IN SURGICAL PROCEDURES and anesthesia involving the aorta, renal dysfunction secondary to ischemic-reperfusion injury is a serious clinical concern (1, 10, 20, 29). Although ischemia itself can cause injury, a significant portion of the injury occurs during the reperfusion period (20). The onset of acute renal failure secondary to ischemic-reperfusion injury implies a poor prognosis and is frequently associated with many other life-threatening complications including sepsis and multiorgan failure (1, 27-29). In high-risk patients undergoing high-risk surgery, the mortality and morbidity rate from perioperative acute renal failure has changed little over the past 30 years (1, 15, 27, 28). The incidence of renal dysfunction in high-risk patients after aorto-vascular surgery has been reported to be as high as 50% (1, 16).

However, recent developments in cardiac physiology indicate that ischemic-reperfusion injury may be an avoidable consequence of revascularization following prolonged ischemia. Murry et al. (31), in 1986, documented and defined the protective effect of “ischemic preconditioning” in cardiac muscle by showing that multiple brief ischemic periods before the prolonged ischemia lessened myocardial dysfunction and infarct size after the reperfusion period. Extensive evidence exists demonstrating the beneficial effects of ischemic preconditioning in cardiac muscle (30, 36). In most animal models, ischemic preconditioning appears to be mediated via preischemic activation of adenosine receptors, specifically A1 adenosine receptors, as exogenous administration of adenosine, or A1 adenosine agonists, mimics ischemic preconditioning in cardiac muscle (26, 30, 42).

Ischemic preconditioning also occurs in noncardiac tissues such as skeletal muscle (22, 23), brain (13), and liver (34). Moreover, adenosine administration in these organs also mimics ischemic preconditioning (13, 22, 23, 34). However, evidence supporting a role for ischemic preconditioning in protecting against ischemic-reperfusion injury in kidneys is scant and controversial (17, 45). Cultured human and porcine proximal tubular cells can also be preconditioned with hypoxia with lessened cellular injury as evidenced by reduced release of lactate dehydrogenase, less production of arachidonic acid metabolites, and better preservation of cellular morphology (45). However, Islam et al. (17) failed to demonstrate protective effects of renal ischemic preconditioning in the rat (4 cycles of 4-min renal ischemia followed by 11-min reperfusion periods) in vivo using radiographic function studies.

Currently, it is unclear whether the kidneys can be protected against ischemic-reperfusion injury with ischemic preconditioning in vivo. The major aims of this study were 1) to determine whether rat kidneys can be preconditioned against ischemic-reperfusion injury, 2) to determine whether preischemic adenosine receptor activation can protect renal function and mimic renal ischemic preconditioning, and 3) to elucidate the role of adenosine receptor subtype(s) in adenosine- and ischemic preconditioning-induced renal protection.

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MATERIALS AND METHODS

All protocols were approved by the Institutional Animal Care and Use Committee of Columbia University. Adult male Wistar rats (225–275 g, Harlan Sprague Dawley, Indianapolis, IN) were used. They had free access to rodent food and water. Rats were anesthetized with intraperitoneal pentobarbital sodium (45 mg/kg body wt, or to effect). Additional pentobarbital sodium was administered as needed based on response to tail pinch. After 500 U heparin were given intraperitoneally, rats were placed on an electric heating pad under a warming light. Body temperature was monitored with a rectal probe and maintained at 37°C. They were allowed to spontaneously breath room air. The right femoral vein was cannulated with heparinized (10 U/ml) polyethylene tubing (PE-50) for intravenous drug access and hydration. The right femoral artery was cannulated with heparinized PE-50 tubing for hemodynamic monitoring and blood sampling.

After a 10-min stabilization period, a midline laparotomy was performed. Right nephrectomy was performed by ligating the vascular pedicle two times with a 2–0 silk, and the left renal artery and vein were isolated. Thirteen separate protocols were performed as described below.

To determine the role of ischemic preconditioning and adenosine pretreatment in renal ischemic-reperfusion injury, rats were subjected to the following protocols after right nephrectomy.

Control group (sham). Rats were subjected to isolation of left renal artery and vein only.

Ischemia-reperfusion group (IR). Rats were subjected to 45 min of left renal ischemia.

Ischemic preconditioning group (IPC). Rats were subjected to four cycles of 8-min left renal ischemia separated by 5-min reperfusion periods before 45 min of left renal ischemia.

Adenosine pretreatment group (ADO). Rats received systemic intravenous infusion of adenosine (1.75 mg·kg⁻¹·min⁻¹ for 10 min) until 2 min before 45 min of left renal ischemia.

To determine the receptor subtypes involved in adenosine-and ischemic preconditioning-induced renal protection, rats were subjected to the following protocols after right nephrectomy.

A₁ adenosine receptor antagonist before adenosine. Rats received intraperitoneal injections of 2 mg/kg 1,3-dipropyl-8-cyclopentylxanthine (DPCPX), a highly selective A₁ adenosine receptor antagonist, 15 min before 10-min adenosine pretreatment followed by 45 min of left renal ischemia.

A₂ adenosine receptor antagonist before adenosine. Rats received intraperitoneal injections of 2 mg/kg 8-(3-chlorostyryl) caffeine (CSC), a highly selective A₂ adenosine receptor antagonist, 15 min before 10-min adenosine pretreatment, followed by 45 min of left renal ischemia.

A₃ adenosine receptor antagonist before adenosine. Rats received intraperitoneal injections of 1 mg/kg 3-ethyl-5-benzylphenylethynyl-6-phenyl-1,4-(+)-dihydropyridine-3,5-dicarboxylate (MRS-1191), a highly selective A₃ adenosine receptor antagonist, 15 min before 10-min adenosine pretreatment followed by 45 min of left renal ischemia.

A₁ adenosine receptor antagonist before ischemic preconditioning. Rats received intraperitoneal injections of 2 mg/kg DPCPX 15 min before ischemic preconditioning treatment followed by 45 min of left renal ischemia.

A₁ adenosine receptor agonist before ischemia and reperfusion. Rats received intraperitoneal injections of 2 mg/kg 4-[(N-ethyl-5’-carbamoyladenosino-2-yl)-aminoethyl]-phenylpropionic acid (CGS-21680), a highly selective A₂ adenosine receptor agonist, 15 min before 45 min of left renal ischemia.

A₂ adenosine receptor agonist before ischemia and reperfusion. Rats received intraperitoneal injections of 1 mg/kg N⁶-(3-iodobenzyl)-N-methyl-5’-carbamoyladenosine (IB-MECA), a highly selective A₂ adenosine receptor agonist, 15 min before 45 min of left renal ischemia.

To further determine the role of A₁ adenosine receptors in renal ischemic-reperfusion injury, rats were subjected to the following protocols after right nephrectomy.

A₁ adenosine receptor antagonist before ischemia and reperfusion. Rats received intraperitoneal injections of 1 mg/kg MRS-1191, a highly selective A₁ adenosine receptor antagonist, 15 min before 45 min of left renal ischemia.

A₁ adenosine receptor agonist alone without ischemia and reperfusion. Rats received intraperitoneal injections of 1 mg/kg IB-MECA, a highly selective A₂ adenosine receptor agonist without being subjected to left renal ischemia.

Materials. Adenosine was dissolved in sterile, isotonic saline. All other drugs were dissolved in 50% dimethyl sulfoxide. Solutions were made daily. All chemicals used were of purest analytical grade. Adenosine and DPCPX were obtained from Sigma Chemical (St. Louis, MO). Pentobarbital sodium was purchased from Henry Schein Veterinary (Indianapolis, IN). All other drugs were obtained from Research Biochemicals (Natick, MA).

Statistical analysis. A one-way ANOVA was used to compare mean values across multiple treatment groups with a Dunnett’s post hoc multiple comparison test (e.g., sham vs. IPC). In all cases, a probability statistic <0.05 was taken to indicate significance. All data are expressed throughout the text as mean ± SE.

RESULTS

Protective effects of renal ischemic preconditioning. As expected, 45 min of renal ischemia and 24 h of reperfusion resulted in significant rises in BUN (149 ± 8 mg/dl, n = 6) and Cr (4.2 ± 0.2 mg/dl, n = 6) compared with the sham-operated group (BUN = 29 ± 5
and Cr = 0.9 ± 0.1 mg/dl, n = 6, P < 0.01, Fig. 1). Ischemic preconditioning (4 cycles of 8-min renal ischemia separated by 5-min reperfusion period) significantly improved renal function (BUN = 95 ± 16 and Cr = 2.7 ± 0.6 mg/dl, P < 0.05, n = 6) after 45 min of renal ischemia and 24 h of reperfusion compared with animals subjected to ischemic-reperfusion injury alone (Fig. 1).

Four cycles of 8-min ischemia is the ideal pretreatment to induce renal ischemic preconditioning. To determine the optimal duration of preconditioning ischemia, pilot studies were performed with 6 or 8 min of ischemic periods separated by 5 min of reperfusion. Ischemic preconditioning with four cycles of 4-min ischemic periods failed to produce protective effects; however, 10 min of renal ischemia are known to produce some degree of cellular injury (17). Therefore, ischemic time intervals of 6 and 8 min were chosen. Four cycles of 6-min ischemia did not protect renal function after 45 min of ischemia and reperfusion (BUN = 129 ± 2 and Cr = 4.8 ± 0.6 mg/dl, n = 3, Fig. 1), whereas four cycles of 8 min ischemia were protective of subsequent prolonged (45 min) ischemia.

To determine the ideal interval between the four cycles of 8-min ischemic preconditioning and the 45 min of renal ischemia (“critical interval”), 5-, 20-, and 60-min intervals were compared. The data (not shown) indicated that no differences among critical intervals of 5, 20, and 60 min existed, suggesting the protective effect of renal ischemic preconditioning begins within 5 min after ischemic preconditioning stimuli and lasts for at least up to 60 min.

Protective effects of systemic adenosine infusion. Preliminary experiments with systemic adenosine at the dose of 350 μg·kg⁻¹·min⁻¹ were performed. At this systemic dose, adenosine failed to produce noticeable hemodynamic effects, and BUN and Cr improved somewhat (data not shown) but inconsistently. Therefore, we increased the dose of systemic adenosine to 1.75 mg·kg⁻¹·min⁻¹. At this dose, adenosine caused moderate bradycardia and hypotension (Fig. 2A), suggesting a significant agonist effect on A₁ adenosine receptors in the heart, and resulted in significant improvements in renal function (BUN = 60 ± 17 and Cr = 1.9 ± 0.6 mg/dl, P < 0.01, n = 6, Fig. 1) after 45 min of renal ischemia and 24 h of reperfusion compared with animals subjected to ischemic-reperfusion injury alone.

A₁ adenosine receptor agonist mimics adenosine-induced renal protection. Figure 3 shows the effects of the A₁ adenosine receptor antagonist DPCPX on adenosine-pretreated (ADO; n = 6) and effect of selective A₁ adenosine agonist [R-N⁶-phenylisopropyladenosine (R-PIA); n = 6] are shown. Mean Cr values are compared. *P < 0.05 vs. sham. $P < 0.05 vs. IR. #Not significantly different from IR. %P < 0.05 vs. ADO. Error bars represent SE. A similar pattern was observed for the comparison of mean BUN. Definitions are as in Fig. 1.
sine-induced renal protection. DPCPX completely abolished the renal protective effects of adenosine (BUN = 131 ± 6 and Cr = 4.0 ± 0.2 mg/dl, n = 6), indicating that A1 adenosine receptors activated by adenosine were responsible for protection from ischemic reperfusion-induced damage. The A1 adenosine receptor agonist R-PIA mimicked the protective effects of adenosine administration (BUN = 51 ± 7 and Cr = 1.1 ± 0.2 mg/dl, n = 6, Fig. 3). In contrast, DPCPX failed to block the renal protection induced by ischemic preconditioning (BUN = 97 ± 19 and Cr = 2.9 ± 0.6 mg/dl, n = 6, Fig. 4). This suggests that, although A1 adenosine receptor activation can protect renal function similar to ischemic preconditioning, not all of the protective effects of ischemic preconditioning are mediated through the A1 adenosine receptor.

Blockade of A3 adenosine receptors protects kidneys from ischemic-reperfusion injury. Highly selective A3 adenosine receptor antagonist MRS-1191 given before systemic adenosine potentiated adenosine’s renal protection (BUN = 32 ± 6 and Cr = 1.2 ± 0.1 mg/dl, n = 6), and the highly selective A3 adenosine receptor agonist IB-MECA significantly worsened renal function (BUN = 190 ± 5 and Cr = 5.0 ± 0.3 mg/dl, n = 6, Fig. 5) after renal ischemia and reperfusion. Moreover, the rats that received the highly selective A3 adenosine receptor antagonist MRS-1191 before the 45 min of renal ischemia demonstrated significant renal protection (BUN = 28 ± 3 and Cr = 1.0 ± 0.1 mg/dl, n = 6), A3 adenosine agonist (IB-MECA) alone without renal ischemia had no effect on renal function.

A2 adenosine receptors are not involved in renal ischemic preconditioning. The highly selective A2 adenosine antagonist CSC (BUN = 75 ± 15 and Cr = 1.9 ± 0.4 mg/dl, n = 6) and the highly selective A2a adenosine agonist CGS-21680 (BUN = 116 ± 9 and Cr = 4.0 ± 0.4 mg/dl, n = 6) failed to block and mimic, respectively, the protection conferred by 10 min of systemic adenosine infusion.

Hemodynamic effects of adenosine, adenosine agonists, and antagonists. Systemic adenosine at 1.75 mg·kg⁻¹·min⁻¹ produced reproducible hypotension (Fig. 2A) and bradycardia. Injections of the selective A1 adenosine agonist R-PIA intraperitoneally produced sustained (3–4 h) bradycardia (heart rate ~150–200 beats/min) and hypotension (systolic blood pressure ~70 mmHg). The A2 adenosine receptor agonist CGS-21680 at 1 mg/kg intraperitoneally produced hypotension (systolic blood pressure ~70 mmHg) and reflex tachycardia (heart rate ~550 beats/min). The A3 adenosine receptor agonist IB-MECA at 1 mg/kg intraperitoneally produced slight reduction in blood pressure (systolic blood pressure ~90 mmHg) without any significant changes in heart rate. Adenosine receptor antagonists themselves did not produce hemodynamic effects. The selective A3 adenosine receptor antagonist DPCPX given intraperitoneally (2 mg/kg) abolished the bradycardic effects of adenosine, verifying antagonism of the A3 adenosine receptor subtype.

Hypotension does not induce hypoxic renal preconditioning. To rule out whether hypotensive effects of systemic adenosine had any protective effects by inducing hypoxic preconditioning (a phenomenon known to occur in cardiac muscle, Ref. 9), sodium nitroprusside was used to induce similar levels of hypotension (40 µg·kg⁻¹·min⁻¹ iv) for 10 min to mimic the hypotensive effects of adenosine infusion (Fig. 2B). The rats were subjected to equivalent duration and degree of hypotension (systolic blood pressure ~75 mmHg) as occurred with adenosine administration. Systemic sodium nitroprusside pretreatment for 10 min did not protect the kidneys against 45 min of renal ischemia and 24 h of reperfusion (BUN = 134 ± 12 and Cr = 3.8 ± 0.1 mg/dl, n = 4, Fig. 1).

Systemic adenosine and ischemic preconditioning improve renal morphology. In Fig. 6, the renal-protective effects of ischemic preconditioning and systemic adenosine are further supported by representative histological slides. Forty-five minutes of renal ischemia followed by 24 h of reperfusion resulted in significant renal injury as evidenced by severe tubular necrosis, medullary congestion and hemorrhage, and development of proteinaceous casts. Ischemic preconditioning and systemic adenosine pretreatment preserved near-normal morphology. The Jablonski scale histology grading
scores are shown in Fig. 7. Forty-five minutes of renal ischemia and 24 h of reperfusion resulted in severe acute tubular necrosis (grade = 3.5 ± 0.4, n = 6). Ischemic-preconditioned (grade = 1.2 ± 0.7, n = 6) and adenosine-pretreated (grade = 0.4 ± 0.4, n = 5) groups showed no statistical differences in histological evaluations compared with the sham-operated (grade = 0.2 ± 0.2, n = 6) group.

DISCUSSION

The major findings of our study were that 1) we demonstrated for the first time that renal ischemic preconditioning and adenosine pretreatment protect against ischemic-reperfusion injury induced by 45 min of global renal ischemia and 24 h of reperfusion; 2) A1 adenosine receptors are involved in adenosine-induced renal protection; 3) an A3 adenosine receptor antagonist protects renal function after ischemia and reperfusion; and 4) although A1 adenosine receptor activation can mimic ischemic preconditioning, not all protective effects of ischemic preconditioning are mediated through the A1 adenosine receptor.

The detrimental effects of ischemic-reperfusion injury are now well recognized in both basic and clinical science arenas (1, 42). Renal ischemic-reperfusion injury secondary to prolonged cessation of blood flow is a significant and common clinical concern (1, 15, 27–29). Surgical procedures involving aorta and renal arteries (e.g., supra- and juxtarenal abdominal aortic aneurysms and renal transplantation, in particular) display significant postoperative renal complications in the forms of acute tubular necrosis and acute renal failure (1, 27–29). Therefore, ways to prevent renal dysfunction following ischemic manipulations have been topics of intense research interest.

In our study, 45 min of renal ischemia followed by 24 h of reperfusion resulted in significant functional (as evidenced by large increases in BUN and Cr) and morphological renal injury. Our protocol of renal ischemic preconditioning significantly attenuated these rises in BUN and Cr and improved renal morphology. This renal protection afforded by ischemic preconditioning significantly attenuates these rises in BUN and Cr and improved renal morphology. This renal protection afforded by ischemic preconditioning significantly attenuates these rises in BUN and Cr and improved renal morphology. This renal protection afforded by ischemic preconditioning significantly attenuates these rises in BUN and Cr and improved renal morphology. This renal protection afforded by ischemic preconditioning significantly attenuates these rises in BUN and Cr and improved renal morphology. 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first to conclusively demonstrate that ischemic preconditioning also occurs in the kidney and may play a crucial role in preserving renal function in patients. There is a limited amount of information in the literature regarding renal ischemic preconditioning. Our study provides the first conclusive evidence to demonstrate the beneficial effects of renal ischemic preconditioning in vivo. Interestingly, investigations to elucidate the effects of varying durations of renal ischemia date back to the early 1960s (38, 43) and received brief revived interest in the early 1980s (3, 51–53). These earlier investigations concluded that brief episodes of finite renal ischemia were actually protective against later and more prolonged ischemia. These results resemble the ischemic preconditioning experiments performed by Murry et al. in 1986 in dog myocardium (31); however, these findings in the kidney failed to generate equivalent research interests and the definition of ischemic preconditioning first occurred in the heart instead of the kidney.

Turman and Bates (45) evaluated hypoxic preconditioning in cultured human proximal tubular cells in vitro. They have determined that hypoxic preconditioned proximal tubular cells demonstrated less cellular injury as evidenced by reduced release of lactate dehydrogenase, less production of arachidonic acid metabolites, and better preservation of cellular morphology under light microscopy. However, until the present study, no evidence of renal ischemic preconditioning in vivo exists. Islam et al. (17) failed to demonstrate protective effects of their ischemic preconditioning in rat kidney ischemic-reperfusion injury models. Their ischemic preconditioning regimen included four cycles of 4-min preconditioning ischemia followed by an 11-min reperfusion period. Using radiographic imaging to study renal function, they failed to demonstrate significant renal protection with their regimen of renal ischemic preconditioning. Unlike the heart, in which the duration of as short as 2 min of ischemia produces myocardial stunning (30) and is sufficient to induce preconditioning, the kidney has a more favorable O2 supply-to-demand ratio. Perhaps 4 min of renal ischemia were insufficient to induce preconditioning in the study by Islam et al. (17).

The precise endogenous mediator of ischemic preconditioning, even in cardiac muscle, is not fully elucidated. However, extensive literature available for review suggests that adenosine pretreatment mimics ischemic preconditioning in cardiac and skeletal muscles, and adenosine appears to be the most attractive endogenous mediator of ischemic preconditioning (22, 26, 36, 38, 51). Adenosine is released in large quantities within seconds after onset of ischemia, including in the kidney (2, 33, 41). The general consensus is that a buildup of endogenous adenosine during the first brief ischemic period (ischemic preconditioning period) may trigger protection via activation of adenosine (specifically A1 adenosine) receptors. In cardiac muscle, exogenous infusion of adenosine or A1 adenosine agonists mimics this ischemic preconditioning process, and infusion of A1 adenosine receptor blockers during the preconditioning period eliminates the protective effects of ischemic preconditioning (26, 42).

This study shows for the first time that adenosine pretreatment protects renal function and morphology and that the A1 adenosine receptor subtype is involved. In our study, 10 min of systemic adenosine pretreatment have beneficial effects on renal function similar to the protective effects of renal ischemic preconditioning. This finding parallels the data from the cardiac literature as preschismic infusion of adenosine mimics myocardial ischemic preconditioning in improving every aspect of cardiac function (3, 26, 42, 51). Similarly, Egan et al. (8) have demonstrated that systemic adenosine pretreatment before 45 min of renal ischemia in rabbits completely prevented rises in BUN and Cr. These protections were associated with complete prevention of histological derangements associated with acute tubular necrosis.

Of the three adenosine receptors known to be present in the kidney (49), the receptor subtype involved in adenosine-induced renal protection is the A1 adenosine receptor subtype as the A3 adenosine antagonist DPCPX blocked adenosine-induced renal protection and the A1 adenosine agonist R-PIA mimicked the protection (Fig. 3). This agrees with findings in heart where preschismic infusion of A1 adenosine-selective agonists mimics and A1 adenosine antagonists block adenosine-induced cardiac protection (26, 42). However, unlike the findings in cardiac muscle, adenosine-induced renal protection may not be equivalent to renal ischemic preconditioning. The fact that an A1 adenosine antagonist failed to block renal ischemic preconditioning indicates either that ischemic preconditioning and adenosine-induced protection follow completely different cellular signaling pathways with a common physiological end point or that multiple endogenous agonists are involved in renal ischemic preconditioning. More recent reports from various animal models of cardiac ischemic-reperfusion injury state that bradykinin (12, 48), phenylephrine (14, 44), ACh (50), and opioid (39) receptors may be involved in ischemic preconditioning. In the current study, the A2a adenosine receptor subtype was shown not to be involved in adenosine-mediated renal protection.

The A3 adenosine receptor subtype is the newest characterized member of adenosine receptor family (32, 46). Although the expression of A3 adenosine receptor subtype in the kidney has been shown (49), its function in the kidney is unknown. In our study, the highly selective A3 adenosine agonist IB-MECA, given before renal ischemia, worsened renal ischemic-reperfusion injury, and the highly selective A3 adenosine antagonist MRS-1191 potentiated the renal-protective effects of systemic adenosine. Moreover, MRS-1191, when given before 45 min of renal ischemia, protected renal function. The mechanism of activation of A3 adenosine receptor leading to worsening of renal injury after ischemia and reperfusion is unclear. We can conclude that A3 adenosine activation must be coupled with ischemic renal insult for it to have an increased detrimental effect on renal function since A3 receptor
agonist alone had no effect on renal function. In cardio-
myocytes (40) and human leukemia cell lines (21), A3
adenosine-selective agonists have been shown to cause
apoptosis by incompletely characterized mechanisms.

Adenosine produces diverse effects in the kidney.
Adenosine has biphasic effects on renal blood flow and
renin release via intrarenal A1 and A2 adenosine recep-
tor activation (6, 35, 41). Adenosine also reduces renal
sympathetic activity, lowers the glomerular filtration
rate (GFR), and controls the modulation of tubular-
glomerular feedback mechanism via A2 adenosine recep-
tor activation. With A2 adenosine receptor activation, it
increases medullary blood flow. The role of A3 adenosine
receptor in the kidney is unknown at the present time.

At first glance, renal effects of adenosine appear to be
detrimental to its function, since A1 adenosine receptor
activation produces effects that appear to “worsen”
renal function: reduced GFR and afferent cortical blood
flow as well as impaired solute transport (37). In our
study, an A1 adenosine receptor agonist and A3 adeno-
sine receptor agonist protected and worsened renal
function, respectively, after 45 min of renal ischemia.
An A3 adenosine receptor antagonist protected renal
function after ischemic renal injury. Several investiga-
tors have reported that nonselective adenosine receptor
agonists such as theophylline have protective ef-
fects against some, but not all, models of ischemic renal
failure (24, 25, 37). The hypothesis was based on the
renal hemodynamic effects of A1 adenosine receptor
stimulation (reduction in GFR, fall in solute transport,
and reduction in renal blood flow via afferent arteriolar
vasoconstriction) and adenosine receptor antagonism
would be renal protective (5). The fact that in our study,
A1 adenosine receptor agonist R-PIA protected renal
function is contradictory to their conclusions. However,
because a nonselective adenosine receptor antagonist
was used in their study, it is unclear which of the three
adenosine receptors’ antagonism protected renal func-
tion in their models of acute ischemic renal failure.
Perhaps they were observing the renal protective ef-
fects of A3 adenosine receptor antagonist in protecting
renal function.

Looking more closely at the renal actions of adeno-
sine, however, adenosine has several protective at-
tributes against renal ischemic reperfusion injury (4, 7).
Reduction in GFR and sympathetic outflow via A1
adenosine receptor activation would reduce renal oxy-
gen consumption, whereas increased renal medullary
blood via A2 adenosine receptor activation flow would
increase oxygen delivery to the kidney. We can specu-
late that renal effects of adenosine may have contrib-
uted to the renal protection in our study.

Plasma renin activity (PRA) increases following re-
nal ischemia, and this increase may play an important
modulatory role in outcomes of renal ischemic injury
(11, 19). Reducing PRA following renal ischemic insult
with β-receptor blockade, for example, has been shown
to retard the degree of renal ischemic-reperfusion
injury (19). As mentioned, adenosine has biphasic
effects on the control of renin release by the juxtaglo-
merular cells; it lowers and increases renin release via
activation of A1 and A2 adenosine receptors, respec-
tively. We can speculate that lowered PRA with infu-
sion of adenosine and A1 adenosine receptor agonist
(R-PIA) may have contributed to the renal protective
effects of these drugs.

In summary, this is the first report of an in vivo
protective effect of ischemic preconditioning in the
kidney. We have demonstrated that brief ischemic
periods or pretreatment with an A1 adenosine receptor
agonist or an A3 adenosine receptor antagonist protects
the kidney from a subsequent prolonged ischemic in-
sult. These findings have potentially profound clinical
significance in the protection of the kidney during
surgical procedures where renal ischemia is unavoid-
able.

We thank Laszlo Virag for his endless help with surgical proce-
dures and encouragement. We also thank Dr. Vivette D’Agati for her
expertise in renal histopathology.

This work was funded in part by intramural grant support from
the Department of Anesthesiology, Columbia University College of
Physicians and Surgeons.

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Received 14 May 1999; accepted in final form 13 September 1999.

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