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Hepatotoxicity, nephrotoxicity, and drug/chemical interaction toxicity of platinum nanoparticles in mice

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Nanomaterials are frequently used in microelectronics, cosmetics, and sunscreens. Platinum reagents are commonly used in disease diagnosis, cosmetics, and the food industry. Although research into the development of nanomaterial-based drug delivery systems has yielded promising results, the toxicity of these materials is not fully understood. We investigated the toxicity and drug interactions of 1- and 8-nm diameter platinum nanoparticles (nPt1 and nPt8, respectively) in mice. Acute hepato-renal toxicity of intravenously administered platinum nanoparticles was evaluated biochemically and histologically. Dose-dependent increases in serum markers of hepato-renal function (serum aminotransferases and blood urea nitrogen) were observed following administration of nPt1, whereas nPt8 had no effect, even at 20 mg/kg. Moreover, nPt1 induced interleukin (IL)-6 and IL-1β production 3 and 6 hours after administration. The effect of nPts on drug-induced toxicity was evaluated in mice injected intraperitoneally with carbon tetrachloride or cisplatin, with or without intravenous administration of platinum nanoparticles. All treatments in the absence of nanoparticles were non-lethal and resulted in moderate toxicity. However, exacerbated toxicity was observed in mice injected with carbon tetrachloride or cisplatin together with nPt1, but not in mice co-injected with nPt8. We found that nPt1 cause hepato-renal damage, and the effect is enhanced by chemical inducers of hepatotoxicity and nephrotoxicity. This is the first report demonstrating that nPt1 not only are hepatotoxic and nephrotoxic but also exacerbate drug toxicity. These findings will be useful for future nanotechnology and nanoscience research.

1. Introduction

The number of products containing nanoparticles and nanomaterials has increased rapidly in recent years. Nanomaterials are frequently used in microelectronics, cosmetics, and sunscreens, and their potential use in drug-delivery systems is also being investigated (Garcia et al. 2007; Caputo et al. 2008; Nohynek et al. 2008). Nanomaterials are typically defined as engineered structures with a size of ≤100 nm in at least one dimension. The smaller size of nanomaterials provides a larger surface area compared with micro-sized materials, and the smaller size, chemical composition, surface structures, solubility, and shapes of nanomaterials impart unique physicochemical properties. Although the large surface area of nanomaterials may be advantageous in some applications, it can result in increased interactions with biological tissues, cells, proteins, and nucleic acids, leading to toxic effects in humans (Oberdorster et al. 2005; Nel et al. 2006; Service 2007). In humans, exposure to nanomaterials is generally accompanied by exposure to other potentially toxic substances, such as dust, food additives, and pharmaceutical agents.

Chemically, platinum is very stable and exhibits high catalytic activity (Wu and Yang 2013). Platinum is used in many products, including industrial catalysts, battery electrodes, electrical appliances, and jewelry (Nawa et al. 1986; Dubiella-Jackowska et al. 2009). The catalytic properties of platinum increase with increasing surface area (Janbey et al. 2003), and so the synthesis of platinum nanoparticles has been the subject of extensive research (Skrabalak and Xia 2009). Platinum-based nanoparticles exhibit excellent antibacterial and antiviral activity, as well as high antioxidant capacity (Sakaue et al. 2010; Tseng et al. 2013). As such, platinum nanoparticles are used in a continually increasing number of products, such as cosmetics, supplements, and fiber products (Horie et al. 2011; Shiraishi et al. 2011). Platinum nanoparticles with a particle diameter of 10 nm are potentially very useful due to their reported antioxidant properties (Kajita et al. 2007; Watanabe et al. 2009). However, very little is known regarding the toxicity and/or potential drug interactions of nanoparticles, particularly platinum nanoparticles.

The field of nano-toxicology has expanded recently as researchers have explored the safety, pharmacology, and pharmacokinetics of nanoparticles. Silica nanoparticles were shown to be cytotoxic, hepatotoxic, and to cause placental injury (Nishimori et al. 2009; Yamashita et al. 2011). Carbon nanotubes reportedly induce mesothelioma of the lung (Park et al. 2011). In addition, the pharmacologic effects resulting from the interaction of nanoparticles with drugs are generally unknown. In the present study, we investigated the toxicity of 1- and 8-nm diameter platinum nanoparticles (nPt1 and nPt8, respectively) in mice and examined whether these nanoparticles synergistically exacerbate the toxicity of chemicals such as carbon tetrachloride (a well-known hepatotoxic reagent) (Weber et al. 2003) or drugs such as cisplatin (a widely used anti-tumor agent) (Ozols and Young 1991; Witjes 1997). Platinum nanoparticles were administered to mice to investigate their safety in mammals; in addition, their safety and interactions when co-administered with drugs and other chemical compounds were also examined.

Abbreviations:
nPt1, 1-nm platinum particles; nPt8, 8-nm platinum particles; CDDP, cisplatin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen

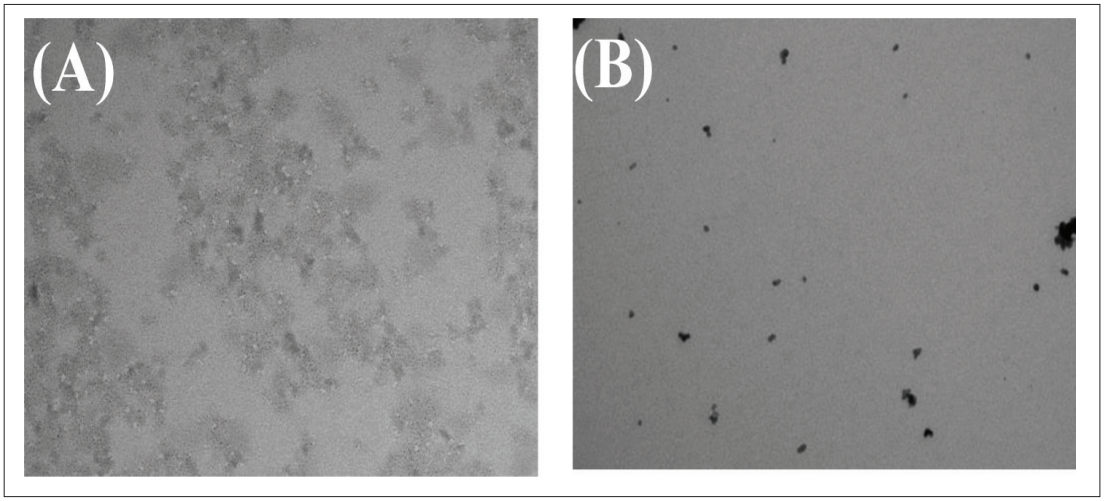

Fig. 1: Ultrastructure of platinum nanoparticles. Electron micrographs of nPt1 (A) and nPt8 (B) nanoparticles.

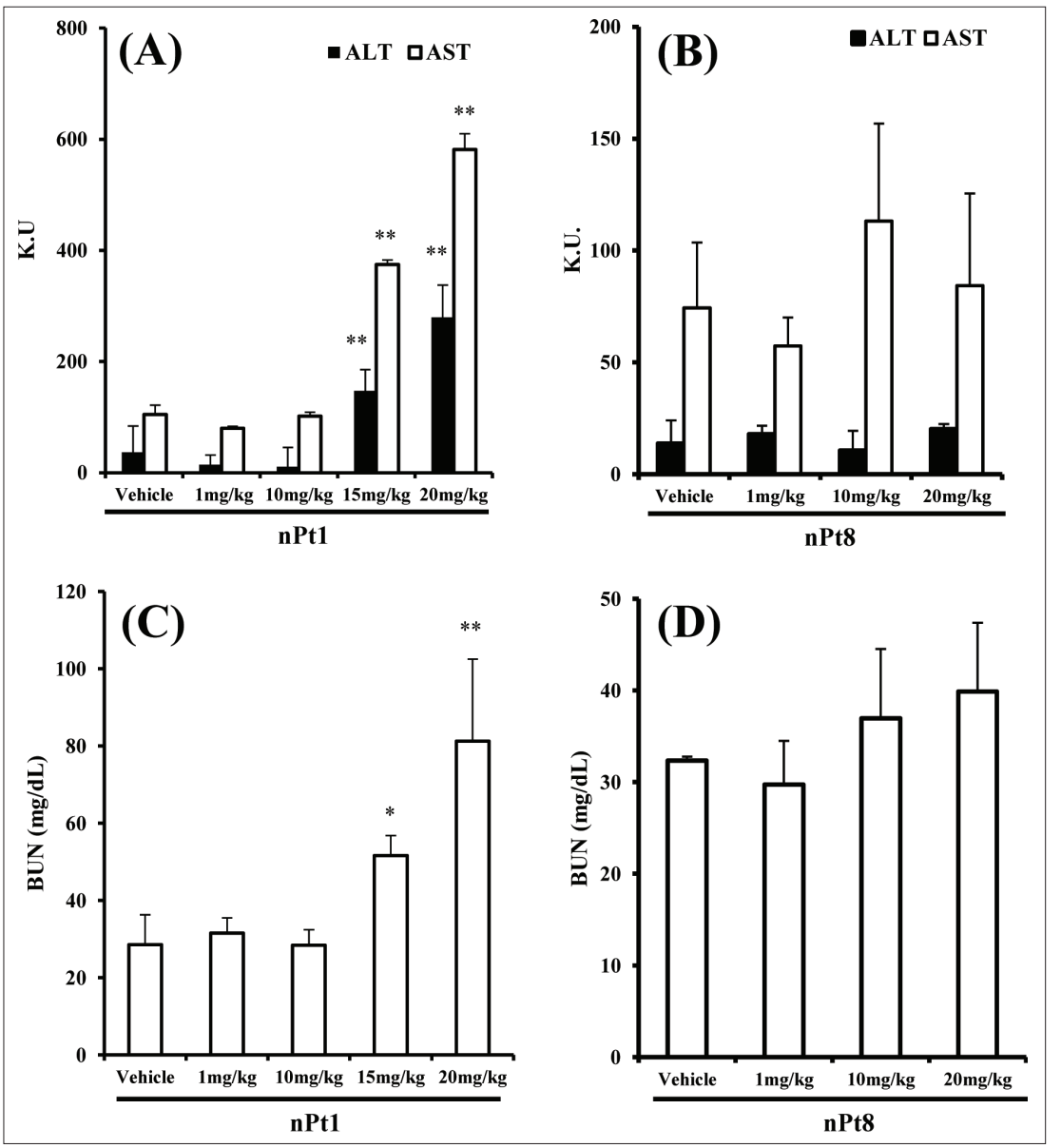

Fig. 2: Dose dependency of nPt1- and nPt8-induced liver and kidney injury. Serum levels of the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) as well as blood urea nitrogen (BUN) were determined using commercially available kits (see '4.6. Biochemical analyses' section) 24 h after i.v. administration of nPt1 (A and C) or nPt8 (B and D) nanoparticles at the indicated doses. Data are presented as mean ± standard error of the mean (S.E.M.; n=4). Significant difference (*$P < 0.05$; **$P < 0.01$) compared with the vehicle-treated group.

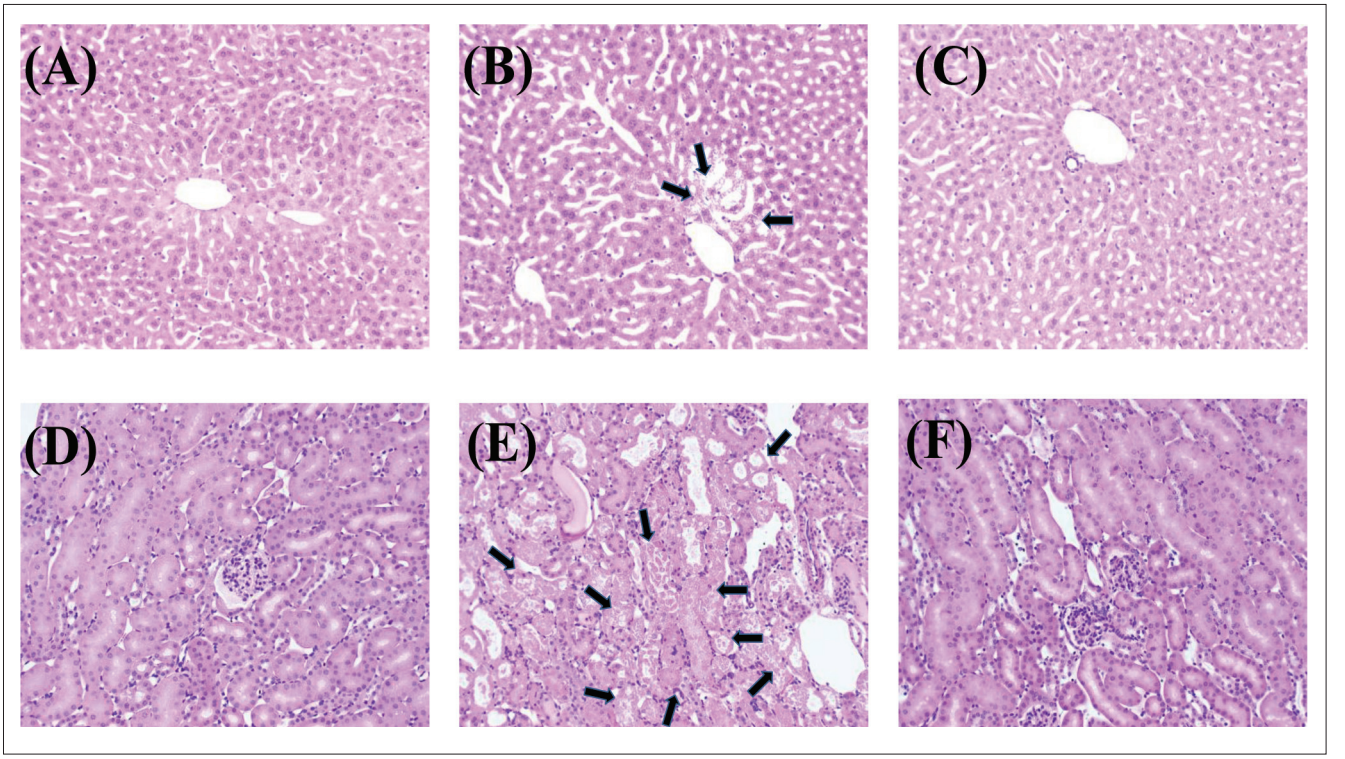

Fig. 3: Histologic analysis of liver and kidney tissues from platinum nanoparticle–treated mice. At 24 h after i.v. administration of vehicle (A and B), nPt1 nanoparticles (C and D), or nPt8 nanoparticles (E and F), tissues were collected, fixed with 4% paraformaldehyde, sectioned, and stained with hematoxylin and eosin. Liver sections (A, B, C) and kidney sections (D, E, F). Arrows designate sites of liver or kidney injury.

2. Investigations and results

2.1. Platinum nanoparticles cause acute hepato-renal injury

We first measured the particle sizes of the platinum nanoparticles using a Zetasizer (Sysmex Co.) and then observed them using transmission electron microscopy. The mean diameters of the nPt1 and nPt8 nanoparticles were 1.11±0.88 and 8.9±8.1 nm, respectively. Furthermore, the electron microscopic images confirmed that the platinum nanoparticles did not aggregate (Fig. 1A, B).

We examined the mice for signs of hepato-renal injury following i.v. administration of nPt1 and nPt8 at concentrations of up to 20 mg/kg. Significant increases in the levels of AST, ALT, and BUN were observed in mice administered nPt1 at doses of 15 and 20 mg/kg (Fig. 2A, C). ALT and AST in mice treated with nPts at a dose of 20 mg/kg increased 7.6- and 5.6-fold, respectively, compared with the vehicle control group. In addition, the BUN level increased 2.8-fold. In contrast, increased levels of markers indicative of hepato-renal injury were not observed in mice administered nPt8 even at the maximum dose (20 mg/kg) (Fig. 2B, D). On histologic evaluation, nPt1-treated mice exhibited lesions indicating of hepato-renal injury; such signs were not observed in nPt8-treated mice (Fig. 3). nPt1 administration resulted in necrosis of hepatocytes and of renal tubular epithelial cells, and urine casts in the kidney were observed (Fig. 3B, E). These data demonstrate that nPt1 cause more severe acute hepato-renal injury than nPt8.

2.2. Cause of platinum nanoparticle–associated hepato-renal injury

We examined the time course of acute hepato-renal injury resulting from nPt1 administration. Maximal ALT and AST levels were observed 24 h after administration and then rapidly recovered by 48 h (Fig. 4A). In contrast, in nPt1-treated mice, the maximal BUN level was observed at 48 h after administration (Fig. 4B). Next, in order to examine the cause of the observed hepato-renal injury in nPt1-treated mice, we measured serum levels of the cytokines IL-6 and IL-1β. Serum IL-6 levels increased significantly 3 h after nPt1 administration (Fig. 5A). Significantly increased IL-1β levels were also observed at both 3 and 6 h after nPt1 administration (Fig. 5B). Neither tumor necrosis factor-α nor interferon-γ could be detected in the serum of the same mice (data not shown).

2.3. Interaction of platinum nanoparticles with carbon tetrachloride

The potential for interaction between nPts and chemical substances was evaluated using carbon tetrachloride. To avoid potential interactions between the test chemical and nPts prior to administration and absorption, carbon tetrachloride was injected intraperitoneally and the nPts were injected intravenously. Carbon tetrachloride was administered to mice at a dose that does not induce hepatic injury (0.01 mL/kg) (Fig. 6A, B). Co-administration of carbon tetrachloride and nPt1/8 caused severe toxicity, with nPt1 causing the most severe toxicity. Co-administration of carbon tetrachloride and nPt1 nanoparticles resulted in increased ALT and AST levels (Fig. 6A, B).

2.4. Interaction of platinum nanoparticles with cisplatin

We next investigated the potential for interaction between nPts and the widely used anti-tumor drug cisplatin. No increases in ALT or AST levels were observed with co-administration of cisplatin (100 μmol/kg) and nPt8. However, co-administration with nPt1 resulted in synergistic elevation of serum ALT levels from 34.7 to 284.3 KU (Fig. 7A), serum AST levels from 193.4 to 578 KU (Fig. 7B), and serum BUN levels from 17.9 to 87.9 mg/dL (Fig. 7C).

2.5. Cause of co-administration–associated hepato-renal injury

Next, to identify the cause of hepato-renal injury associated with co-administration of nPt1 and carbon tetrachloride or cisplatin, we determined levels of the oxidative stress marker 8-OHdG, which provides an indication of DNA damage caused by reactive oxygen species (ROS). As shown in Fig. 8, co-administration of nPt1 (1

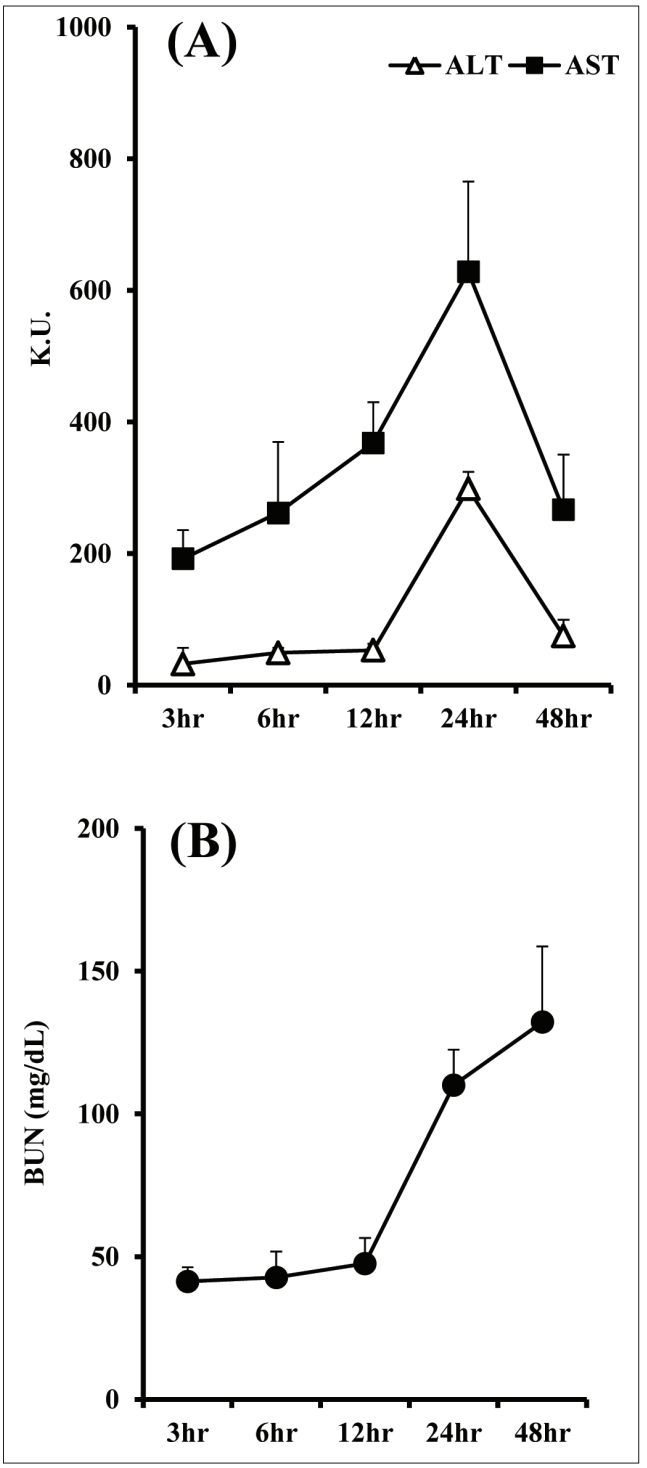

Fig. 4: Time course of sPt1-associated toxicity. Mice were intravenously injected with nPt1 nanoparticles at a dose of 20 mg/kg. Blood was recovered at 3, 6, 12, 24, and 48 h after injection. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (A) and blood urea nitrogen (BUN) (B) were measured using commercially available kits, as described in the '4.6. Biochemical analyses' section. Data are mean ± standard error (S.E.; n=4).

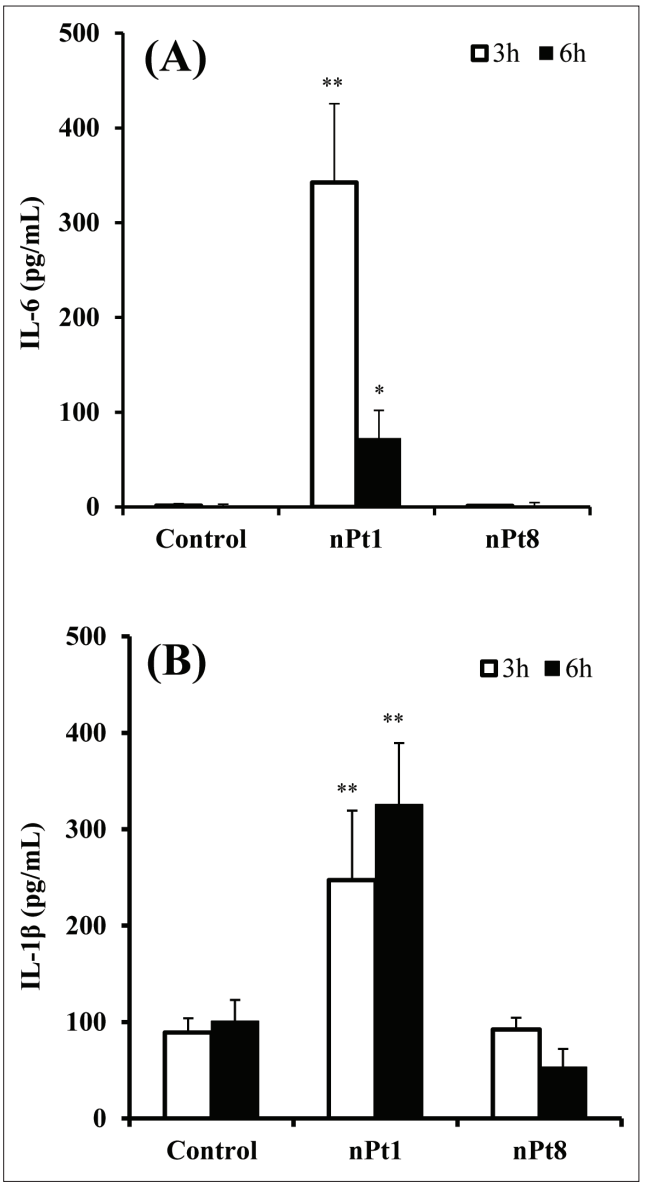

Fig. 5: Changes in serum interleukin (IL)-6 (A) and IL-1β (B) levels, as measured by ELISA. Mice received an i.v. injection of nPt1 or nPt8 nanoparticles. Cytokine levels were measured 3 and 6 h after administration. Values are the mean ± standard error (S.E.; n=4). $*P < 0.05$ or $**P < 0.01$ compared with vehicle-treated controls.

mg/kg) with carbon tetrachloride (0.01 mL/kg) or cisplatin (100 µmol/kg) led to elevated serum 8-OHdG levels. 8-OHdG levels were more than 6-fold higher with co-administration compared with administration alone (Fig. 8).

3. Discussion

This study examined hepato-renal injury in mice resulting from the administration of nPt1 and nPt8 alone or in combination with CCl_4 or cisplatin. We found that nPt1 induce hepato-renal injury alone and as a result of interaction with carbon tetrachloride or cisplatin. No hepato-renal injury was noted in mice treated with nPt8.

The nPt1 induced hepato-renal injury in mice at a dose as low as 15 mg/kg (Fig. 1A, C), whereas the nPt8 nanoparticles did not exhibit cytotoxicity even at a dose of 20 mg/kg (Fig. 1B, D). Previously, we reported that silica nanoparticles induce hepatotoxicity in a particle size–dependent manner (Isoda et al. 2013). Separately, Hirai et al. (2011) reported that silica nanoparticles with a diameter of 100 nm or less exhibit size-dependent immunomodulatory effects. Moreover, Inoue et al. (2011) reported that 14-nm diameter carbon black nanoparticles cause more severe acute lung injury than 56-nm diameter carbon black nanoparticles. These data, in conjunction with our results showing that smaller-diameter nPts induce hepato-renal injury while larger-diameter platinum nanoparticles do not, suggest that there is a strong correlation between hepato-renal injury and nanoparticle size. More detailed examinations are needed to clarify this relationship.

Our results indicate that hepato-renal injury resulting from administration of nPt1 is mediated by IL-6 and IL-1β, which is in agreement

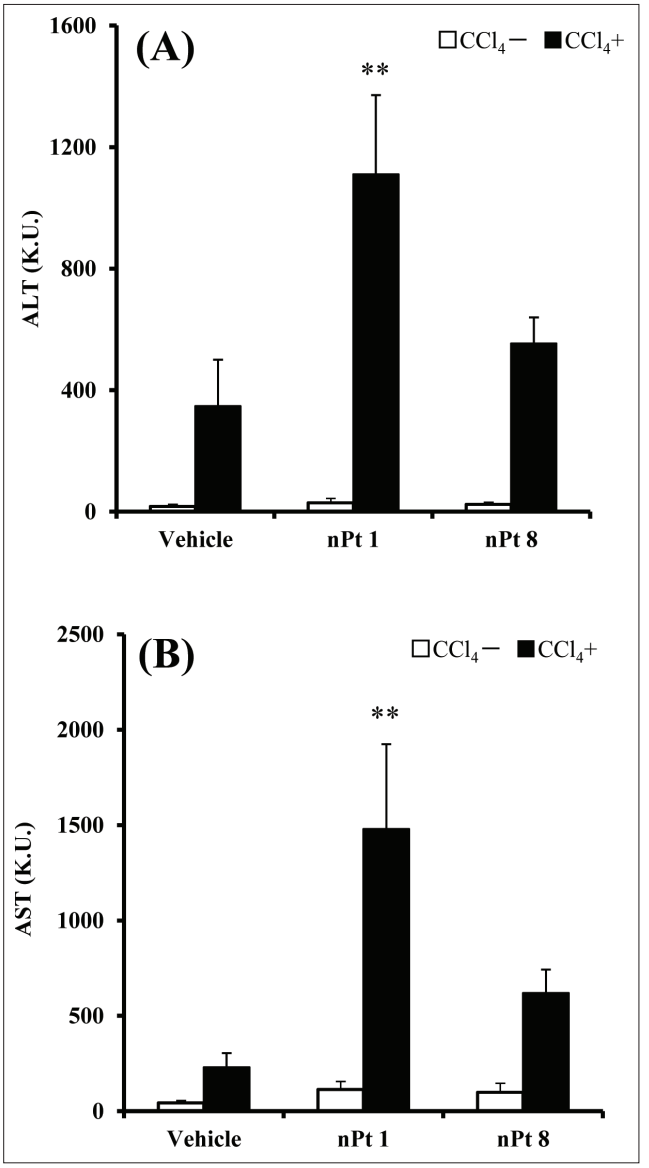

Fig. 6: Effect of nPt1 nanoparticles on carbon tetrachloride (CCl_4)-induced toxicity. Mice were injected intraperitoneally with CCl_4 at 0 (open bars) or 0.01 mL/kg (solid bars) together with i.v. injection of vehicle or platinum nanoparticles (5 mg/kg). At 24-h post-injection, serum levels of the liver enzymes alanine aminotransferase (ALT; panel A) and aspartate aminotransferase (AST; panel B) were determined using commercially available kits (see '4.6. Biochemical analyses' section). Data are representative of three independent experiments and are presented as mean ± standard error of the mean (S.E.M.; n=4). Significant difference (**$P < 0.01$) between vehicle- and CCl_4-treated groups.

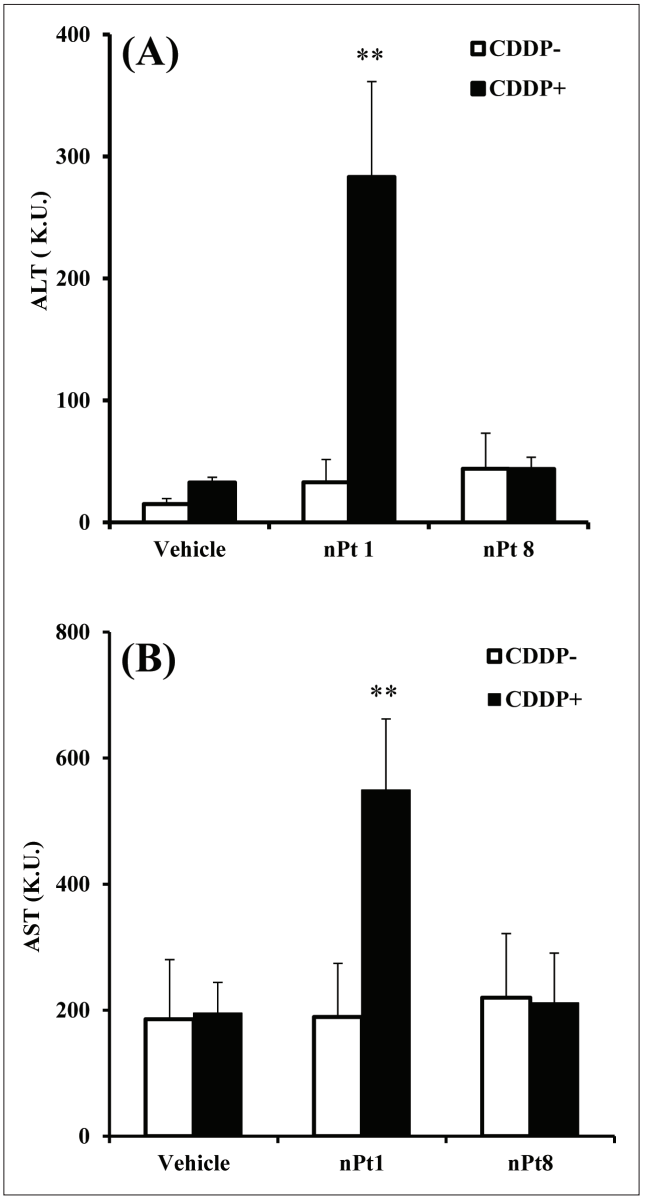

Fig. 7: Effect of nPt1 nanoparticles on cisplatin-induced toxicity. Mice were injected intraperitoneally with cisplatin (CDDP) at 0 (open bars) or 100 µmol/kg (solid bars) together with i.v. injection of vehicle or platinum nanoparticles (5 mg/kg). At 24-h post-injection, serum levels of the liver enzymes alanine aminotransferase (ALT; panel A) and aspartate aminotransferase (AST; panel B) and plasma levels of blood urea nitrogen (BUN; panel C) were determined using commercially available kits (see '4.6. Biochemical analyses' section). Data are presented as mean ± standard error of the mean (S.E.M.; n=4). Significant difference (*$P < 0.05$) between vehicle- and CDDP-treated groups.

than 56-nm diameter carbon black nanoparticles. These data, in conjunction with our results showing that smaller-diameter nPts induce hepato-renal injury while larger-diameter platinum nanoparticles do not, suggest that there is a strong correlation between hepato-renal injury and nanoparticle size. More detailed examinations are needed to clarify this relationship.

Our results indicate that hepato-renal injury resulting from administration of nPt1 is mediated by IL-6 and IL-1β, which is in agreement with previous reports indicating that IL-6 is involved in liver injury. Cao et al. (1998) reported that IL-6 is involved in concanavalin A–induced acute liver failure. In addition, IL-1β is reportedly involved in the induction of renal failure (Berry and Clatworthy 2012; Nakamura et al. 2012). This suggests that in mice treated with nPt1, liver injury is associated with IL-6 and kidney injury with IL-1β. Our data indicate that nPt1 induce increased expression of IL-6 and IL-1β, but the mechanisms through which these cytokines induce cytotoxicity in cells is unknown. Bauza et al. (2012) reported that IL-6 causes liver injury by inducing the expression of particular transcription factors in hepatocytes. We considered the involvement of cell-specific transcription factors in IL-6–induced liver injury. We believe that it will be necessary to examine the mechanism of platinum nanoparticle–associated cytotoxicity in more detail.

We co-administered platinum nanoparticles with carbon tetrachloride or cisplatin and examined the effect on the liver and kidneys. Carbon tetrachloride is widely known as a compound that damages the liver, whereas cisplatin is used globally as an anti-cancer agent. Because nanoparticles reportedly enhance the production of ROS, we also examined the interaction of nPts with carbon tetrachloride or cisplatin (Wu et al. 1999). Liver injury associated with carbon tetrachloride administration was more severe in mice co-administered nPts (Fig. 6). Both liver and kidney injury associated with cisplatin were exacerbated due to

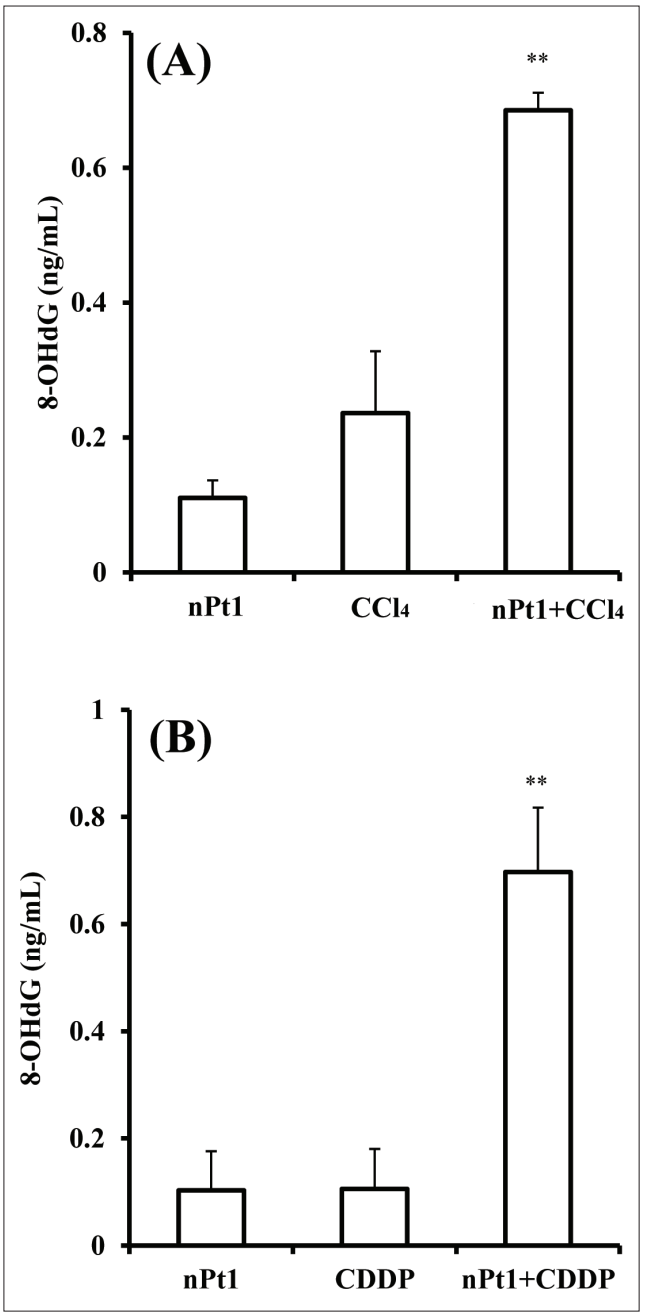

Fig. 8: Changes in 8-OHdG levels as measured by ELISA. Mice were injected intraperitoneally with carbon tetrachloride (CCl_4) at 0.01 mL/kg (A) or cisplatin (CDDP) at 100 µmol/kg (B) together with i.v. injection of vehicle or platinum nanoparticles (5 mg/kg). At 24-h post-injection, serum levels of 8-OHdG were determined using a commercially available kit (see '4.6. Biochemical analyses' section). Data are representative of three independent experiments and are presented as mean ± standard error of the mean (S.E.M.; n=4). Significant difference (**$P < 0.01$) between vehicle- and CCl_4- or CDDP-treated groups.

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4. Experimental

4.1. Materials

Platinum nanoparticles with diameters of 1 or 8 nm (nPt1 and nPt8, respectively) were obtained from Polytech & Net GmbH (Rostock, Germany). The size distribution of the particles, as analyzed using a Zetasizer (Sysmex Co., Kobe, Japan), indicated mean diameters of 1.6 and 8.9 nm, respectively. Both nPt1 and nPt8, which were spherical and nonporous, were formulated and stored at a concentration of 5 mg/mL in aqueous suspension. Prior to administration, the suspensions were thoroughly dispersed by sonication and then diluted with water. Identical volumes of suspension were injected in each experiment. The geometric sizes of the particles were characterized using a TEM JEOL JEM-1011 transmission electron microscope. Carbon tetrachloride (Wako Pure Chemical Industries, Osaka, Japan) was dissolved in olive oil. Cisplatin (Wako Pure Chemical Industries) was dissolved in saline and stored at −20 ºC until use. All reagents were research grade.

4.2. Animals

Eight-week-old BALB/c male mice were purchased from Funabashi Farm Co., Ltd. (Chiba, Japan). Animals were maintained in a controlled environment (temperature: 23±1.5 ºC; light: 12-h light/dark cycle) with free access to standard rodent chow and water. The mice were given 1 week to acclimate before the experiments were conducted. The experimental protocols conformed to the ethical guidelines of the Teikyo Heisei University Graduate School of Pharmaceutical Sciences, compiled from the Guidelines for Animal Experimentation of the Japanese Association for Laboratory Animal Sciences.

4.3. Preparation and administration of the test items

The test item nPt1 was suspended in distilled water for injection and administered intravenously to mice at doses of 1, 10, 15, and 20 mg/kg body weight. nPt8 was prepared similarly and administered intravenously at doses of 1, 10, and 20 mg/kg body weight. Blood was recovered 24 hours after administration.

4.4. Dose dependency of nPt1 and nPt8

nPt1 was administered to mice intravenously at a dose of 20 mg/kg body weight. Blood was recovered 3, 6, 12, 24, and 48 hours after administration, and then the mice were sacrificed (n = 4 for each group).

4.5. Drug interactions of platinum nanoparticles

nPt1 or nPt8 were suspended in water for injection and administered intravenously at a dose of 5 mg/kg body weight; simultaneously, carbon tetrachloride (0.01 mL/kg) or cisplatin (100 µmol/kg) was administered intraperitoneally. Blood was recovered 24 hours after the co-administration. The doses of cisplatin and carbon tetrachloride were previously determined experimentally and did not induce toxicity.

4.6. Biochemical analyses

Serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), and blood urea nitrogen (BUN) were measured using commercially available kits (Wako Pure Chemical Industries) according to the manufacturer's protocols. Briefly, collected serum (10 mL) was combined with 1 mL of color A reagent (including urease) and incubated at 37 ºC for 15 min. Following the addition of 1 mL of color B reagent, the sample was incubated at 37 ºC for 10 min. Absorbance was measured at a wavelength of 570 nm. Interleukin (IL)-1β and IL-6 were analyzed using an enzyme-linked immunosorbent assay (ELISA) kit (BioSource International, CA, USA). Serum 8-hydroxy-2'-deoxyguanosine (8-OHdG) was determined using a Check ELISA kit (Japan Institute for the Control of Aging, Fukuroi, Japan). All analyses were performed in strict accordance with the manufacturer's instructions.

4.7. Histologic analyses

For animals dosed either intravenously or intraperitoneally with snPt1 or snPt8, the kidney and liver were removed at 24 h post-injection and fixed with 4% paraformaldehyde. Thin tissue sections were stained with hematoxylin and eosin for histologic observation.

4.8. Statistical analyses

Statistical analyses were performed with Statcel add-in forms on Excel software, 3rd edition (EMS Publication Co., Ltd., Saitama, Japan). All data are presented as mean ± SEM. Significant differences between control and experimental groups were determined using the Dunnett test; a P value less than 0.05 was considered significant.

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Conflicts of interest: None declared.

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