than an effect of other co-expressed P2 receptors, is that the $P2X_7$ ligand BzATP has a much greater cyst-reducing effect than other nucleotides, such as ATP and UTP [26]. Attempts to define the mechanisms by which $P2X_7$ receptors mediate this reduction in cyst formation in vitro have so far found no significant alteration in markers of cell turnover, proliferation or apoptosis, supporting an alternative role for the receptor in this model. Ultimately, the biological importance of this in vitro effect could be tested by observing the frequency and severity of renal cysts in offspring of crosses between the $P2X_7$ knockout and *cpk/cpk* mice.

Conclusion

The current literature describes the presence of this unique P2X molecule in various cell types of the urinary tract, and leads to some interesting proposals as to the function on the $P2X_7$ receptor in the kidney. Work is currently underway to determine whether these receptors are functional in vivo and if so, to determine which of the receptors' many biological effects are important.

Recent identification of a common polymorphism in the $P2X_7$ receptor C-terminus in the human population, which not only alters receptor function, but also disease progression in chronic lymphocytic leukemia, is the first evidence for a potentially functional role of the $P2X_7$ receptor in human disease [18]. Identification of $P2X_7$ receptor-mediated functions in the kidney, particularly in the context of disease, may lead to the discovery of new therapeutic targets: manipulation of ATP signaling might be utilized to alter cyst expansion, and if the $P2X_7$ receptor has a role in cell death, this pathway could be targeted to reduce loss of functioning renal tissue in a wide range of pathological renal conditions.

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