Control of epithelial transport via luminal P2 receptors

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Leipziger, Jens. Control of epithelial transport via luminal P2 receptors. Am J Physiol Renal Physiol 284: F419–F432, 2003; 10.1152/ajprenal.00075.2002.—P2 membrane receptors are specifically activated by extracellular nucleotides like ATP, ADP, UTP, and UDP. P2 receptors are subdivided into metabotropic P2Y and ionotropic P2X receptors. They are expressed in all tissues and induce a variety of biological effects. In epithelia, they are found in both the basolateral and the luminal membranes. Their widespread luminal expression in nearly all transporting epithelia and their effect on transport are summarized. The P2Y2 receptor is a prominent luminal receptor in many epithelia. Other luminal P2 receptors include the P2X7, P2Y4, and P2Y6 receptors. Functionally, luminal P2Y2 receptor activation elicits differential effects on ion transport. In nearly all secretory epithelia, intracellular Ca2+ concentration-activated ion conductances are stimulated by luminal nucleotides to induce Cl−, K+, or HCO3− secretion. This encompasses respiratory and various gastrointestinal epithelia or tissues like the conjunctiva of the eye and the epithelium of sweat glands. In the distal nephron, all active transport processes appear to be inhibited by luminal nucleotides. P2Y2 receptors inhibit Ca2+ and Na+ absorption and K+ secretion. Commonly, in all steroid-sensitive epithelia (lung, distal nephron, and distal colon), luminal ATP/UTP inhibits epithelial Na+ channel-mediated Na+ absorption. ATP is readily released from epithelial cells onto their luminal aspect, where ecto-nucleotidases promote their metabolism. Adenosine generated by the action of 5′-nucleotidase may elicit further effects on ion transport, often opposite those of ATP. ATP release from epithelia continues to be poorly understood. Integrated functional concepts for luminal P2 receptors are suggested: 1) luminal P2 receptors are part of an epithelial “secretory” defense mechanism; 2) they may be involved in the regulation of cell volume when transcellular solute transport is out of balance; 3) ATP and adenosine may be important autocrine/paracrine regulators mediating cellular protection and regeneration after ischemic cell damage; and 4) ATP and adenosine have been suggested to mediate renal cyst growth and enlargement in polycystic kidney disease.

P2Y; P2X; chloride secretion; sodium absorption; epithelial sodium channel; potassium secretion

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be considered whether leakage of a “luminally” active substance may have occurred and whether the receptor site is actually on the basolateral membrane. Nonetheless, the use of immunocytochemistry and sided perfusion of high-resistance epithelia, like the collecting duct, has unequivocally demonstrated the existence of luminal membrane receptors and defined some important aspects of their biological function (34, 125). Certainly, the most convincing evidence comes from studies in which the same agonist leads to different effects when applied to either the luminal or basolateral side of the epithelium (54, 58, 82, 125). One prominent and well-established example of the control of epithelial transport via a luminal agonist and its corresponding luminal receptor is guanylin. This intestinal peptide hormone binds to the luminal guanylate cyclase receptor to stimulate cGMP elevations and subsequently G kinase-II-mediated CFTR activation and Cl− secretion (27). The guanylate cyclase receptor is also the target for Escherichia coli heat-stable enterotoxin that mediates severe secretory diarrhea (26).

For the mammalian nephron, a number of luminal agonists, such as PGE2 (125), vasopressin (52), or ANG II (104), have been described. Significant attention has recently focused on luminal ANG II and luminal AT1 receptors. Remarkably high intratubular proximal ANG II concentrations could be identified and are apparently generated by the proximal tubule itself. Luminal ANG II was shown to regulate Na+ and HCO3− absorption in the proximal and distal tubule, and thus ANG II obviously also travels along with the tubular fluid (104).

This review focuses attention on one specific family of receptors, namely, those activated by extracellular nucleotides like, e.g., ATP, ADP, UTP, or UDP. These P2 or purinergic receptors have come to the awareness of almost every researcher in biology, because they are ubiquitously expressed and are involved in a myriad of different cellular functions (113). Mammalian P2 receptors are subdivided into metabotropic (G protein-coupled) P2Y (P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, P2Y12, and P2Y13) and ionotropic P2X (P2X1-7 and P2XM) receptors (28, 113, 151, 161). One prominent feature of P2 receptors is their extraordinarily frequent expression, especially in the luminal membrane of epithelia. Extracellular luminal nucleotides have been shown to be prominent regulators of ion transport. The widespread epithelial P2 receptor expression is the reason for summarizing the present state of knowledge. This review tries to comprehensively summarize the evidence for luminal P2 receptors in intact epithelia and their functional effects on the various transport processes. More elaborate attention will be directed toward the mammalian nephron, and finally some integrative functional implications for luminal P2 receptors will be discussed.

**THE DISCOVERY OF LUMINAL P2 RECEPTORS**

Possibly the first experimental description of a luminal P2 receptor-mediated effect was documented in 1969, when Kohn et al. (65) investigated the transmural potential in the small intestine and showed that luminal (and basolateral) ATP stimulated a serosal positive-voltage change. The authors concluded that this reflected “stimulation of ion transport” but assumed an “intracellular action of ATP.” They speculated that “this might represent a direct stimulation of the electronegative sodium pump at the serosal pole of the epithelial cells” but were puzzled by the fact that they failed to demonstrate a significant depression of the response in Mg2+-free saline, although there is an absolute requirement for Mg2+ by the ATPase system. At that time, P2 receptors were yet to be discovered. Starting in the early 1990s, the work of a number of groups has led to a nearly comprehensive cloning and characterization of the large and diverse family of P2 receptors (113). Interestingly, the characterization of the luminal enterocyte P2 receptors in the small intestine still remains poorly defined, except that the P2Y4 receptor seems to be one possible candidate (15).

After the recognition of the P2 receptor family, it was the work of Wong (159) that led to the discovery that the isolated perfused rat epididymis responds to luminal ATP with Cl− secretion, e.g., movement of NaCl and H2O into the ductal lumen. Because no effect was detected with basolateral ATP, the authors concluded that a luminal P2 receptor is responsible for this effect. Obviously, the most important question was to establish the source of luminal ATP in the epididymis. The authors suggested that the high ATP concentrations present in the spermatozoa could be released, thereby stimulating Cl− secretion and fluidity of the local environment and thus facilitating sperm transport. Evidence for this is still pending, but present theories follow these lines and propose that extracellular ATP in general is a local paracrine/autocrine regulator (42). Thus the epididymis was the first intact epithelial tissue in which luminal P2 receptors were described, leading subsequent investigators to describe the effect of luminal ATP or other nucleotides in nearly all epithelial tissues. Noteworthy here is an early study by Simmons (137), who in 1981 described a luminal ATP-stimulated effect on Cl− secretion and correctly assumed that P2 receptors were localized at “each of the cellular membranes of this epithelium.” Table 1 summarizes the epithelial organs expressing luminal P2 receptors, the most likely P2 receptor subtype, and the regulated ion transport process.

**LUMINAL P2 RECEPTORS IN RESPIRATORY EPITHELIUM**

Not long after the results in epididymis appeared (159), the respiratory epithelium was discovered to be a remarkably rich source of the expression of luminal P2 receptors (64, 100). Activation of luminal P2 receptors in respiratory epithelium has two distinct effects on ion transport: 1) it activates NaCl secretion (46, 53, 100) and 2) it inhibits electrogenic Na+ absorption (18, 53, 93). Figure 1 shows a simplified schematic cell model of a secretory respiratory epithelial cell. Nucle-
<table>
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<tr>
<th>Epithelial Tissue</th>
<th>Species</th>
<th>Luminal Receptor</th>
<th>Agenist</th>
<th>Regulated Function</th>
<th>Intracellular Signal</th>
<th>Reference No(s.)</th>
</tr>
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<tr>
<td>Stria vascularis, vestibular dark cells</td>
<td>Gerbil</td>
<td>P2Y&lt;sub&gt;4&lt;/sub&gt;</td>
<td>ATP/UTP</td>
<td>K&lt;sup&gt;+&lt;/sup&gt; secretion ↓</td>
<td>PKC</td>
<td>88, 97, 98, 123</td>
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<tr>
<td>Stria vascularis, strial marginal cells</td>
<td>Gerbil</td>
<td>P2Y&lt;sub&gt;4&lt;/sub&gt;</td>
<td>ATP/UTP</td>
<td>K&lt;sup&gt;+&lt;/sup&gt; secretion ↓</td>
<td>PKC</td>
<td>88, 123</td>
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<tr>
<td>Outer hair cells</td>
<td>Guinea pig</td>
<td>P2X&lt;sub&gt;2&lt;/sub&gt;</td>
<td>ATP</td>
<td>Endocochlear potential ↓</td>
<td>Subapical</td>
<td>48</td>
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<tr>
<td></td>
<td>Guinea pig</td>
<td>P2Y</td>
<td>ATP</td>
<td>?</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
<td>95</td>
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<tr>
<td>Hensen cells</td>
<td>Guinea pig</td>
<td>P2X</td>
<td>ATP</td>
<td>?</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
<td>71</td>
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<tr>
<td>Reissner membrane epithelial cells</td>
<td>Guinea pig</td>
<td>P2X&lt;sub&gt;2&lt;/sub&gt;</td>
<td>ATP</td>
<td>Endocochlear potential ↓</td>
<td>60</td>
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<td>Conjunctival epithelium</td>
<td>Rabbit</td>
<td>P2X&lt;sub&gt;2&lt;/sub&gt;</td>
<td>ATP</td>
<td>ApoA</td>
<td>?</td>
<td>87, 111, 136</td>
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<td>Salivary gland duct</td>
<td>Rat</td>
<td>P2X&lt;sub&gt;2&lt;/sub&gt;</td>
<td>ATP, Bz-ATP</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
<td>79, 150</td>
</tr>
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<td>Salivary acinar submandibular cells (PartC10)*</td>
<td>Rat</td>
<td>P2X&lt;sub&gt;2&lt;/sub&gt;</td>
<td>UTP</td>
<td>I&lt;sub&gt;Na&lt;/sub&gt; ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
<td>79</td>
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<td>Sweat gland acinar cells&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Horse</td>
<td>P2Y&lt;sub&gt;2&lt;/sub&gt;, P2Y&lt;sub&gt;6&lt;/sub&gt;</td>
<td>ATP/UTP, UDP</td>
<td>Na&lt;sup&gt;+&lt;/sup&gt; secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
<td>156</td>
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<td>Nasal, bronchial</td>
<td>Human</td>
<td>P2Y&lt;sub&gt;2&lt;/sub&gt;</td>
<td>ATP=UTP</td>
<td>Na&lt;sup&gt;+&lt;/sup&gt; absorption ↓</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>18, 93, 100</td>
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<td>Trachea</td>
<td>Mouse</td>
<td>P2Y&lt;sub&gt;2&lt;/sub&gt;, P2Y&lt;sub&gt;6&lt;/sub&gt;</td>
<td>ATP=UTP, UDP</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>P2X&lt;sub&gt;1&lt;/sub&gt;/P2X&lt;sub&gt;5&lt;/sub&gt;</td>
<td>α,β-meth-ATP, Bz-bz-ATP</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
<td>146</td>
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<td>Primary culture</td>
<td>Rat</td>
<td>P2X&lt;sub&gt;2&lt;/sub&gt;</td>
<td>UTP/ATP</td>
<td>Na&lt;sup&gt;+&lt;/sup&gt; absorption ↓</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>51</td>
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<td></td>
<td>Rabbit</td>
<td>P2X&lt;sub&gt;2&lt;/sub&gt;</td>
<td>UTP/ATP</td>
<td>Na&lt;sup&gt;+&lt;/sup&gt; absorption ↓</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>56</td>
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<td>Distal bronchi</td>
<td>Pig</td>
<td>P2X&lt;sub&gt;2&lt;/sub&gt;</td>
<td>UTP/ATP</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
<td>66, 92</td>
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<td>Distal fetal lung</td>
<td>Rat</td>
<td>P2X&lt;sub&gt;2&lt;/sub&gt;</td>
<td>UTP</td>
<td>Na&lt;sup&gt;+&lt;/sup&gt; absorption ↓</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>114</td>
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<td>Mouse</td>
<td>P2X&lt;sub&gt;2&lt;/sub&gt;, P2X&lt;sub&gt;6&lt;/sub&gt;</td>
<td>ATP=UTP</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
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<td>Duodenum (villus cells)</td>
<td>Rat</td>
<td>P2X&lt;sub&gt;7&lt;/sub&gt;</td>
<td>Apoptosis (?)</td>
<td>?</td>
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<td>Guinea pig</td>
<td>P2X&lt;sub&gt;2&lt;/sub&gt;</td>
<td>ATP=UTP</td>
<td>HCO&lt;sub&gt;3&lt;/sub&gt; absorption ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
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<td>Rat</td>
<td>P2X&lt;sub&gt;2&lt;/sub&gt;, P2X&lt;sub&gt;4&lt;/sub&gt;</td>
<td>ATP=UTP, UDP</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
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<td>ATP=UTP, UDP</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
<td>91</td>
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<td>PDECA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Dog</td>
<td>P2X&lt;sub&gt;2&lt;/sub&gt;</td>
<td>ATP</td>
<td>Mucin secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
<td>105</td>
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<td>CFAPC-1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Human</td>
<td>P2X&lt;sub&gt;2&lt;/sub&gt;/P2Y&lt;sub&gt;4&lt;/sub&gt;</td>
<td>ATP=UTP/ATP</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
<td>8</td>
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<tr>
<td>Gall bladder</td>
<td>Mouse</td>
<td>P2Y&lt;sub&gt;2&lt;/sub&gt;/P2Y&lt;sub&gt;6&lt;/sub&gt;</td>
<td>ATP=UTP/UDP</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
<td>15</td>
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<td></td>
<td>Mouse</td>
<td>P2X&lt;sub&gt;2&lt;/sub&gt;</td>
<td>ATP</td>
<td>HCO&lt;sub&gt;3&lt;/sub&gt; secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
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<td>Necturus</td>
<td>P2Y&lt;sub&gt;2&lt;/sub&gt;</td>
<td>ATP</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>cAMP↑, ↑</td>
<td>152</td>
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<td></td>
<td>Rat</td>
<td>P2Y&lt;sub&gt;2&lt;/sub&gt;, P2Y&lt;sub&gt;6&lt;/sub&gt;, P2Y&lt;sub&gt;6&lt;/sub&gt;, 2-MeSATP</td>
<td>ATP, UTP, UDP, ADP, 2-MeSATP</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
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<td>Colon</td>
<td>Rat</td>
<td>P2Y&lt;sub&gt;2&lt;/sub&gt;/P2Y&lt;sub&gt;4&lt;/sub&gt;</td>
<td>ATP=UTP/ATP</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
<td>126, 129</td>
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<td></td>
<td>Rat, mouse</td>
<td>P2Y&lt;sub&gt;2&lt;/sub&gt;/P2Y&lt;sub&gt;4&lt;/sub&gt;</td>
<td>ATP=UTP/ATP</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
<td>58</td>
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<td>Caco-2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Human</td>
<td>P2X&lt;sub&gt;2&lt;/sub&gt;/P2Y&lt;sub&gt;4&lt;/sub&gt;, P2Y&lt;sub&gt;6&lt;/sub&gt;</td>
<td>ATP=UTP/ATP</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
<td>101</td>
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<td>Epididymis</td>
<td>Rat</td>
<td>P2X&lt;sub&gt;2&lt;/sub&gt;</td>
<td>ATP</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
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<td>Cortical collecting duct</td>
<td>Mouse</td>
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<td>ATP</td>
<td>Na&lt;sup&gt;+&lt;/sup&gt; absorption ↓</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
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<td>M-1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Mouse</td>
<td>P2X&lt;sub&gt;2&lt;/sub&gt;</td>
<td>ATP</td>
<td>K&lt;sup&gt;-&lt;/sup&gt; secretion ↓</td>
<td>PKG↑</td>
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<td>MDCK-C7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Dog</td>
<td>P2Y</td>
<td>ATP</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
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<td>MDCK-1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Dog</td>
<td>P2Y</td>
<td>ATP</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
<td>16, 147</td>
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<td>Primary culture&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Rabbit</td>
<td>P2Y</td>
<td>ATP</td>
<td>K&lt;sup&gt;-&lt;/sup&gt; secretion ↓</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
<td>83, 158</td>
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<td>Primary cultured PKD cyst</td>
<td>Rat</td>
<td>P2X</td>
<td>ATP</td>
<td>Na&lt;sup&gt;+&lt;/sup&gt; absorption ↓</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>68</td>
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<tr>
<td>epithelial cells</td>
<td>Human, mouse</td>
<td>P2Y and P2X</td>
<td>ATP=UTP, ATP</td>
<td>K&lt;sup&gt;-&lt;/sup&gt; secretion ↑</td>
<td>[Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sup&gt;2&lt;/sup&gt;↑, ↑</td>
<td>135</td>
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</table>

[Ca<sup>2+</sup>]<sup>2</sup>, intracellular Ca<sup>2+</sup> concentration; I<sub>Na</sub>, short-circuit current; MDCK, Madin-Darby canine kidney cells; IMCD, inner medullary collecting duct; PKD, polycystic kidney disease. Whether these or other luminal P2 receptors are expressed in the corresponding intact tissues may be still uncertain. P2 receptor expression shows significant alterations under the different culture and developmental conditions (110, 149). * Cultured cell line. † Activation. ‡ Silberberg SD, personal communication.
Luminal P2 receptors in Gastrointestinal Tract Epithelia

In addition to the lung and the epididymis, the activation of ion secretion is also a hallmark of luminal P2 receptor stimulation in the gastrointestinal (GI) tract. In the GI tract, this comprises the activation of K⁺ secretion in the distal colon (58) and gallbladder (13); HCO₃⁻ secretion in the gallbladder (11), intrahepatic bile duct (22), and pancreatic duct (54); and Cl⁻ secretion in biliary duct cells (118, 129), gallbladder (13, 152), small intestine (15), and cultured pancreatic duct cells (8, 105).

Luminal Nucleotides in GI Tract Glandular Secretion

For salivary (78), bile (22, 118), and pancreatic (54) juice formation, the following has been suggested and extends the two-step model (acinar production and ductal modification) of glandular secretion by a luminal P2 receptor component. In an initial step, ATP could be secreted by the acinar cells [salivary gland acini, hepatocytes, or pancreatic acini (54, 79, 91)]. Second, ATP, as it travels along the duct, would find luminal P2 receptors and influence ion transport to modify the specific composition of the digestive juices. In support of this concept, recent results provide evidence for carbachol-stimulated ATP release from rat pancreatic acini (138). Thus a physiological stimulus for the formation of primary pancreatic juice triggers ATP release for further intraductal pancreatic juice modification. A stimulating effect of luminal ATP/UTP on HCO₃⁻ secretion was recently shown in isolated guinea pig pancreatic ducts (54). Interestingly, addition of basolateral ATP/UTP inhibited HCO₃⁻ secretion in this tissue. The luminal P2 receptor in guinea pig pancreatic duct appears to be the P2Y₂ subtype (54). In rat pancreatic duct, evidence for a P2X₇ receptor (54) was recently reported (43, 91). It was also proposed that duct cells themselves participate in luminal ATP release and thus would regulate secretion in an autocrine or paracrine fashion (54, 118).

In addition, ATP and UTP stimulate Cl⁻ secretion in biliary duct cells (118, 129), gallbladder (13, 152), small intestine (15), and cultured pancreatic duct cells (8, 105).

Luminal P2 Receptors in Large and Small Intestine

It is noteworthy that similarly to airway epithelium, luminal P2Y₂/P2Y₄ receptor stimulation also inhibits generating sufficient concentration to stimulate luminal P2 receptors (73). Physical stimuli are potent stimulators of luminal ATP release in respiratory epithelia, and this release occurs without an effect on cell viability. Thus a mechanosensitive mechanism for ATP release could be important and may be a component of the “cough reflex” (72). The irritant and the cough could stimulate ATP release into the luminal surface liquid, and subsequently the machinery of mucociliary clearance would be activated.

otide-mediated activation of secretion in the airways was later also shown to encompass activation of K⁺ secretion (10). Rapidly, a number of essential steps forward were made, driven by the putative therapeutic role of inhaled luminal nucleotides in the treatment of cystic fibrosis (CF). Luminal P2 receptor stimulation activates mucociliary clearance in three ways: by their effects on ion transport, resulting in an increased hydration of the respiratory surface; by stimulation of mucin secretion from goblet cells (85); and by an increase in ciliary beat frequency (67). A knockout study confirmed previous pharmacological data and identified the P2Y₂ receptor subtype as the crucial luminal P2 receptor in respiratory epithelium (15). In addition to this, but of minor importance, a luminal P2Y₆ receptor is expressed in the luminal membrane of respiratory epithelia (75). Activation of luminal P2Y₂ (or P2Y₆) receptors increases intracellular Ca²⁺ concentration ([Ca²⁺]ᵢ), and subsequently Ca²⁺-activated Cl⁻ channels are stimulated, resulting in Cl⁻ secretion. Because in CF this “alternative Cl⁻ channel” is not defective, it may serve to bypass the secretory defect when epithelium is stimulated with luminal nucleotides. The important question of the source of ATP in the luminal epithelial fluid continues to be poorly understood and will be discussed below. Constitutive basal release of ATP has been described as possibly
electrogenic Na⁺ absorption in the mouse distal colon (81). The distal mammalian colon is an aldosterone-sensitive epithelium that will absorb Na⁺ via epithelial Na⁺ channels (ENaCs) in salt-restricted states (70). In distal colon from normal and CF animals, luminal ATP/UTP does not activate the alternative Cl⁻ secretory pathway discussed above, because CFTR appears to be the only apical Cl⁻ channel in this tissue (35). Nonetheless, the stimulation of luminal P2Y receptors in the colon (activation of K⁺ secretion and inhibition of Na⁺ absorption) and small intestine (activation of Cl⁻ secretion) will result in luminal fluid accumulation. As suggested for the airway epithelium, luminal P2 receptors may thus serve a purpose in host defense reactions. Intraluminal intestinal bacterial overgrowth could be one source of luminal ATP/UTP, which would result in an associated diarrhea response.

A recent immunocytochemical localization of luminal P2X7 receptors in duodenal villus tip cells suggests yet another functional role of luminal P2 receptors. P2X7 receptors have been associated with apoptosis in a large variety of cells (113, 131). Epithelia in the urinary bladder or intestinal mucosa are rapidly regenerating mammalian tissues. In the intestinal mucosa, stem cells are located in the crypt base and, after having moved toward the surface, undergo programmed cell death and get exfoliated into the intestinal lumen. “Dying” cells eventually will release ATP and may therefore provide an extracellular death signal. P2X7 receptors thus appear strategically located to ensure small intestinal epithelial regeneration (37).

OTHER EPITHELIUM EXPRESSING LUMINAL P2 RECEPTORS

The ubiquitous nature of luminal P2 receptor expression in nearly all epithlia is apparent from the long list shown in Table 1. Another organ with prominent luminal P2 receptor expression is the scala media in the inner ear. The entire epithelial lining of the scala media in the inner ear [vestibular dark cells and strial marginal cells of the stria vascularis organ (97, 98, 123), the Reissner membrane epithelium (60), the Hensen cells (71), and the sensory outer hair cells (48)] shows expression of different luminal P2 receptors. For a comprehensive description, the interested reader is referred to a recent review by Housley (48). Other epithelia with luminal P2 receptors not mentioned before include sweat gland acinar cells (156) and the conjunctival epithelium of the eye (87). In both tissues, stimulation of these receptors induce Cl⁻ secretion. An understanding of the role of P2 receptors in these and other tissues awaits further studies.

LUMINAL P2 RECEPTORS ALONG THE NEPHRON

An increasing number of studies have focused on P2 receptors in renal epithelia, an issue recently reviewed comprehensively (134). The fact that renal epithelial cells may also express luminal P2 receptors has been suggested by a number of studies using cultured cells of distal tubular origin (16, 34, 102, 135). In cultured renal epithelial cells, the functional responses resemble those of the respiratory or other secretory epithelia. Luminal nucleotides increase [Ca²⁺]ᵢ, activate Cl⁻ secretion, and inhibit Na⁺ and Ca²⁺ absorption (16, 34, 68, 102, 135). Most recently, the luminal expression of a P2Y₂ receptor in the intact isolated perfused cortical collecting duct of the mouse was demonstrated (17, 80). Pharmacological screening suggested that this receptor is the only luminal P2 receptor subtype expressed in the distal nephron. High-resolution confocal imaging unequivocally demonstrated that the P2Y₂ receptor was located in principal cells. It is presently uncertain whether rat intercalated cells also express luminal P2 receptors. For rabbit cortical collecting duct, the functional expression of luminal P2Y₃/P2Y₄ on intercalated cells has recently been reported (158). The expression of luminal P2Y₂ receptors appears to occur along the entire distal nephron, down to the inner medullary collecting duct (17, 62, 68, 83). Apparently, mice, rats, and rabbits show this luminal receptor expression. In the intact collecting duct, luminal ATP/UTP inhibited electrogenic Na⁺ transport. A transepithelial electrical signal indicative of Ca²⁺-activated Cl⁻ secretion, however, was not observed in the native epithelium (80, 128). It is therefore assumed that Ca²⁺-activated Cl⁻ channels are not expressed in native cortical collecting duct principal cells. This situation is reminiscent of a number of studies in colonic epithelia, where CFTR is localized to principal cells. It is presently uncertain whether rat intercalated cells also express luminal P2 receptors. For rabbit cortical collecting duct principal cells also inhibited apical K⁺ secretion, how-
and further studies are required. Noteworthy is a recent study in which the so-called P2X_{cilia} (possibly P2X{sub}j) receptor was shown to be only capable of activation if extracellular Na{sup}+ was low (92).

Luminal ATP and Flow-Dependent Regulation of Tubular Transport?

An increase in tubular flow in the nephron is known to increase K{sup}+ secretion (33, 59, 94) and Na{sup}+ absorption (127). This effect is thought to reflect in part the increased delivery of Na{sup}+ to more distal nephron segments and subsequent apical membrane depolarization with the resulting increase in driving force for K{sup}+ exit via luminal ROMK channels (31). In addition, activation of maxi-K{sup}+ channels mediated by increased tubular flow was recently shown (144, 157). Regarding Na{sup}+ absorption, evidence suggests that an increase in flow could lead to direct “mechanical” activation of ENaC channels (127). In addition, one may suggest that luminal ATP contributes to flow-dependent K{sup}+ and Na{sup}+ transport. Even though the mechanism of ATP release continues to be obscure, we have learned that different nonexcitable cells display constitutive ATP release (73, 145). Assuming that this is also true for the nephron, one could envisage that an increase in flow could wash out luminal ATP and thus relieve a proposed tonic inhibition of luminal ROMK and ENaC channels. In conflict with this is the flow-dependent increase in K{sup}+ secretion via maxi-K{sup}+ channels (157). The authors also showed that elevation of flow increased [Ca{sup}2+]_{i} (157). It has been shown for endothelial cells that an increase in flow can result in an increase in ATP release (74). It may thus be speculated that tubular flow increase triggers luminal ATP release and subsequent activation of maxi-K{sup}+ channels. This issue has recently been addressed from yet another angle. The functional significance of the rather obscure central luminal cilium was investigated in Madin-Darby canine kidney cells, and a mechanosensory role was proposed (112). Increasing superfusion flow or bending the central cilium directly triggered [Ca{sup}2+]_{i} elevations and hyperpolarized the cell. Indirect arguments are presented that ATP release is not involved in this effect. Thus the activation of maxi-K{sup}+ channels may involve a mechanosensory event independently of ATP release. In summary, K{sup}+ secretion induced by increased flow could be composed of independent but concerted events: 1) increased delivery of Na{sup}+ to more distal nephron segments; and 2) mechanosensitive activation of maxi-K{sup}+ channels. In addition, washout of luminal ATP could contribute to this effect.

PREVALENCE OF LUMINAL P2Y{sub}2 RECEPTORS

It is a prominent finding that nearly all native tissues described above respond equally well to ATP and UTP. Inspection of the extensive list of epithelial tissues shown in Table 1 indicates that the P2Y{sub}2 receptor is a very prevalent luminal P2 receptor in transporting epithelia. Importantly, however, one needs to consider that the similar “agonist profile” of the P2Y{sub}2 and P2Y{sub}4 receptors makes a functional discrimination between them difficult (113). A recent P2Y{sub}2 receptor knockout study has clarified some issues in this context. Whereas in respiratory epithelium the P2Y{sub}2 receptor indeed appears to be the critical player in luminal nucleotide-stimulated effects, it is apparently of no importance for the small intestinal effects (15). Also, in the stria vascularis of the inner ear it was previously thought that a luminal P2U receptor mediated inhibition of K{sup}+ secretion (98) with novel evidence showing a luminal P2Y{sub}4 receptor in this tissue (97, 123). An inspection of Table 1 also clearly shows that the existence of numerous other luminal P2 receptors (P2Y{sub}1, P2Y{sub}4, P2Y{sub}6, P2X{sub}2, P2X{sub}4, P2X{sub}5, P2X{sub}7) has been suggested. It is therefore apparent that epithelial cells commonly (if not always) express multiple P2 receptors (P2X and P2Y) and these may be present in the same membrane domain (9, 22, 43, 51, 58, 82, 91, 101, 134, 146). In renal epithelium, so far the only luminal P2 receptor was the P2Y{sub}2 subtype (see Table 1). However, not all epithelia express luminal P2Y{sub}2 receptors. Two examples here are Calu-3 cells (secretory cell line derived from submucosal bronchial glands) (49) and rat submandibular gland duct cells (79).

SOURCE AND FATE OF LUMINAL NUCLEOTIDES

Source

The luminal expression of P2 receptors has triggered the important question of the source of luminal nucleotides. In the absence of any other specific source (e.g.,
nerve endings), a larger number of studies have led to the accepted proposal that the epithelial cell itself is a source of the released nucleotide. ATP release has been shown for a variety of epithelia and other cells, and in epithelia release appears to occur preferentially onto the luminal side. A number of reviews have recently summarized the present state of knowledge (41, 118, 145). Any mechanical perturbation (touching the cell with a glass pipette (12, 24), increasing superfusion flow (74, 99, 124), cell swelling with hypomolar solutions (145, 153), or just mechanical shaking of a culture dish (38, 42, 76)) has been shown to induce ATP or UTP release without apparent cellular damage. The release pathway from epithelial cells has been assumed to be either by a conductive pore (23), a specialized membrane transporter, or vesicular release and exocytosis (118). CFTR anion channels and ABC transporters like MDR1 were suggested to conduct/transport ATP (118, 133), but subsequent studies could not confirm that CFTR functions directly as an ATP-conductive pore (38, 86, 115, 154). Importantly, in CF epithelia ATP release is absent (116), and CFTR has been suggested to regulate an associated ATP channel in epithelia (57, 142). A recent study using mutational alterations to change the substrate specificity of the MDR1 transporter reported no effect on ATP release (119). Thus the authors argue that MDR1 is not likely to function as an ATP transporter. However, upregulation of MDR1 augmented ATP release in hepatoma cells, implying a possible indirect mechanism of MDR1 on ATP release (119). Whether ATP release can occur via vesicular fusion and exocytosis will need further studies, but evidence supporting this concept has been presented (99, 103, 116, 138).

Even though ATP release has been demonstrated to occur preferentially onto the luminal side of epithelial cells, basolateral ATP release has also been shown. This basolateral ATP release has been suggested to occur after “luminal damage” (e.g., a kidney stone in the ureter) and may convey information to the central nervous system via P2X2/P2X3 receptors located on sensory nerves. Thus a basolateral release has been suggested to play a role in mechanosensory transduction (7).

The propagation of [Ca\(^{2+}\)], increases from cell to cell is a widely distributed phenomenon attributed to the spread of inositol 1,4,5-trisphosphate through gap junctions (30, 39). In addition, in epithelial and non-epithelial cells released ATP has been discovered to act as an extracellular signal responsible for “traveling [Ca\(^{2+}\)] waves” (12, 24, 130). ATP release is triggered from a site of initiation (e.g., by touching a cell with a pipette) and diffuses to neighboring cells. This, in turn, stimulates P2 receptors, which induce intracellular [Ca\(^{2+}\)] signals and again ATP release, resulting in a traveling [Ca\(^{2+}\)] or extracellular ATP wave. In poorly gap junctional-coupled cell lines, the expression of different connexons (Cx43, Cx32, Cx26) was recently shown to greatly augment ATP release (12). At the same time, it was also noticed that connexons (hemichannels) can be functional channels and allow the permeation of Lucifer yellow when lowering extracellular Ca\(^{2+}\) (44). A recent study in astrocytes presented evidence that ATP is directly conducted through connexon hemichannels. Dye flux was molecular weight specific, induced by mechanical stimulation, and blocked by Gd\(^{3+}\) and flufenamic acid (140). Certainly, these results demand further rigorous experimental proof, but on the basis of these novel results, one might speculate that connexon hemichannels could be localized in the apical membrane of epithelia and thus provide an exit pathway for secreted ATP. This hypothesis, however, includes a contradiction because [Ca\(^{2+}\)], waves mediated by ATP release were described to be uninfluenced by gap junctional blockers (12).

**Fate**

After their release, nucleotides will be metabolized. This is executed by membrane surface-located ecto-nucleotidases. The field of extracellular surface enzymes involved in metabolizing extracellular nucleotides is presently expanding rapidly (163). Ecto-nucleotidases encompass several families with partially overlapping substrate specificities. The most prominent family encompasses the ecto-nucleotidase triphosphate diphosphohydrolases (NTPDases, etc. syn: CD39 or apyrase), which hydrolyze ATP and ADP to generate AMP (162). Subsequently, ecto-5′-nucleotidase will generate the nucleoside and phosphate (77, 163). Other ectonucleotidases encompass the alkaline phosphatase and the ecto-phosphodiesterase/pyrophosphatase family. A comprehensive review of this issue is not intended here, and the reader is directed to pertinent reviews in the field (42, 73, 77, 162–164). However, it should be mentioned that the metabolism of extracellular nucleotides is more complicated than initially assumed. Nucleotides cannot only be degraded but also upgraded (by “ecto-kinases”). The identification of extracellular nucleoside diphosphokinase has revealed this phenomenon. In the presence of ATP and UDP, for example, this enzyme can mediate the formation of ADP and UTP (73). In addition, matters are further complicated by the recognition that not only nucleotides but also their metabolizing enzymes (NTPDase, nucleoside diphosphokinase) can be secreted into the extracellular space as soluble proteins (21, 163). In the context of this review, it is important to note that luminal ecto-nucleotidases have been identified and localized, for example, in respiratory epithelium (21) and rat pancreatic duct (106). In the kidney, early data from 1972 indicated that isolated tubule segments were able to hydrolyze added ATP (120). Later proximal tubule brush-border membrane and basolateral membrane vesicles were described to exhibit ecto-ATPase activity (122). CD39 was recently shown in the renal vasculature but not in medullary nephron segments (84). More comprehensive data are available for the localization of ecto-5′-nucleotidase in the nephron. It is noteworthy that ecto-5′-nucleotidase belongs to the phosphatidylinositol-anchored proteins, which are localized specifically in the luminal membrane of epithelia (77). It is thus expressed in the
luminal membrane of proximal tubules and distal tubular intercalated cells but apparently not in the thick ascending limb of Henle (77). Thus the luminal side of epithelia including the nephron contains important established components of the “ATP-signaling machinery,” i.e., P2 receptors, released agonists, and metabolizing enzymes.

RELEASED LUMINAL ATP AS PRECURSOR FOR ADENOSINE-REGULATED ION TRANSPORT

The preceding comments imply that epithelial transport is not only regulated by the different nucleotides but also by adenosine as a degradation product of ATP (29). Evidence for this has been presented, for example, in T84 enterocytes, where luminal ATP exerts a Cl− secretory effect via A2 adenosine receptors and is associated with an increase in cAMP (141). Evidence for ecto-ATPase activity on the luminal side of the small intestine has been presented (132), and most likely a luminal ecto-5′-nucleotidase is also present on the luminal side of intestinal epithelia (141). A similar phenomenon was observed in Calu-3 cells, a cell line derived from submucosal respiratory glands. Calu-3 cells do not express luminal P2Y2 receptors but release ATP after mechanical stimulation. Adenosine is subsequently generated, stimulates A2b adenosine receptors, and then a cAMP-mediated Cl− secretion occurs via CFTR. The authors also present the interesting finding that cAMP-mediated signaling in response to A2b receptor activation is localized to the subapical membrane of these airway epithelial cells (49). In the kidney, the urinary excretion of adenosine is well documented and increases strongly during renal ischemia (3, 108). In the mammalian nephron, no evidence to date suggests that luminal adenosine modulates epithelial transport (77). In the Xenopus laevis renal epithelial A6 cell line, however, luminal A1 adenosine receptors have been identified (1, 20), and it may well be that luminal adenosine receptors will be discovered in the intact mammalian nephron in the near future.

FUNCTIONAL IMPLICATIONS FOR LUMINAL P2 RECEPTORS IN EPITHELIA

Given their ubiquitous expression, one is tempted to search for a common functional purpose of luminal P2 receptors in epithelia. Present knowledge makes this task difficult, and different organ systems are likely to have developed luminal P2 receptors for specific purposes. The formulation of one common function is certainly hampered by the lack of essential pieces in this puzzle. Receptor identification is likely to be incomplete, the molecular release mechanism and its precise regulation are obscure, and the fate of released ATP processed by the increasingly growing family of nucleotide-metabolizing enzymes awaits further specification. Nonetheless, the above-mentioned findings make it possible to extract common denominators for functional integrative schemes. Some suggestions for an integrated functional role of luminal P2 receptors are elaborated below. Emphasis will be given to renal tissue.

Luminal P2 Receptors Involved in a Nonspecific Epithelial Defense Mechanism

This concept was originally postulated for the respiratory epithelium (72) but may extend to other epithelial tissues. In the respiratory tract, the outer eye, and the intestinal tract, luminal nucleotides stimulate ion secretion. These epithelia are vulnerable body surfaces, where exogenous harmful particles or bacteria can produce extensive local damage. Each of these epithelial organs has specific armaments to counteract potential threats on their luminal surface. It is proposed that the epithelial defense mechanisms also involve luminal P2 receptors. A noxious particle would mechanically trigger nucleotide release. Luminal ATP could also originate from a bacterial source or from dying defense cells, which have migrated into the epithelial lumen. Subsequently, P2Y2 receptor-mediated secretion/inhibition of absorption would be stimulated. Larger amounts of luminal fluid would be generated and therefore would help to flush away the luminal irritant. For example, large amounts of purulent sputum in bacterial bronchitis may well be explained by the stimulation and activation of mucociliary clearance via luminal P2Y2 receptors.

P2 Receptors and the Regulation of Cell Volume

Cell volume regulation is an important property of all cells. It is likely to be of extraordinary importance in epithelial cells, where rapid changes in transcellular flux of fluid and solutes occur. It is easy to conceive that any imbalance of luminal uptake and basolateral excretion will compromise cell volume. This is beautifully exemplified in macula densa cells. Reduction of apical ion influx via the Na+−K+−Cl− cotransporter isoform 2 (NKCC2) reduces cell volume and vice versa (32). A role for extracellular ATP and P2 receptors has recently been demonstrated in rat hepatoma (153) and bile duct epithelia (118). In both cell types, cell swelling was shown to release ATP, activate P2 receptors and, subsequently, Ca2+-activated K+ and Cl− conductances. The resulting cellular KCl loss mediates regulatory volume decrease (45). In an extrapolation from these results, luminal P2 receptors may serve to regulate cellular volume in transporting epithelia. P2 receptor-mediated activation of K+ and Cl− channels is also seen in cultured renal epithelia (1, 5, 16). However, to date there is no evidence for Ca2+-activated Cl− channels in intact nephron segments, and it is uncertain whether the mechanism described applies to renal tubules. However, another mechanism to regulate cellular volume via luminal P2 receptors can be postulated. A common functional consequence of extracellular ATP action in the distal tubule is the inhibition of the major transport processes. Thus increases in transcellular transport would increase cell volume, elicit regulated ATP release, and so induce autocrine activation of luminal (and basolateral) P2 receptors.
This would downregulate apical substrate influx and thus provide a negative-feedback regulation of cellular volume. This hypothesis requires rigorous testing. One beautiful example that illustrates the issue of volume regulation, ATP release, and regulated cell function deserves mentioning here. Using A1 receptor knockout mice, it has recently been shown that adenosine is the extracellular mediator of tubuloglomerular feedback (TGF) (6, 143). In TGF, the macula densa senses the distal tubular sodium load via the NKCC2 cotransporter. This probably occurs via a change in cellular volume because macula densa cells strongly change their volume in response to luminal electrolyte uptake (32). Cell volume increases induced by increasing luminal NaCl concentration have recently been shown to stimulate ATP release into the basolateral interstitial space (4). Released ATP is suggested to be broken down, and the adenosine formed by the 5′-nucleotidase will subsequently constrict preglomerular arterioles (148). This feedback is disrupted by knockout of A1 receptors. These results highlight the importance of cell swelling-induced release of ATP in TGF regulation.

ATP and Ischemic Protection in the Kidney

In the intact distal nephron, a consistent finding has been that all major transporting activity is downregulated when luminal and/or basolateral P2Y receptors are activated (61, 68, 80, 89). For more proximal tubular segments, this has not been studied in any detail, and it might be a peculiar property of the distal nephron. In the distal tubule, at least, it is proposed that extracellular (luminal) ATP acts as a luminal signaling molecule and serves to protect the tubular epithelium under ischemic conditions (Fig. 3). The sequence of events could be as follows. In ischemia, epithelial cells will suffer energy depletion and therefore swell. ATP is subsequently released from epithelial cells by cell swelling (69, 73, 145). This, in turn, will trigger regulated ATP release and autocrine or paracrine P2 receptor stimulation. The released ATP could enter the tubular fluid and move along the nephron to autoinhibit energy-consuming transport processes in more distal tubular segments and so protect them. Basolateral P2 receptors could mediate a similar process. Obviously, nucleotides could also originate from the vascular space and enter the nephron via glomerular filtration.

In renal ischemia, increased amounts of adenosine are released into the urine (108), but it is likely that ATP is the primary metabolite released from ischemic cells and that it is then converted to adenosine (see above). In addition, extracellular ATP acting via P2 receptors has been shown to stimulate cell growth and division in a number of renal (40, 50, 55, 109) and nonrenal tissues (47). An intriguing preliminary study suggests that shortly after renal ischemia, ion transport processes are downregulated, whereas expression of the P2Y2 receptor itself is upregulated (63). It is therefore suggested that ATP acts as an “intelligent” extracellular signaling molecule that can prevent ischemic damage almost before it occurs but which can also assist in cell recovery and regeneration after damage has happened.

It has been indicated above that the focus on P2 receptors and ATP implies a rather crude simplification of matters, because released ATP will provide the source for the formation of adenosine with numerous effects mediated via adenosine receptors. Recently, A2b adenosine receptors were shown to play an important role as a physiological feedback mechanism for the limitation and termination of both tissue-specific and systemic inflammatory responses (29, 107). This is worth mentioning in this context because P1 and P2 receptors may serve a common purpose in a concerted effort to limit tissue damage by noxious events of different origin.

Luminal P2 Receptors in Polycystic Kidney Disease

Luminal P2 receptors have been suggested to play an important role in the course of polycystic kidney disease (PKD) (135, 155). PKD is associated with the formation of cysts derived from renal tubular epithelia. It is the expansion of cysts that determines the progression of disease and development of renal failure. Expansion of cysts is driven by two processes, cellular proliferation and fluid secretion, leading to progressive cyst enlargement. Although cysts can arise from any portion of the renal tubule, evidence from models of autosomal dominant PKD in both mice (90) and rats (14) suggests that cysts originate mainly from proximal tubular cells; the same also seems to be true in the recessive form of this disease (96). It has been suggested that a variety of different locally released

**Fig. 3.** Schematic model of “ischemic protection hypothesis.” Proximal endotubular ATP is proposed to lead to distal tubular transport inhibition and thus epithelial protection.
factors acting as autocrine or paracrine regulators stimulate renal cyst growth and expansion (117). Intriguingly, primary cultured PKD cyst epithelial cells were recently shown to express luminal P2Y and P2X receptors and secrete ATP onto the luminal side (i.e., into the cyst lumen) (135). In PKD, epithelial luminal ATP was also shown to stimulate Cl− secretion (135). Furthermore, it was shown that cyst fluid contains significant concentrations of ATP (155). Thus ATP could be one of the local factors involved in progression of PKD cysts.

I appreciate comments on improving this manuscript from Dr. Ivana Novak, August-Krogh-Institute, Copenhagen, Denmark.

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