Protective Effects of KW-3902, an Adenosine A₁-Receptor Antagonist, against Cisplatin-Induced Acute Renal Failure in Rats

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ABSTRACT—We investigated possible renal protective and therapeutic effects of KW-3902 (8-(noradamantan-3-yl)-1,3-dipropylxanthine), a novel and potent adenosine A₁-receptor antagonist, on cisplatin-induced acute renal failure (ARF). ARF was induced in rats by a single injection of cisplatin (5 mg/kg, i.v.). Prophylactic treatment with KW-3902 (0.01–1 mg/kg, p.o., twice a day) significantly attenuated the increases of serum creatinine (S-CRE) and urea nitrogen (S-UN) induced by cisplatin. On the other hand, neither furosemide nor trichlormethiazide showed any ameliorating effects against the cisplatin-induced ARF. In the clearance study, the cisplatin-treatment induced marked decreases of glomerular filtration rate (GFR), renal plasma flow (RPF), and reabsorptions of water, sodium and potassium at tubular sites, in comparison with those in untreated normal rats. KW-3902 (0.1 mg/kg, p.o., twice a day) significantly improved these deteriorated glomerular and tubular functions. In the rats with established cisplatin-induced ARF, KW-3902 ameliorated the cisplatin-induced reductions of GFR, RPF, and reabsorptions of water, sodium and potassium at tubular sites. These results suggest that activation of adenosine A₁-receptors is involved in the pathogenesis of cisplatin-induced ARF. The adenosine A₁-receptor antagonist may be useful for the treatment of cisplatin-induced ARF.

Keywords: KW-3902, Adenosine A₁-receptor antagonist, Renal protective effect

Cisplatin has been proved to be a useful agent for the treatment of solid tumors (1). In spite of its potent and dose-dependent anti-tumor activity (2), high doses of cisplatin induce various adverse effects, including nephrotoxicity (3), which limit its clinical usefulness. In the rat, single intravenous administration of cisplatin reduces the glomerular filtration rate (GFR) and inhibits reabsorptions of water and sodium at tubular sites (4, 5). The decrease of GFR in cisplatin-induced acute renal failure (ARF) has been ascribed to reduced renal plasma flow (RPF) and effective filtration (5). The main site of morphologic changes due to cisplatin is the renal proximal tubule, while the glomerulus remains unaffected (6). Dobyan et al. (7) reported that cisplatin exerts its nephrotoxic effect specifically on the S₃ segment of the proximal tubule located in the outer medulla, whereas gentamicin damages the S₁ segment and glycerol degenerates the whole renal tubule (8). Secretion of cisplatin may lead to its selective accumulation in the proximal tubule and direct toxic effect on the epithelial cells lining the S₃ segment (7).

To prevent the nephrotoxicity induced by cisplatin, a variety of maneuvers, such as volume-induced diuresis (9), inhibition of tubular cisplatin secretion with probenecid (10) and treatment with oxygen free-radical scavengers (11), have been attempted. Recently, Heidemann et al. (12) reported that aminophylline, a non-selective adenosine antagonist, prevented cisplatin-induced ARF in rats. Furthermore, the study by Knight et al. (13) demonstrated that the prophylactic treatment with 8-cyclopentyl-1,3-dipropylxanthine (DPCPX), an adenosine A₁-receptor antagonist, can ameliorate the severity of cisplatin-induced ARF in rats. Thus, adenosine is thought to be one of the mediators responsible for the cisplatin-induced nephrotoxicity. Prior to the present study, however, the therapeutic effect of the adenosine receptor antagonist has not been reported.

KW-3902 (8-(noradamantan-3-yl)-1,3-dipropylxanthine) is a newly synthesized specific adenosine A₁-receptor antagonist and the most potent one reported to date (14). In receptor-binding studies, dissociation constant values of KW-3902 for adenosine A₁-receptor and A₂-receptor are

1.3 and 380 nM, respectively (14). Furthermore, in anesthetized rats, KW-3902 potently antagonizes the 5'-N-ethylcarboxamidoadenosine (NECA)-induced bradycardic response mediated via adenosine A₁-receptors with little influence on the NECA-induced hypotensive response mediated via adenosine A₂-receptors (15). We have previously reported that KW-3902 exhibits renal protective effects against glycerol- (15), gentamicin- (16) or cephaloridine- (17) induced ARF in rats.

In the present study, we have examined possible renal protective effects of KW-3902 against cisplatin-induced ARF in rats, with special emphasis on the renal function as examined by the clearance study. Moreover, to investigate the therapeutic effect, we determined the effects of KW-3902 on the renal function in rats with established cisplatin-induced ARF.

MATERIALS AND METHODS

Experimental animals

Male Wistar rats (Japan Shizuoka Laboratory Animal Center, Inc., Hamamatsu), weighing 200–350 g, were used for the present experiments. The rats were kept at 22°C under a 12-hr light-dark cycle, and they had free access to tap water and commercial chow.

Drugs

KW-3902 (8-(noradamantan-3-yl)-1,3-dipropylxanthine) (14) was synthesized in our laboratories. Cisplatin was purchased from Nippon Kayaku Co., Ltd. (Tokyo). Creatinine (CRE) and *N*-1-naphthyl-*N*-diethylethylene diamine oxalate (Tsuda reagent) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka). *p*-Aminohippuric acid (sodium salt, PAH) was purchased from Sigma Chemical Co. (St. Louis, MO, USA). Furosemide was purchased from Tokyo Kasei Co., Ltd. (Tokyo) and trichlormethiazide (TCM) was from Aldrich Chemical Co., Ltd. (Milwaukee, WI, USA). All other chemicals and solvents were used in their analytical pure form.

Prophylactic effects against cisplatin-induced ARF

Cisplatin-induced ARF was produced according to the previous method (12). In brief, ARF was induced in rats by an intravenous injection of cisplatin at a dose of 5 mg/kg. KW-3902 (0.001–1 mg/kg), furosemide (30 mg/kg) or TCM (1 mg/kg) was orally administered to rats 1 hr before and at 12-hr intervals until 72 hr after the injection of cisplatin. Drugs were suspended in 0.3% carboxymethylcellulose containing 0.25% Tween 80, and the suspension was orally administered to rats at a volume of 5 ml/kg. Five days after the injection of cisplatin (i.e., 2 days after the termination of drug treatment), saline, not containing drugs, was orally administered to rats at a

volume of 25 ml/kg, and the rats were individually placed in metabolic cages without food or water. Urine was collected for 4 hr. Immediately after the urine collection, blood was collected from the tail vein, and serum was separated by centrifugation (3,000 rpm, 10 min, 4°C). Concentrations of serum CRE (S-CRE) and urea nitrogen (S-UN) were measured. Urine volume and concentrations of CRE, sodium and potassium in urine were also determined.

At the end of the experiment, the left kidney was removed of adhering connective and fat tissues. Coronal slices of the kidney from the non-treated and the cisplatin-treated rats were fixed in 10% buffered formalin (pH 7.25). Transverse kidney slices were embedded in paraffin, sectioned at 4-μm thickness by a microtome and stained with hematoxylin/eosin for light microscopy.

The clearance study was performed with a separate series of animals. KW-3902 was orally administered to rats at a dose of 0.1 mg/kg with the same schedule as described above. Ninety-six hr after the injection of cisplatin, the rats were anesthetized with urethan (1.3 g/kg, s.c.). The left carotid artery, right femoral vein and urinary bladder were cannulated for blood collection, infusion and urine collection, respectively. After the surgery, saline containing 0.5% PAH and 0.001% CRE was intravenously infused at a rate of 2 ml/hr/rat with a constant flow infusion pump (Pump 22; Harvard Apparatus Inc., South Natick, MA, USA). After the equilibration period, urine was collected for 1 hr. Heparinized blood was collected at the midpoint of the urine collection period, and plasma was separated by centrifugation (3,000 rpm, 10 min, 4°C). Urine volume was determined gravimetrically. The concentrations of CRE, PAH, sodium and potassium in the plasma and urine were measured.

Therapeutic effects against established cisplatin-induced ARF

In rats with established cisplatin-induced ARF, by employing the clearance technique, the acute effects of KW-3902 on the renal functions were determined. Four days before the experiment, the rats were injected with cisplatin at the dose of 5 mg/kg. Cisplatin-treated rats were anesthetized with urethane (1.3 g/kg, s.c.), and the same surgery as described above was performed. After the surgery, saline containing 0.5% PAH and 0.001% CRE was infused at a rate of 2 ml/hr/rat. In the KW-3902-treated group, vehicle and 0.001, 0.01, 0.1 mg/kg (i.v.) of KW-3902 were cumulatively administered to the rat every 1 hr after the equilibration period. In the control group, only the vehicle was administered to the rat 4 times every 1 hr. KW-3902 was dissolved in saline containing 1% dimethylsulfoxide and 0.01 N NaOH (vehicle), and the solution

was intravenously administered to the rat at a volume of 1 ml/kg. Urine was collected 4 times every 1 hr, and blood was collected at the midpoint of each urine collection period. Plasma was separated immediately after the blood collection. Concentrations of sodium, potassium, CRE and PAH in the urine and plasma were determined.

Analytical procedures

The concentration of CRE and UN in the urine and plasma (serum) were determined by an autoanalyzer (AU510; Olympus, Tokyo). The concentrations of sodium and potassium in the urine and plasma were measured by flame photometry (775-A; Hitachi Ltd., Tokyo). The concentration of PAH in the urine and plasma was determined by the Bratton-Marshall method (18). For the analysis of the plasma, 0.25 ml of plasma was added with 1 ml of 7.5% trichloroacetic acid (TCA) to precipitate the proteins, and the supernatant was obtained by centrifugation (12,000 rpm, 5 min, room temperature). One milliliter of the supernatant was supplemented with 1 ml of distilled water and used for assay. For the analysis, a urine sample was first diluted 200-fold with distilled water. A 1-ml aliquot of the diluted urine was added with 1 ml of 7.5% TCA and used for the assay. Plasma or urine test solution was added with 0.1 ml of 2 N HCl and 0.2% Na₂NO₂. After 3 min, 0.1 ml of 25% urea solution was added, and the mixture was allowed to stand 10 min. Subsequently, 0.1 ml of 0.2% Tsuda reagent was added and the mixture was allowed to stand for another 10 min. Two milliliters of ethanol was added to the resultant mixture to stop the reaction, and the absorbance was measured at a wavelength of 570 nm with an Auto Shipper Photometer (U-1080; Hitachi, Ltd., Tokyo).

Standard formulas were used to calculate creatinine clearance (C_{CRE}) as an index of GFR and PAH clearance (C_{PAH}) as an index of RPF. Reabsorption rates of water, sodium and potassium at tubular sites were calculated from the following formulas:

Reabsorption rate of water (%)

$$= \frac{C_{CRE}(\text{ml/kg/hr}) - \text{Urine volume}(\text{ml/kg/hr})}{C_{CRE}(\text{ml/kg/hr})} \times 100$$

Reabsorption rate of Na (%)

$$= \frac{C_{CRE}(\text{ml/kg/hr}) \times \text{Plasma Na}(\mu\text{Eq/ml}) - \text{Na excretion}(\mu\text{Eq/kg/hr})}{C_{CRE}(\text{ml/kg/hr}) \times \text{Plasma Na}(\mu\text{Eq/ml})} \times 100$$

Reabsorption rate of K (%)

$$= \frac{C_{CRE}(\text{ml/kg/hr}) \times \text{Plasma K}(\mu\text{Eq/ml}) - \text{K excretion}(\mu\text{Eq/kg/hr})}{C_{CRE}(\text{ml/kg/hr}) \times \text{Plasma K}(\mu\text{Eq/ml})} \times 100$$

Statistical analyses

Data are presented as means $\pm$ S.E. Statistical significance was estimated by Student's *t*-test or analysis of variance (ANOVA) followed by Dunnett's test. P values of less than 0.05 were considered statistically significant.

RESULTS

Prophylactic effects against cisplatin-induced ARF

Table 1 shows the effects of prophylactic treatment with KW-3902, furosemide or TCM on cisplatin-induced ARF in rats. Five days after the injection of cisplatin, S-CRE and S-UN in the control group markedly increased as compared with those in the normal group. KW-3902 significantly ameliorated the increases of S-CRE and S-UN at doses of 0.01 mg/kg and higher. On the other hand, furosemide did not show any effects against the

Table 1. Effects of prophylactic treatments with KW-3902, furosemide and TCM on cisplatin-induced ARF in rats

	S-CRE (mg/dl)	S-UN (mg/dl)	C_{CRE} (ml/kg/4 hr)
Normal	0.57 $\pm$ 0.02**	15.8 $\pm$ 0.6**	1268.7 $\pm$ 47.8**
Control	3.54 $\pm$ 0.43	156.0 $\pm$ 24.2	75.6 $\pm$ 36.1
KW-3902 0.001 mg/kg (p.o.)	3.95 $\pm$ 0.50	157.2 $\pm$ 21.7	108.8 $\pm$ 35.1
KW-3902 0.01 mg/kg (p.o.)	1.83 $\pm$ 0.26*	70.2 $\pm$ 8.2**	354.7 $\pm$ 58.8**
KW-3902 0.1 mg/kg (p.o.)	1.78 $\pm$ 0.18**	69.4 $\pm$ 10.1**	494.8 $\pm$ 49.8**
Furosemide 30 mg/kg (p.o.)	3.07 $\pm$ 0.32	146.2 $\pm$ 18.4	86.7 $\pm$ 21.6
TCM 1 mg/kg (p.o.)	5.88 $\pm$ 0.16**	250.8 $\pm$ 6.1**	12.9 $\pm$ 1.4

Values represent means $\pm$ S.E. of 7 animals. S-CRE: serum creatinine, S-UN: serum urea nitrogen, C_{CRE} : creatinine clearance. *P < 0.05, **P < 0.01, when compared with the control value.

Fig. 1.

Table 2. Influences of cisplatin on glomerular and tubular functions and the protective effects of KW-3902 against cisplatin-induced ARF in rats

Variable	Non-treated	Cisplatin-treated	
		Control	KW-3902 (0.1 mg/kg, p.o.)
C _{CRE} (ml/kg/hr)	236 ± 16***	18 ± 1	83 ± 6***
C _{PAH} (ml/kg/hr)	869 ± 18***	48 ± 10	321 ± 37**
Urine volume (ml/kg/hr)	1.13 ± 0.13	1.14 ± 0.15	1.08 ± 0.09
Na excretion (μEq/kg/hr)	82 ± 10	113 ± 13	102 ± 6
K excretion (μEq/kg/hr)	207 ± 23**	74 ± 6	141 ± 14**
Reabsorption rats (%)			
of water	99.5 ± 0.03**	93.7 ± 0.82	98.7 ± 0.06**
of sodium	99.8 ± 0.02***	95.6 ± 0.42	99.1 ± 0.06***
of potassium	79.7 ± 1.1***	1.7 ± 0.2	58.2 ± 4.9***

Cisplatin was injected at a dose of 4 mg/kg (i.v.) 4 days before the clearance measurement. Values represent means ± S.E. of 5 animals. C_{CRE}: creatinine clearance, C_{PAH}: p-aminohippuric acid clearance. **P < 0.01, ***P < 0.001, when compared with the value in cisplatin-treated control rats.

cisplatin-induced ARF. TCM markedly potentiated the increases in S-CRE and S-UN in cisplatin-treated rats. In the control group, C_{CRE} was markedly decreased following the injection of cisplatin. KW-3902 at doses higher than 0.01 mg/kg ameliorated the depressed C_{CRE} in a dose-dependent manner.

Figures 1A and 1B show typical microphotographs of the kidney from normal and cisplatin-induced ARF rats, respectively. The cortex and the proximal tubule were evidently affected in the kidney of cisplatin-induced ARF rats. Necrosis and regeneration of proximal tubular epithelium, tubular dilation and delayed lumen were observed especially in the cortical tubules. On the other hand, the glomerulous medulla and papilla were histologically intact in the kidney of cisplatin-induced ARF rats. Figure 1C shows a typical microphotograph of the kidney of cisplatin-induced ARF rats treated with KW-3902 (0.1 mg/kg). KW-3902 attenuated the damage of the proximal tubule.

Table 2 shows the protective effect of KW-3902 (0.1 mg/kg, p.o.) against cisplatin-induced ARF, as examined by the clearance study. C_{CRE} and C_{PAH} in the control group were prominently depressed in comparison with those in the normal group. On the other hand, urine volume and sodium excretion were not different between the control group and the normal group. Potassium excre-

tion was prominently reduced by cisplatin-treatment. Tubular reabsorption rates of water, sodium and potassium in the control group were significantly reduced in comparison with those in the normal group. C_{CRE} and C_{PAH} in the KW-3902 (0.1 mg/kg, p.o.)-treated group were significantly higher than those in the control group. KW-3902 significantly improved the reduced potassium excretion. Additionally, KW-3902 significantly improved the reduced tubular reabsorption rates of water, sodium and potassium, which were observed in the control group.

Therapeutic effects against established cisplatin-induced ARF

As was the case with the result described above, cisplatin induced marked decreases in C_{CRE} (15.2 ± 4.4 ml/kg/hr) and C_{PAH} (39.3 ± 13.9 ml/kg/hr) in comparison with those (C_{CRE}: 236 ± 16 ml/kg/hr, C_{PAH}: 869 ± 18 ml/kg/hr) in the normal group. Urine volume and sodium excretion were not different between cisplatin-treated and non-treated rats, while potassium excretion was severely depressed. Reabsorption rates of water, sodium and potassium were significantly reduced compared with those of non-treated rats.

Figure 2 illustrates the effects of KW-3902 on C_{CRE} and C_{PAH} in the rats with cisplatin-induced ARF. Following the repeated treatments (4 times) with the vehicle, sig-

Fig. 1. Light microphotographs of the kidney from normal (A), cisplatin-treated (B) and cisplatin and KW-3902 (0.1 mg/kg, p.o.)-treated (C) rats. The rats in the ARF group received a single injection of cisplatin at 5 mg/kg through the tail vein on day 0. The normal rat received a saline solution (10 ml/kg body weight). Magnification × 100.

Fig. 2. Effects of KW-3902 on creatinine clearance (C_{CRE}) and *p*-aminohippuric acid clearance (C_{PAH}) in anesthetized rats with established cisplatin-induced acute renal failure. Values represent means $\pm$ S.E. of 5 animals. * $P < 0.05$, ** $P < 0.01$, when compared with the basal value.

nificant changes were not observed in all the parameters. KW-3902 produced dose-dependent improvement of C_{CRE} and C_{PAH} . The highest dose (0.1 mg/kg, i.v.) of KW-3902 produced about 75 and 100% increases of C_{CRE} and C_{PAH} as compared with the basal values.

Figure 3 illustrates the effects of KW-3902 on urine volume, sodium and potassium excretions in cisplatin-treated rats. KW-3902 dose-dependently and prominently increased urine volume and sodium excretion with minimal change in potassium excretion. The highest dose (0.1 mg/kg, i.v.) of KW-3902 produced about 220% and 1100% increases in urine volume and sodium excretion, respectively. In contrast, the maximal increase in potassium excretion was about 104%, which was observed at 0.01 mg/kg (i.v.) of KW-3902.

Reabsorption rates of water, sodium and potassium at tubular sites are presented in Fig. 4. KW-3902 dose-dependently decreased reabsorption rates of water and sodium. In contrast, the reabsorption rate of potassium was significantly increased by the injection of KW-3902 (0.1 mg/kg, i.v.).

Fig. 3. Effects of KW-3902 on urine volume and excretions of sodium and potassium in anesthetized rats with established cisplatin-induced acute renal failure. Values represent means $\pm$ S.E. of 5 animals. * $P < 0.05$, ** $P < 0.01$, when compared with the basal value.

DISCUSSION

Recently, Knight et al. (13) reported that the adenosine A_1 -receptor blockade by DPCPX ameliorates cisplatin-induced ARF in rats, suggesting that adenosine plays a role in the pathophysiology of cisplatin-induced ARF. In the present study, KW-3902 also prevented the development of cisplatin-induced ARF, as examined by the determina-

Fig. 4. Effects of KW-3902 on reabsorption rates of water, sodium and potassium in anesthetized rats with established cisplatin-induced acute renal failure. Values represent means $\pm$ S.E. of 5 animals. * $P < 0.05$, ** $P < 0.01$, when compared with the basal value.

tion of S-CRE, S-UN and CCRE. Moreover, KW-3902 (0.1 mg/kg, p.o.) tended to ameliorate the tubular damage, as determined by histological observations. Our results as well as those reported by Knight et al. (13) suggest that adenosine may be involved in the pathogenesis of cisplatin-induced ARF. In fact, the serum adenosine in the renal vein tended to be increased in the cisplatin-induced ARF (K. Nagashima et al., unpublished data). Thus the increased adenosine could contribute to the ag-

gravation of cisplatin-induced ARF, as was the case with glycerol-induced ARF (19). Taken together, KW-3902 might have ameliorated the cisplatin-induced ARF by antagonizing adenosine A₁-receptors in the kidney. Further investigation, however, is necessary to clarify this point.

There are some reports about the renal glomerular function in cisplatin-induced ARF. RPF, but not mean arterial blood pressure, was decreased in rats with cisplatin-induced ARF, suggesting that the decrease of RPF was due to the increase of renovascular resistance (5). Reduced RPF and increased renovascular resistance were also observed in dogs and humans with cisplatin-induced ARF (20, 21). It is well known that exogenous adenosine constricts the afferent arteriole and reduces GFR (22). The increase of renovascular resistance and decrease of GFR by exogenous adenosine resemble those induced by cisplatin (23), suggesting that in the kidney with cisplatin-induced ARF, adenosine may be involved in the constriction of the afferent arteriole, resulting in the reduced RPF and GFR. Thus, KW-3902 might have improved the depressed renal function by antagonizing the adenosine A₁-receptor. However, the blockade of adenosine A₁-receptors did not perfectly suppress cisplatin-induced ARF, suggesting that endogenous substances other than adenosine might also be responsible for it. For example, BN52021, a PAF antagonist (24), and superoxide dismutase (11) are reported to be effective for cisplatin-induced ARF.

KW-3902 is reported to induce diuretic action by inhibiting reabsorptions of water and sodium at the proximal tubule (15, 23). The diuretic action of KW-3902 might also have contributed to the amelioration of cisplatin-induced ARF, since the diuresis can lead to the dilution of cisplatin in the proximal tubule, which is the major site of injury following cisplatin (25). The aggravating effect of TCM may be due to its diuretic action at the distal tubule and the following decreases of RPF and GFR, via the tubuloglomerular feed back mechanism (26). In this study, furosemide, a loop diuretic, did not show any effects against the cisplatin-induced ARF. In contrast, Ward et al. (27) previously found that rats could be partially protected against the ARF by administration of furosemide 30 min before cisplatin injection. The pretreatment with furosemide diminished the renal tubular necrosis and the azotemia. On the other hand, LeHane et al. (28) were unable to confirm the renal protective effect of furosemide and, in fact, found that the diuresis aggravated the nephrotoxicity of cisplatin. It is thus still controversial whether diuresis ameliorates cisplatin-induced ARF or not. In any case, further studies are necessary to determine the mechanism involved in the protective effect of KW-3902 against cisplatin-induced ARF.

Our present results showed that adenosine A₁-receptor blockade with KW-3902 ameliorated the decreased tubu-

lar reabsorptions of water and electrolytes, which were observed in the rats with cisplatin-induced ARF. The reduced tubular reabsorption rates of water and electrolytes following cisplatin treatment can, at least partly, be ascribed to the reduced RPF and GFR. Thus, the amelioration of the decreased tubular reabsorptions of water and electrolytes by the prophylactic treatment with KW-3902 might be the secondary event following the improvement of RBF and GFR by this drug.

One of the interesting new findings of the present study is that the adenosine A_1 -receptor blockade with KW-3902 produced a dose-dependent improvement of renal glomerular and tubular functions in rats with established cisplatin-induced ARF, as demonstrated by the clearance study. Though KW-3902 at the diuretic dose does not affect RPF and GFR in normal anesthetized rats (15), this drug significantly ameliorated the depressed RPF and GFR in the rats with established cisplatin-induced ARF (this study). These observations suggest that in the kidney suffering from cisplatin-induced ARF but not in the normal kidney, adenosine functions as an endogenous vasoconstrictor in the renal arteriole. The increases of urine volume and excretions of sodium and potassium by KW-3902 treatment seem to, at least partly, be due to the increased RPF and GFR. In contrast, furosemide, at the dose inducing diuretic effects in normal rats, does not induce any diuretic effect in rats with established cisplatin-induced ARF (8). These results suggest a possibility that KW-3902 can be the diuretic agent with a property of improving renal function in cisplatin-induced ARF.

In summary, the present study demonstrates that KW-3902, an adenosine A_1 -receptor antagonist, prevents the development of cisplatin-induced ARF. Additionally, KW-3902 significantly ameliorated the depressed glomerular and tubular functions in rats with established cisplatin-induced ARF. These results suggest that activation of adenosine A_1 -receptors plays an important role in the pathogenesis of cisplatin-induced ARF. The adenosine A_1 -receptor antagonist may be a prophylactic regimen as well as a diuretic drug for the patients treated with cisplatin.

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