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Attenuation of cisplatin nephrotoxicity by inhibition of soluble epoxide hydrolase

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Abstract Cisplatin is a highly effective chemotherapeutic agent against many tumors; however, it is also a potent nephrotoxicant. Given that there have been no significant advances in our ability to clinically manage acute renal failure since the advent of dialysis, the development of novel strategies to ablate nephrotoxicity would represent a significant development. In this study, we investigated the ability of an inhibitor of soluble epoxide hydrolase (sEH), *n*-butyl ester of 12-(3-adamantan-1-yl-ureiido)-dodecanoic acid (nbAUDA), to attenuate cisplatin-induced nephrotoxicity. nbAUDA is quickly converted to AUDA and results in maintenance of high AUDA levels in vivo. Subcutaneous administration of 40 mg/kg of nbAUDA to C3H mice every 24 h resulted in elevated blood levels of AUDA; this protocol was also associated with attenuation of nephrotoxicity induced by cisplatin (intraperitoneal injection) as assessed by BUN levels and histological evaluation of kidneys. This is the first report of the use of sEH inhibitors to protect against acute nephrotoxicity and suggests a therapeutic potential of these compounds.

Keywords Cisplatin · Nephrotoxicity · Soluble epoxide hydrolase

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Introduction

Cisplatin is a chemotherapeutic agent with a broad range of antitumor activity against lung, ovary, testicular, bladder, and head/neck tumors (Go and Adjei 1999; Lokich 2001). The nephrotoxicity of cisplatin was first demonstrated in preclinical trials (Schaeppi et al. 1973) and has long been recognized in clinical patients (Ries and Klastersky 1986; Kintzel 2001). It is estimated that renal failure occurs in 5–10% of patients (Lokich 2001). The nephrotoxicity

induced by cisplatin is dose-related and may be observed after either single or cumulative drug treatments (Arany and Safirstein 2003). The hallmark of cisplatin nephrotoxicity is damage to the S3 segment of the proximal tubules. A number of pathways critical to nephrotoxicity have been identified, including endoplasmic reticulum stress (Peyrou and Cribb 2007; Peyrou et al. 2007), metabolism via cysteine-*S*-conjugate β-lyase (Townsend et al. 2003), oxidative damage (Baliga et al. 1999), and renal inflammation, most notably mediated by tumor necrosis factor alpha (TNF-α; Ramesh and Reeves 2002). Amifostine may attenuate cisplatin/ifosfamide nephrotoxicity in patients with solid tumors (Hartmann et al. 2000). However, this strategy is associated with adverse, but often reversible, side effects (Genvresse et al. 2001). Therefore, it is important to develop new therapeutic strategies to attenuate cisplatin-induced nephrotoxicity.

In mammals, the soluble epoxide hydrolase (sEH) represents a single known gene product with over 90% homology between rodent and human. While sEH initially was thought to be only involved in xenobiotic metabolism, it has been well established that fatty acid epoxides are excellent substrates for this enzyme (Zeldin et al. 1993). Several classes of inhibitors have been developed for the enzyme, the most notable based on the 1,3-disubstituted urea pharmacophores (Morisseau et al. 1999, 2002). The finding that $sEH^{-/-}$ mice are viable (Sinal et al. 2000) suggests that serious side effects from the therapeutic use of sEH inhibitors are minimal. sEH inhibitors have been shown to normalize blood pressure in spontaneously hypertensive rats (Yu et al. 2000) and in rats challenged with angiotensin (Imig et al. 2002). Furthermore, the sEH inhibitors have been found to be strongly anti-inflammatory in several in vivo bioassays (Smith et al. 2005; Schmelzer et al. 2005; Liu et al. 2005; Inceoglu et al. 2006; Schmelzer et al. 2006; Xu et al. 2006). Arachidonic acid epoxides [epoxyeicosatrienoic acids (EETs)] are endogenous regulators that influence inflammation (Node et al. 1999) and blood pressure (Roman 2002) in the kidney; both inflammation and renal blood flow are critical mediators of cisplatin-mediated acute kidney injury (Jo et al. 2005; Winston and Safirstein 1985). Given that sEH inactivates the anti-hypertensive and anti-inflammatory effects of EETS (Imig et al. 2002; Hennig et al. 2002), we hypothesized that a sEH inhibitor, such as the *n*-butyl ester of 12-(3-adamantan-1-yl-ureido)-dodecanoic acid (nbAUDA), will attenuate cisplatin-induced nephrotoxicity.

Methods

Animals

Animal studies were conducted in accordance with the Guide for Care and Use of Laboratory Animals. For the nbAUDA pharmacokinetic studies, mice were exposed to varying concentrations of nbAUDA (dissolved in corn oil) subcutaneously. Serial tail blood samples (<5 μl) were collected at various time points (5 min to 24 h) after administration (Watanabe et al. 2006). Blood was transferred to a 1.5-ml microcentrifuge tube. The blood samples were weighed and mixed with 100 μl of purified water and 25 μl of internal standard [1-cyclohexyl-3-tetradecyl urea (CTU) at 500 ng/ml in methanol]. The samples were then extracted with 500 μl of ethyl acetate. The ethyl acetate layer was transferred into a clean 1.5-ml Eppendorf microcentrifuge tube and then dried under nitrogen. The residues were reconstituted in 25 μl of methanol and analyzed by liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS). For the cisplatin studies, male C3H mice (20–25 g; Charles River) were maintained in the College of Medicine animal care facility and given food and water ad libidum. Mice were injected with cisplatin [20 mg/kg; dissolved in phosphate-buffered saline (PBS), total injection volume 250 μl, i.p.] and killed 48, 72, or 96 h after challenge. In certain experiments, mice were given nbAUDA subcutaneously [40 mg/kg in 96:4 corn oil/dimethyl sulfoxide (DMSO) mixture] every 24 h with the first dose delivered 1 day before cisplatin challenge. After anesthesia (isoflurane), the abdominal cavity was opened, blood was obtained via cardiac puncture, and the kidneys were removed.

AUDA levels measurement

For the stability studies, rat liver microsomal proteins (0.05 mg) were brought to a final volume of 890 μl in 100 mM sodium phosphate buffer at pH 7.4. This protein solution was pre-incubated for 5 min in open glass tubes immersed in a shaking bath at a constant temperature of 37°C. After this pre-incubation, 10 μl

of a 100 μM solution of nbAUDA in methanol was added, and the reaction was initiated by the addition of 100 μl of the nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH) generating system (total volume 1 ml). The NADPH regenerating system consisted of 2 mM NADP, 57 mM glucose 6-phosphate, 3.5 units/ml glucose-6-phosphate dehydrogenase, and 50 mM magnesium chloride dissolved in 100 mM sodium phosphate buffer at pH 7.4. Each incubation mixture was incubated in a shaking water bath kept at 37°C for 5, 10, 20, 30, 40, and 60 min. A control (t=0) was prepared by the addition of 1 ml of ethyl acetate just after adding the NADP generating system. Reactions were terminated by the addition of 1 ml of cold ethyl acetate and kept in ice water until isolation. A 200-μl aliquot of 500 ng/ml CTU was added to the sample. The samples were then vortexed and centrifuged at 6,000 rpm (4,000×g) for 5 min. The aqueous phases were extracted twice with ethyl acetate; extracts were combined and dried under nitrogen. The residue was reconstituted in 1 ml of methanol. Aliquots (5 μl) were injected onto the LC/MS/MS system.

AUDA levels were measured using LC/MS/MS as previously described by Watanabe et al. (2006). The LC/MS/MS analysis was performed using a Micromass Quattro Ultima triple quadrupole tandem mass spectrometer (Micromass, Manchester, UK) equipped with atmospheric pressure ionization source [atmospheric z-spray pressure chemical ionization or electrospray ionization (ESI) interface]. The mass spectrometer was coupled to an high performance liquid chromatography system consisting of a Waters-2790 separations module (Waters, Milford, MA) including an auto-sampler with refrigerated sample compartment and inline vacuum degasser, and a Waters-2487 dual λ absorbance detector. For optimization of tandem MS conditions, samples were directly and continuously infused into the mass spectrometer. Data were analyzed with MassLynx software (Ver. 3.5). The ESI mass spectrometer was operated in the positive ion mode with a capillary voltage at 1.0 kV. Cone gas (N_2) and desolvation gas (N_2) were maintained at flow rates of 130 and 630 l/h, respectively. The source and the desolvation temperature were set at 100 and 300°C, respectively. Optimum cone voltages were set at 50 V for nbAUDA, 80 V for AUDA, and 100 V for CTU (internal standard). Mass spectra of the precursor ions were obtained by syringe pump infusions at the flow rate of 10 μl/min, while scanning over the range of 50 to 500 m/z at 3 s per scan. Data were acquired in the multichannel analysis mode and continuum mode. Quantitative analysis was performed in the multiple reaction monitoring mode with a dwell time of 600 ms. Ultrapure argon (99.9999%) was used as a collision gas at a pressure of 2.5 mTorr for collision-induced dissociation. An XTerra™MS C18 column (30×2.1 mm ID, 3.5 μm; Waters) was used with a flow rate of 0.3 ml/min at ambient temperature. Chromatographic separation was performed using a two-solvent linear gradient system. Both solvents A (water) and B (acetonitrile) contained 0.1% formic acid. Solvents were filtered through a 0.45-μm membrane and degassed before use. Mobile phases were mixed with a linear gradient from 40% B to 100% B in 5 min and then isocratic for 8 min with 100% B. The column was equilibrated back to the initial conditions for 1 min before the next run. Five microliters of standard and the extracted blood samples were injected onto the column.

Renal function and structure

Blood urea nitrogen (BUN) was assessed in collected blood samples using a commercially available kit (Sigma) as previously used by our laboratory (Jiang et al. 2004). Ten microliters serum were added to a tube and incubated in 37°C water bath for 10 min. At this time, 1 ml phenol nitroprusside solution, 1 ml alkaline hypochlorite solution (6 mM), and 5 ml deionized H_2O were added to each tube. The reaction was allowed to develop at room temperature 30 min before spectrophotometric analysis. Creatinine was also assessed with a commercially available kit (Sigma) as previously used by our laboratory (Jiang et al. 2004). Three hundred microliters of sample were added to a cuvette. To all cuvettes, 3 ml of alkaline picrate solution was added and incubated at room temperature for 10 min. Absorbance was read at 500 nm. After measurement, 0.1 ml acid reagent was added, and the sample was incubated for 5 min at room temperature. Absorbance was then read again at 500 nm; the difference in absorbance before and after acidification correlates with the amount of creatinine.

Kidneys were sliced with a razor blade into four sagittal sections and placed in 4% paraformaldehyde for 24 h. The sections were then rinsed repeatedly

with PBS and placed in 70% ethanol for embedding. Five-micrometer sections from the paraffin-embedded tissues were used for histological evaluation after hematoxylin/eosin staining.

Statistical analysis

Data were expressed as mean±SEM. An analysis of variance was performed, and a Wilcoxon rank sum test was used to assess significant differences between groups ($p<0.05$).

Results

The free acid AUDA and several of its esters inhibit the soluble epoxide hydrolase with IC50s of 2–10 nM. Thus, the *n*-butyl ester can be considered a prodrug for AUDA, which is itself a highly potent sEH inhibitor. Initial pharmacokinetic studies were designed to demonstrate the stability of nbAUDA. As shown in Fig. 1a, nbAUDA is rapidly cleaved to the *n*-butyl ester and AUDA. Subcutaneous administration of nbAUDA is associated with the maintenance

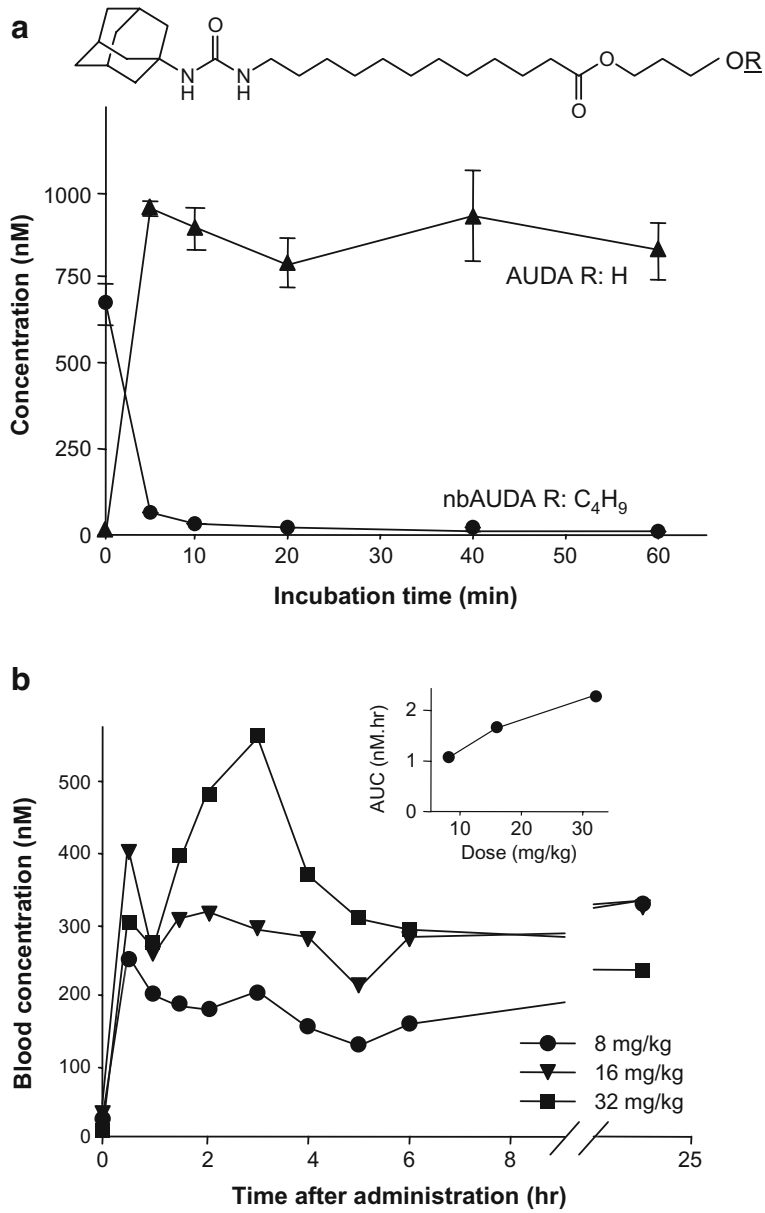

Fig. 1 Metabolic stability and pharmacokinetics of nbAUDA. **a** The stability of nbAUDA in rat hepatic microsomes. nbAUDA is rapidly converted to free AUDA and *n*-butyl alcohol. **b** Pharmacokinetic profiles of the nbAUDA metabolite (*AUDA*) after subcutaneous administration to mice. nbAUDA dissolved in olive oil (oleic-acid-rich triglyceride) was administered subcutaneously to mice and levels measured at the indicated times. *Inset* AUC (area under curve from 0 to 6 h post-treatment) values were calculated by using WinNonlin software

of high concentrations of AUDA over 24 h (Fig. 1b). As shown in the inset, the amount of AUDA reaching the bloodstream, as assessed by area under the curve analysis, increased with injected dose.

To evaluate potential protective effects of nbAUDA on cisplatin-induced renal injury, male C3H mice (25 g) were administered nbAUDA (40 mg/kg) subcutaneously in 96:4 corn oil/DMSO mixture 24 h before cisplatin (20 mg/kg) challenge. The mice were re-administered nbAUDA every 24 h and killed 48, 72, and 96 h after cisplatin challenge. As shown in Fig. 2, nbAUDA administration increased the serum concentration of AUDA at each time point, suggesting that the dosing regimen was successful. The high variability in the cisplatin+nbAUDA most likely reflects alterations in clearance due to impaired renal function. Importantly, nbAUDA significantly attenuated cisplatin-induced nephrotoxicity as assessed by BUN levels (Fig. 3). While the protection afforded by nbAUDA was not complete, cisplatin-induced increases in BUN levels were significantly reduced by nbAUDA at all time points. This effect is independent of vehicle because DMSO+corn oil had no effect on BUN values in control mice or mice challenged with cisplatin. In addition, analysis of serum creatinine at 96 h showed significant protection by nbAUDA (control=0.24±0.04; nbAUDA=0.24±0.04; cisplatin=0.41±0.04; cisplatin+nbAUDA=0.26±002; all values mg/dl, n=6 per group).

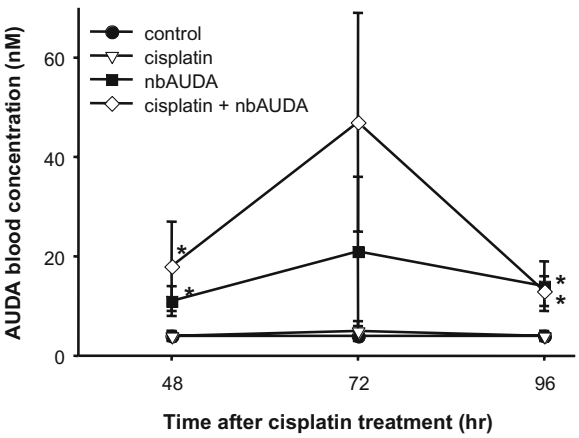

Fig. 2 Blood concentration profiles of AUDA. Mice were administered nbAUDA (40 mg/kg) every 24 h beginning 1 day before cisplatin challenge (20 mg/kg). Mice were harvested 48–96 h after cisplatin challenge, and AUDA concentrations were measured by LC/MS. Each datum point represents the mean± SD of three (control) or six (treated) animals; *Asterisk* indicates a significant difference from control (p<0.05)

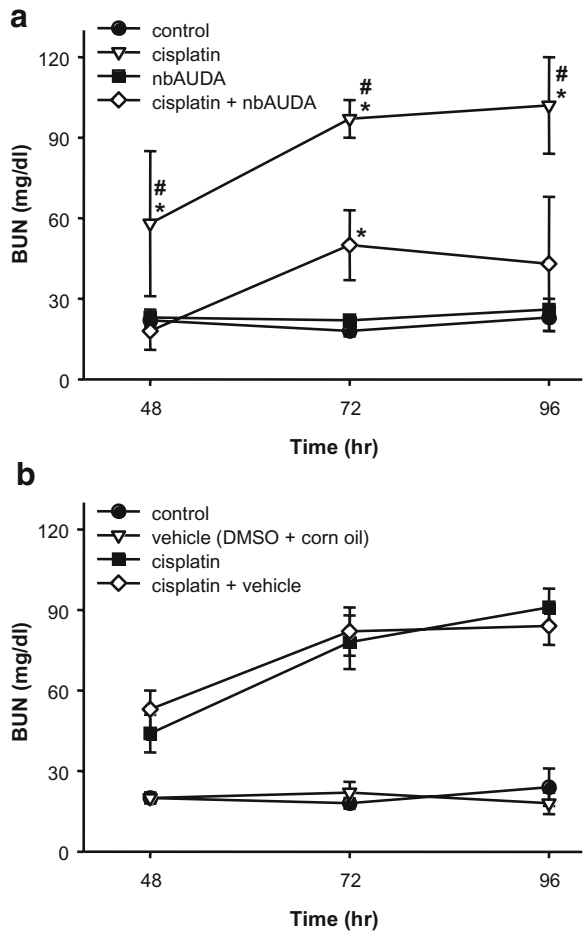

Fig. 3 The impact of nbAUDA on cisplatin-induced increases in BUN. **a** Mice were administered nbAUDA (40 mg/kg) every 24 h beginning 1 day before cisplatin challenge (20 mg/kg). Mice were harvested 48–96 h after cisplatin challenge, and BUN levels were evaluated. Each datum point represents the mean±SD of three (control) or six (treated) animals; *asterisk* indicates a significant difference from control (p<0.05), *number symbol* indicates a significant difference from cisplatin+nbAUDA (p<0.05). Similar results were seen in three independent experiments. **b** Mice were administered DMSO+corn oil as a vehicle control in the absence (control) or presence of 20 mg/kg cisplatin. Mice were harvested at 48, 72, and 96 h for assessment of BUN. Each datum point represents the mean+SD of six animals. Similar results were seen in two independent experiments

The kidneys were also examined by histology. Sections from paraformaldehyde-fixed tissues were stained with hematoxylin and eosin. The sections

were first evaluated at low magnification (×10 objective) to examine the impact of nbAUDA on cisplatin-induced nephrotoxicity. Cisplatin was associated with overt damage to the kidney 96 h after challenge (Fig. 4). Clear evidence of damage is seen in the cortex with damage confined to the tubules. Higher magnification further demonstrates the tubular damage elicited by cisplatin, with the tubular structure almost completely lost, marked by the loss of tubular epithelial cells. However, tubules from nbAUDA/cisplatin mice look remarkably normal. Similar results were seen in four animals from each group and at earlier time points (72 h; data not shown), further supporting the conclusion that nbAUDA affords protection against cisplatin-induced nephrotoxicity.

Discussion

The free acid AUDA and its *n*-butyl ester are both highly potent as inhibitors of the recombinant, affinity-purified murine and human sEHs (Morisseau et al. 1999, 2002). Both compounds are high melting lipophilic solids and thus difficult to formulate. The more polar-free acid can be formulated as a complex with hydroxypropyl beta cyclodextran in water, while the *n*-butyl ester is more lipid soluble and gives sustained blood levels after subcutaneous or intraperitoneal injection in triglyceride. The butyl ester was selected from a set of esters evaluated and used rather than the free acid AUDA because it is more easily formulated in triglyceride for oral, subcutaneous, or

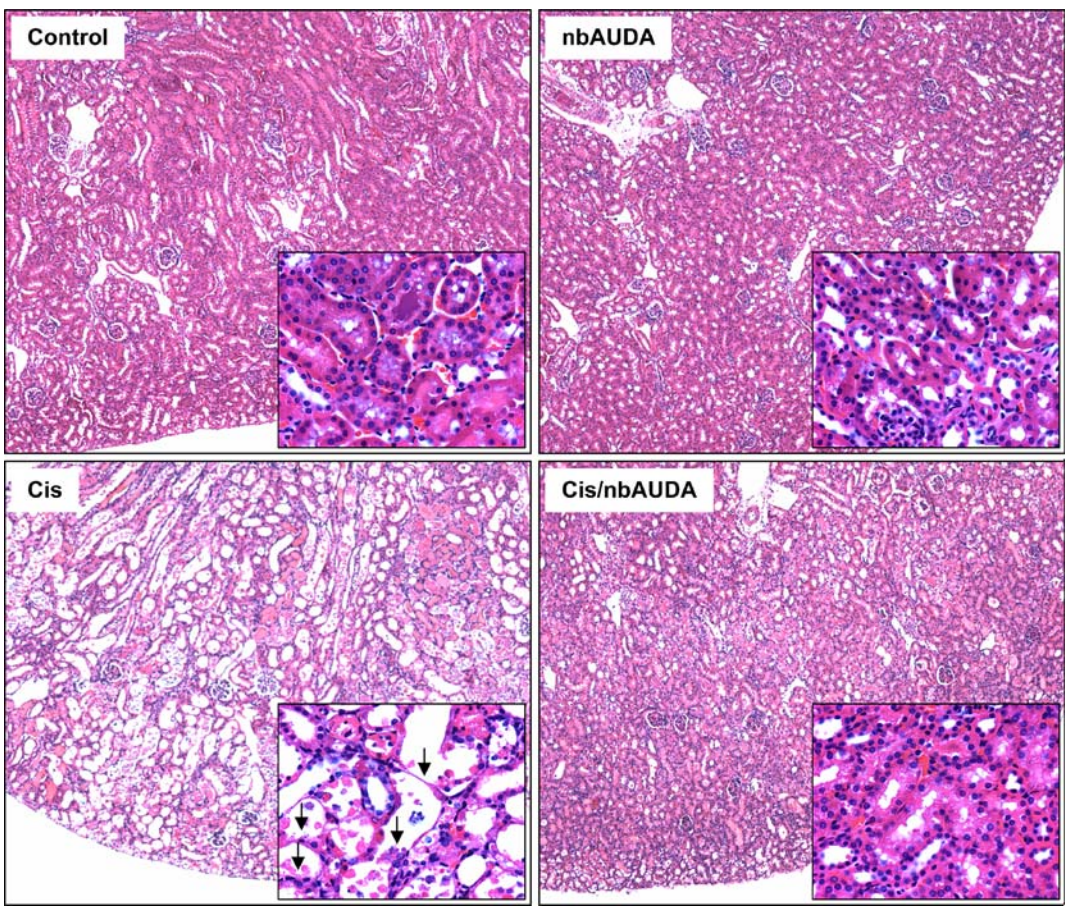

Fig. 4 The impact of nbAUDA on cisplatin-induced renal damage. Mice were administered nbAUDA (40 mg/kg) every 24 h beginning 1 day before cisplatin challenge (20 mg/kg). Mice were harvested 96 h after cisplatin challenge, and histological evaluation was performed in a blinded fashion. Cisplatin is associated with significant damage to the tubules, while nbAUDA affords remarkable protection. *Arrows* demonstrate areas of detachment of tubular epithelial cells from the basement membrane. The width of the field is 870 μm; 220 μm for the insets

intraperitoneal injection or formulated in a wax bead for a sustained release formulation (Kim et al. 2007). Once the compounds are in solution, the *n*-butyl ester is rapidly hydrolyzed, and the free acid undergoes rapid beta oxidation to shorter side chains of reduced inhibitory activity. In these studies, nbAUDA was effective in attenuating cisplatin-induced renal injury; the protective effect of AUDA was marginal and highly variable (data not shown). Although both AUDA and its butyl ester have been found to be effective in vivo in other systems (Smith et al. 2005; Schmelzer et al. 2005; Liu et al. 2005; Inceoglu et al. 2006; Schmelzer et al. 2006; Xu et al. 2006), it is not surprising that the free acid is less effective under conditions where it needs to be continually available to protect the kidney.

Using a combination of in vitro and in vivo models, many mechanisms of cisplatin nephrotoxicity have been elucidated. A role for organic cation transport in the accumulation of cisplatin has been demonstrated (Ludwig and Oberleithner 2004) as well as the contributions of γ-glutamyl transpeptidase and metabolism by proximal tubular epithelial cells in nephrotoxicty (Hannigan and Devarajan 2003). Both oxidative stress (Chirino et al. 2008) and nitric oxide (Chirino et al. 2007) have been implicated in the nephrotoxicity of cisplatin. Elegant studies have identified many of the molecular pathways that are involved in cisplatin toxicity, including cAMP response element binding-mediated transcription (Arany et al. 2008), p53-mediated regulation of caspases (Yang et al. 2008), and the PI3K-AKT pathway (Kuwana et al. 2008). Several studies have also focused on gene regulation by cisplatin in the kidney (Huang et al. 2001; Thompson et al. 2004); our finding that inhibition of sEH attenuates cisplatin-induced renal injury is also supported by recent data demonstrating that the same dose of cisplatin induces a 15-fold increase in sEH messenger RNA expression in mice (Hung et al. 2007). However, we hypothesize that the protective effects of sEH inhibition are related to the role of inflammation in cisplatin-induced nephrotoxicity.

The role of inflammation in cisplatin nephrotoxicity is becoming more apparent (Ramesh and Reeves 2002; Jo et al. 2005; Ramesh et al. 2007; Zager et al. 2007). Both the Jun N-terminal kinase (Francescato et al. 2007) and peroxisome proliferator-activated receptor (Li et al. 2005; Lee et al. 2006) pathways have been shown to mediate the production of inflammatory cytokines; interestingly, inhibition of these pathways is protective against cisplatin-induced nephrotoxicity (Lee et al. 2006; Francescato et al. 2007). We hypothesize that the anti-inflammatory effects of sEH inhibition are responsible for the protection against cisplatin-induced nephrotoxicity. Arachidonic acid epoxides (EETs) are endogenous regulators that influence inflammation (Node et al. 1999) and blood pressure (Roman 2002) in the kidney. It has been established that sEH inactivates the anti-hypertensive and anti-inflammatory effects of EETS (Hennig et al. 2002; Imig et al. 2002; Schmelzer et al. 2005; Imig 2008). Therefore, the impact of sEH inhibition on cisplatin-induced inflammation represents a logical approach to future studies and suggests that these inhibitors may be protective against other number of insults responsible for acute kidney injury, given the role of inflammation in this pathophysiology (Bonventre 2007). Taken together, our data demonstrate that sEH inhibitors represent a novel approach to attenuating cisplatin-induced acute kidney injury.

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