A2A adenosine receptor: a novel therapeutic target in renal disease

MARK D. OKUSA
Division of Nephrology, Department of Medicine, University of Virginia Health System, Charlottesville, Virginia 22908

Okusa, Mark D. A2A adenosine receptor: a novel therapeutic target in renal disease. Am J Physiol Renal Physiol 282: F10–F18, 2002.—Present strategies in the treatment of inflammatory renal injury have focused on developing agents that specifically target individual mechanisms thought to contribute toward the pathogenesis of the disease. Such an approach is hindered by redundancies in the inflammatory cascade, rendering intervention suboptimal. The A2A adenosine receptor (A2A-AR) is a member of the family of guanine nucleotide binding proteins and has become a focus of major interest primarily because of its ability to broadly inactivate the inflammatory cascade. This review summarizes our present knowledge regarding the molecular biology and pharmacology of A2A-ARs as well as the physiological effects of activation of A2A-ARs in the kidney. We also review our recent experience in targeting this receptor subtype in abrogating the inflammatory cascade in ischemia-reperfusion injury.

inflammation; ATL-146e; ZM-243185; ischemia-reperfusion; acute renal failure

Adenosine, generated locally in tissue by conditions that produce hypoxia, ischemia, or inflammation, mediates a variety of physiological functions. The renal effects mediated by adenosine are heterogeneous, due in part to activation of multiple adenosine receptor subtypes that are localized in different regions of the kidney. Traditionally, adenosine has been thought to play a critical role in the local regulation of blood flow, but more recently, evidence has been accumulating that adenosine also has potent effects in modulating inflammatory processes. This review summarizes present knowledge on the characteristics of one subtype, the A2A adenosine receptor (A2A-AR) and its potential role in treating and preventing renal injury.

PHARMACOLOGY AND MOLECULAR BIOLOGY OF A2A ADENOSINE RECEPTORS

Adenosine Receptor Subtypes

Adenosine and adenine nucleotides bind to P1 and P2 receptors, respectively (9). P2 receptors that bind adenosine nucleotides, uracil nucleotides, and/or diadenine polyphosphates are composed of ligand-gated channels (P2X) and guanine nucleotide binding protein (G protein)-coupled receptors (P2Y) (43). Adenosine, on the other hand, binds to P1 purinergic receptors, which are members of the G protein-coupled receptor family. Four subtypes of adenosine receptors have been cloned: A1, A2A, A2B, and A3 (for a review, see Refs. 41 and 51). The four subtypes have the hallmark structural characteristics that are common to G protein-coupled receptors, including seven putative transmembrane-spanning domains, an extracellular NH2 terminus, cytoplasmic COOH terminus, and a third intracellular loop that is important in binding G proteins. The first adenosine receptors to be cloned, RDC7 (38) and RDC8 (39), were originally isolated as “orphan” cDNAs. On the basis of their binding properties to pharmacological agents and their effects on adenyl cyclase, RDC7 and RDC8 were shown to encode canine A1- and A2A-ARs, respectively. Subsequently, adenosine receptor orthologs and homologs were identified in other species, including humans (40, 57, 66–68, 84). When the amino acid sequences of all four human adenosine receptor subtypes were compared, they were found to have an
overall identity of 30% and a transmembrane domain identity of 45%. They were also found to have pharmacological properties distinct from those of other species. The human A1-, A2A+, A2B-, and A3-ARs are proteins comprising 326, 412, 332, and 318 amino acids, respectively (42). The receptors can be distinguished pharmacologically by their ability to bind selective ligands and their use of distinct signaling pathways (41, 51). Table 1 summarizes ligands and their affinities to adenosine receptor subtypes as well as major signaling pathways.

**A2A Adenosine Receptors**

The A2A-AR cDNA, which has been cloned from several species including humans (53), encodes a protein of ~45 kDa, larger than the molecular masses of the other subtypes. This is primarily due to the additional 80–90 amino acids of the COOH-terminal tail. The overall amino acid identity is >90% among species, with most of the differences occurring in the second extracellular loop and the long COOH-terminal domain. The COOH-terminal domain has several serine and threonine residues that are potential phosphorylation sites. It is well known the A2A-ARs undergo rapid agonist-induced desensitization associated with phosphorylation of the receptor (55). A2A-ARs stimulate adenylyl cyclase and increase the production of cAMP by coupling to stimulatory G proteins (Gs) or to Gq in certain tissues in which Gq is expressed as the primary stimulatory G protein (29). In addition to the cAMP-protein kinase A (PKA) pathway, recent studies indicate that serine/threonine protein phosphatase (61), mitogen-activated protein kinase (MAP kinase) (71, 72), PKC (56), and phospholipase D (83) may participate in mediating the effects of A2A-AR activation.

**LOCALIZATION AND FUNCTIONAL EFFECTS OF A2A ADENOSINE RECEPTORS IN THE KIDNEY**

Determining the adenosine receptor subtypes that mediate specific effects of adenosine in the kidney has been difficult for several reasons. First, the low abundance of multiple subtypes in many tissues, including kidney, hinders detection by standard methods. Second, specific pharmacological reagents for the characterization of adenosine receptor subtypes have been largely unavailable. For example, selective reagents for A2B and A3 receptors have yet to be developed, and only recently have selective antagonists for A2A-AR been developed (53). The cloning of adenosine receptor subtypes enabled the development of highly specific reagents for receptor localization, using in situ hybridization, ligand binding autoradiography, RT-PCR of microdissected nephron segments, and immunohistochemistry. Although these techniques have been useful for the localization of adenosine receptors in other tissue, such as brain, very little information exists regarding the precise localization within kidney tissue. Weaver and Reppert (87) used radiolabeled probes to determine the localization of A1- and A2A-ARs in the kidney. A1-AR mRNA was expressed in collecting ducts of the inner medulla and cells of the juxtaplomerular apparatus. A2A-AR mRNA was expressed in the outer medullary descending vasa recta (OMDVR). Antibodies have been used successfully to localize A2A-ARs in the brain (64). More recently, a peptide antibody was developed that identified A1-ARs in afferent arterioles, mesangial cells, proximal convoluted tubules, medullary collecting ducts, and papillary surface epithelium of the kidney (75).

The functional effects of adenosine on renal hemodynamics have been reviewed recently (45). Drury and Szent-Gyorgi (19) reported in 1929 that adenosine produced a marked reduction in renal blood and urine flow. Early studies demonstrated biphasic effects of adenosine with an initial transient vasoconstriction followed by vasodilation, effects mediated by A1- and A2-ARs, respectively (45). Defining the functional effects of the A2A-AR subtype has become possible with the availability of selective A2A agonists. Infusion of CGS-21680, a selective A2A agonist, produced an increase in renal blood flow and glomerular filtration rate (37). With the use of a laser Doppler probe, CGS-21680 was found to increase medullary blood flow to 184% of control without a change in cortical blood flow (37). Because all blood flow to the renal medulla must pass through the OMDVR, Silldorff et al. (73) isolated OMDVR from rats, perfused them in vitro, and examined the vasoactive properties of CGS-21680. They

### Table 1. Comparative affinities of A2A ligands for human adenosine receptor subtypes and signaling elements

<table>
<thead>
<tr>
<th>Agonist/Agonist</th>
<th>A2A AR (Coupled)</th>
<th>A2B AR</th>
<th>A2B AR</th>
<th>A2B AR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potency order</td>
<td>NECA &gt; R-PIA &gt; CPA &gt; S-PIA</td>
<td>NECA &gt; R-PIA &gt; S-PIA</td>
<td>NECA &gt; CGS-21680</td>
<td>CPA &gt; R-PIA &gt; S-PIA</td>
</tr>
<tr>
<td>NECA (55)</td>
<td>45</td>
<td>&gt;1,000</td>
<td>&gt;1,000</td>
<td></td>
</tr>
<tr>
<td>CGS-21680 (50)</td>
<td>60</td>
<td>&gt;1,000</td>
<td>1,000</td>
<td></td>
</tr>
<tr>
<td>ZM-243185 (50)</td>
<td>1.4</td>
<td>269</td>
<td>31</td>
<td>536</td>
</tr>
<tr>
<td>G proteins (42)</td>
<td>Gs, G</td>
<td>G0, Gs, G</td>
<td>G0, Gs, G</td>
<td></td>
</tr>
<tr>
<td>Signaling (42)</td>
<td>cAMP</td>
<td>cAMP</td>
<td>Mobilizes Ca2+</td>
<td>Activates K+ channels; inhibits Ca2+ channels</td>
</tr>
</tbody>
</table>

Shown are inhibition constant values (μM) to inhibit radioligand binding to recombinant human adenosine receptors (ARs), with reference nos. in parentheses. Affinity of ATL-146e, a newly developed, highly selective A2A agonist, and CGS-21680, an A2A-AR agonist, for A2B-ARs was considered for binding to A2A high-affinity sites (50). ZM-243185, a selective A2A antagonist; MAPK, mitogen-activated protein kinase; CPA, N6-cyclopentyladenosine; NECA, 5’N-ethylcarboxamidoadenosine; R-PIA, R-N-phenylisopropyladenosine.
found that the vasoconstrictive effects of angiotensin II were inhibited in the presence of CGS-21680 but that CGS-21680 had no effect when applied to vessels alone in the absence of angiotensin II. These results indicate that A2A-ARs are expressed in the OMDVR and mediate vasodilation in constricted vessels. Recently, Nishiyama et al. (46) examined afferent and efferent arteriolar response to adenosine in an in vitro blood-perfused juxtaglomerular nephron preparation. They found that afferent and efferent vasodilatory responses to adenosine are blocked by KF-17837, a novel A2A antagonist, suggesting the presence of A2A-ARs in both afferent and efferent arterioles. These results indicate the important renal hemodynamic effects are mediated by A2A-ARs. Moreover, the expression of A2A-ARs in afferent and efferent arterioles, which permits critical control of glomerular filtration, could serve as a potential target for therapeutic intervention.

A2A ADENOSINE RECEPTORS IN INFLAMMATION

A2A Adenosine Receptor Expression on Hematopoietic Cells

In addition to the renal vascular and hemodynamic effects of adenosine, studies over the last 10 years have indicated that adenosine has a direct effect on hematopoietic and endothelial cells to reduce inflammation (for a review, see Ref. 42). Given the fact that A2A-ARs are expressed in a variety of hematopoietic cell types, i.e., monocytes, lymphocytes, neutrophils, basophils, and mast cells, all of which share a common stem cell source in the bone marrow (23), this receptor subtype is ideally suited to modulate inflammatory processes. Evidence for an anti-inflammatory role of A2A-AR activation comes from a variety of studies both in vivo and in vitro.

A large body of evidence suggests that the major signaling pathway that links A2A-receptor activation and reduction of inflammation is the cAMP-PKA pathway (23, 78). A2A agonists increase cAMP in a dose-dependent manner, an effect that is enhanced in the presence of a phosphodiesterase (PDE) inhibitor (29). Furthermore, several studies indicate that inhibitors of PDE block the anti-inflammatory action of A2A agonists (44, 49, 79). In tumor necrosis factor (TNF)-α-activated human neutrophils, ATL-146 ester (e) in the presence of rolipram, a PDE type IV (PDE 4) inhibitor, increased cAMP and decreased human neutrophil oxidative activity. These results suggest that the decrease in neutrophil oxidative activity produced by the selective activation of A2A-ARs expressed on neutrophils may be due to increased cAMP and activation of PKA.

Effect of A2A Activation on Reactive Oxygen Species

For the past decade, adenosine has been known as a molecule that mediates an anti-inflammatory effect through the activation of A2A-ARs (13, 70, 77). This physiological role of endogenous adenosine became apparent after the demonstration that activated neutrophils or endothelial cells release and respond to adenosine (5, 14, 15, 25). Neutrophils play a critical role in the inflammatory process. They are the most abundant leukocyte in blood and the first to arrive at a site of injury. Several groups of investigators have demonstrated that adenosine, largely through A2A-ARs, acts on activated neutrophils (17, 23) to reduce oxygen metabolites such as superoxide anion or hydrogen peroxide (14, 17, 63, 69, 70, 79). These data provide compelling evidence that selective activation of A2A-ARs decreases neutrophil oxidative activity. Tissue damage is induced, in part, by the migration of neutrophils into damaged tissue and the release of these reactive oxygen species. Adenosine’s effect through A2A-ARs is thought to limit tissue damage (12).

Effect of A2A Activation on Neutrophil Adherence

Adenosine also reduces neutrophil adherence to endothelial cells through an effect attributed to A2A-ARs (8, 16, 22, 89). Adhesion of neutrophils to endothelial cells occurs through a complex series of events that may involve several classes of adhesion molecules, including selectins, mucin, and other selectin ligands, integrins, and the immunoglobulin superfamil (24, 33, 58, 59). In particular, the role of intercellular adhesion molecule (ICAM)-1 has been well studied. ICAM-1 (CD-54) is expressed on endothelial cells and binds to counterreceptors on neutrophils, lymphocyte function antigen (LFA-1; CD11a/CD18), and Mac-1 (CD11b/CD18). Abundant data have accumulated that demonstrate convincingly that CD11/CD18 integrins and ICAM-1 are important in the pathogenesis of ischemic renal injury (11, 18, 26, 32, 33, 58, 59). P-selectin and E-selectin, adhesion molecules expressed on endothelial cells thought to be responsible for leukocyte rolling, have also been found to mediate ischemia-reperfusion injury (74). In human umbilical vein endothelial cells, adenosine reduces the expression of the adhesion molecules E-selectin and vesicular cell adhesion molecule-1 in a dose-dependent manner (7).

There is accumulating evidence that adenosine regulates adhesion molecule expression. Using monoclonal antibodies and flow cytometry, N-formylmethionyl-leucylphenylalanine-induced expression of neutrophil Mac-1 was inhibited by a selective A2A agonist (88). More recently, in vivo studies using a selective A2A agonist, ATL-146e, reduced the heightened expression of renal endothelial cell expression of ICAM-1 and P-selectin induced by ischemia-reperfusion injury (48). On the other hand, adenosine paradoxically mediates neutrophil chemotaxis via A1-ARs (13, 63). Such a dual effect might protect endothelial cells from the deleterious effects of activated neutrophils yet allow chemotaxis to the site of infection (13). These data from the use of selective agonists of A1 and A2A-ARs suggest a complex interaction between adenosine receptor subtypes and neutrophil adhesion. Adenosine, acting on A2A-ARs, may reduce inflammation by inhibiting adhesion molecule expression and subsequent neutrophil adherence to endothelial cells. The precise signaling
pathways whereby adenosine reduces neutrophil adherence are not known.

**A₂A Activation and Cytokines**

Monocytes accumulate more slowly at sites of inflammation than neutrophils and contribute to the inflammatory process by producing and releasing cytokines. The results of several studies indicate that the proinflammatory cytokine TNF-α, is regulated by A₂A-ARs. Mononuclear cells (15–20% monocytes and 80–85% lymphocytes) were cultured in vitro and stimulated with endotoxin (78). Endotoxin-induced stimulation of TNF-α production was inhibited with 5′-N-ethylcarboxamido-adenosine and CGS-21680 in a dose-dependent manner. This effect by the selective A₂A agonists was inhibited completely with the addition of ZM-243185, a selective A₂A antagonist. Other studies have also demonstrated that adenosine or adenosine analogs reduce TNF-α production by A₂A-AR activation (6, 20, 28, 60). In human monocytes, lipopolysaccharide-induced production of the proinflammatory cytokines interleukin (IL)-6 and IL-8 was also inhibited by A₂A receptor activation (6).

In activated monocytes/macrophages, binding of selective A₂A-AR agonists leads to an inhibition of the proinflammatory cytokine IL-12 (27, 44). The rank-order potency for the inhibition of IL-12 was CGS-21680 > IB-N⁶-(3-iodobenzyl)-adenosine-5′-N-methyluronamice > 2-chloro-N⁶-cyclopentyl adenosine (27). The observation that the inhibitory effect of A₂A-AR agonists on IL-12 is blocked by PKA inhibitors suggests the involvement of the cAMP-PKA pathway (44). Regulation of IL-12 is not thought to be due to activation of p38 and p42/p44 MAP kinase or phosphorylation of c-Jun terminal kinase (27). These studies demonstrate the ability of the activation of a single receptor subtype to broadly regulate a number of proinflammatory cytokines.

**A₂A Adenosine Receptors Activation Reduces Tissue Injury**

On the basis of the evidence that activation of A₂A-ARs regulates factors that attenuate inflammation, studies have been performed using selective A₂A agonists in nonrenal tissue to determine whether activation of A₂A-ARs confers tissue protection. In many of these studies, the observation that A₂A agonist-induced tissue protection was associated with a reduction of factors associated with inflammation suggested that A₂A agonists contribute to tissue protection by attenuating inflammation. Although a direct causal relationship between tissue protection and attenuation of inflammation by A₂A agonists has not been proven, the abundant data suggest this direct link. In dog heart, CGS-21680, a highly selective A₂A agonist, reduced myocardial tissue injury, an effect associated with a decrease in neutrophil accumulation, superoxide generation, and neutrophil adherence to endothelium (31). Recently, using a lung transplantation model, ATL-146e, an agonist that is 50 times more potent than CGS-21680 (62), reduced neutrophil sequestration and microvascular permeability in parallel with a reduction in tissue injury (65). The role of A₂A-ARs in neuroprotection appears to be more complex due to the role of A₂A-ARs in neural function. Both by immunohistochemistry using a selective A₂A-AR monoclonal antibody and by in situ hybridization, A₂A-ARs have been localized to the striatum, nucleus accumbens, and globus pallidus (53, 86). A₂A agonists lead to the release of neurotoxic chemical mediators such as glutamate which may augment cerebral ischemia-reperfusion. In contrast, A₂A antagonists, when given before ischemia-reperfusion, can lead to a decrease in the release neurotoxic chemicals, leading to a reduction of cerebral damage (86). This finding is in sharp contrast to what is known about the effects of A₂A agonists on neutrophil function and reperfusion injury in other tissues (31, 48). Because leukocyte accumulation occurs after the ischemic period and during reperfusion, cerebral tissue protection achieved by A₂A agonists (52) is typically optimal when given during the reperfusion period and not before the ischemic period (86).

**A₂A ADENOSINE RECEPTORS IN RENAL DISEASE**

Given the possibility of multiple functional consequences by nonspecific activation of adenosine receptors, agents that are targeted to specific A₂A-AR subtypes are potentially important novel therapeutic agents. The foregoing discussion demonstrating the protective effect of A₂A activation in other tissues strongly suggests that selective A₂A agonists could provide a means of reducing tissue injury in kidney. One such compound is ATL-146e, which has been developed and extensively characterized (62, 79) by chemically modifying the structure of adenosine. The high selectivity of ATL-146e for A₂A-ARs is due to substitutions at the C2 and 5′ positions. Radioligand binding studies indicate that ATL-146e has a higher affinity for A₂A-ARs than the acid form (ATL-146 acid) and a higher affinity and selectivity for A₂A-ARs than the commercially available CGS-21680, a highly selective A₂A agonist (Table 1, Ref. 30).

**Acute Ischemic Renal Failure**

We tested the potential role of A₂A-AR activation in reducing renal injury in a model of acute ischemic renal failure (48–50). This model was chosen because of the well-characterized effects of reperfusion on the inflammatory cascade associated with renal ischemia-reperfusion injury (36, 76, 82). Although the pathogenic role of neutrophils in ischemia-reperfusion injury of the kidney has been controversial, many studies have clearly shown that neutrophils and other inflammatory cells accumulate in kidneys subjected to ischemia-reperfusion (10, 54, 80). We studied both rats and mice and found that ATL-146e, when administered before ischemia and during the period of reperfusion, produced a 70% reduction in the elevation of plasma creatinine produced by ischemia-reperfusion (49). Significant protection was also observed when ATL-146e administration was delayed and begun immediately at the onset of reperfusion (50). ATL-146e-induced pres-
ervation of renal function was associated with pronounced histological preservation as well (50). Figure 1 shows the dose-dependent reduction in plasma creatinine by ATL-146e in mice subjected to 32 min of ischemia followed by 24 h of reperfusion (49). Maximal protection was observed with doses of ATL-146e between 1 and 10 ng kg\(^{-1}\) min\(^{-1}\), an effect that was blocked by coadministration of a selective A\(_2\)A antagonist (50) or absent in A\(_2\)A-knockout mice (Okusa MD, unpublished observations). These results indicate that the effect of ATL-146e in reducing renal injury is A2A receptor mediated.

Additional studies have been performed to elucidate the mechanism of protection by ATL-146e. These studies demonstrate that A\(_2\)A activation reduces neutrophil accumulation, a result that may be due to a decrease in P-selectin and ICAM-1 expression (48). Furthermore, studies in neutrophils indicate that ATL-146e decreased neutrophil oxidative activity and neutrophil adherence factors (48). Figure 2 summarizes potential targets for A\(_2\)A agonists in reducing renal injury. Evidence from in vitro and in vivo studies suggest that A\(_2\)A receptor activation regulates tissue-specific function. Activation of A\(_2\)A-ARs on leukocytes could attenuate inflammation by reducing the release of leukocyte free radicals and hydrogen peroxide (14, 17, 63, 69, 70, 79), the releasing of various leukocyte proteases, and reducing the expression of adhesion molecules such as Mac-1 (88). Characterization of A\(_2\)A-AR expression by microvascular endothelial cells is lacking; however, certain microvascular endothelial cell adhesion molecules may be directly or indirectly regulated by A\(_2\)A agonists (48). There is evidence that reduction of cytokine release by activation of A\(_2\)A-ARs on other inflammatory cells such as monocyte/macrophages may potentially reduce renal injury (27, 44). Although there are several targets for A\(_2\)A agonists in mediating tissue protection, not all necessarily participate in the protection observed in ischemia-reperfusion injury of the kidney. Differentiating effects on inflammatory cells and endothelial/smooth muscle cells could lead to a further understanding of the mechanism of action of A\(_2\)A agonists as well as of the pathogenesis of ischemia-reperfusion injury. The generation of chimeric mice in which the bone marrow of wild-type mice is ablated and repopulated with stem cells from A\(_2\)A-knockout mice could address this issue.

The cellular mechanism by which A\(_2\)A-ARs produce these effects is likely through an increase in intracellular cAMP and PKA activation, as the effects of A2A activation on neutrophil oxidative activity were blocked by a PKA inhibitor (48). An intriguing observation with potential therapeutic implications is the observation that the effects of A\(_2\)A activation on neutrophil oxidative activity and adherence were potentiated in the presence of a PDE 4 inhibitor. Both A\(_2\)A agonists and PDE inhibitors act along different pathways to increase intracellular cAMP accumulation. We evaluated the effects of combination therapy and found

**Fig. 1.** Adenosine receptor subtype (A\(_2\)A) activation reduces renal injury in mouse kidneys subjected to ischemia-reperfusion. Mouse kidneys were subjected to 32-min ischemia and 24 h of reperfusion. Vehicle or selective A\(_2\)A agonist (ATL-146e; 0.1, 0.5, 1, and 10 ng kg\(^{-1}\) min\(^{-1}\)) was administered continuously via osmotic minipump beginning 5 h before ischemia and continuing through the 24-h period of reperfusion. Plasma creatinine was measured after 24 h of reperfusion (adapted from Ref. 49).

**Fig. 2.** Cellular model depicting potential targets of A\(_2\)A agonists in mediating tissue protection from ischemia-reperfusion injury. Circulating leukocytes and tissue-resident mast cells or macrophages express A\(_2\)A adenosine receptors (ARs). Activation of A\(_2\)A-ARs results in stabilization of these cell types (23). Smooth muscle cells of the descending vasa recta vasodilate in response to A\(_2\)A agonists (73). Last, an effect mediated by A\(_2\)A agonists in endothelial cells may regulate adhesion molecules (48) and cytokines (7). ROS, reactive oxygen species; MØ, macrophages; TNF-α, tumor necrosis factor-α; NO, nitric oxide.
that treatment with both compounds in combination has a greater effect in reducing renal injury and neutrophil accumulation than the use of either compound alone (49). Combination therapy using low doses of each agent might be a useful strategy for providing maximal tissue protection by blocking the inflammatory cascade while minimizing the risk of side effects (Fig. 3). These studies indicate a novel approach to reducing renal injury that takes advantage of the ability of a single receptor to broadly abrogate the inflammatory cascade.

**A2A Adenosine Receptors in Other Renal Diseases**

Recent evidence also suggests the potential utility of A2A agonists in renal transplantation. All renal allografts encounter substantial injury due to the transplant process, which may enhance the antigenicity of the transplanted organ and initiate rejection (18). Reducing reperfusion injury by A2A-AR activation may enhance allograft survival. Independent of the effects of A2A-agonists on reperfusion injury, we have recently shown that activation of A2A-ARs reduces human leukocyte antigen class I and II expression on human lymphocytes (47). Direct effects on human leukocyte antigen expression by A2A agonists may reduce the antigenicity of allografts and provide an additional mechanism for enhanced graft survival.

Additional potential therapeutic applications of A2A agonists include reducing renal injury associated with nephrotoxins. Contrast-induced acute renal failure is thought to be due in part to renal vasoconstriction (1) and to oxidant injury (3). The latter mechanism forms the basis for the use of N-acetylcysteine in the prevention of acute renal failure from contrast agents (81), whereas adenosine agonists could be protective by intervention of either mechanism. Experimental studies point to adenosine as a candidate in mediating renal vasoconstriction (1), a hypothesis supported by the finding that theophylline, a nonselective adenosine receptor antagonist, prevents the reduction of glomerular filtration rate associated with contrast agents (1, 21). A2A-ARs are expressed in afferent and efferent arterioles and induce vasodilation when activated (46); thus selective A2A-agonists could potentially prevent a contrast-induced decrease in glomerular filtration rate. Furthermore, because of the known effects of adenosine in reducing oxidative injury, A2A agonists could mediate renal protection by reducing the oxidant damage produced by contrast agents.

Cisplatin is an anticancer therapeutic agent that is associated with significant nephrotoxicity due to hemodynamic changes and oxidant injury (4). Antagonizing A1-ARs with a selective antagonist, 8-cyclopentyl-1,3-dipropylxanthine, has been shown to decrease renal injury associated with cisplatin (34). Thus the potential exists for using selective A2A agonists to counteract oxidant injury and renal vasoconstriction in reducing cisplatin-induced nephrotoxicity.

The known anti-inflammatory effects of A2A agonists on both neutrophils and mononuclear cells may permit wide-ranging effects on other types of acute inflammatory renal injury. Among these, the involvement of the inflammatory cascade in glomerulonephritis may be a likely target for similar anti-inflammatory strategies with A2A-AR agonists. Previous studies have demonstrated the potential role of PDE inhibition in suppressing the injury associated with mesangial proliferative glomerulonephritis (85). This finding along with the foregoing discussion establish the potential for the use of A2A agonists in glomerulonephritis. The expression of A2A-ARs on key structures involved in the regulation of glomerular filtration such as afferent and efferent arterioles and mesangial cells could provide the foundation for studies examining chronic models of glomerular disease.

**CONCLUSION**

Although various strategies have been employed to abrogate the inflammatory cascade of renal injury, activation of A2A-ARs has emerged as a novel therapeutic approach. Newer agents have been synthesized that are potent and selective for this receptor subtype. Their further development awaits their use in human clinical trials.
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