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The selective adenosine A_1 receptor antagonist KW-3902 prevents radiocontrast media-induced nephropathy in rats with chronic nitric oxide deficiency

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Abstract

Several studies have recently suggested a principal role of adenosine in the pathogenesis of radiocontrast media-induced nephropathy. In the present experiments, we therefore investigated the renal protective effects of 8-(noradamantan-3-yl)-1,3-dipropylxanthine (KW-3902), a potent and selective adenosine A_1 receptor antagonist, on radiocontrast media-induced nephropathy in the model of the *N*-ϖ-nitro-L-arginine methyl ester (L-NAME) hypertensive, chronic nitric oxide (NO)-depleted rat. Chronic NO depletion was induced by pretreatment with L-NAME, 50 mg/ml, added to drinking water for 8 weeks. Clearance experiments were performed in anesthetized rats and glomerular filtration rate was assessed prior to and following the application of high osmolar radiocontrast media (sodium diatrizoate, 3 ml/kg, i.v.) or an equivalent volume of isoosmolar mannitol to examine the role of hyperosmolarity in radiocontrast media-induced nephropathy. Subgroups received KW-3902 (0.1 mg/kg, i.v.), 20 min prior to radiocontrast media administration. Age-matched, untreated rats served as controls. Radiocontrast media application induced a significant decline in glomerular filtration rate in L-NAME hypertensive animals, whereas no effects were observed in control rats. KW-3902 fully prevented the drop in glomerular filtration rate in response to radiocontrast media in L-NAME hypertensive rats. No renal hemodynamic alterations were observed in mannitol-infused animals. The present experiments demonstrate that the decrease in glomerular filtration rate following radiocontrast media occurred independently of the osmotic load, and that KW-3902 effectively prevented the radiocontrast media-induced deterioration in renal function. KW-3902 may be especially beneficial in patients at high risk for developing acute renal failure following radiocontrast media application or in patients in which extracellular fluid volume expansion is limited by clinical conditions such as congestive heart failure.

Keywords: Renal hemodynamic; Radiocontrast medium; Adenosine; Adenosine A_1 receptor antagonism; KW-3902

1. Introduction

Radiocontrast media are recognized to induce profound alterations in renal hemodynamics, clinically ranging from a transient decline in glomerular filtration rate up to the development of acute renal failure (Salomon, 1998). The administration of radiocontrast media results in a biphasic renal vascular response, characterized by a transient initial vasodilation followed by a pronounced vasoconstriction with a decline in glomerular filtration rate, persisting after recovery of renal blood flow (Sherwood and Lavender, 1969; Katzberg et al., 1983).

Different mediators of radiocontrast media-induced nephropathy have been suggested, among which adenosine plays a principal role. Theophylline, an unselective adenosine receptor antagonist, has proven effective in the prevention of radiocontrast media-induced nephropathy in both animals (Arend et al., 1987; Erley et al., 1997) and humans (Erley et al., 1994; Katholi et al., 1995). Arakawa et al. (1996) demonstrated an activation of adenosine A_1 receptors to be involved in the renal hemodynamic response to radiocontrast media. Pretreatment with the selective adenosine A_1 receptor antagonist, 8-cyclopentyl-1,3-

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dipropylxanthine (DPCPX), prevented the decline in glomerular filtration rate and renal blood flow following radiocontrast media application in rats (Erley et al., 1997). These observations suggest, that a selective blockade of adenosine A_1 receptor activation may significantly attenuate the nephrotoxic effects of radiocontrast media.

8-(Noradamantan-3-yl)-1,3-dipropylxanthine (KW-3902) is a novel potent and selective adenosine A_1 receptor antagonist (Suzuki et al., 1992), with a dissociation constant value (k_D) of 0.19 and 170 nM for adenosine A_1 and A_2 receptor subtypes, respectively (Nonaka et al., 1996). The selectivity ratios of DPCPX for the A_1 receptor were 240 vs. the A_{2A} receptor and 110 vs. A_{2B} receptor whereas the ratios of KW-3902 were 890 vs. the A_{2A} and 270 vs. the A_{2B} receptor (Nonaka et al., 1996). KW-3902 is the most potent and selective A_1 antagonist. In anesthetized rats, KW-3902 is a potent antagonist of adenosine A_1 receptor-mediated responses with little effect on actions mediated via the adenosine A_2 receptor subtype (Mizumoto et al., 1993). KW-3902 exhibits renal protective effects in various models of immunologic and xenobiotic-induced acute renal injury (Mizumoto et al., 1993; Yao et al., 1994; Nagashima et al., 1994, 1995). KW-3902 exhibited the 10-fold more potent nephroprotective effects against glycerol-induced acute renal failure than DPCPX (Suzuki et al., 1992).

In the present investigations, the effects of KW-3902 on radiocontrast media-induced renal functional impairment were assessed in a novel animal model of radiocontrast media-induced nephropathy (Erley et al., 1997). In this model, animals are chronically nitric oxide (NO) depleted by pretreated with the NO synthase inhibitor *N*-ϖ-nitro-L-arginine methyl ester (L-NAME), and demonstrate comparable renal hemodynamic effects in response to radiocontrast media as observed in humans. In addition, the effects of isoosmolar mannitol on renal hemodynamic were assessed to examine the role of hyperosmolarity in radiocontrast media-induced nephropathy. Since KW-3902 is under clinical development, it was desirable to test its efficacy first in an accepted animal model of radiocontrast media-induced nephropathy before application in patients.

2. Methods

Experiments were conducted in male Sprague–Dawley rats (150–220 g, Charles River, Sulzfeld, FRG). Animals were fed on pelleted standard rat chow (Altromin 1320, Lage, FRG) with free access to drinking water. The rats in control groups were given regular tap water during the entire pre-experimental period. The rats in L-NAME-treated groups received L-NAME (Sigma, St. Louis, MO, USA) for 8 weeks, added to the drinking water in a concentration of 50 mg/l, corresponding to a daily dose of approximately 5 mg/kg/day.

For clearance experiments, rats were anesthetized with thiobutabarbital, 120 mg/kg i.p. (Inactin®, RBI, Natick, MA, USA) and placed on a servo-controlled, heated table to maintain body temperature at 37°C. Following tracheostomy, the right jugular vein was cannulated with three polyethylene catheters for infusion of saline (0.85 g/dl), tritium-labeled inulin (1.33 μCi/h; DuPont, Bad Homburg, FRG) and study drugs. Total infusion rate was 1.2 ml/h/100 g body wt. throughout the experiment. The right femoral artery was cannulated for continuous monitoring of arterial blood pressure and a catheter was inserted into the bladder for collection of urine. Plasma and urinary concentrations of inulin were measured by liquid scintillation counting (Packard, Meridian, CT, USA), and glomerular filtration rate calculated using standard formulas.

Following equilibration, baseline values for urine volume, urinary Na^+ excretion and glomerular filtration rate were assessed in two consecutive 20 min periods. Hereafter, KW-3902 (Kyowa Hakko Kogyo, Tokyo, Japan), 0.1 mg/kg body wt. or an equivalent volume of vehicle (0.85% saline containing NaOH 0.01 N and 1% dimethylsulfoxide (DMSO)) was applied as a slow bolus injection over 3 min. Following another 20-min clearance period, radiocontrast media (sodium diatrizoate, Urografin®, 214 mgI/ml; diluted with sterile water; Schering, Berlin, FRG) or isoosmolar mannitol (1100 mosM/l, Mannitol-Loesung 20%, Pharma Hameln, Hameln, FRG) was administered at a dose of 3 ml/kg body wt. i.v. over a period of 3 min and another three clearance periods were performed (Fig. 1).

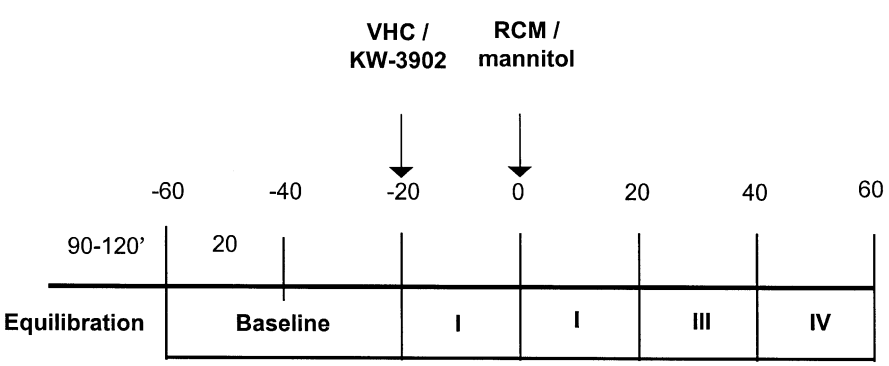

Fig. 1. Experimental protocol. VHC: Vehicle, 1% DMSO, 0.01 N NaOH, in saline; KW-3902, 0.1 mg/kg; RCM, radiocontrast media (sodium diatrizoate).

Table 1
Mean arterial pressure, glomerular filtration rate (GFR), urine volume and Na^+ excretion at baseline

	n	Mean arterial pressure (mm Hg)	GFR (ml/min/100 g)	Urine volume (μl/min/100 g)	Na^+ excretion (μmol/min/100 g)
(A) L-NAME groups					
VHC + mannitol	6	120.5 ± 7.0[a]	0.657 ± 0.045	17.9 ± 2.3	1.97 ± 0.25
VHC + RCM	6	123.0 ± 7.2[a]	0.710 ± 0.035	17.9 ± 2.7	1.76 ± 0.29
KW-3902 + mannitol	6	114.3 ± 10.5[a]	0.627 ± 0.051	15.4 ± 2.1	1.05 ± 0.31
KW-3902 + RCM	6	115.2 ± 3.9[a]	0.720 ± 0.038	18.2 ± 1.7	1.84 ± 0.20
(B) Control groups					
VHC + mannitol	6	83.5 ± 6.3	0.743 ± 0.059	23.4 ± 3.5	2.69 ± 0.82
VHC + RCM	6	92.5 ± 2.7	0.701 ± 0.041	24.3 ± 4.6	2.11 ± 0.55
KW-3902 + mannitol	6	82.3 ± 6.2	0.751 ± 0.061	21.5 ± 4.4	2.01 ± 0.65
KW-3902 + RCM	6	86.0 ± 6.1	0.778 ± 0.042	24.9 ± 5.5	1.44 ± 0.46

Values are means ± S.E.M. of $n = 6$ animals/group.
[a] $P < 0.05$ vs. respective control groups.

The single dose 0.1 mg/kg (i.v.) of KW-3902 was determined so that the dose exhibited a diuretic effect not by the change in the renal hemodynamics, but by the inhibition of water and Na^+ reabsorption in tubular site (Mizumoto et al., 1993).

2.1. Statistical analysis

All data were pressed as means ± S.E.M. The data were analyzed using computer and statistical analysis software (SAS, version 6.12, SAS Institute, Cary, NC). Statistic analysis were performed using analysis of variance for nested model, followed by paired *t*-test for paired comparisons between baseline and each period, and Student's *t*- or Aspin–Welch test for unpaired comparison between radiocontrast media and respective mannitol-infused groups at each period. *P* values of < 0.05 were considered statistically significant.

3. Results

3.1. Effects of L-NAME pretreatment

Mean arterial pressure was significantly elevated in L-NAME hypertensive animals, as compared to the respective control groups and remained elevated throughout the course of the experiments. Baseline glomerular filtration rate as well as urine volume and urinary Na^+ excretion were slightly, but not significantly, lower in L-NAME-treated animals, as depicted in Table 1.

3.2. Effects of KW-3902, radiocontrast media or mannitol on renal hemodynamics

Radiocontrast media application induced a significant decline in glomerular filtration rate in L-NAME hypertensive animals (0.71 ± 0.04 to 0.42 ± 0.08 ml/min/100 g, $p < 0.05$), without affecting mean arterial pressure. The time course of the changes in glomerular filtration rate is depicted in Fig. 2A. The administration of an equivalent volume of mannitol solution isoosmolar to radiocontrast

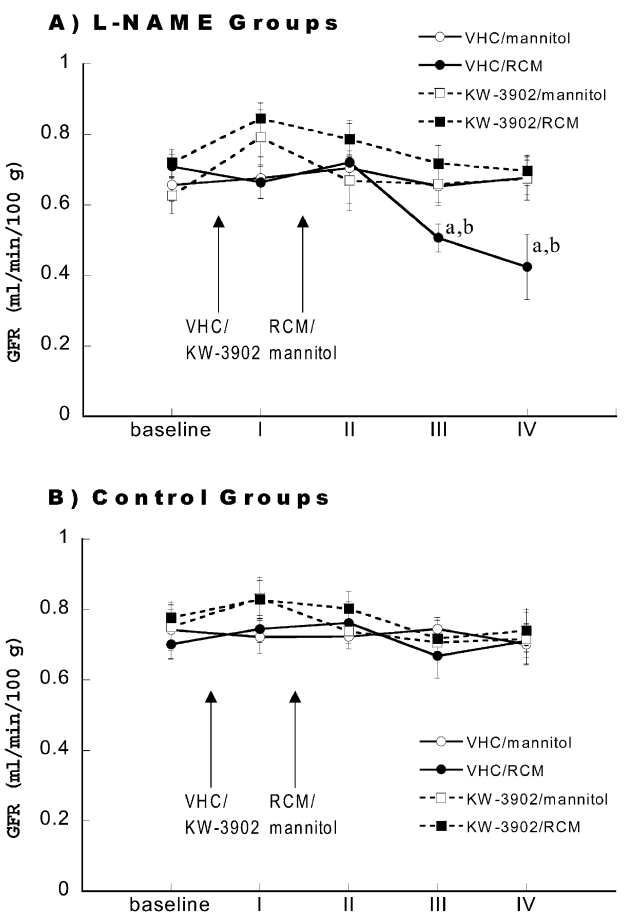

Fig. 2. (A, B) Time course of the changes in glomerular filtration rate throughout the experiment in (A) L-NAME animals and (B) control animals. Values are means ± S.E.M. of $n = 6$ animals/group, (a) $P < 0.05$ vs. baseline, (b) $P < 0.05$ vs. respective mannitol infused groups. No significant difference vs. baseline or respective mannitol in control animals (B).

media was without significant effect on renal or systemic hemodynamics.

Pretreatment with KW-3902 fully prevented the drop in glomerular filtration rate following radiocontrast media administration, as compared to the respective vehicle-treated groups (Fig. 2A). KW-3902, radiocontrast media and mannitol were without significant systemic or renal hemodynamic effect in untreated control animals (Fig. 2B).

3.3. Effects of KW-3902, radiocontrast media or mannitol on tubular function

Pretreatment with KW-3902 induced a significant increase in urine volume and urinary Na^+ excretion in both, L-NAME hypertensive and untreated control rats, as depicted in Figs. 3 and 4, respectively. Subsequent administration of radiocontrast media resulted in a transient additional increase in urine flow and urinary Na^+ excretion, with values returning to baseline levels within 60 min. The time course of urine volume and urinary Na^+ excretion in the respective groups is depicted in Figs. 3A,B and 4A,B.

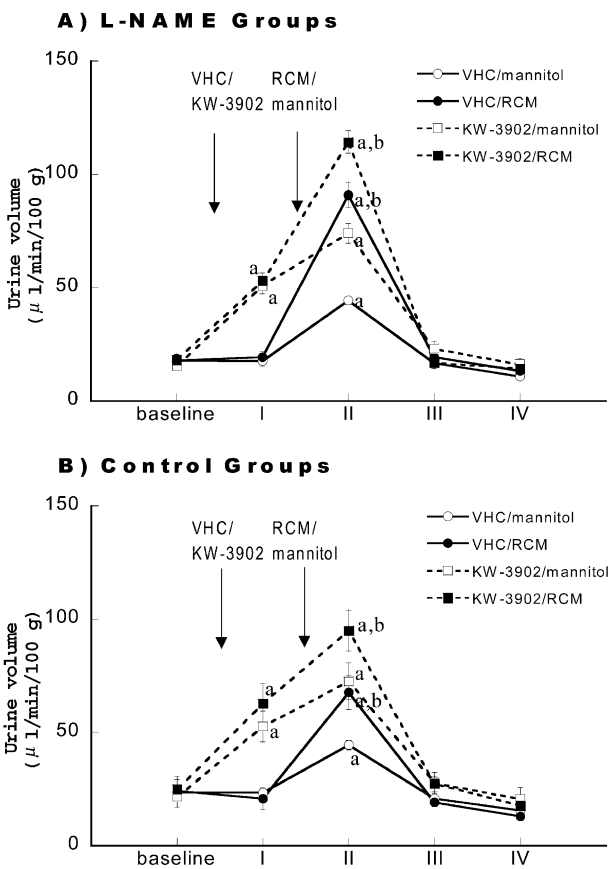

Fig. 3. (A, B) Time course of the changes in urine volume throughout the experiment in (A) L-NAME animals and B) control animals. Values are means ± S.E.M. of $n = 6$ animals/group, (a) $P < 0.05$ vs. baseline, (b) $P < 0.05$ vs. respective mannitol infused groups.

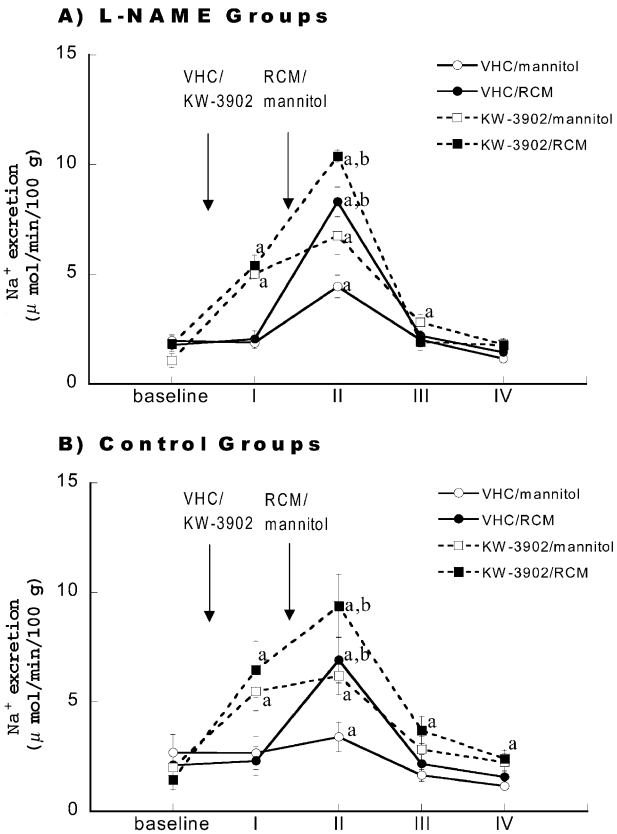

Fig. 4. (A, B) Time course of the changes in urinary Na^+ excretion throughout the experiment in (A) L-NAME animals and (B) control animals. Values are means ± S.E.M. of $n = 6$ animals, (a) $P < 0.05$ vs. baseline, (b) $P < 0.05$ vs. the respective mannitol infused group.

A markedly less pronounced effect during the comparable time course was observed in mannitol-infused animals.

4. Discussion

Renal functional deterioration, up to the development of acute renal failure is a major clinical complication following the application of radiocontrast media. To date, a number of risk factors for the development of renal functional deterioration have been identified such as dehydration, extracellular volume contraction, congestive heart failure, diabetes mellitus or preexisting renal insufficiency [***] (Barrett, 1994). Different clinical strategies have been proposed for the prevention of radiocontrast media-induced nephropathy, among which hydration of the patient prior to the application of radiocontrast media has proven most effective. However, in cases where hydration of the patient is limited due to time or to clinical settings, alternative therapeutic approaches have to be found. Since KW-3902 is under clinical development in safety studies and as a diuretic substance, its potential efficacy as a nephroprotective drug after radiocontrast media in humans needs to

be analyzed before testing in patients. In the present study, we examined the effects of KW-3902 on radiocontrast media-induced nephropathy in in vivo conditions and not in isolated perfused kidney preparation used by Oldroyd et al. (2000).

In the kidney under in vivo conditions, adenosine induces significant vasoconstriction and a drop in glomerular filtration rate and renal blood flow (Osswald et al., 1978, 1997). Several studies have demonstrated adenosine to contribute to the renal functional deterioration in response to radiocontrast media (Arend et al., 1987; Arakawa et al., 1996; Oldroyd et al., 2000); the exact pathomechanisms of radiocontrast media-induced nephropathy, however, are still not completely understood.

In the present experiments, we employed the model of L-NAME hypertensive, chronic NO-depleted rat to assess the effects of a selective adenosine A_1 receptor antagonist in the prevention of radiocontrast media-induced nephropathy. Originally described as a model for arterial hypertension, the L-NAME hypertensive, chronic NO-depleted rat was recently established as a model for radiocontrast media-induced nephropathy by Erley et al. (1997, 1998). The chronic inhibition of NO synthase and thus inhibition of a potent vasodilating stimulus apparently unmasks the renal hemodynamic response to radiocontrast media and enables the study of the pathophysiology of radiocontrast media-induced nephropathy without prior reduction in renal mass or concomitant application of other nephrotoxic substances.

The data of the present experiments demonstrate a significant decline in glomerular filtration rate in L-NAME-treated rats following application of radiocontrast media. No significant alterations in renal hemodynamics were observed in control rats, indicating that radiocontrast media-induced vasoconstriction is compensated for by vasodilating autacoids such as an increased NO production under physiologic conditions. The fact that chronic NO synthase inhibition resulted in a significant renal functional impairment indicates that the buffering capacity of the NO system is enormous in rats under control conditions. The effect of chronic NO deficiency suggests that the direct action of radiocontrast media may be vasoconstriction at afferent arterioles, which is masked by NO under control conditions. To what extent an enhanced production of oxygen radicals may contributes to the toxicity of radiocontrast media during chronic NO synthase remains to be elucidated. This notion is supported by data from Agmon et al. (1994), demonstrating NO and vasodilatory prostanoids to attenuate radiocontrast media nephrotoxicity in the rat. The selective adenosine A_1 receptor antagonist KW-3902 completely blocked the radiocontrast media-induced drop in glomerular filtration rate in L-NAME hypertensive animals, extending previous studies with theophylline or DPCPX and demonstrating a central role for adenosine A_1 receptor activation in the pathogenesis of radiocontrast media-induced nephropathy (Arend et al., 1987; Erley et al., 1994, 1997, 1998). Recently, Oldroyd et al. (2000) demonstrated that KW-3902 prevented the radiocontrast media-induced decrease in glomerular filtration rate, in the isolated perfused rat kidney. The authors of this publication used the isolated perfused rat kidney preparation of rats which, however, is of somewhat of limited value to predict pathophysiological mechanisms in experimental nephropathy. The filtration fraction in this isolated perfused rat kidney (Oldroyd et al., 2000) was about 2% whereas normal kidneys have a filtration fraction of 20–30%. In addition, they infused constantly the radiocontrast media to the perfusion fluid of the isolated perfused rat kidney. The authors state that their model with high concentration of radiocontrast media in the perfusate "was not chosen to simulate clinical doses" but "to elicit a significant response" in the isolated perfused rat kidney preparation. Thus, the data obtained by Oldroyd et al. (2000) cannot be compared directly to our data or to the situations of patients. Therefore, it appeared to be desirable to confirm that the drop in glomerular filtration rate after radiocontrast media administration as seen in the isolated perfused rat kidney and the protective effect of KW-3902 are also present in in vivo conditions. In the present study, renal blood flow was not measured, and further experiments are necessary to clear the effects of KW-3902 on renal hemodynamics in radiocontrast media-induced nephropathy.

In our experiments, infusion of hypertonic mannitol solution was employed as an osmotic challenge isoosmolar to radiocontrast media in order to examine the role of hyperosmolarity in radiocontrast media-induced nephropathy. Mannitol infusion was without significant effect on glomerular filtration rate in both, control and L-NAME-treated rats, indicating that alterations in renal hemodynamics following radiocontrast media occur independently of the osmotic load. These results suggest that the main cause of the increase in intrarenal adenosine might not be entirely osmolar-dependent response to radiocontrast media.

Significant differences occurred, however, in the tubular function. Radiocontrast media-induced diuresis and natriuresis was significantly higher compared to isoosmolar mannitol. This difference might indicate a direct cytotoxic effect of radiocontrast media on tubular epithelium. Various studies have confirmed a direct tubular damage by radiocontrast media at both proximal and distal tubular sites (Janzen, 1982; Humes et al., 1987; Bakris et al., 1990). The subsequent impaired Na^+ reabsorption upstream of the macula densa would result in an activation of the tubuloglomerular feedback and a reduction in glomerular filtration rate (Schnermann et al., 1970; Spielman and Arend, 1991). In addition, cellular damage and a drop in the ATP/ADP ratio would augment adenosine generation and adenosine-mediated vasoconstriction (for reference, see Osswald and Vallon, 1998). KW-3902 had an additive effect on fluid- and electrolyte excretion in both mannitol

and radiocontrast media-infused animals. KW-3902 has been shown to prevent the damage of proximal tubules from chemical-induced acute renal failure (Mizumoto et al., 1993; Nagashima et al., 1994, 1995; Yao et al., 1994). KW-3902 may directly protect the proximal tubular against radiocontrast media. Whether KW-3902, besides antagonizing renal adenosine actions, reduces radiocontrast media uptake and cellular toxicity by a direct inhibition of Na^+ transport in the proximal tubule remains to be determined.

In summary, our data demonstrate adenosine, via adenosine A_1 receptor activation, to play a major role in the pathogenesis of radiocontrast media-induced acute renal failure. The selective adenosine A_1 receptor antagonist KW-3902 fully prevented the renal hemodynamic alterations in response to radiocontrast media. In addition, whether KW-3902 reduces tubular damage and diminishes intrarenal adenosine generation remains to be determined. In clinical settings, where hydration of the patient is limited or may not suffice due to the presence of additional risk factors, KW-3902 could present a promising novel therapeutic approach in the prevention of radiocontrast media-induced nephropathy.

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