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Adenosine and protection from acute kidney injury

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Abstract

Purpose of Review—Acute Kidney Injury (AKI) is a major clinical problem without effective therapy. Development of AKI among hospitalized patients drastically increases mortality, and morbidity. With increases in complex surgical procedures together with a growing elderly population, the incidence of AKI is rising. Renal adenosine receptor (AR) manipulation may have great therapeutic potential in mitigating AKI. In this review, we discuss renal AR biology and potential clinical therapies for AKI.

Recent Findings—The 4 AR subtypes (A_1AR, A_{2A}AR, A_{2B}AR and A_3AR) have diverse effects on the kidney. The pathophysiology of AKI may dictate the specific AR subtype activation needed to produce renal protection. The A_1AR activation in renal tubules and endothelial cells produces beneficial effects against ischemia and reperfusion (IR) injury by modulating metabolic demand, decreasing necrosis, apoptosis and inflammation. The A_{2A}AR protects against AKI by modulating leukocyte-mediated renal and systemic inflammation whereas the A_{2B}AR activation protects by direct activation of renal parenchymal ARs. In contrast, the A_1AR antagonism may play a protective role in nephrotoxic AKI and radiocontrast induced nephropathy by reversing vascular constriction and inducing naturesis and diuresis. Furthermore, as the A_3AR-activation exacerbates apoptosis and tissue damage due to renal IR, selective A_3AR antagonism may hold promise to attenuate renal IR injury. Finally, renal A_1AR activation also protects against renal endothelial dysfunction caused by hepatic IR injury.

Summary—Despite the current lack of therapies for the treatment and prevention of AKI, recent research suggests that modulation of renal ARs holds promise in treating AKI and extrarenal injury.

Keywords

Apoptosis; inflammation; ischemia and reperfusion injury; necrosis

Introduction

Acute Kidney Injury (AKI) is a common problem in hospitalized patients and dramatically increases in mortality [1]. AKI costs more than $10 billion per year in the United States and no effective treatment exists [1]. Clinical outcomes of AKI are poor and have not improved over the past 50 years [2]. The incidence of AKI in Intensive Care Units (ICU) ranges from 1 to 25% in the United States, with mortality rates ranging between 15 and 60% [3]. With rapid increases in surgical and radiological procedures performed coupled with a growing elderly population, the incidence of AKI has risen over the last 10–15 years [4–6]. AKI

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commonly progresses to chronic kidney disease and is frequently associated with other life-threatening complications including sepsis and multiorgan failure [2,4,5]. Approximately 14% of surviving patients will go on to require renal replacement therapy, however the prognosis remains poor: mortality in patients treated with dialysis is 50–60% [2–6]. Unfortunately, there are no drugs that are FDA-approved to treat or prevent AKI.

Consequently, novel therapeutic and preventative measures for AKI are under intense investigation. Research on adenosine signaling in the kidney is one area with significant clinical therapeutic potential. This brief review will focus on renal adenosine signaling, the action of renal adenosine receptors (ARs) and their therapeutic potential in AKI and extrarenal injury.

Definitions and Causes of Acute Kidney Injury

AKI is defined as a rapid loss of kidney function (hours to days), resulting in the retention of metabolic waste products and oftentimes oliguria. Stages of kidney failure are defined clinically according to either the RIFLE or AKIN criteria [3]. The RIFLE acronym describes the increasing severity classes Risk, Injury, Failure, defined by rising serum creatinine and decreased urine output, and the two outcome classes Loss and End stage kidney disease, defined by the duration of loss of kidney function, 4 weeks and 3 months respectively [3]. However, the concern over conservative serum creatinine definitions in the RIFLE-classification system, when increases as little as 0.3 mg/dL could be indicative of early stages of AKI and with more than 50% increase in mortality [1], led to the AKI-Network (AKIN) staging system [3].

Renal ischemia and reperfusion (IR) injury, along with sepsis and nephrotoxin injury, are the leading causes of AKI for patients undergoing surgery involving the kidney, liver or aorta with the incidence of renal dysfunction in high-risk patients approaching 70–80% [4,7]. Of these, ischemic AKI is the best studied with highly reproducible experimental models. The basic mechanisms of ischemic AKI involve renal tubular and endothelial cell necrosis, apoptosis and inflammation [8]. Other leading causes of AKI include sepsis and nephrotoxins [4,9]. Drugs in the kidney tubular lumen are concentrated by reabsorption and have a direct toxic effect on the tubules. Radiocontrast dyes, antibiotics, non-steroidal anti-inflammatory drugs, chemotherapeutics and heavy metals are among the more common nephrotoxic agents. AKI occurs in 20% of patients with sepsis and in over 50% of patients with septic shock [4]. AKI also frequently co-manifests with injuries of other organs including the heart, liver, and lungs [9,10]. These extra-renal systemic complications secondary to AKI are the leading causes of mortality in the ICU [11]. Indeed, clinical studies show that patients with AKI complicated by extra-renal organ dysfunction have worsened prognosis compared to patients with isolated AKI [12].

Adenosine Generation in the Kidney

Adenosine is produced by all mammalian cells and regulates a wide variety of physiological activities [8,13]. In the kidney, adenosine regulates renin release, glomerular filtration rate (GFR) and renal vascular tone [13]. Adenosine is also a critical regulator of tubular glomerular feedback (TGF) [13,14]. Adenosine levels are enhanced during states of negative energy balance when the rate of adenosine triphosphate (ATP) hydrolysis is increased with respect to the rate of ATP synthesis. Hence, increased renal ATP consumption, impaired renal perfusion and hypoxia rapidly enhance adenosine formation within the kidney. Adenosine therefore accumulates during pathological insults to the kidney.

Extracellular adenosine is primarily derived from enzymatic phosphohydrolysis of ATP in the extracellular space. High levels of intracellular ATP (>5mmol/L) may be released into

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the extracellular space during hypoxic conditions, inflammation or acute injury by destabilizing apoptotic/necrotic cellular membranes [8,15]. Adenosine precursors may also be transported into the extracellular space via nucleotide release mechanisms, such as the release of ADP by granular release from activated platelets or inflammatory cells [8,16]. ATP and ADP are enzymatically phosphohydrolyzed by ectonucleoside-triphosphate-diphosphohydrolase-1 (also known as ectopyrase, CD39), yielding AMP [17,18]. AMP is then converted to adenosine by the surface enzyme ecto-5′-nucleotidase (CD73) (Figure 1) [16,19]. In addition, degradation of AMP to adenosine by CD73 activation decreases the availability of extracellular ATP, a recently recognized danger signal that promotes tissue injury and cell death [15,20,21]. In the extracellular space, ATP acts to attract leukocytes to the site of tissue injury and serve as a strong pro-inflammatory stimulus [22]. Therefore, stimulation of CD73 may serve the dual protective role of utilizing/removing cytotoxic extracellular ATP for the generation of cytoprotective adenosine.

Adenosine Receptors and AKI

The extracellular adenosine generated by CD39 and CD73 phosphohydrolysis mediates a variety of cellular effects through G-protein coupled purinergic receptors (A_1AR, A_{2A}AR, A_{2B}AR and A_3AR, Fig. 1) [8,13]. The high-affinity receptors, A_1AR, A_{2A}AR, and A_3AR, are activated by physiological levels of adenosine (10–100nM) whereas the A_{2B}AR is a low affinity receptor, activating at concentrations above 1μM [13,23]. Such high levels of adenosine are seen only during pathological conditions [24]. While the expression levels of AR subtypes vary in cell types and locations in the kidney (Table 1, Figure 3), expression levels also have been known to change during ischemic, hypoxic or inflammatory conditions [8]. Renal adenosine generation and manipulating ARs have the potential to mitigate AKI.

1) A_1 Adenosine Receptors

The A_1AR is widely expressed in the kidney, especially in the distal afferent arterioles, mesangial cells, proximal convoluted tubules, medullary collecting ducts, and papillary surface epithelia [8] (Figure 3). The A_1AR regulates renal vascular tone, TGF and renin secretion [13,14]. Endogenous or exogenous adenosine via A_1AR causes renal arteriolar vasoconstriction, thus lowering GFR and stimulates NaCl, HCO_3^-, phosphate and fluid reabsorption. The A_1AR signaling is mediated by pertussis toxin-sensitive G-protein transduced coupling to protein kinase C, extracellular signal-regulated protein kinase mitogen-activated protein kinase (ERK MAPK) and Akt (Figure 2) [25].

In addition to its renal hemodynamic effects and critical role in TGF, manipulation of A_1AR has significant therapeutic potential in protection against AKI. Clinical benefit of activation or blockade of the A_1AR is dictated by the etiology and pathophysiology of the AKI. Selective A_1AR activation protects against renal IR injury and septic AKI in mice by reducing inflammation, necrosis and apoptosis [26–30].

As activation of renal A_1ARs reduces GFR and afferent cortical blood flow through mediation of TGF, some investigators have implicated A_1AR activation in the reduction of renal function due to nephrotoxic AKI, and perhaps due to ischemic and septic AKI [13]. These experimental results and interpretations may be conditioned by whether the outcomes tested are changes in GFR or indicators of tubular damage. However, decrease in GFR, renin, sympathetic outflow and active solute transport associated with A_1AR activation would, in theory, reduce renal oxygen consumption in the setting of ischemic and nephrotoxic renal injury. The metabolic effects may differ between different models of AKI as a lower GFR might protect in certain models (e.g., ischemic AKI) and inhibition of transport may provide more protection in other experimental models (e.g., nephroxin induced AKI).

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Indeed, we demonstrated that A_1AR agonist produced powerful renal protection against ischemic AKI in mice [29,30]. Conversely, mice deficient in A_1AR or wild type mice treated with an A_1AR antagonist had increased renal dysfunction after ischemic- or septic-AKI [28,30]. We also demonstrated that transient activation of renal A_1AR led to acute as well as delayed protective effects against renal IR injury via distinct signaling pathways [25]. In the acute phase, A_1AR activation led to phosphorylation of ERK MAPK, Akt and heat shock protein 27 (HSP27), whereas the delayed protective effects observed several hours after A_1AR activation may be the result of a dramatic induction of HSP27.

In contrast to the powerful renal protection against ischemic AKI with selective A_1AR agonists, selective A_1AR antagonists may protect against nephrotoxin-induced AKI and radiocontrast nephropathy [13,31]. A selective A_1AR antagonist (DPCPX) or genetic deletion of A_1ARs protected against radiocontrast nephropathy in mice [31]. Selective A_1AR antagonists also promote natriuresis without kaliuresis and may also have a therapeutic potential as a diuretic in patients with congestive heart failure [32,33]. However, despite theoretical benefits for cardiorenal syndrome, recent clinical trials have shown that A_1AR antagonists increased renal dysfunction rather than improving it [34]. Selective and non-selective A_1AR antagonists prevented renal injury due to other nephrotoxins including glycerol, uranyl nitrate, cisplatin and gentamicin [13,14,35]. Meta-analysis of clinical trial data concluded that theophylline may reduce the incidence of radiocontrast media-induced nephropathy [13,35,36]. In mitigating radiocontrast induced renal injury, saline hydration and AR antagonists are effective, though the benefits are not additive. AR antagonists such as theophylline may be advantageous in conditions of poor renal blood flow when additional hydration may be deleterious (i.e. congestive heart failure, chronic renal insufficiency [13,35].

2) A_{2A} Adenosine Receptors

In the kidney, the A_{2A}AR receptor is located predominantly in the glomerular epithelium and adjacent vasculature [8] (Figure 3). In contrast to the A_1AR-receptor, the A_{2A}AR-receptor activation vasodilates deep cortical glomerular vessels and increases blood flow in the renal medulla [37,38]. A_{2A}AR-activation has also been shown to increase renin release (Table 1) [13]. A_{2A}AR-coupled G_s-mediated stimulation of adenylate cyclase and protein kinase A results in CREB-mediated cytoprotection against AKI (Figure 2) [37,39,40].

The A_{2A}AR activation leads to increased medullary blood flow and oxygenation, and lowers medullary transport activity [13]. Consistent with these effects, treatment with A_{2A}AR agonists has been shown to improve medullary hypoxia or hypoperfusion after renal IR injury [38,41]. The A_{2A}ARs are also well known for their ability to regulate hyperactive inflammatory cascade associated with AKI. A_{2A}AR produces immuno-modulatory effects, notably on macrophages and neutrophils, that limit tissue damage [37,41,42]. In IR injury, renal protection by A_{2A}AR-activation is independent of macrophage activation [42]. However in glomerulonephritis, A_{2A}AR-agonists reduce inflammation by diminishing macrophage-derived pro-inflammatory cytokine release including TNF-α, IL-6 and IL-8 [43]. The A_{2A}AR-activation also reduces neutrophil adhesion, infiltration and myeloperoxidasese activity and release of reactive oxygen metabolites likely through increased cAMP and activation of PKA in neutrophils [37,42].

3) A_{2B} Adenosine Receptors

The A_{2B}AR receptors are found predominantly in the renal vasculature with scant expression in renal epithelia under normal physiologic conditions [44,45] (Table 1, Figure 3). Similar to the A_{2A}ARs, the A_{2B}ARs cause vascular dilatation, increased renin secretion, increased NO production and reduced tissue inflammation through G_s and cAMP signaling

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pathways (Figure 2) [13]. Grenz *et al*. demonstrated in a murine model of renal IR injury that kidney ischemic preconditioning was absent in A_{2B}AR deficient mice [46]. In contrast, ischemic preconditioning was produced in mice with specific deletion of A_1AR, A_{2a}AR or A_3AR. Consistent with these findings, they also showed that wild type mice treated with a selective A_{2B}AR agonist (BAY 60–6583) were protected against ischemic AKI. In addition, an A_{2B}AR selective antagonist (PSB1115) blocked the renal protective effects of kidney ischemic preconditioning. They also found that renal A_{2B}ARs rather than leukocyte A_{2B}ARs conferred renal protection against IR injury using A_{2B}AR bone-marrow chimera model. Therefore, unlike the A_{2A}ARs that regulate infiltrating pro-inflammatory leukocytes, the A_{2B}ARs target renal parenchymal (endothelial and/or tubular epithelia) cells to attenuate ischemic AKI.

4) A_3 Adenosine Receptors

The A_3AR is the least characterized AR subtype in the kidney [47]. The specific location of A_3ARs in the kidney is still unclear, as are the mechanisms of A_3AR signal transduction [13]. Under normal physiological conditions, A_3AR does not affect TGF, GFR or solute excretion [48]. Both pro- and anti-inflammatory effects have been attributed to A_3AR activation [49–51]. We have determined that mice genetically deficient in A_3ARs or blocking A_3ARs in wild-type mice resulted in significant renal protection from ischemic or myoglobinuric renal failure [50]. Moreover, we demonstrated in rats that selective A_3AR activation or inhibition worsened or protected, respectively, against ischemic AKI [52]. In contrast, A_3AR-activation diminishes inflammation and attenuates mortality and renal and hepatic injury in mice subjected to septic AKI [53]. Therefore, similar to A1AR, A3AR differentially modulates renal function depending on the type of renal injury.

The mechanism(s) by which the A_3AR activation or inhibition exacerbates or protects against, respectively, ischemic AKI remains to be determined. The A_3AR activation degranulates resident mast cells, which results in the release of stored inflammatory mediators including histamine and proteolytic enzymes [54,55]. We also demonstrated that the A_3AR agonist IB-MECA profoundly increases plasma histamine levels in C57 mice (~45 fold increase) [50]. In addition, A_3AR agonists cause apoptosis and calcium overload in multiple cell lines including cardiomyocytes, human leukemia cell lines and human proximal tubule (HK-2) cells [56–58]. Chronic A_3AR activation or overexpression is detrimental to cell survival [59]. Moreover, overexpression of A_3AR is embryologically lethal in mice with prominent fragmentation of DNA.

Remote Organ Injury Induced AKI, AKI-Induced Extrarenal Injury and Modulation by Adenosine Receptors

A host of changes occur during AKI that may cause distant injury to the brain, lungs, pancreas, liver, intestine, heart and vasculature. Leukocyte activation and trafficking, inflammation, oxidative stress, and changes to expression levels of cytokines, chemokines, sodium and water channels all lead to AKI-induced injury to distant organs, including the brain, lungs, intestines, liver, heart and circulation [10,60]. Inflammatory cytokines including TNF-α, IL-6 and IL-17A are released after ischemic AKI from small intestine and liver leading to additional renal, intestinal and liver injury [61]. A_1AR activation protects against AKI and also reduces liver and intestinal injury after renal IR injury [62]. We recently demonstrated that severe hepatic IR causes AKI with rapid renal endothelial apoptosis and leukocyte infiltration [63,64]. Endogenous and exogenous activation of renal A_1ARs protect against liver and kidney injury after in vivo liver IR via pathways involving Akt activation [62,63]. Therefore, protecting the kidney reduces liver IR injury and selective

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overexpression of cytoprotective A_1ARs in the kidney leads to protection of both liver and kidney after hepatic IR.

Allosteric Manipulation of Adenosine Receptors

The ubiquitous expression of ARs may limit selective activation of renal ARs. One promising therapy has been the use of allosteric activators with endogenous adenosine [65,66]. During AKI, adenosine levels dramatically increase in the kidney, and allosteric drugs may locally protect the kidney from AKI by potentiating the activation of desired ARs [65]. Potential side effects of selective AR agonists can be mitigated by application of AR allosteric enhancers. An AR allosteric enhancer selectively increases the efficacy of endogenous adenosine in tissues (e.g., ischemic kidney producing increased localized adenosine) thereby avoiding potential systemic side effects of AR agonists. At present, AR allosteric modulators (e.g., T-62 for chronic pain and migraine headache) are in various stages of human clinical trials [65].

Conclusions

Manipulation of AR activation has therapeutic potential in mitigating AKI and AKI-induced extrarenal injury. The pathophysiology of the AKI dictates whether activation or inactivation of a particular receptor subtype is beneficial. Modulating AR activation in AKI may also protect against AKI-induced extrarenal injury. While the AR agonists and antagonists may have pharmacological benefit, allosteric-binding drugs may offer the most targeted effects with limited side effects. Therapeutics involving ARs are increasing in scope and value, and will certainly play a role in clinical innovations for treating AKI and other conditions.

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Abbreviations

ADP	Adenosine Diphosphate
AKI	Acute Kidney Injury
AMP	Adenosine Monophosphate
AR	Adenosine Receptor
ATN	Acute Tubular Necrosis
ATP	Adenosine Triphosphate
CD39	Ectonucleoside Triphosphate Diphosphohydrolase 1
CD73	Ecto-5′-nucleotidase
ERK MAPK	Extracellular Signal-Regulated Protein Kinase Mitogen Activated Protein Kinase
GFR	Glomerular Filtration Rate
ICU	Intensive Care Unit
IR	Ischemia and Reperfusion

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TGF Tubular Glomerular Feedback

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Key Points

- Each of the AR subtypes (A_1AR, A_{2A}AR, A_{2B}AR or A_3AR) produces different effects on the kidney when activated. Modulating ARs in treatment of AKI should be based on the pathophysiology of renal injury.
- Under hypoxic or ischemia conditions, activating the A_1AR, A_{2A}AR or A_{2B}AR receptors is beneficial: this reduces metabolic demand and inflammation, and increases renal perfusion. Under nephrotoxin-induced AKI, A_1AR-antagonism appears to be therapeutic.
- A_1AR and A_{2B}AR protect against AKI by directly targeting kidney parenchymal cells. A_{2A}AR activation produces immunomodulatory effects on circulating and infiltrating leukocytes. A_3AR-activation may exacerbate apoptosis and tissue damage during ischemic AKI.
- Mitigating AKI reduces the risk and severity of extrarenal injury, and may also be accomplished through AR manipulation.

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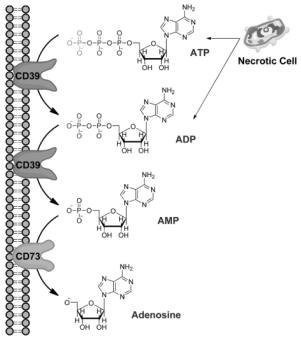

Figure 1.

Cell death by apoptosis and necrosis releases ATP into the extracellular space. Adenosine is then generated from cleavage of ATP and ADP into AMP by the surface enzyme ecto-nucleoside-triphosphate-disphosphohydrolase1 (E-NTPDase1 or CD39) highly expressed in the kidneys. AMP is then dephosphorylated to adenosine by ecto-5′-nucleotidase (CD73). Phosphohydrolysis of AMP by CD73 is the rate-limiting step in this pathway.

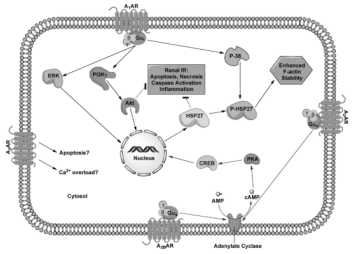

Figure 2.

Mechanisms of action of adenosine receptor (AR) subtype activation modulating renal cytoprotection. A_1AR-activation results in pertussis toxin-sensitive G_i-mediated activation of mitogen-activated protein kinases (ERK, P-38) and phosphoinositide 3-kinases (PI3K) resulting in Heat Shock Protein 27 (HSP27) phosphorylation and induction leading to reduced apoptosis and inflammation. A_{2A}AR and A_{2B}AR couple with G_s and stimulates adenylate cyclase, raising cAMP and activating Protein Kinase A (PKA). PKA then causes nuclear translocation of cAMP Response-Element Binding (CREB) protein to produce cytoprotection. Mechanism of A_3AR activation is still unknown. A_3AR activation appears to stimulate apoptosis and calcium overload leading to enhanced renal injury after ischemia and reperfusion.

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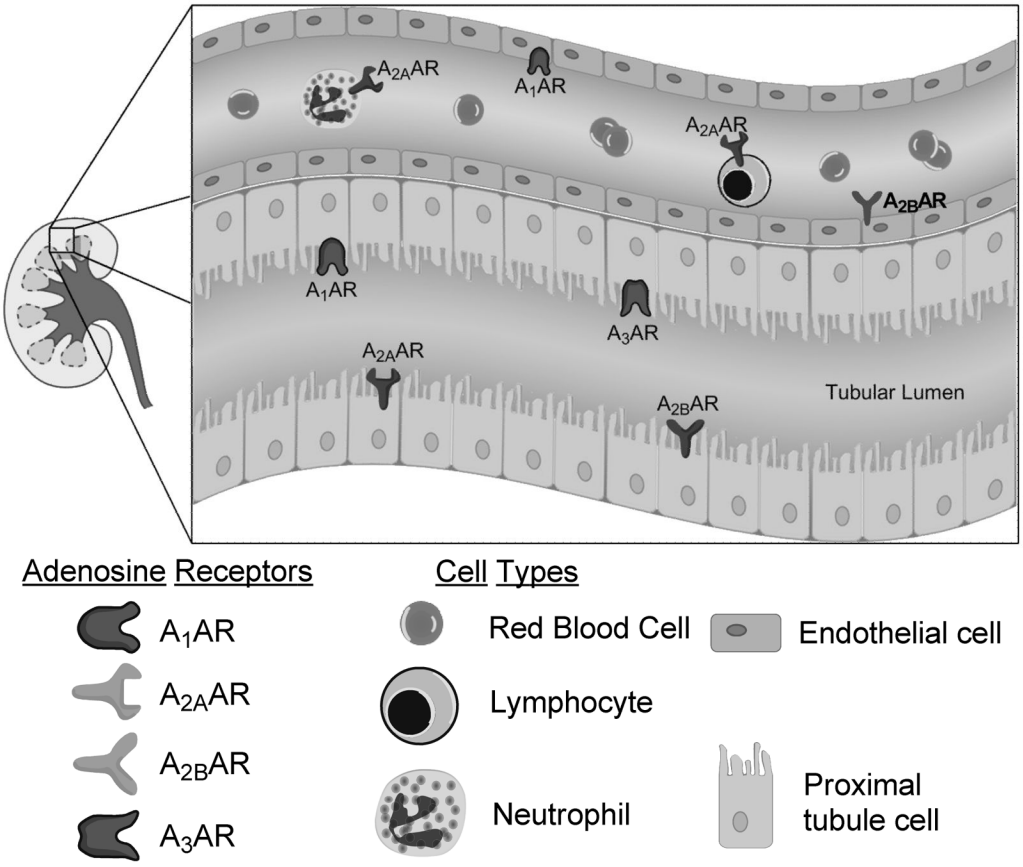

Figure 3.

Location of adenosine receptors (ARs) in the kidney mediating cytoprotection. Endothelial and tubular A_1AR activation produces cytoprotection. A_{2A}ARs are found in leukocytes (e.g., neutrophils and lymphocytes) and protect against renal injury by reducing inflammation. Renal tubular and endothelial A_{2B}ARs may also produce renal protection. A_3ARs appear to be expressed in many cell types (e.g., epithelial and endothelial cells) in the kidney. Selective A_3AR antagonist produces renal protection against ischemia and reperfusion injury.