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Adenosine Receptors and Renal Ischemia Reperfusion Injury

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Abstract

One of the frequent clinical complications that results in billions of dollars in health care costs annually in the United States is acute kidney injury (AKI). Ischemia reperfusion (IR) injury is a major cause AKI. Unfortunately, no effective treatment or preventive measure for AKI exists. With increased surgical complexity coupled with increasing number of elderly, the incidence of AKI is becoming more frequent. Adenosine is a metabolic breakdown product of adenosine triphosphate (ATP) and contributes to the regulation of multiple physiological events. Extracellular adenosine activates 4 subtypes of adenosine receptors (AR) including A_1AR, A_{2A}AR, A_{2B}AR and A_3AR. In the kidney, adenosine regulates glomerular filtration rate, vascular tone, renin release and is an integrative part of tubular glomerular feedback signal to the afferent arterioles. In addition, each AR subtype powerfully modulates renal IR injury. The A_1AR activation protects against ischemic insult by reducing apoptosis, necrosis, and inflammation. Activation of A_{2A}AR protects against renal injury by modulating leukocyte-mediated inflammation as well as directly reducing renal tubular inflammation. Activation of A_{2B}AR acts via direct activation of renal parenchymal as well as renovascular receptors and is important in kidney preconditioning. Finally, activation of A_3AR exacerbates renal damage following renal IR injury while A_3AR antagonism attenuates renal damage following ischemic insult. Latest body of research suggests that kidney AR modulation may be a promising approach to treat ischemic AKI. This brief review focuses on the signaling pathways of adenosine in the kidney followed by the role for various AR modulations in protecting against ischemic AKI.

Keywords

Acute kidney injury; acute renal failure; apoptosis; inflammation; necrosis

Renal ischemia reperfusion injury –clinical significance and pathobiology

Acute kidney injury (AKI) involves a complex series of events that are associated with high health care costs and as well as very high mortality and morbidity rates in hospitalized patients (Chertow et al. 2005). Outcomes from AKI are poor without any significant improvements in the past 50 years (Jones & Lee 2008). The incidence of AKI in critically ill

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patients is increasing in the US with mortality rates approaching 60% (Srisawat et al. 2010). For over a decade, the incidence of kidney injury due to ischemia has been increasing in the United States due to the rise in major surgical procedures in conjunction with an increasing elderly population (Hoste & Kellum 2007; Kellum & Hoste 2008; Hoste et al. 2010). Prognosis from AKI continues to be poor with mortality rates of patients requiring hemodialysis approaching 60% (Hoste & Kellum 2007; Jones & Lee 2008; Kellum & Hoste 2008; Srisawat et al. 2010; Hoste et al. 2010). AKI usually develops into chronic kidney disease and often correlated with severe extrarenal complications including multi-organ dysfunction and sepsis (Jones & Lee 2008; Kellum & Hoste 2008; Hoste et al. 2010). Presently, there are no drugs or therapies for the treatment of AKI. Therefore, therapies to prevent or accelerate renal recovery during and after ischemic AKI are critically needed.

Renal ischemia reperfusion (IR) injury is a leading cause of perioperative AKI (Jones & Lee 2008). Renal IR injury leading to AKI involves a complex series of events orchestrated by renal tubular cells, endothelial cells and leukocytes. The pathophysiology of IR injury involves initial cellular and tissue damage caused by compromised blood flow (ischemia) resulting in tubular and endothelial necrosis and apoptosis (Kusch et al. 2013). Restoration of blood flow (reperfusion) exacerbates renal injury due to the inflammatory response accompanied by chemokines and cytokines derived from renal tubular proximal tubule cells, resident intrarenal leukocytes (e.g., dendritic cells, macrophages) as well as infiltration bone-marrow derived-leukocytes (e.g., neutrophils, lymphocytes) (Kinsey et al. 2008).

Directly related to protection against renal IR injury, studies over the past 2 decades revealed that adenosine via activation of cell surface adenosine receptors (ARs) plays a major role in protection against ischemic AKI (Day et al. 2004; Lee et al. 2004a; Gallos et al. 2005; Kinsey et al. 2012).

Adenosine generation and function in the kidney

Adenosine, a nucleoside comprised of a ribose sugar and adenine base, is generated by all mammalian cells (Vallon & Osswald 2009). Renal adenosine levels accumulate due to increased consumption of renal ATP, hypoxia and impairment of kidney perfusion. During hypoxia or ischemia, high levels of intracellular ATP or adenosine diphosphate (ADP) are released, typically from apoptotic or necrotic cells, into the extracellular milieu (Trautmann 2009). In addition, with increased renal tubular solute transport activity and increased ATP consumption due to increased ATPase activity, adenosine generation is accelerated (Vallon et al. 2006; Vallon & Osswald 2009).

In the extracellular milieu, adenosine is derived from the phosphohydrolysis of adenosine triphosphate (ATP) and adenosine monophosphate (AMP) (Figure 1). Metabolism of ATP and ADP and subsequent adenosine generation is achieved via a 2 step enzymatic reaction. The first step encompasses the enzymatic phosphohydrolysis of ATP and/or ADP by ectonucleoside-triphosphate-diphosphohydrolase-1 (also known as ectopyrase or CD39), which can either elicit the conversion of ATP to ADP and consequently yields adenosine monophosphate (AMP) (Colgan et al. 2006; Grenz et al. 2007). Subsequently, the conversion of AMP to adenosine is accomplished by the surface enzyme ecto-5’-

nucleotidase (CD73). CD73 is present in virtually all cell types and particularly in high concentrations of CD73 are present in the kidney. CD73 and adenosine generation serves to protect against inflammatory and ischemic tissue injury (Colgan et al. 2006). Furthermore, activation of CD73 reduces ATP in the extracellular space – a recently recognized danger signal molecule that accelerates cell death and tissue injury (Chen et al. 2006; Trautmann 2009; McDonald et al. 2010). Indeed, recent studies show that ATP not only serves as a robust pro-inflammatory stimulus but also attracts leukocytes to the site of injury (Stagg & Smyth 2010). Consequently, the activation of CD73 may indirectly function as a protective mechanism via the utilization or removal of extracellular ATP in exchange for generating cytoprotective adenosine.

Adenosine plays a major physiological role in the kidney by regulating the release of renin, glomerular filtration rate (GFR) and renal vascular tone (Vallon & Osswald 2009). Additionally, adenosine plays a major role in tubular glomerular feedback (TGF). In the kidney, TGF is triggered by changes in NaCl concentration that are detected by the macula densa cells at the end of the thick ascending limb of Henle's loop which in turn triggers a change in the vascular tone of the afferent arteriole of the juxtaglomerular apparatus resulting in subsequent changes in GFR and renin secretion (Osswald et al. 1997). Adenosine is the factor that mediates the TGF response in the macula densa and afferent arterioles and TGF can be inhibited by selective AR antagonists (Osswald et al. 1996; Osswald et al. 1997; Vallon et al. 2006; Vallon & Osswald 2009).

Adenosine receptor signaling and renal IR injury

Extracellular adenosine signals through 4 G-protein coupled purinergic adenosine receptors (ARs) and includes A_1AR, A_{2A}AR, A_{2B}AR and A_3AR (Bauerle et al. 2011; Yap & Lee 2012) (Figure 1). These G protein-coupled receptors comprise a seven transmembrane domain in which the A_1AR and A_3AR receptors are coupled with the G_i subunit to inhibit adenylyl cyclase and the cyclic AMP (cAMP) pathway. In contrast, the A_{2A}AR and A_{2B}AR stimulate adenylyl cyclase and cAMP production by coupling with the G_s subunit (Hasko et al. 2008; Vallon & Osswald 2009). Physiological levels of adenosine (10–100nM) can activate the high affinity receptors A_1AR, A_{2A}AR and A_3AR. In contrast, the low affinity A_{2B}AR receptor is activated upon pathophysiological conditions (e.g., ischemia or hypoxia) where higher adenosine concentrations (>1μM) are generated (Hasko et al. 2008; Vallon & Osswald 2009). During pathophysiological conditions such as ischemia, inflammation and hypoxia, AR expression changes in various areas of the kidney. Thus, recent studies show that adenosine generation and AR modulation have the potential to attenuate renal IR injury, which will be discussed further in this review.

A_1AR and renal IR injury

In the kidney, the A_1AR is located in the distal afferent arteriole, glomerulus, proximal tubules, mesangial cells and collecting ducts (Freissmuth et al. 1987; Weaver & Reppert 1992; Jackson et al. 2002; Vallon et al. 2006; Vallon & Osswald 2009) (Figure 2). Facilitation of A_1AR signaling is achieved via the pertussis toxin-sensitive G-proteins and is coupled to protein kinase C, extracellular signal-regulated protein kinase mitogen-activated

protein kinase (ERK MAPK) and Akt pathways (Figure 3) (Joo et al. 2007). The A_1AR activation regulates kidney vascular tone, TGF and renin secretion by reducing cAMP levels and by decreasing the activity of protein kinase A (PKA) with resultant increase in intracellular calcium concentration due to decrease in its sequestration (Vallon et al. 2006; Vallon & Osswald 2009). Renal A_1AR activation lowers GFR by directly causing arteriolar vasoconstriction and stimulates NaCl, HCO_3^-, phosphate and fluid reabsorption (Vallon & Osswald 2009; Bauerle et al. 2011).

In addition to its important role in renal physiology by modulating renal hemodynamics and TGF, renal A_1AR activation with a selective A_1AR agonist 2-chlolo-cyclopentyladenosine (CCPA) protects against renal IR injury by decreasing renal tubular necrosis, apoptosis and the inflammatory response while global genetic deletion of this receptor increases renal injury following IR (Lee et al. 2004a; Lee et al. 2004c). Moreover, pretreatment with a selective A_1AR antagonist 1,3-dipropyl-8-cyclopentylxanthine (DPCPX) after renal IR resulted in increased renal dysfunction with marked renal tubular necrosis, inflammation as well as apoptosis.

Previous work also showed that A_1AR activation directly protects cultured renal tubules against necrosis as well as apoptosis (Lee et al. 2007a). Furthermore, overexpression of the A_1AR in renal tubule cell line protected against peroxide induced necrosis and apoptosis induced by tumor necrosis factor-α (TNF-α) and cycloheximide, via upregulation of total and phosphorylated heat-shock protein 27 (HSP27) expression via p38 MAPK activation. Moreover, proximal tubule cells obtained from A_1AR deficient mice exhibited enhanced hydrogen peroxide-induced necrosis and apoptosis compared to proximal tubule cells obtained from wild-type mice (Lee et al. 2007a).

Proximal tubule specific genetic ablation of the A_1AR increased renal IR injury suggesting that endogenous activation of the renal proximal tubular A_1AR is renoprotective (Kim et al. 2013a). Furthermore, reconstitution of renal A_1AR with intrarenal injection of A_1AR lentivirus injection resulted in a lower plasma creatinine, indicative of improved renal function, and reduced tubular inflammation shown by reduced leukocyte infiltration and pro-inflammatory cytokine production following renal IR (Kim et al. 2009). Thus, renal tubular A_1AR plays a major role in mediating the cytoprotective effects of adenosine in the kidney.

Recent studies suggest a critical role for activation of additional cytoprotective pathways in A_1AR-mediated protection against ischemic AKI (Park et al. 2012; Kim et al. 2013a). The A_1AR activation results in increased renal tubular interleukin-11 (IL-11) synthesis via ERK MAPK activation (Kim et al. 2013a). Furthermore, renal tubular A_1AR activation protects against ischemic AKI via induction of sphingosine kinase-1 (SK-1) synthesis and sphingosine 1-phosphate generation (Park et al. 2012). IL-11 as well as SK1 synthesis was critical for A_1AR-mediated renal tubular protection as mice deficient in IL-11 or SK-1 were not protected against ischemic AKI with a specific A_1AR agonist. Consistent with these findings, recent studies have shown that IL-11 receptor activation directly induces new SK-1 synthesis to increase cytoprotective S1P generation (Kim et al. 2013a).

Activation of renal A_1ARs leads to both acute and delayed protection from renal ischemic insult via separate signaling pathways (Joo et al. 2007). In particular, acute activation of A_1AR leads to the phosphorylation of HSP27, Akt, and ERK MAPK to protect against renal IR injury whereas the delayed phase of renal protection with A_1AR activation occurs several hours later via induction of new HSP27 synthesis (Joo et al. 2007).

In summary, the A_1AR activation protects against ischemic insult by decreasing necrosis, apoptosis and inflammation making it a promising candidate in improving renal function after renal IR injury. Intense efforts have been made to investigate several A_1AR agonists and antagonists to demonstrate renoprotective effects in both animal models and in human subjects. Challenge remains; however, as A_1AR activation produces wide-ranging pharmacological effects on different organs (bradycardia, sedation, hypotension) potentially limiting their use systemically.

A_{2A}AR and renal IR injury

The location of A_{2A}AR in the kidney includes the vasculature and glomerular epithelium (Bauerle et al. 2011) as well as proximal tubules (Lee & Emala 2002a; Wengert et al. 2005; Jackson et al. 2006). In contrast to the A_1AR, A_{2A}AR activation dilates blood vessels in the kidney and stimulates renin release (Okusa et al. 2000; Okusa 2002a) (Vallon & Osswald 2009). In particular, A_{2A}AR activation increases blood flow and oxygenation to the renal medulla while reducing solute transport activity in the medulla (Vallon & Osswald 2009). Consistent with these physiological effects, previous studies have demonstrated that A_{2A}AR activation ameliorates hypoxia or hypoperfusion after ischemic renal injury (Okusa et al. 2000; Day et al. 2003).

The A_{2A}ARs are well recognized for their ability to modulate the inflammatory response after renal IR injury. Indeed, A_{2A}AR activation reduces cytokine and chemokine expression in renal tubules cells as well as in leukocytes including macrophages, lymphocytes as well neutrophils (Okusa 2002a; Day et al. 2003; Day et al. 2005). The anti-inflammatory effects of A_{2A}AR activation is a critical component of renal protection with selective A_{2A}AR agonists (Linden 2006; Hasko et al. 2008). In terms of signal transduction, the A_{2A}AR-coupled G_s-mediated stimulation of adenylyl cyclase and PKA results in cAMP response element-binding protein (CREB)-mediated cytoprotection against renal IR injury (Figure 3) (Lee & Emala 2001; Okusa 2002a; Lee & Emala 2002b). Indeed, A_{2A}AR-mediated cAMP induction and PKA activation powerfully reduces renal inflammation as well as promotes medullary vasorelaxation after IR (Okusa et al. 2001; Linden 2006).

Adenosine may powerfully suppress inflammation via A_{2A}AR activation in regulatory T-cells (Tregs) (Kinsey et al. 2012). Adoptive transfer of Tregs deficient in CD73, the enzyme that produces extracellular adenosine from AMP, or transfer of A_{2A}AR deficient Tregs led to inhibition of Treg function. Therefore, these studies show that simultaneous ability to generate and respond to adenosine is required for Tregs to suppress innate immune responses in renal IR injury. Recent studies further demonstrate that A_{2A}AR activation in dendritic cells plays a critical role in protection against ischemic AKI (Li et al. 2012). Indeed, mice with specific deletion of A_{2A}ARs in dendritic cells had exacerbated renal

injury after IR. Furthermore, dendritic cell A_{2A}AR deficient mice were not protected against renal IR injury with specific A_{2A}AR agonist treatment. Furthermore, exogenous administration of dendritic cells treated *ex vivo* with A_{2A}AR agonist was protective against renal IR injury by suppressing natural killer T-cell mediated inflammation.

In summary, recent studies have shown that selective A_{2A}AR agonists attenuate inflammation and protect against kidney IR injury by PKA activation. However, additional investigations are necessary to increase the understanding of mechanisms of A_{2A}AR agonist-mediated reduction in inflammation and tissue damage.

A_{2B}AR and renal IR injury

The A_{2B}AR receptors are located in renal vasculature as well as in the renal epithelia (Lee & Emala 2002a; Wengert et al. 2005; Linden 2006; Jackson et al. 2006; Eckle et al. 2008) (Figure 2). Similar to the A_{2A}ARs, the A_{2B}ARs cause renovascular dilatation and increased renin secretion and decreased tissue inflammation via G_s and cAMP signaling pathways (Figure 3) (Vallon & Osswald 2009). In a murine model, the - renoprotective effects of ischemic preconditioning against ischemic AKI (intermittent ischemia and reperfusion before more prolonged ischemic insult) was lost in A_{2B}AR deficient mice (Grenz et al. 2008). On the contrary, ischemic preconditioning was preserved in animals lacking A_1AR, A_{2a}AR or A_3AR. Moreover, wild type animals given BAY 60–6586 (a selective A_{2B}AR agonist) were protected from AKI induced by warm renal IR injury with reduced renal tubular necrosis and inflammation. Consistent with the renoprotective effects of A_{2B}AR in renal ischemic preconditioning, PSB-1115 (a selective A_{2B}AR antagonist) abolished the renoprotective effects of kidney ischemic preconditioning. Bone marrow chimera studies conducted in mice also showed that bone marrow-derived leukocyte A_{2B}ARs do not play an important role in renal protection against IR injury. Therefore, unlike the A_{2A}ARs that regulate infiltrating pro-inflammatory leukocytes including Tregs and dendritic cells, the A_{2B}ARs target renal parenchymal (renal tubular cells and/or renal endothelial cells) cells to attenuate renal IR injury.

TNF-α plays a major role in renal IR injury as mice treated with TNF-α neutralizing antibody or mice deficient in TNF-α are protected against ischemic AKI (Donnahoo et al. 1999; Grenz et al. 2012b). The A_{2B}AR activation also plays a critical role in modulating neutrophil production of TNF-α during and after renal IR (Grenz et al. 2012b). The A_{2B}AR deficient mice generated significantly increased renal TNF-α after IR injury. Neutrophils are the source of exacerbated TNF-a generation after renal IR as neutrophil depletion or reconstituting A_{2B}AR deficient mice with TNF-α deficient neutrophils significantly attenuated renal injury.

Endothelial A_{2B}AR activation also plays a critical role in renal protection against IR injury by improving post-ischemic renal peritubular capillary blood flow (Grenz et al. 2012a). Adenosine generated during renal ischemia is rapidly removed through equilibrative nucleoside transporters (ENT). Indeed, Pharmacological ENT blockade or genetic deletion significantly increased renal adenosine levels and profoundly protected against renal IR injury in mice. The renal protection with ENT blockade mediated by activation of vascular

endothelial A_{2B}ARs as mice deficient in vascular endothelial A_{2B}ARs were not protected against renal IR injury with ENT blockade. Vascular endothelial A_1AR, A_{2A}AR and A_3ARs do not appear to play a role in improved post-ischemic renal blood flow after IR injury. Therefore, crosstalk between renal ENTs and the A_{2B}AR in vascular endothelia is critical in regulating post-ischemic no-reflow phenomenon.

In summary, A_{2B}AR is drastically induced during and after inflammation and ischemia. A_{2B}AR activation protects against renal ischemic injury with decreased renal tubular necrosis and inflammation as well as by modulating neutrophil TNF-α signaling. Thus, potentiating A_{2B}AR activation could be show promise in improving renal function after IR injury.

A_3AR and renal IR injury

The A_3AR is the least studied AR subtype in the kidney (Linden 2001). Although transcripts of A_3AR can be detected throughout the kidney, the specific function of A_3ARs in the kidney is still unknown as A_3AR activation does not affect solute excretion, TGF or GFR (Mozaffari et al. 2000; Vallon & Osswald 2009). In several cell lines, A_3ARs couple to both G_i and G_q for signal transduction (Fredholm et al. 2011). Interestingly, selective A_3AR activation increases renal tubular necrosis, apoptosis and inflammation after renal IR injury (Lee et al. 2003; Mabley et al. 2003; Young et al. 2004). Conversely, mice genetically deficient in A_3ARs or wild type mice treated with a specific A_3AR antagonist had improved kidney function and reduced renal injury after IR (Lee & Emala 2000; Lee et al. 2003).

The mechanism of A_3AR-mediated modulation of ischemic renal injury is unclear. The A_3AR activation has been shown to degranulate mast cells and increases the release of several inflammatory mediators including proteolytic enzymes and histamine (Fozard et al. 1996; Reeves et al. 1997), consistent with our findings that administration of a selective A_3AR agonist (IB-MECA) significantly increased the plasma histamine levels in mice, worsening renal function after renal IR injury (Lee et al. 2003). Therefore, mast cell activation may play a role in A_3AR-mediated exacerbation of renal IR injury. Furthermore, A_3AR activation increases calcium influx and induces apoptosis in several cell types including human proximal tubule cells, cardiomyocytes and leukocyte cell lines (HK-2) cells (Kohno et al. 1996; Shneyvays et al. 1998; Jacobson 1998). Finally, A_3AR overexpression is embryonically lethal with increased DNA fragmentation and chronic activation is detrimental to cell survival (Zhao et al. 2002). These mechanisms may also play a role in A_3AR-mediated modulation of renal IR injury.

Although substantial progression has been made in investigating the physiological significance of AR subtypes, the role for renal A_3ARs remains unclear. Studies utilizing knockout A_3AR mice as well as pharmacological agonists and antagonists have identified this receptor to potentiate ischemic injury by promoting necrosis and apoptosis.

Role of adenosine receptors in volatile anesthetic-mediated protection against ischemic AKI

Inhalation volatile anesthetics are one of the most widely used drugs during the perioperative period. Several clinically utilized volatile anesthetics including sevoflurane and isoflurane protects against renal IR injury via directly reducing renal tubular necrosis, inflammation and apoptosis (Lee et al. 2004b; Lee et al. 2007b). Recent studies suggest that adenosine plays a critical role in isoflurane-mediated protection against renal IR injury (Kim et al. 2013b). Isoflurane treatment induced CD73 induction in cultured proximal tubule cells as well as in mouse kidney with significantly increased renal tubular adenosine generation. Furthermore, isoflurane-mediated induction of CD73 and adenosine generation was critical for protection against ischemic AKI in mice as mice treated with a selective CD73 inhibitor or mice deficient in CD73 were not protected against renal injury after IR with isoflurane anesthesia. Therefore, these studies imply that isoflurane-mediated modulation of renal epithelial CD73 induction and adenosine generation may have important therapeutic implications to protect against renal IR injury.

Conclusions

Ischemic AKI continues to be a major clinical problem in hospitalized patients. Ischemic AKI is characterized by renal tubular cell death due to necrosis and apoptosis. Renal injury is further compounded by massive inflammatory response due to renal tubular cytokine and chemokine generation followed by infiltration of several pro-inflammatory leukocytes including T-lymphocytes, neutrophils and macrophages (Okusa 2002b; Kinsey et al. 2008). Modulation of renal AR activation has exciting potential to protect against renal injury by targeting various aspects of pathophysiology of ischemic AKI by reducing renal tubular necrosis and apoptosis and by dampening leukocyte-mediated inflammation. Specifically, renal tubular A_1AR activation reduces necrosis and apoptosis after renal IR (Lee et al. 2004a). Several leukocytes are targeted by A_{2A}AR activation including neutrophils, Tregs and dendritic cells (Kinsey et al. 2008; Li et al. 2012; Kinsey et al. 2012; Grenz et al. 2012b). Renal vascular A_{2B}AR also play a major role in improving post-ischemic kidney blood flow (Grenz et al. 2012a). The A_3AR activation, in contrast exacerbates renal IR injury and therefore, A_3AR antagonist therapy may be useful to protect against ischemic AKI (Lee & Emala 2000; Lee et al. 2003). Furthermore, renal AR activation appears to play a role in anesthetic-induced reduction in renal tubular inflammation and necrosis after IR (Kim et al. 2013b). More studies are required to better understand the mechanisms and distal signaling molecules generated with renal AR activation to translate these experimental studies to clinical setting.

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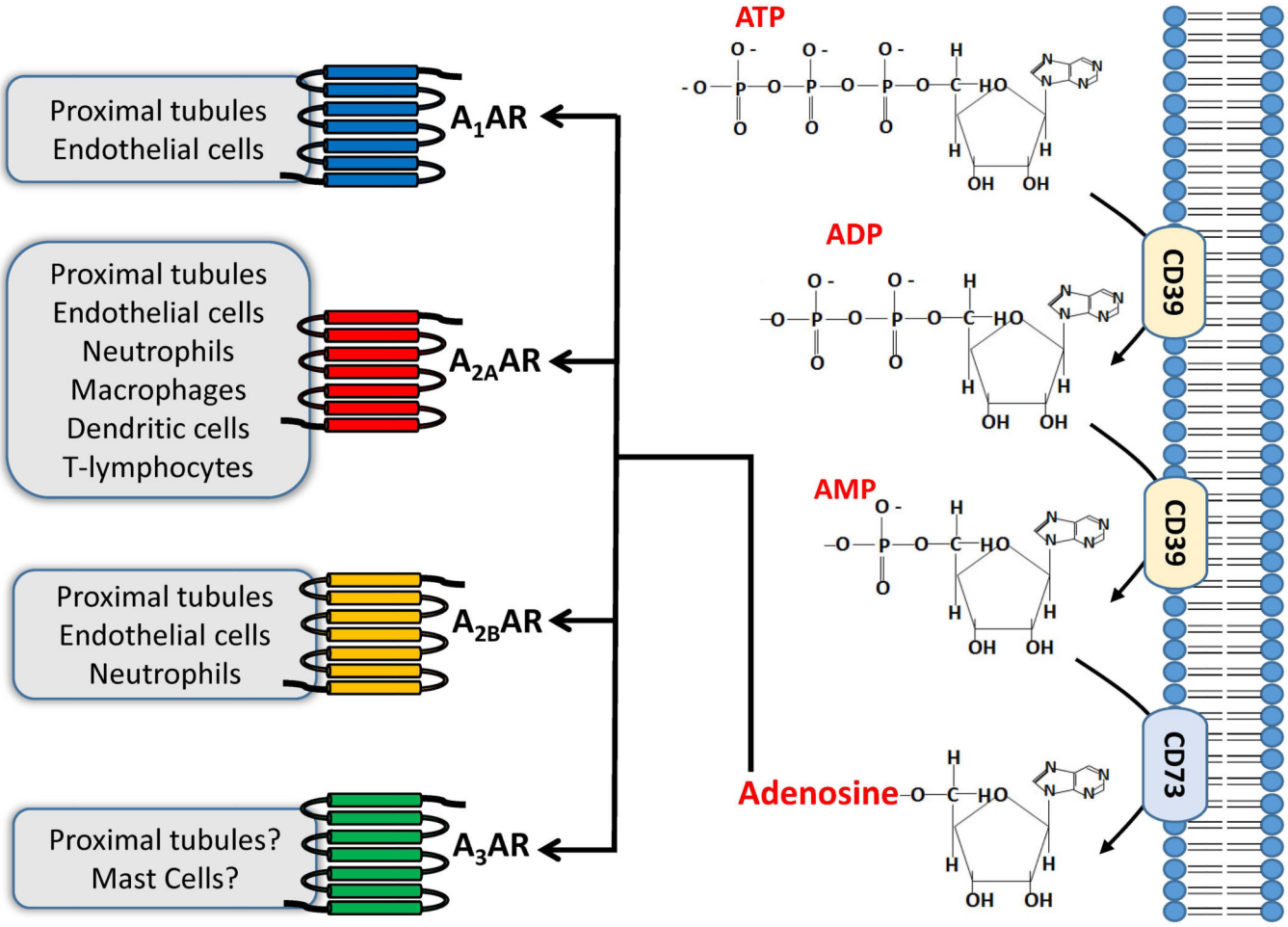

Figure 1.

Renal adenosine production is initiated by cleaving ATP and ADP molecules into AMP by the enzyme ecto-nucleoside-triphosphate-disphosphohydrolase1 (E-NTPDase1 or CD39). Following the cleavage to AMP, dephosphorylation occurs to yield adenosine by ecto-5'-nucleotidase (CD73) which is the rate-limiting step in adenosine synthesis. Adenosine generated then activates 4 distinct purinergic adenosine receptor subtypes (A_1AR, A_{2A}AR, A_{2B}AR and A_3AR). The A_1AR has been demonstrated to protect against renal IR injury by targeting kidney proximal tubules and endothelial cells. The A_{2A}AR modulates ischemic AKI by targeting both renal parenchymal cells as well as multiples subtypes of leukocytes including neutrophils, T-lymphocytes including regulatory T-cells, dendritic cells and macrophages. The A_{2B}AR reduces renal IR injury by targeting proximal tubules and endothelial cells as well as modulating TNF-α synthesis from kidney infiltrating neutrophils. The specific cell types(s) targeted by A_3AR activation in the kidney is unclear. However, a selective A_3AR agonist induces epithelial apoptosis most likely via calcium overload and also induces mast cell degranulation and histamine release to promote the inflammatory response.

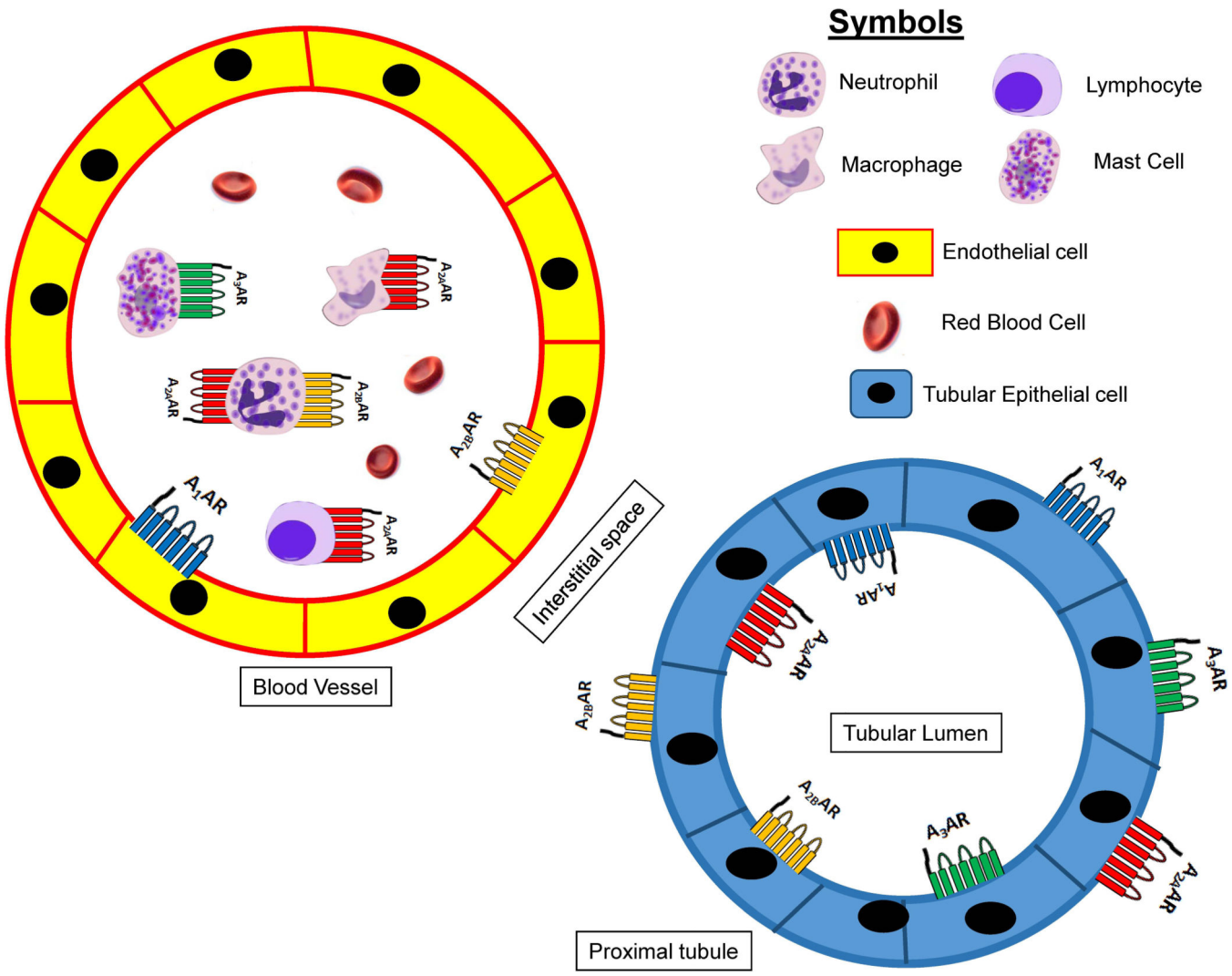

Figure 2.

Adenosine receptors (ARs) in the kidney mediating cytoprotection. A_1AR activation in endothelial and renal tubular cells produces cytoprotection. Neutrophil and lymphocyte A_{2A}AR activation protect against renal injury by reducing inflammation. Renal tubular and endothelial A_{2B}ARs protect from ischemic insult by attenuating inflammation and improving blood flow to the kidney, respectively. A_{2B}AR activation in neutrophils also decreases kidney injury after IR by downreguating neutrophil TNF-α synthesis. A_3ARs are expressed in various cell types (e.g., epithelial and endothelial cells) in the kidney as well as in mast cells. Selective antagonists of A_3AR protect against ischemic AKI.

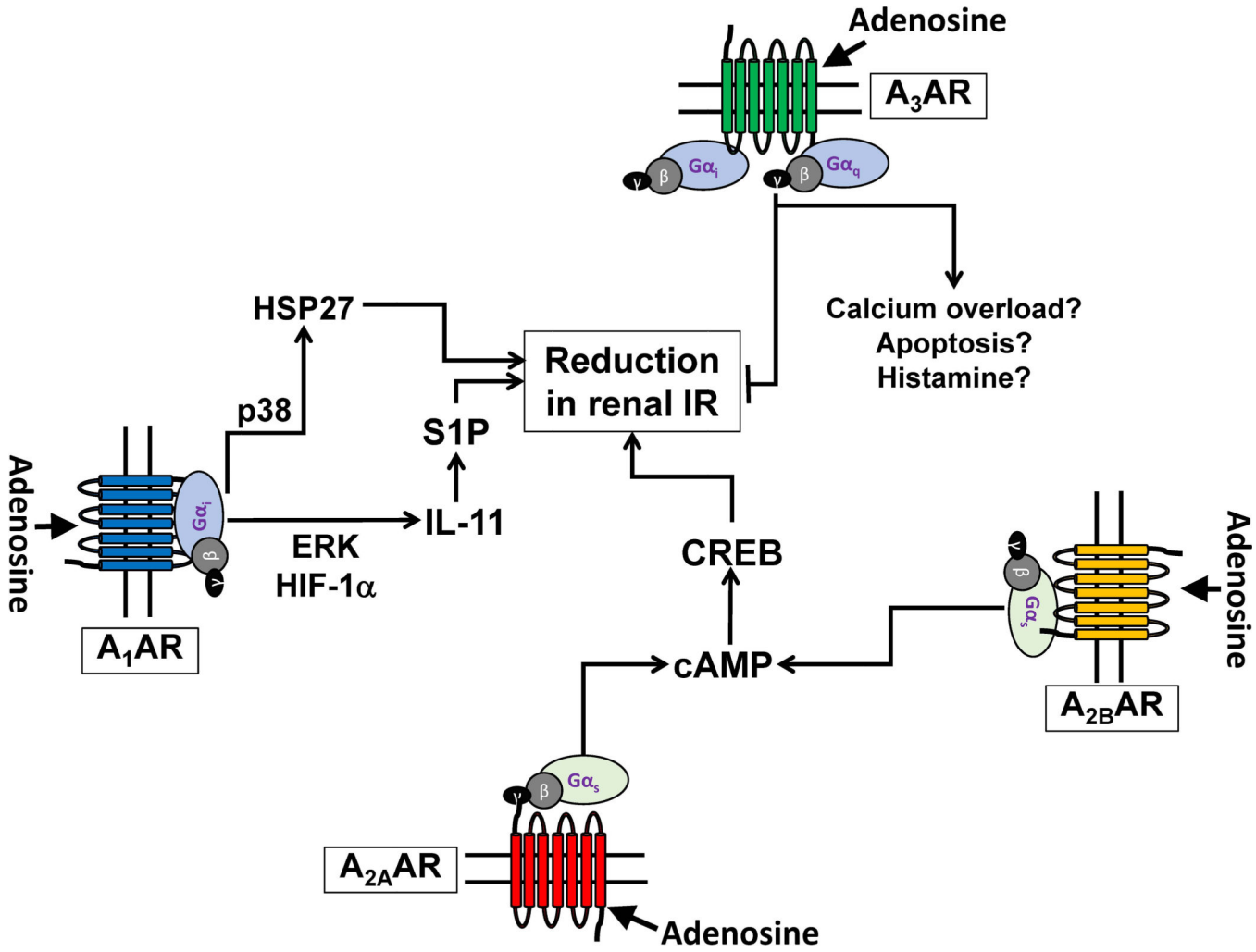

Figure 3.

Summary of mechanisms of adenosine receptor (AR)-mediated modulation of renal IR injury. Activation of A_1AR yields G_i-mediated activation of ERK and hypoxia inducible factor 1-alpha to synthesize a cytoprotective cytokine interleukin-11 (IL-11). IL-11 then subsequently induces the synthesis of another cytoprotective molecule sphingosine 1-phosphate (S1P) via upregulation of sphingosine kinase-1 synthesis. The A_1AR also phosphorylates and induces cytoprotective heat shock protein 27 (HSP27) synthesis via p38 MAPK activation resulting in decreased renal tubular apoptosis and inflammation. The $A_{2A}AR$ and the $A_{2B}AR$ couple with cholera toxin-sensitive G_s and stimulates adenylyl cyclase, raising cAMP and activating Protein Kinase A (PKA). Following PKA activation, nuclear translocation of cAMP Response-Element Binding (CREB) protein occurs to generate renal protection against IR injury by targeting renal tubules as well as leukocytes. The mechanisms of A_3AR activation leading to exacerbation of renal IR injury are still unknown. The A_3AR activation may stimulate apoptosis, calcium overload and degranulate mast cells leading to enhanced ischemic AKI.