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Adenosine Receptors and the Kidney

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Abstract

The autacoid, adenosine, is present in the normoxic kidney and generated in the cytosol as well as at extracellular sites. The rate of adenosine formation is enhanced when the rate of ATP hydrolysis prevails over the rate of ATP synthesis during increased tubular transport work or during oxygen deficiency. Extracellular adenosine acts on adenosine receptor subtypes (A_1, A_{2A}, A_{2B}, and A_3) in the cell membranes to affect vascular and tubular functions. Adenosine lowers glomerular filtration rate by constricting afferent arterioles, especially in superficial nephrons, and thus lowers the salt load and transport work of the kidney consistent with the concept of metabolic control of organ function. In contrast, it leads to vasodilation in the deep cortex and the semihypoxic medulla, and exerts differential effects on NaCl transport along the tubular and collecting duct system. These vascular and tubular effects point to a prominent role of adenosine and its receptors in the intrarenal metabolic regulation of kidney function, and, together with its role in inflammatory processes, form the basis for potential therapeutic approaches in radiocontrast media-induced acute renal failure, ischemia reperfusion injury, and in patients with cardiorenal failure.

Keywords

Adenosine receptors electrolyte; Kidney; Tubuloglomerular feedback; Renin; Fluid and transport; Metabolic control; Acute renal failure; Acute kidney injury; Radiocontrast media; Ischemia reperfusion injury; Heart failure

1 Introduction

Adenosine is a tissue hormone that is locally generated in many organs and that binds to cell surface receptors to mediate various aspects of organ function. Many of these effects revolve around a role of adenosine in metabolic control of organ function, including local matching of blood flow with energy consumption. According to this concept, the interstitial concentration of adenosine rises when cells are in negative energy balance. Adenosine locally activates vasodilatory adenosine A_2 receptor (A_2AR) and adjusts blood flow to meet demand. The role of adenosine in the kidney is analogous but, as a consequence of the specific renal structural organization and function, more complicated than its role in other organs. We will first describe the differential effects of adenosine on the renal cortical and medullary vascular structures, and its role in tubuloglomerular feedback (TGF), the regulation of renin secretion and in transport processes in the tubular and collecting duct

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system. These issues are subsequently discussed with regard to a potential role of adenosine receptors as new potential targets in the treatment of patients with radiocontrast media-induced acute renal failure, ischemia-reperfusion injury, and in patients with acute decompensated heart failure or cardiorenal failure. Please see recent reviews on the expression of adenosine receptors in the kidney and the role of adenosine in kidney function in general (Vallon et al. 2006), and in acute renal failure (Osswald and Vallon 2008) and fluid retention in particular (Welch 2002; Modlinger and Welch 2003; Vallon et al. 2008).

2 Vascular Effects of Adenosine in Kidney Cortex and Medulla

In contrast to other organs, blood flow into the cortex of the kidney generates, via the formation of an ultrafiltrate, the metabolic burden for tubular electrolyte transport and thus the demand for energy. Hence, to recover from negative energy balance in the kidney, a mechanism is required that lowers glomerular filtration rate (GFR) or the ratio between glomerular filtration rate and cortical renal blood flow. In comparison, blood flow in the renal medulla is nutritive. It derives from the postglomerular circulation of deep nephrons, and due to the way the kidney concentrates the urine, blood flow and O_2 supply are low in this area, although active NaCl reabsorption in the medullary thick ascending limb is essential for function. With regard to metabolic control, this requires a *vasodilator* to prevent hypoxic injury in the renal medulla. As outlined in the following, adenosine is a vasodilator in the renal medulla but induces cortical vasoconstriction and lowers GFR.

2.1 Activation of A_1AR Lowers Glomerular Filtration Rate

Healthy volunteers responded to an intravenous infusion or direct application of adenosine into the renal artery with a reduction in GFR of 15–25% while blood pressure and renal blood flow were unchanged (Edlund and Sollevi 1993; Edlund et al. 1994; Balakrishnan et al. 1996). Adenosine infusion into the renal artery of rats or dogs reduced single-nephron GFR (SNGFR) in superficial nephrons to a larger extent than whole-kidney GFR, indicating that deep-cortical vasodilation (see below) counteracts superficial vasoconstriction (Osswald et al. 1978a, b; Haas and Osswald 1981). Adenosine lowers SNGFR in superficial nephrons due to afferent arteriolar vasoconstriction (Osswald et al. 1978b; Haas and Osswald 1981) (Fig. 1). Direct videometric assessment of pre- and postglomerular arteries using the “split-hydronephrotic” rat kidney technique revealed adenosine-induced constriction of afferent arterioles via high-affinity A_1AR and dilation via activation of both high-affinity A_{2A}AR and low-affinity A_{2B}AR (Tang et al. 1999). Whereas activation of A_1AR led to the constriction of mainly afferent arterioles near the glomerulus, A_2AR activation lead to the dilation of mainly postglomerular arteries (Holz and Steinhausen 1987; Dietrich and Steinhausen 1993; Gabriels et al. 2000). A_1AR-mediated afferent arteriolar constriction involves a pertussis toxin-sensitive Gi protein and subsequent activation of phospholipase C, presumably through βγ subunits released from Gαi (Hansen et al. 2003b). A_{2A}AR-mediated renal vasodilation may involve activation of ATP-regulated potassium channels (Tang et al. 1999) and endothelial nitric oxide synthase (Hansen et al. 2005).

Oral application of the A_1AR antagonist (+)-(*R*)-[(*E*)-3-(2-phenylpyrazolo [1,5-*a*]pyridin-3-yl)acryloyl]-2-piperidine ethanol (FK-453) to healthy male subjects increased GFR by

~20% without significantly altering effective renal plasma flow or mean arterial blood pressure (Balakrishnan et al. 1993), providing evidence that *endogenous* adenosine elicits a tonic suppression of GFR through the activation of A_1AR. Consistent with a prominent role of adenosine in the regulation of afferent arteriolar tone, autoregulation of renal blood flow and glomerular filtration rate (i.e., their constancy in spite of changes in renal perfusion pressure) is dependent upon the activation of A_1AR (Hashimoto et al. 2006).

2.2 Factors Modulating Adenosine-Induced Cortical Vasoconstriction

Suppression of the renin–angiotensin system by dietary salt or pharmacological means reduces or blocks the renal vasoconstrictive action of adenosine (Osswald et al. 1975, 1982; Spielman and Osswald 1979; Arend et al. 1985; Macias-Nunez et al. 1985; Dietrich et al. 1991; Dietrich and Steinhausen 1993). In contrast, activation of the renin–angiotensin system potentiates adenosine-induced vasoconstriction and lowering of GFR (Osswald et al. 1975, 1978a, 1982). Further studies identified a mutual dependency and cooperation of adenosine and angiotensin II in producing afferent arteriolar constriction (Weihprecht et al. 1994; Traynor et al. 1998; Hansen et al. 2003a). Adenosine enhances angiotensin II-induced constriction of afferent arterioles by receptor-dependent and -independent pathways. The latter involves adenosine uptake and intracellular effects that increase the calcium sensitivity by phosphorylating the myosin light chain (Lai et al. 2006; Patzak et al. 2007). Moreover, inhibiting the synthesis of vasodilators like nitric oxide (NO) (Barrett and Droppleman 1993; Pflueger et al. 1999b) or prostaglandins (Spielman and Osswald 1978; Pflueger et al. 1999a) increases the sensitivity of the kidney to adenosine-induced vasoconstriction. The outlined interactions can be of clinical relevance.

2.3 Activation of A_2AR Induces Medullary Vasodilation

Intrarenal adenosine infusion in rats initially induces vasoconstriction in all cortical zones; this is followed by persistent superficial cortical vasoconstriction but *deep cortical* vasodilation (Macias-Nunez et al. 1983; Miyamoto et al. 1988). While A_1AR-mediated afferent arteriolar constriction dominates in *superficial* nephrons, *deep cortical* glomeruli, which supply the blood flow to the renal medulla, can respond to adenosine with A_2AR-mediated vasodilation (Inscho et al. 1991; Weihprecht et al. 1992; Inscho 1996; Yaoita et al. 1999; Nishiyama et al. 2001). In accordance, renal interstitial infusion in rats of the A_2AR agonist 2-[*p*-(2-carboxyethyl)phenethylamino]-5′-*N*-ethylcarboxamido adenosine (CGS-21680) increased medullary blood flow (Agmon et al. 1993), whereas intramedullary infusion of the selective A_2AR antagonist 3,7-dimethyl-1-propargylxanthine (DMPX) (but not the A_1AR antagonist 1,3-dipropyl-8-cyclopentylxanthine (DPCPX)) decreased medullary blood flow (Zou et al. 1999). This indicates that *endogenous* adenosine dilates medullary vessels and sustains medullary blood flow via activation of A_2AR (Fig. 1).

2.4 Adenosine is a Mediator of Tubuloglomerular Feedback via Activation of A_1AR

The mammalian kidney has a rather high GFR (~180 l per day in humans). About 99% of the filtered fluid and NaCl are subsequently reabsorbed along the tubular and collecting duct system, such that urinary excretion closely matches intake. As a result, GFR is a significant determinant of renal transport work, and GFR and re-absorption have to be closely coordinated to avoid renal loss or retention of fluid and NaCl. The tubuloglomerular

feedback (TGF) is a mechanism that helps to coordinate GFR with the tubular transport activity or capacity. In this mechanism, specialized tubular cells, the macula densa, sense the tubular NaCl load at the end of the thick ascending limb (TAL; where about 85% of the filtered NaCl has been reabsorbed), and induce a change in afferent arteriolar tone such that an inverse relationship is established between the tubular NaCl load and SNGFR of the same nephron. This way, the TGF stabilizes the NaCl load to further distal segments, where the fine regulation of NaCl and fluid balance takes place under *systemic* neurohumoral control.

The TGF response, in other words an inverse change in SNGFR or glomerular capillary pressure in response to changes in the NaCl concentration at the macula densa, is inhibited by unselective adenosine receptor blockers like theophylline or 1,3-dipropyl-8-sulfophenylxanthine (DPSPX) (Schnermann et al. 1977; Osswald et al. 1980; Franco et al. 1989), as well as by selective A_1AR antagonists like DPCPX, 8-(noradamantan-3-yl)-1,3-dipropylxanthine (KW-3902, rolofylline), CVT-124 (the *S*-enantiomer of the highly selective racemic A_1AR antagonist 1,3-dipropyl-8-[2-(5,6-epoxynorbornyl)] xanthine), or 6-oxo-3-(2-phenylpyrazolo [1,5-*a*]pyridin-3-yl)-1(6*H*)-pyridazinebutanoic acid (FK838) (Franco et al. 1989; Schnermann et al. 1990; Kawabata et al. 1998; Wilcox et al. 1999; Thomson et al. 2000; Ren et al. 2002a). Mice with gene knockout for A_1AR lack the TGF response (Brown et al. 2001; Sun et al. 2001; Vallon et al. 2004), and have an impaired ability to stabilize the Na^+ delivery to the distal tubule (Vallon et al. 2004). Most importantly, an intact TGF response requires local concentrations of adenosine to fluctuate depending on the NaCl concentration in the tubular fluid at the macula densa, indicating that adenosine serves as a *mediator* of TGF (Thomson et al. 2000).

In 1980, Osswald and colleagues proposed that adenosine may be a mediator of TGF. Figure 2 illustrates a current model. Changes in luminal concentrations of Na^+, K^+, and Cl^- alter NaCl uptake by macula densa cells via the furosemide-sensitive Na–K–2Cl cotransporter in the luminal membrane. This triggers basolateral ATP release (Bell et al. 2003; Komlosi et al. 2004) as well as transport-dependent hydrolysis by basolateral Na^+–K^+-ATPase (Lorenz et al. 2006) of ATP to AMP. Plasma membrane-bound ectonucleoside triphosphate diphosphohydrolase 1 (CD39) converts ATP and ADP to AMP (Oppermann et al. 2008) and ecto-5′-nucleotidase (CD73) converts extracellular AMP to adenosine (Thomson et al. 2000; Castrop et al. 2004; Ren et al. 2004; Huang et al. 2006). Part of the extracellular adenosine involved in the TGF response is generated independent of ecto-5′-nucleotidase and may reflect direct adenosine release from macula densa cells (Huang et al. 2006). Extracellular adenosine binds to A_1AR at the surface of extraglomerular mesangial cells (Olivera et al. 1989; Weaver and Reppert 1992; Toya et al. 1993; Smith et al. 2001) and increases cytosolic Ca^{2+} concentrations (Olivera et al. 1989). Gap junctions between extraglomerular mesangial cells and smooth muscle cells of glomerular arterioles can transmit intracellular Ca^{2+} transients to these target structures, inducing afferent arteriolar constriction (Iijima et al. 1991; Ren et al. 2002b). Potential candidates for the formation of gap junctions in the juxtaglomerular apparatus include connexins 37, 40, and 43 (Wagner et al. 2007; Takenaka et al. 2008a, b).

3 Activation of A_1AR Inhibits Renin Secretion

Tagawa and Vander reported in 1970 that adenosine infusion into the renal artery of salt-depleted dogs inhibited the renal secretion of renin into the venous blood (Tagawa and Vander 1970). This was confirmed in various species including humans (Edlund et al. 1994). Most notably, a single application of the A_1AR antagonist FK-453 increased plasma renin concentrations in humans (Balakrishnan et al. 1993), indicating a tonic inhibition of renin secretion by A_1AR activation. In accordance, knockout mice for A_1AR have increased renal mRNA expression and content of renin (Schweda et al. 2003) as well as greater plasma renin activity (Brown et al. 2001; Rieg et al. 2007) compared with wild-type mice.

Jackson and coworkers proposed an extracellular cyclic adenosine monophosphate (cAMP)-adenosine pathway in the control of renin release: the increase in intracellular cAMP in renin-secreting cells causes efflux of cAMP, the latter being converted to adenosine in the extracellular space. The generated adenosine, by acting on A_1AR on the renin-secreting cells, then acts as a negative-feedback control on renin release (Jackson and Raghvendra 2004). In addition, *high* NaCl concentrations in the tubular lumen enhance adenosine generation in a macula densa-dependent way, and the adenosine generated inhibits renin release via activation of A_1AR (Itoh et al. 1985; Weihprecht et al. 1990; Lorenz et al. 1993; Kim et al. 2006) (Fig. 2). In contrast to A_1AR stimulation, activation of A_2AR can increase renin secretion (Churchill and Churchill 1985; Churchill and Bidani 1987). The latter may have contributed to the observation that the unselective adenosine receptor antagonist caffeine reduced plasma renin concentration in mice lacking A_1AR (Rieg et al. 2007).

4 Differential Effects of Adenosine on Fluid and Electrolyte Transport

In addition to its effects on renal blood flow, GFR, and renin release, adenosine induces *direct* effects on fluid and electrolyte transport along the tubular and collecting duct system.

4.1 Activation of A_1AR Increases Reabsorption in the Proximal Tubule

Endogenously formed adenosine can *stimulate* proximal tubular reabsorption of fluid, Na^+, HCO_3^-, and phosphate by activation of A_1AR (Takeda et al. 1993; Cai et al. 1994, 1995; Tang and Zhou 2003). Importantly, systemic application of selective A_1AR antagonists (such as CVT-124, DPCPX, KW-3902, or FK-453) elicits diuresis and natriuresis predominantly by inhibiting reabsorption in the proximal tubule in rats and humans (Mizumoto and Karasawa 1993; Balakrishnan et al. 1993; van-Buren et al. 1993; Knight et al. 1993b; Wilcox et al. 1999; Miracle et al. 2007), indicating a tonic stimulation of proximal tubular reabsorption via A_1AR activation (Fig. 1). As a consequence, selective A_1AR antagonists are being developed as eukaliuretic natriuretics in Na^+-retaining states such as heart failure (see below). A_1AR-mediated increases in proximal tubular reabsorption may involve increases of intracellular Ca^{2+} (Di Sole et al. 2003), reductions of intracellular cAMP levels (Kost Jr et al. 2000), and activation of the Na^+–H^+ exchanger (NHE3) (Di Sole et al. 2003).

Similar to selective A_1AR blockade, systemic application or consumption of the unselective adenosine receptor antagonist theophylline or caffeine induces natriuretic and diuretic responses. These responses to theophylline and caffeine are absent in mice lacking A_1AR,

strongly suggesting that A_1AR blockade mediates the natriuresis and diuresis in response to these compounds (Rieg et al. 2005).

4.2 Activation of A_1AR Inhibits Reabsorption in Medullary Thick Ascending Limb

In contrast to the proximal tubule, adenosine via activation of A_1AR inhibits NaCl reabsorption in medullary TAL (Torikai 1987; Burnatowska-Hledin and Spielman 1991; Beach and Good 1992). Medullary TAL is a site of adenosine release, and adenosine release in this segment is transport dependent (Beach et al. 1991; Baudouin-Legros et al. 1995) and enhances significantly during hypoxic conditions (Beach et al. 1991). Studies using pharmacological inhibition (Zou et al. 1999) or gene knockout (Vallon et al. 2004) are consistent with a tonic inhibition of Na^+ re-absorption in medullary TAL by A_1AR activation (Fig. 1). This is relevant since the renal medulla has a low partial oxygen pressure (Brezis and Rosen 1995), and the described inhibitory effects of adenosine on transport work together with its A_2AR-mediated renal medullary vasodilation (see above) to maintain metabolic balance in the renal medulla.

4.3 Effects of Adenosine on Transport in Distal Convolution and Cortical Collecting Duct

In general, natriuretics that act proximal to the aldosterone-sensitive distal nephron stimulate K^+ secretion in the latter segment and thus increase renal K^+ excretion. The natriuretic but eukaliuretic effect of A_1AR inhibitors suggests an additional site of action in the aldosterone-sensitive distal nephron, but the exact site of action and the involved mechanisms are unclear.

A_1AR activation can stimulate Mg^{2+} and Ca^{2+} uptake in the cortical collecting duct in vitro (Hoenderop et al. 1998, 1999; Kang et al. 2001), but the clinical relevance (e.g., during pharmacological inhibition of A_1AR) is not known.

4.4 Activation of A_1AR Counteracts Vasopressin Effects in Inner Medullary Collecting Duct

Extracellular adenosine feedback can inhibit vasopressin-induced cAMP-mediated stimulation of Na^+ and fluid reabsorption in the inner medullary collecting duct (IMCD) (Yagil 1990; Yagil et al. 1994; Rieg et al. 2008) and decrease vasopressin-stimulated electrogenic Cl^- secretion through the activation of A_1AR (Moyer et al. 1995). Vasopressin-induced adenosine may derive from the extracellular cAMP–adenosine pathway (Jackson et al. 2003) or follow the cellular release and breakdown of ATP (Vallon 2008). Studies on water transport in knockout mice indicate efficient compensation by other pathways in the absence of A_1AR, including upregulation of ATP-sensitive $P2Y_2$ receptors (Rieg et al. 2008).

5 Adenosine and Metabolic Control of Kidney Function

The above outlined functions of adenosine can be integrated into the concept of metabolic control of renal function (Fig. 1). Adenosine-induced vasoconstriction via A_1AR activation is predominant in the outer cortex by increasing the resistance of afferent arterioles, which lowers GFR and thus renal transport work. Under physiological conditions, adenosine-induced afferent arteriolar constriction primarily derives from tonic activation of the TGF,

for which adenosine acts as a mediator. Adenosine via A_1AR tonically stimulates NaCl reabsorption in the cortical proximal tubule, which is a tubular segment with a relatively high basal oxygen supply, thereby limiting the NaCl load to downstream medullary segments. In the deep cortex and medulla, adenosine induces vasodilation via A_2AR activation, which is associated with an increase of medullary blood flow and thus increased medullary oxygenation. Moreover, adenosine inhibits NaCl reabsorption in medullary TAL and IMCD (i.e., nephron segments with relatively low oxygen delivery). In addition, the A_2AR-mediated rise in medullary blood flow lowers medullary transport activity by washing out the high osmolality in the medullary interstitium (Zou et al. 1999). In accordance, interstitial infusion of adenosine in rat kidney decreased partial pressure of O_2 in the cortex but increased it in the medulla, consistent with an important regulatory and protective role of adenosine in renal medullary O_2 balance (Dinour and Brezis 1991).

6 Adenosine and Acute Renal Failure

The renal effects of adenosine fit into the concepts of acute renal failure (ARF) in as much as adenosine is an *intrarenal* metabolite that accumulates in the kidney during renal ischemia and that can lower GFR. In addition, ischemia or nephrotoxins can inhibit renal transport activity, with the resulting increase in the NaCl concentration at the macula densa further lowering GFR (Fig. 3). Moreover, experimental models of ARF can be associated with increased expression of A_1AR in glomeruli, which may contribute to depressed GFR (Smith et al. 2000). Thus, inhibition of adenosine vasoconstrictor actions in the kidney could be beneficial in conditions of ARF. On the other hand, the ARF-associated reduction in GFR and thus in tubular NaCl load may, to some extent, protect the tubular system—especially the medulla—from hypoxic injury, and the body from excess NaCl loss. Moreover, adenosine can induce direct cytoprotective effects in renal cells. Therefore, inhibition of adenosine receptors in ARF could be a two-sided sword. In the following we discuss the role of adenosine in ARF induced by radiocontrast media and ischemia-reperfusion, respectively.

6.1 Radiocontrast Media-Induced Acute Renal Failure: Theophylline and A_1AR Antagonists Induce Protective Effects

Application of radiocontrast media to humans can lead to an impairment of renal function, including a fall in GFR. Concomitant volume and NaCl depletion increases the severity and can result in ARF. Unselective or A_1AR-selective antagonists can prevent renal impairment induced by radiocontrast media, as shown in dogs (Arend et al. 1987), rats (Erley et al. 1997), mice (Lee et al. 2006), and, most importantly, in humans (Erley et al. 1994; Katholi et al. 1995; Kolonko et al. 1998; Kapoor et al. 2002; Huber et al. 2002, 2003). In accordance, mice lacking A_1AR preserved kidney function better, and had lesser renal cortical vacuolization and enhanced survival 24 h after radiocontrast media treatment compared with wild-type mice (Lee et al. 2006). In comparison, dipyridamole, which increases extracellular adenosine concentrations, augmented the severity of renal impairment in response to radio-contrast media in dogs (Arend et al. 1987) and humans (Katholi et al. 1995). Two studies indicated that the unselective adenosine receptor antagonist theophylline is as effective as saline hydration at preventing ARF in response to contrast media, but the benefits of the two maneuvers are not additive (Abizaid et al. 1999; Erley et al. 1999). Thus, use of theophylline

can be beneficial in patients where sufficient hydration may be impossible or in patients with a concomitant decrease in renal blood flow (e.g., congestive heart failure or chronic renal insufficiency (Erley et al. 1999; Huber et al. 2002)). A recent meta-analysis of clinical trials concluded that theophylline may reduce the incidence of radiocontrast media-induced nephropathy, and recommended a large, well-designed trial to more adequately assess the role of theophylline in this condition (Bagshaw and Ghali 2005). Notably, unselective or A_1AR-selective antagonists can also prevent renal impairment in response to other nephrotoxic substances (Table 1).

6.2 Ischemia-Reperfusion Injury

Ischemia-reperfusion injury plays a major role in delayed graft function and long-term changes after kidney transplantation. It has become evident that the cellular and molecular mechanisms that operate during ischemia and reperfusion resemble an acute inflammatory response (Gueler et al. 2004). To what extent the acute cellular alterations persist and affect organ function later on remains unclear.

In the kidney, extracellular adenosine derives to a large extent from the extracellular breakdown of ATP and ADP to AMP and adenosine via ectonucleoside triphosphate diphosphohydrolases (ENTPDases) and CD73 (Grenz et al. 2007a, b). Using knockout mouse models for these ectoenzymes, Grenz et al. showed that CD39-dependent nucleotide phosphohydrolysis as well as CD73-dependent adenosine formation serve to protect against renal ischemia-reperfusion injury and to increase the ischemia tolerance of the kidney. In addition, the authors presented evidence that treatment with apyrase or soluble 5′-nucleotidase to increase extracellular adenosine concentrations could serve as potential novel pharmacological approaches to renal diseases precipitated by limited oxygen availability (Grenz et al. 2007a, b).

6.2.1 Theophylline Induces Protective Effects—Different animal studies assessed the effect of a *single* application of the unselective adenosine receptor antagonist theophylline in ischemia-reperfusion injury. Animals were pretreated with theophylline or it was given at day 5 after the renal ischemic/hypoxemic event. Pretreatment with a single dose of theophylline in rats attenuated the reduction in renal blood flow and GFR observed during the initiation phase of postischemic ARF as determined 1 h after releasing a 30 or 45 min occlusion of the renal artery (Lin et al. 1986). Similar results were obtained with theophylline in the rabbit (Gouyon and Guignard 1988). In rats subjected to 60 min occlusion of the left renal artery, theophylline given i.v. 20 min before the release of the renal artery clamp in doses which antagonize the renal actions of adenosine in vivo improved the recovery of renal function after ischemic injury by increasing urinary flow rate, GFR (measured by inulin clearance), and histology, as assessed by morphometric quantification of tubular damage, tubular obstruction and pathologic alteration of glomeruli at 3 h after initiating reperfusion (Osswald et al. 1979; Helmlinger 1979). In contrast, pretreating rats prior to renal artery occlusion for 30 min with dipyridamole, which increases extracellular adenosine concentrations, intensified the fall in renal blood flow and GFR determined about 1 h after releasing the clamp, and this impairment was blocked by theophylline (Lin et al. 1987).

Notably, single-dose pretreatment of rats with theophylline during a 30 min renal artery occlusion lead to increased renal blood flow and GFR during the maintenance phase of ARF after five days, indicating that the effects of theophylline in the acute phase affected the outcome in the maintenance phase. Similarly, a single dose of theophylline, given early after birth in asphyxiated full-term infants, has beneficial effects in reducing the renal involvement and fall in GFR as determined over the first five days (Bakr 2005). Finally, acute theophylline treatment given at five days after ischemia acutely increases renal blood flow and GFR in previously untreated rats, indicating that adenosine contributes to the suppression of renal blood flow and GFR in the maintenance phase of ischemia-reperfusion injury (Lin et al. 1988). These data provide strong evidence that pretreatment with theophylline can exert beneficial effects in the initiation and maintenance phase of ischemia-reperfusion injury.

6.2.2 Adenosine Induces Protective Effects via A_1AR and A_2AR—Similar to theophylline, systemic intravenous infusion of adenosine (1.75 mg kg^{-1} min^{-1} ×10 min, intravenously) 2 min before a 45 min ischemic insult protected renal function against ischemia and reperfusion injury, as indicated by lower blood urea nitrogen and creatinine and improved renal morphology after 24 h of reperfusion. The effects of adenosine were proposed to be mediated by A_1AR (Lee and Emala 2000), involve $G_{i/o}$ proteins and protein kinase C activation (Lee and Emala 2001a), and include a reduction in inflammation, necrosis, and apoptosis (Lee et al. 2004a). Direct cytoprotective effects of endogenous A_1AR activation in renal proximal tubules involve modulation of heat-shock protein (HSP)27 due to A_1AR-mediated enhancement of p38 and AP2 mitogen-activated protein kinase activities (Lee et al. 2007). In comparison, mice lacking A_1AR exhibited significantly higher plasma creatinines and worsened renal histology compared with wild-type mice at 24 h after renal ischemia for 30 min (Lee et al. 2004b). Similarly, wild-type mice pretreated with an A_1AR antagonist or agonist demonstrated worsened or improved renal function, respectively, after ischemia-reperfusion that was associated with increased or reduced markers of renal inflammation, respectively (Lee et al. 2004b) (Fig. 3). More recent work indicated that A_1AR activation produces not only acute but also delayed renal protection; i.e., pretreatment with a selective A_1AR agonist 24 h before renal ischemia was also protective against renal ischemia-reperfusion injury. Furthermore, the study showed that acute protection from A_1AR activation is dependent on protein kinase C and Akt activation, whereas the delayed protection is dependent on Akt activation and induction of HSP27 (Joo et al. 2007).

Continuous application in the reperfusion period of 4-(3-(6-amino-9-(5-ethylcarbamoyl-3,4-dihydroxytetrahydrofuran-2-yl)-9*H*-purin-2-yl)prop-2-ynyl) cyclohexanecarboxylic acid methyl ester (DWH-146e), a selective A_{2A}AR agonist, protected kidneys from ischemia-reperfusion injury, as evidenced by a lower rise in serum creatinine and blood urea nitrogen following 24 and 48 h of reperfusion. Histological examination revealed widespread tubular epithelial necrosis and vascular congestion in the outer medulla of vehicle-treated rats. These lesions were significantly reduced in DWH-146e-treated animals (Okusa et al. 1999). Similarly, systemic adenosine given after 45 min of renal ischemia but before reperfusion protected renal function, as indicated by lower rises in creatinine and less histologically

evident renal tubular damage. Pharmacological maneuvers indicated that these effects of adenosine were mediated by A_{2A}AR activation (Lee and Emala 2001b). Whereas A_{2A}AR activation could improve medullary hypoxia, other studies suggested that protection from renal ischemia-reperfusion injury by A_2AR agonists or endogenous adenosine requires activation of A_2AR expressed on bone marrow-derived cells (Day et al. 2003). Activation of A_{2A}AR on macrophages was also shown to inhibit inflammation in a rat model of glomerulonephritis (Garcia et al. 2008). Moreover, activation of A_{2B}AR in the renal vasculature contributes to the increased ischemia tolerance produced by the procedure of renal ischemic preconditioning (Grenz et al. 2008).

Finally, A_3AR stimulation in rats deteriorated renal ischemia-reperfusion injury, whereas inhibition of A_3AR protected renal function as efficiently as preconditioning (Lee and Emala 2000). In accordance, mice lacking A_3AR presented significant renal protection, functionally and morphologically, from ischemic or myoglobinuric renal failure (Lee et al. 2003). The mechanisms of these A_3AR-mediated effects are not understood at present.

In summary, beneficial effects on GFR and renal morphology beyond 3–24 h of reperfusion after ischemia can be induced by (1) pretreatment with the unselective adenosine receptor antagonist theophylline, (2) pretreatment or treatment immediately before reperfusion with adenosine, (3) pretreatment with A_1AR agonists, (4) treatment immediately before or during reperfusion with A_{2A}AR agonists, (5) treatment with A_{2B}AR agonists, and (6) deficiency of A_3AR. In comparison, the outcome is worsened by (1) pretreatment with A_1AR antagonists or deficiency of A_1AR, (2) pretreatment with A_{2B}AR antagonists or deficiency of A_{2B}AR, and (3) pretreatment with A_3AR agonists. The findings appear contradictory because theophylline can inhibit both A_1AR and A_{2A}AR, and possibly acts as an agonist at A_3AR (Ezeamuzie 2001). Further studies are necessary to resolve this issue, which may relate to the nature of adenosine being a double-edged sword in ARF, and the situation being further complicated by the role of adenosine in inflammatory responses.

7 A_1AR Antagonists in the Treatment of Cardiorenal Failure

Concomitant renal dysfunction is one of the strongest risk factors for mortality in ambulatory heart failure patients (Dries et al. 2000; Hillege et al. 2000; Mahon et al. 2002). In patients hospitalized for decompensated heart failure, worsening of renal function further predicts an adverse outcome (Forman et al. 2004). Intravenous loop diuretics are the mainstay of therapy for patients with both systemic volume overload and acute pulmonary edema decompensated heart failure. Treatment, however, may be complicated by diuretic resistance and/or worsening of renal function, indicating the need for alternative approaches.

Volume overload heart failure in dogs increases myocardial adenosine release (Newman et al. 1984), and circulating levels of adenosine can be increased in patients with chronic heart failure (~200 vs 60 nM) (Funaya et al. 1997) (Fig. 4). Whether this increases circulating adenosine to an extent that affects afferent arteriolar tone and thus GFR is unclear. Nonetheless, the renal vasculature in heart failure patients can be sensitized to the GFR-lowering effects of adenosine by the associated activation of the renin–angiotensin system and/or impairment of the local formation of NO (endothelial dysfunction) or prostaglandins

(see above and Fig. 4). In addition, impaired renal perfusion and hypoxia enhance adenosine formation within the kidney (Nishiyama et al. 1999). As a consequence, the normally homeostatic adenosine system may become maladaptive and overshoots with regard to the downregulation of GFR in patients with heart failure. Fluid retention is further potentiated by stimulation of NaCl and fluid reabsorption in the proximal tubule, a mechanism also mediated by A_1AR activation (see above and Fig. 4). Based on this concept, pharmacological blockade of A_1AR could improve kidney function and fluid retention in heart failure. Since adenosine (through the activation of A_1AR) mediates TGF, the expected TGF-induced reduction in GFR in response to inhibition of proximal reabsorption by A_1AR antagonists should be blunted. In accordance, a study in rats showed that A_1AR antagonism with KW-3902 prevented the GFR-lowering effect of the proximal diuretic benzolamide, a carbonic anhydrase inhibitor (Miracle et al. 2007).

7.1 Animal Studies

Lucas et al. used a pig model of systolic dysfunction and induction of chronic heart failure by pacer-induced tachycardia. They observed that *acute* application of the selective A_1AR antagonist 1,3-dipropyl-8-[2-(5,6-epoxynorbornyl)xanthine (BG9719) (CVT-124) increased creatinine clearance and urinary flow rate and sodium excretion. This was associated with lower pulmonary capillary wedge pressure and pulmonary vascular resistance in the absence of significant changes in mean arterial blood pressure, heart rate or cardiac output compared with vehicle control (Lucas Jr et al. 2002). Similar effects were described by Jackson et al. in aged, lean SHHF/Mcc-fa(cp) rats, a rodent model of hypertensive dilated cardiomyopathy in response to the same compound (Jackson et al. 2001). The rats were pretreated for 72 h before experiments with the loop diuretic furosemide to mimic the clinical setting of chronic diuretic therapy, and were given 1% NaCl as drinking water to reduce dehydration/sodium depletion. *Acute* application of BG9719 increased GFR and urinary fluid and sodium excretion. In comparison, acute application of furosemide decreased renal blood flow and GFR and increased fractional potassium excretion. Neither drug altered afterload or left ventricular systolic function ($+dP/dt$ (max)); however, furosemide, but not BG9719, decreased preload and attenuated diastolic function (decreased $-dP/dt$ (max), increased tau). Thus, in the setting of left ventricular dysfunction, chronic salt loading and prior loop diuretic treatment, selective A_1AR antagonists are effective diuretic/natriuretic agents that do not induce potassium loss and have a favorable renal hemodynamic/cardiac performance profile (Jackson et al. 2001).

7.2 Human Studies

Gottlieb et al. compared the *acute* effects of furosemide and BG9719 on renal function in 12 patients categorized as New York Heart Association (NYHA) functional classes II, III or IV (Gottlieb et al. 2000). Both BG9719 and furosemide increased sodium excretion compared with placebo. However, only furosemide lowered GFR. Subsequently, Gottlieb et al. compared BG9719 and furosemide in 63 patients categorized as NYHA functional classes II, III or IV, which despite receiving standard therapy, including furosemide (at least 80 mg daily) and angiotensin-converting enzyme inhibitors, remained edematous (Gottlieb et al. 2002). Patients received 7 h infusions of placebo or BG9719 to yield serum concentrations of 0.1, 0.75, or 2.5 μg ml^{-1}. BG9719 tripled urine output without lowering GFR or inducing

kaliuresis. In comparison, furosemide increased urine output eightfold and increased potassium excretion while reducing GFR. Notably, when BG9719 was given with furosemide, GFR remained unaltered compared with placebo and sodium excretion increased further. These results indicate that A_1AR antagonism can preserve renal function while simultaneously promoting natriuresis during *acute* treatment of heart failure (Gottlieb et al. 2002).

Similar results were more recently reported in studies using the A_1AR antagonist KW-3902 in patients with congestive heart failure and impaired renal function (Dittrich et al. 2007; Givertz et al. 2007). Dittrich et al. assessed baseline GFR and renal plasma flow 3 h before and over 8 h following the intravenous administration of furosemide along with KW-3902 (30 mg) or placebo. After a washout period of 3–8 days (median six days), the crossover portion of the study was performed. KW-3902 increased GFR by 32% and renal plasma flow by 48% compared with placebo. Notably, subjects who initially received KW-3902 had a statistically significant 10 ml min^{-1} increase in GFR when they returned for the crossover phase compared with the previous baseline. Thus, the increase in GFR persisted for several days longer than predicted by pharmacokinetics. These findings suggest that KW-3902 reset the complex network that determines kidney function in these patients, and provided first evidence for potential longer-term benefits of using A_1AR antagonists (Dittrich et al. 2007). Greenberg et al. assessed the effects of the selective A_1AR antagonist 1,3-dipropyl-8-[1-(4-propionate)-bicyclo-[2,2,2]octyl)]xanthine (BG9928) given orally for ten days to 50 patients with heart failure and left ventricular systolic dysfunction who were receiving standard therapy (Greenberg et al. 2007). BG9928 (3–225 mg per day) increased sodium excretion without causing kaliuresis or reducing GFR. Notably, these effects were maintained over the ten-day period. BG9928 at doses of 15, 75, or 225 mg also reduced body weight at the end of the study compared with placebo (Greenberg et al. 2007).

In summary, the abovedescribed acute and short-term studies employing A_1AR antagonists in patients with heart failure yielded promising results. Since A_1AR blockade may increase transport in the semihypoxic medullary TAL, combining A_1AR antagonists with furosemide may potentiate natriuresis while helping to prevent transport-induced medullary hypoxia (Fig. 4). Whereas the presented animal and human studies were *acute* or *short-term* treatments, it remains to be determined whether longer-term application of A_1AR antagonism has beneficial effects. These studies should also reveal whether a clinically relevant effect of A_1AR blockade on renin release occurs. Consideration should also be given to the evidence that A_1AR activation is potentially important for protection in response to ischemia of the kidney (see above) and the heart (Cohen and Downey 2008). Apart from these issues, A_1AR blockade is unique in inducing natriuresis without potassium loss and lowering renal vascular resistance independent of all other organs. With regard to preserving renal function, this is an advantage over all vasodilator heart failure therapies that have been tried so far.

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Abbreviations

AA	Afferent arteriole
ADO	Adenosine
ARF	Acute renal failure
A_XAR	Adenosine receptor subtype x
B	Bowman's capsule
BG9719	1,3-Dipropyl-8-[2-(5,6-epoxynorbornyl) xanthine
BG9928	1,3-Dipropyl-8-[1-(4-propionate)-bicyclo-[2,2,2]octyl)]xanthine
BM	Basement membrane
BS	Bowman's space
cAMP	Cyclic adenosine monophosphate
CD39	Ecto-nucleoside triphosphate diphosphohydrolase-1
CD73	Ecto-5′-nucleotidase
CGS21680	2-[*p*-(2-Carboxyethyl)phenethylamino]-5′-*N*-ethylcarboxamido adenosine
CVT-124	*S*-Enantiomer of 1,3-dipropyl-8-[2-(5,6-epoxynorbornyl)] xanthine
DMPX	3,7-Dimethyl-1-propargylxanthine
DPCPX	1,3-Dipropyl-8-cyclopentylxanthine
DPSPX	1,3-Dipropyl-8-sulfophenylxanthine
DWH 146e	4-(3-(6-Amino-9-(5-ethylcarbamoyl-3,4-dihydroxytetrahydrofuran-2-yl)-9*H*-purin-2-yl)prop-2-ynyl)cyclohexanecarboxylic acid methyl ester
EA	Efferent arteriole
EGM	Extraglomerular mesangium
ENTPDase	Ectonucleoside triphosphate diphosphohydrolase
FK-453	(+)-(*R*)-[(*E*)-3-(2-Phenylpyrazolo[1,5-*a*]pyridin-3-yl)acryloyl]-2-piperidine ethanol
FK-838	6-Oxo-3-(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)-1(6*H*)-pyridazinebutanoic ‘acid
GFR	Glomerular filtration rate
HSP27	Heat-shock protein 27
IMCD	Inner medullary collecting duct

KW-3902	8-(Noradamantan-3-yl)-1,3 dipropylxanthine
MBF	Medullary blood flow
MC	Mesangium cells
mTAL	Medullary thick ascending limb
NHE	Na + − H+ exchanger
NKCC2	Na + − K+ −2Cl− cotransporter
NO	Nitric oxide
NYHA	New York Heart Association
pO2	Partial oxygen pressure
PT	Proximal tubule
SNGFR	Single nephron glomerular filtration rate
TAL	Thick ascending limb
TGF	Tubuloglomerular feedback
TNa	Transport of sodium
VSMC	Vascular smooth muscle cells

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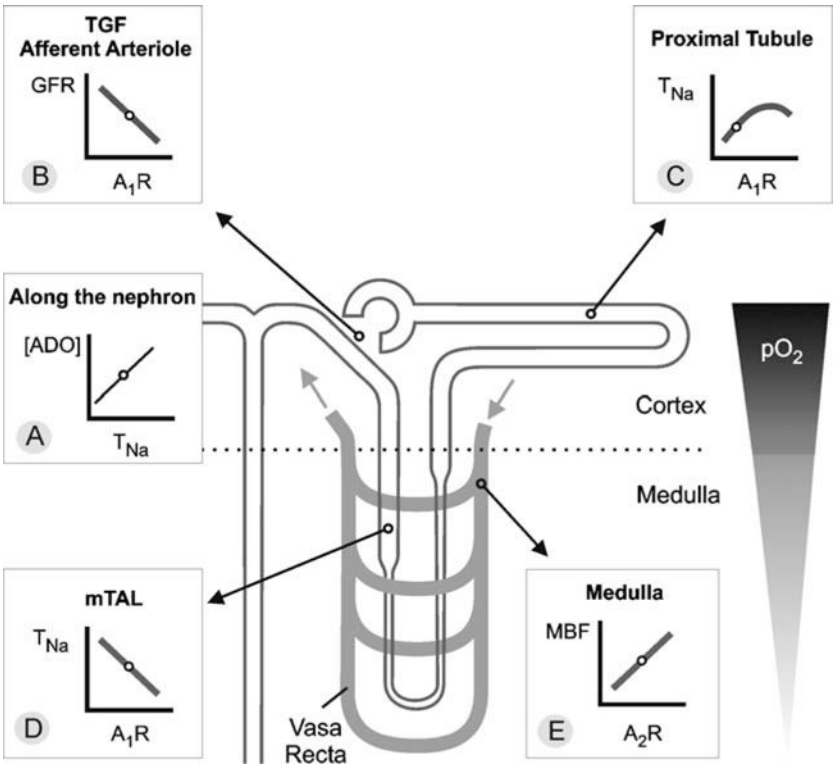

Fig. 1.

a–e Control of renal hemodynamics and transport by adenosine (*ADO*). The *line plots* illustrate the relationships between the given parameters. *Small circles* on these lines indicate ambient physiological conditions. In general, the medulla is at greater risk for hypoxic damage than the cortex due to a lower partial oxygen pressure (pO_2). **a** In every nephron segment, an increase in reabsorption or transport of sodium (T_{Na}) increases extracellular ADO. **b** ADO via A_1AR mediates tubuloglomerular feedback (*TGF*) and constricts the afferent arteriole to lower GFR. **c** In the proximal tubule, ADO via A_1AR stimulates T_{Na} and thus lowers the Na^+ load to segments residing in the semihypoxic medulla. **d** In contrast, ADO via A_1AR inhibits T_{Na} in the medulla, including medullary thick ascending limb (*mTAL*). **e** In addition, ADO via A_2AR enhances medullary blood flow (*MBF*), which increases O_2 delivery and further limits O_2-consuming transport in the medulla (adapted from Vallon et al. 2006)

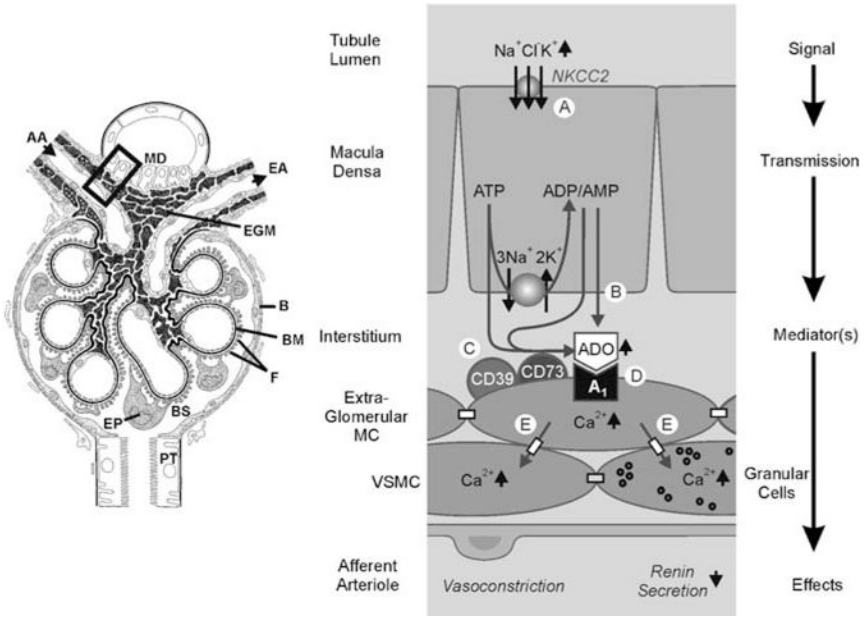

Fig. 2.

a–e Adenosine is a mediator of the tubuloglomerular feedback: a proposed mechanism. *Left panel*: schematic drawing illustrating the macula densa (*MD*) segment at the vascular pole with the afferent arteriole (*AA*) entering and the efferent arteriole (*EA*) leaving the glomerulus; extraglomerular mesangium (*EGM*); glomerular basement membrane (*BM*); epithelial podocytes (*EP*) with foot processes (*F*); Bowman's capsule (*B*) and space (*BS*), respectively; proximal tubule (*PT*). (Adapted from Kriz, Nonnenmacher and Kaissling). *Right panel*: schematic enlargement of area in rectangle. An increase in concentration-dependent uptake of Na^+, K^+ and Cl^- via the furosemide-sensitive $Na^+ - K^+ - 2Cl^-$ cotransporter (*NKCC2*) **a** leads to transport-related, intra- and/or extracellular generation of adenosine (*ADO*) **b**, **c**. Extracellular ADO activates A_1AR, triggering an increase in cytosolic Ca^{2+} in extraglomerular mesangium cells (*MC*) **d**. The intensive coupling between extraglomerular MC, granular renin-containing cells, and vascular smooth muscle cells (*VSMC*) of the afferent arteriole by gap junctions allows propagation of the increased Ca^{2+} signal **e**, resulting in afferent arteriolar vasoconstriction and inhibition of renin release (adapted from Vallon et al. 2006)

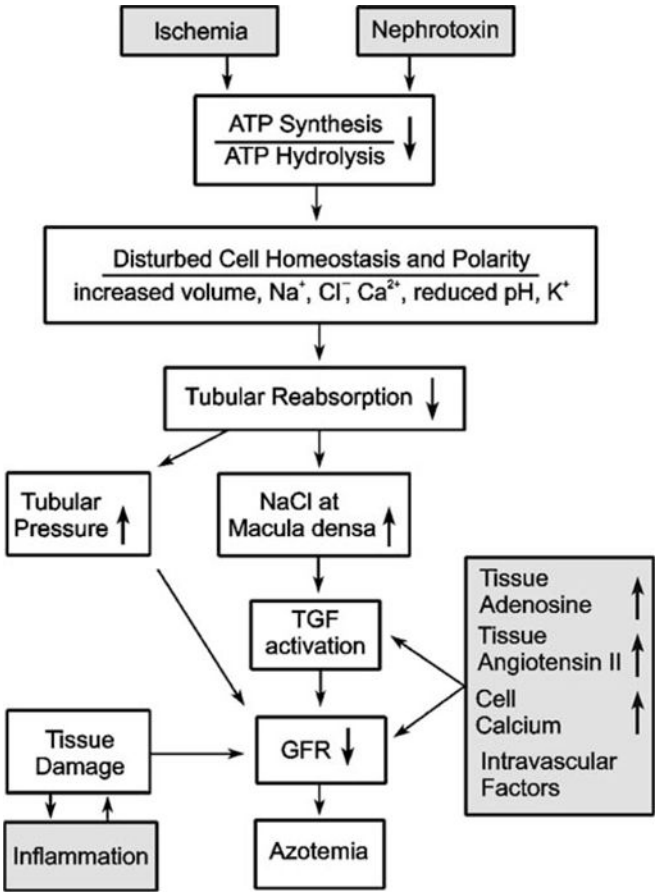

Fig. 3.

Schematic illustration of intrarenal mechanisms in acute renal failure. See text for further explanation (adapted from Osswald and Vallon 2008)

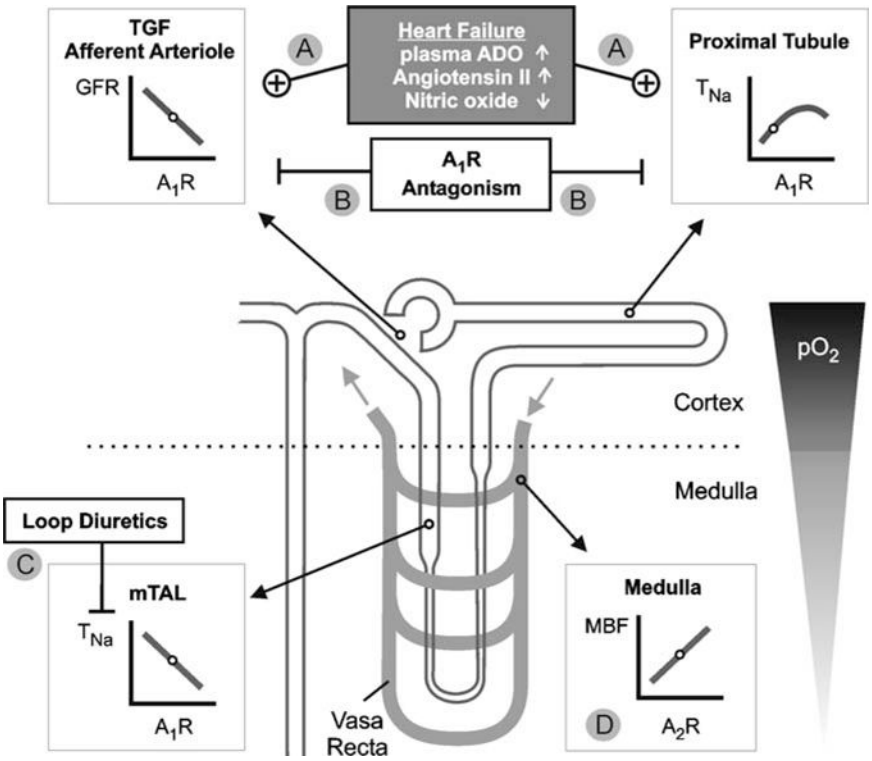

Fig. 4.

a–d Basis for a therapeutic effect of A_1AR antagonism in heart failure. The basic effects of adenosine on renal functions are outlined in the legend to Fig. 1. **a** Heart failure can be associated with increased plasma concentrations of adenosine (*ADO*) and angiotensin II, and endothelial dysfunction can impair nitric oxide (*NO*) formation, all of which can enhance the A_1AR-mediated lowering of GFR and may, in addition, stimulate proximal reabsorption. **b** A_1AR antagonism induces natriuresis and diuresis by inhibiting proximal reabsorption and preserving or increasing GFR. **c** A_1AR antagonism can enhance sodium transport (T_{Na}) in semihypoxic medullary thick ascending limb (*mTAL*). This is prevented by coadministration of loop diuretics, and diuresis and natriuresis are potentiated. **d** A_2AR-mediated medullary vasodilation is preserved (adapted from Vallon 2008)

Table 1

Adenosine receptor antagonists improve renal function in various models of nephrotoxic acute renal failure (ARF)

Models of ARF	Species	Adenosine antagonist	References
Glycerol	Rat	Theophylline	Bidani and Churchill (1983); Bidani et al. (1987)
Injection		8-Phenyl-theophylline	Bowmer et al. (1986); Yates et al. (1987) Kellett et al. (1989); Panjehshahin et al. (1992)
		DPCPX	
		FK-453	Ishikawa et al. (1993)
		KW-3902	Suzuki et al. (1992)
Uranyl nitrate	Rat	Theophylline	Osswald et al. (1979)
Cisplatin	Rat	Theophylline	Heidemann et al. (1989)
	Human	DPCPX	Knight et al. (1991)
		KW-3902	Nagashima et al. (1995)
		Theophylline	Benoehr et al. (2005)
Contrast media	Dog	Theophylline	Arend et al. (1987)
	Human	Theophylline	Erley et al. (1994); Katholi et al. (1995); Kolonko et al. (1998); Kapoor et al. (2002); Huber et al. (2002, 2003)
	Rat	DPCPX, KW3902	Erley et al. (1997); Yao et al. (2001)
Endotoxin	Rat	DPCPX	Knight et al. (1993a)
Amphotericin B	Rat	Theophylline	Heidemann et al. (1983)
	Dog	Theophylline	Gerkens et al. (1983)
Gentamicin	Rat	KW-3902	Yao et al. (1994)

8-Cyclopentyl-1,3-dipropylxanthine (DPCPX), (+)-(*R*)-[(*E*)-3-(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)acryloyl]-2-piperidine ethanol (FK-453) and 8-(noradamantan-3-yl)-1,3 dipropylxanthine (KW-3902) are A_1AR-selective antagonists. Adapted from Vallon et al. (2006)