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Combined toxicity of Fe_3O_4 nanoparticles and cadmium chloride in the liver of mice by oral route

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Abstract: The combined toxicity of Fe_3O_4 nanoparticles (nano-Fe_3O_4) and $CdCl_2$ in the liver of mice was reported. The organ coefficient, histopathological changes, serum biochemical parameters and oxidative stress responses were determined in the liver of mice after oral administration of nano-Fe_3O_4 and/or $CdCl_2$ for 7 d. The results show that nano-Fe_3O_4 and $CdCl_2$ mutually competitively inhibit Fe and Cd uptake in the liver. Oral nano-Fe_3O_4 (50 mg/kg BW) does not induce obvious injury in mice. In contrast, oral $CdCl_2$ (2.0 mg/kg BW) causes signigicant oxidative damage in the liver. Co-administration of nano-Fe_3O_4 with $CdCl_2$ significantly attenuates $CdCl_2$-induced damage in the liver through reduction of oxidative stress. The inhibition of Cd-induced deprivation of tissue Fe and decrease in Cd accumulation after co-administration of nano-Fe_3O_4 with $CdCl_2$ might play two key roles in the protective effect of nano-Fe_3O_4 on $CdCl_2$-induced oxidative damage. Nano-Fe_3O_4 may be used as a perfect MRI contrast agent and drug carrier for patients with Cd poisoning, since it not only acts as an MRI contrast agent or drug carrier, but also simultaneously attenuates Cd-induced toxicity.

Key words: nano-Fe_3O_4; Cd; joint toxicity; liver

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口服纳米四氧化三铁和氯化镉对小鼠肝脏的联合毒性

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摘要:报道了纳米四氧化三铁和氯化镉对小鼠肝脏的联合毒性.在连续7d给小鼠灌胃给药纳米四氧化三铁、氯化镉或二者混合物(纳米四氧化三铁+氯化镉)后,测定了肝脏的脏器系数、组织病理学变化、血清生化参数和氧化应激反应.结果表明,纳米四氧化三铁和氯化镉会竞争性抑制小鼠肝脏对铁和镉的摄取.口服纳米四氧化三铁(50 mg/kg体重)没有对小鼠肝脏产生明显的毒性,而口服氯化镉(2.0 mg/kg体重)对小鼠肝

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脏产生显著的氧化应激损伤. 同时口服纳米四氧化三铁与氯化镉后,纳米四氧化三铁能够显著降低由氯化镉诱导的肝的氧化应激,从而显著减少氯化镉对肝脏的损伤. 同时口服纳米四氧化三铁与氯化镉后,纳米四氧化三铁不仅能显著减少镉在肝脏的积累,而且能抑制由镉引起的肝脏中铁的缺乏,这是纳米四氧化三铁保护肝脏免遭氯化镉诱导氧化损伤的两个关键作用机制. 纳米四氧化三铁可以作为镉中毒患者完美的磁共振造影剂和药物载体,因为它在发挥磁共振造影剂和药物载体功能的同时,可以减少镉的毒性.

关键词: 纳米四氧化三铁; 镉; 联合毒性; 肝

0 Introduction

With the rapid development of nanotechnology over the last decade, nanomaterials with unique physicochemical properties such as high surface area, small size and high reactivity have been used in various fields on a global scale. There is increasing concern about the potential risk of nanomaterials to human health[1]. Among a wide variety of nanomaterials, magnetite iron oxide nanoparticles (MION) have found extensive biomedical applications such as site-specific drug delivery, contrast agents for magnetic resonance imaging (MRI), and hyperthermia[2]. The complementary functions of MION as imaging agents and carriers for drug delivery are of high clinical significance. With the wide applications of MION, much research has been carried out to assess the toxicity of MION, and the results indicate that MION shows low toxicities in vitro and in vivo experiments[3].

Cadmium (Cd) is a ubiquitous contaminant of the natural environment and dietary products[4] and has been recognized as one of the top 20 hazardous substances priority list[5]. The primary sources of cadmium exposure are cigarette smoke, food intake and ambient air, particularly in the vicinity of battery, electroplating, pigment and plastic manufactories[6]. Chronic exposure to Cd results in accumulation of the metal mainly in the liver and kidneys, while acute exposure leads to accumulation of Cd mainly in the liver[7]. When the amount of Cd in the liver and kidneys exceeds the binding capability of metallothionein (MT) that has a high affinity for Cd, the non-MT-bound Cd ions can induce reactive oxygen species (ROS)[8], which results in oxidative deterioration to lipids, proteins and DNA[9]. Chronic Cd exposure is responsible for a wide range of human diseases ranging from cancer, hepatotoxicity to severe kidney failure[10].

With the wide applications of MION and the ubiquitous Cd contamination, it is necessary to identify the synergistic effect of co-exposure to MION and Cd on human health. The development and clinical application of MION as an MRI agent and carrier for drug delivery has increased the interest for evaluation of the synergistic toxicity of co-exposure to MION and Cd. Such an investigation is critically important for the application of Fe_3O_4 nanoparticles (nano-Fe_3O_4) in clinical diagnosis and therapy of Cd poisoning. MION are suitable candidates as oral delivery of therapeutic agents and MRI contrast agents for the diseases of the gastrointestinal tract organs[11]. The oral route is one of the main entry portals for nanomaterials and Cd into the body. Herein, we investigated the synergistic acute toxicity of nano-Fe_3O_4 and cadmium chloride in mice by oral route. The results indicate that the co-exposure to nano-Fe_3O_4 and Cd has a negative cooperative effect on the biodistribution of both Fe and Cd, and that nano-Fe_3O_4 is able to protect against the $CdCl_2$-induced liver injury in mice. Therefore, nano-Fe_3O_4 may be used as an ideal MRI contrast agent for patients with Cd poisoning.

1 Experimental

1.1 Materials

Nano-Fe_3O_4 and bovine serum albumin were purchased from Sigma-Aldrich (St Louis, MO, USA). Nano-Fe_3O_4 was characterized by

transmission electron microscopy (JEM-2010, JEOL Ltd, Japan). $CdCl_2$ and nitric acid (ultrapure grade) were purchased from Shanghai Chemical Reagent Co. Ltd. (Shanghai, China). All other reagents used were of analytical grade from commercial sources.

1.2 Animals and treatment

6～8 week old male Kun Ming mice (21g±2g, Animal Center of Anhui Medical University) were housed in polycarbonate cages with filter tops under standard conditions (22℃ ± 2℃; relative humidity at 55% ± 5%; 12 h light/dark cycle). Distilled water and sterilized food for mice were available ad libitum. They were acclimated to the environment for 5 d prior to dosing. All experiments were conducted in accordance with the guidelines of the University of Science and Technology of China for the care and use of laboratory animals. Mice were randomly divided into four groups with 8 male mice in each group: control group (treated with saline) and three experimental groups (50 mg/kg BW nano-Fe_3O_4, 2.0 mg/kg BW $CdCl_2$, 50 mg/kg BW nano-Fe_3O_4 + 2.0 mg/kg BW $CdCl_2$). We chose to work with the doses of $CdCl_2$ (2.0 mg/kg BW) that was suggested by Jurczuk et al.[12] and Jin et al.[13], and nano-Fe_3O_4 (50 mg/kg BW) that was suggested by the OECD guidelines 420[14]. Before treatment, animals were fasted overnight. Nano-Fe_3O_4 and $CdCl_2$ were suspended into physiological saline, respectively. The suspensions were sonicated for 25 min at 60 W (KQ 3200 ultrasonic cleaner, Kunshan Ultrasonic Instrument Co., Ltd.). Chemicals were administered to mice by intragastric feeding respectively, once a day for 7 consecutive days. For co-administration, nano-Fe_3O_4 were administered 2h before the administration of $CdCl_2$. The symptom and mortality were observed and recorded carefully every day. After the last oral administration, the mice were fasted overnight. After anaesthetization with ether, the blood samples were collected, and then the mice were sacrificed by cervical dislocation. The livers were excised, washed thoroughly with 95% saline, weighed and stored at -80℃. The coefficient of liver to body weight was calculated as the ratio of organ (wet weight, mg) to body weight (g).

1.3 Fe and Cd content analysis

The liver tissues (0.1～0.3 g) were weighed and digested with ultrapure nitric acid overnight, respectively. Then the solutions were heated at 120℃ to remove the remaining nitric acid until they were colorless and clear. Finally, the remaining solutions were diluted to 5 mL with 2 % nitric acid. The Fe and Cd concentrations in sample solutions were determined by inductively coupled plasma-atomic emission spectrometry (ICP-AES) (Perkin Elmer Corporation, USA). Data were expressed as micrograms per gram fresh tissue.

1.4 Biochemical parameter assay of serum

Liver function was evaluated with serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin (TBIL). All serum biochemical parameters were determined by commercial kits (Roche Ltd., Switzerland) using biochemical autoanalyzer (Roche Modular DPP, Roche Ltd., Switzerland).

1.5 Measurement of oxidative stress makers

The liver tissues were assayed for the oxidative biomarkers by the conventional methods as described previously[15]. The activities of glutathione peroxidase (GPx), superoxide dismutase (SOD), and the level of lipid peroxidation product malondialdehyde (MDA) were determined using commercial kits (Nanjing Jiancheng Bioeng Inst., Nanjing, China) following the manufacturer's protocol.

1.6 Histopathological examination

For pathological studies, all histopathological examinations were performed using standard laboratory procedures. The tissues of liver were

sampled, immobilized in 10% formaldehyde solution, embedded in paraffin blocks, sliced into 5 mm in thickness and placed onto glass slides. After hematoxylin-eosin (HE) staining, the slides were observed and the photos were taken using optical microscope (Nikon U-III Multi-point Sensor System, USA).

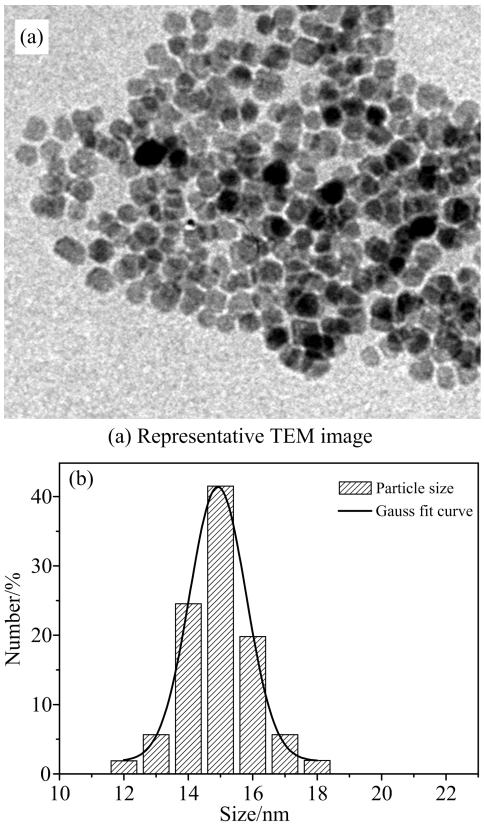
1.7 Statistical analysis

All results were expressed as means ± SD. Data were analyzed using one-way analysis of variance (ANOVA). Differences were considered significant when $p<0.05$.

2 Results

2.1 Characterization of nano-Fe_3O_4

The size and morphology of nano-Fe_3O_4 were characterized by TEM (Fig. 1). The TEM image of nano-Fe_3O_4 revealed that the particles had an approximately spherical morphology with an average size of about 15.0 nm± 0.5 nm.



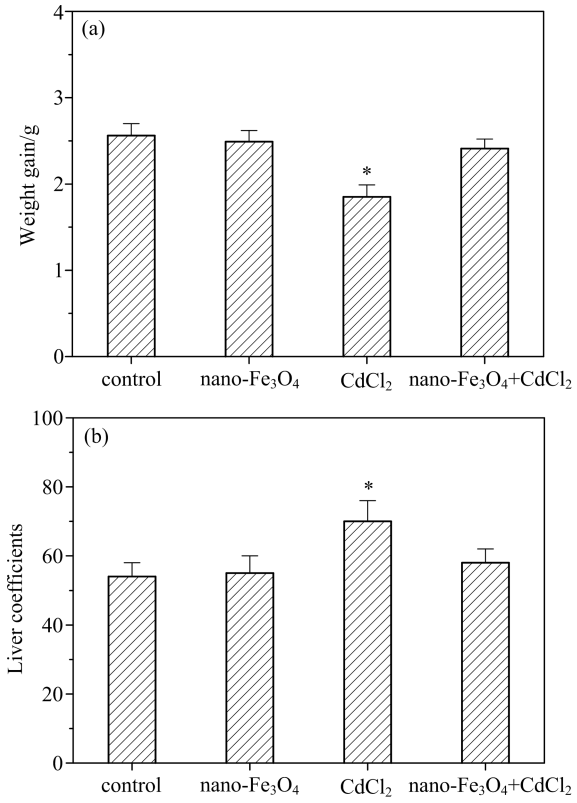
(a) Representative TEM image

(b) size distribution profile

Fig. 1 TEM image of nano-Fe_3O_4 with a mean size of 15.0nm±0.5 nm

2.2 Effects of co-administration on coefficient of liver

During the whole exposure, the mice were all at a growth state. The daily behavior such as eating, drinking and activity in the nano-Fe_3O_4 group and the nano-Fe_3O_4 + $CdCl_2$ group were as normal as the control group, while the mice treated with $CdCl_2$ alone exhibited passive behaviors such as unwillingness to move and depression after oral administration. Fig. 2 showed the net weight increase and the coefficient of the liver to the body weight. No obvious differences were found in net weight increase between the control and nano-Fe_3O_4 groups, whereas the net weight increase in the $CdCl_2$ group was significantly reduced ($p<0.05$) compared with that of the control. Interestingly, the net weight increase in the nano-Fe_3O_4 + $CdCl_2$ group was similar to the control. These results suggested that $CdCl_2$ obviously slowed down the growth of mice and nano-Fe_3O_4 significantly alleviated the harmful effect of $CdCl_2$.

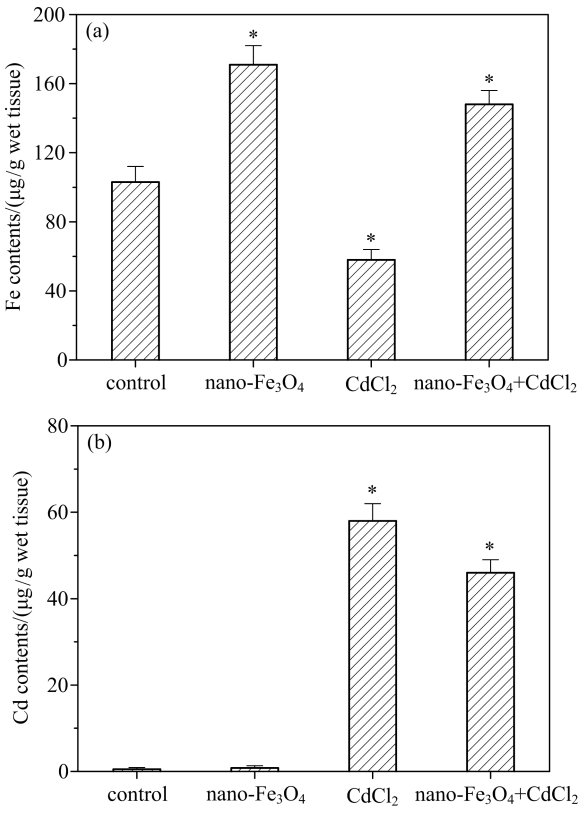


Data were shown as mean±SD, $n = 6$. * $p < 0.05$ *versus* the control

Fig. 2 The weight gain (a) and the liver coefficients (b) of mice after 7 d oral administration of nano-Fe_3O_4

2.3 Fe and Cd content analysis

Fig. 3 showed the contents of Fe and Cd in the liver of mice. Oral nano-Fe_3O_4 resulted in a significant increase in Fe content in the liver. In contrast, oral $CdCl_2$ resulted in a significant decrease in Fe content in the liver. In the nano-Fe_3O_4 + $CdCl_2$ group, the content of Fe was significantly lower than the nano-Fe_3O_4 group ($p<0.05$). The contents of Cd in the control group and the nano-Fe_3O_4 group were beyond the limit of detection of ICP-AES. Oral $CdCl_2$ resulted in a significant increase in Cd content in the liver. In the nano-Fe_3O_4 + $CdCl_2$ group, the content of Cd was significantly lower than that of the $CdCl_2$ group ($p<0.05$). These results revealed that co-administration of nano-Fe_3O_4 with $CdCl_2$ had a negative cooperative effect on the uptake of Fe and Cd in the liver.

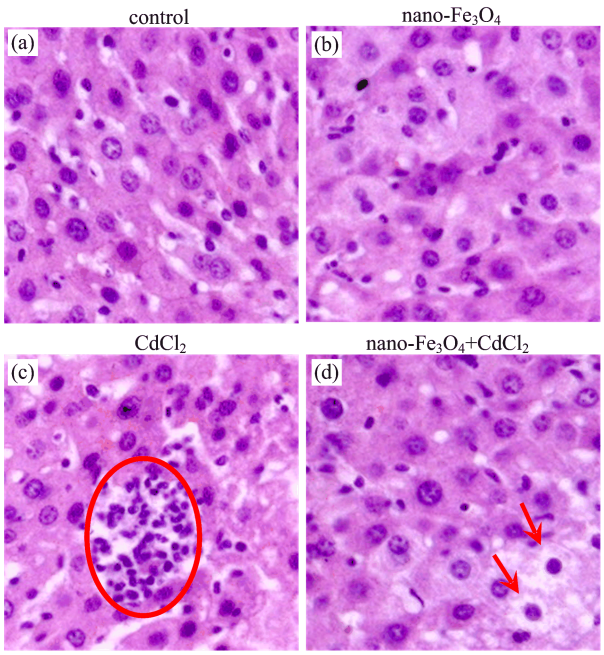


Mice were orally administrated with nano-Fe_3O_4 and/or $CdCl_2$ for 7 d. Results were presented as mean±SD, $n = 6$. $^*p < 0.05$ *versus* the control

Fig. 3 The contents of Fe (a) and Cd (b) in the liver measured with ICP-AES

2.4 Histopathological examination

The histopathological photomicrographs of liver tissues were shown in Fig. 4. There were no abnormal pathological changes in the liver tissues in the control or nano-Fe_3O_4 group. However, in the $CdCl_2$ group, the piecemeal necrosis was observed in the liver tissue. In the nano-Fe_3O_4 + $CdCl_2$ group, although a few hepatocytes showed hydropic degeneration, no piecemeal necrosis was observed in the liver tissue. The results indicated that nano-Fe_3O_4 can protect the liver cells from $CdCl_2$-induced liver damage.



(a) normal liver tissue in the control group; (b) the nano-Fe_3O_4 group shows normal liver tissue; (c) the $CdCl_2$ group shows the spotty necrosis (oval); (d) the nano-Fe_3O_4 + $CdCl_2$ group shows the hydropic degeneration of hepatocytes (arrows).

Fig. 4 Histopathological sections of the liver tissue in mice following oral administration of nano-Fe_3O_4 and/or $CdCl_2$ for 7 d

2.5 Biochemical analysis of liver function

In order to further evaluate the protection of Cd^{2+}-induced hepatotoxicity in mice by nano-Fe_3O_4, the serum biochemical parameters in the mice after administration nano-Fe_3O_4 and/or $CdCl_2$ were determined and shown in Tab. 1. In the nano-Fe_3O_4 group, there were no significant differences in all tested serum biochemical parameters compared with the control group,

except for a slight increase in AST level, revealing that oral nano-Fe_3O_4 didn't affect the liver function. In the $CdCl_2$ group, the levels of ALT, AST and LDH significantly increased ($p<0.05$) and the level of TBIL significantly decreased ($p<0.05$) compared with the control group, indicating $CdCl_2$-induced hepatic injury. In the nano-Fe_3O_4 + $CdCl_2$ group, the levels of AST and LDH significantly increased ($p<0.05$) compared with the control group. However, compared with the $CdCl_2$ group, in the nano-Fe_3O_4 + $CdCl_2$ group, there were significant decreases in the levels of ALT, AST and LDH, and a significant increase in the level of TBIL, suggesting that nano-Fe_3O_4 significantly attenuated $CdCl_2$-induced damage in the liver.

Tab. 1 The mice were orally administrated with nano-Fe_3O_4 and/or $CdCl_2$ for seven consecutive days

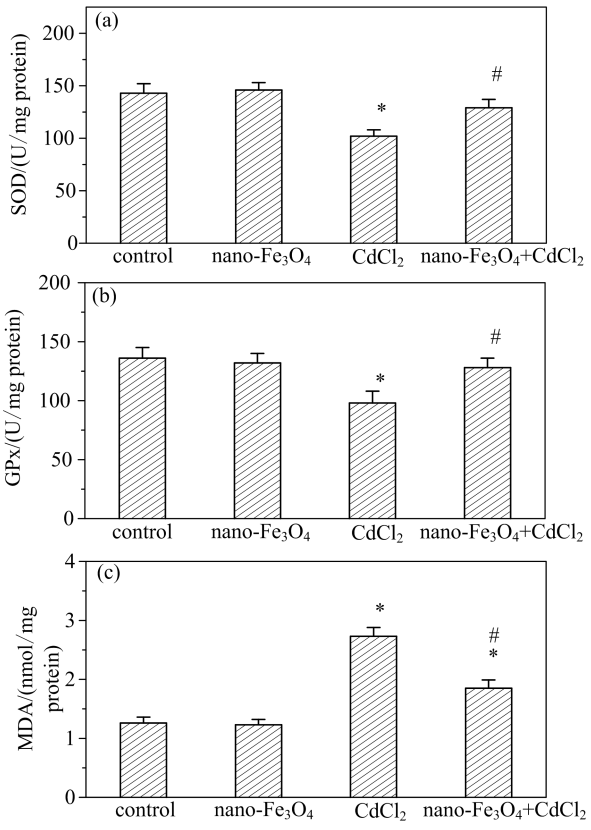
Indexes	Control	nano-Fe_3O_4	$CdCl_2$	nano-Fe_3O_4+$CdCl_2$
ALT/(U·L^{-1})	43.2±3.1	46.1±3.3	91.5±8.1*	48.7±4.2#
AST/(U·L^{-1})	87.4±6.2	102±8*	283±15*	121±4*#
ALP/(U·L^{-1})	92.7±5.4	95.3±8.4	98.6±5	96.1±4.2
LDH/(U·L^{-1})	781±62	832±56	1153±92*	898±73*#
TBIL/(μmol·L^{-1})	1.85±0.25	1.82±0.21	1.35±0.14*	1.65±0.19

[Note] Data were expressed as mean±SD($n=6$). * $p<0.05$ *versus* the control; # $p<0.05$ *versus* the $CdCl_2$ group.

2.6 Measurement of oxidative stress makers

The endogenous antioxidative enzymes, SOD and GPx in the liver were determined after oral administration of nano-Fe_3O_4 and/or $CdCl_2$ for 7 d. As shown in Fig. 5(a) and (b), oral nano-Fe_3O_4 didn't cause significant changes in the activities of SOD and GPx, suggesting that oral nano-Fe_3O_4 didn't induce an obvious oxidative stress in the liver. However, oral $CdCl_2$ caused significant decreases in the activities of SOD and GPx, suggesting that oral $CdCl_2$ induced an oxidative stress in the liver. Interestingly, the activities of SOD and GPx only slightly decreased in the nano-Fe_3O_4 + $CdCl_2$ group, compared with the control group. Co-administration of nano-Fe_3O_4 with $CdCl_2$ significantly increased the activities of SOD and GPx compared with the $CdCl_2$ group, indicating that nano-Fe_3O_4 significantly reduced $CdCl_2$-induced oxidative stress in the liver.

MDA is the product of lipid peroxidation, which is one of the main manifestations of oxidative damage. As shown in Fig. 5(c), oral nano-Fe_3O_4 didn't cause significant changes in the level of MDA, suggesting that oral nano-Fe_3O_4 didn't induce an obvious oxidative stress in the



Data were shown as mean ± SD, $n = 6$.

* $p < 0.05$ *versus* the control; # $p < 0.05$ *versus* the $CdCl_2$ group.

Fig. 5 The activities of antioxidative enzymes, SOD and GPx and the level of MDA in the liver of mice after oral administration of nano-Fe_3O_4 and/or $CdCl_2$ for 7 d

liver. However, oral $CdCl_2$ caused significant increase in the level of MDA, suggesting $CdCl_2$-induced lipid peroxidation in the liver. In the nano-Fe_3O_4 + $CdCl_2$ group, although the level of MDA significantly increased ($p < 0.05$) compared with the control group, co-administration of nano-Fe_3O_4 with $CdCl_2$ significantly decreased the level of MDA compared with the $CdCl_2$ group, indicating that nano-Fe_3O_4 significantly attenuated $CdCl_2$-induced oxidative stress in the liver.

3 Discussion

In this study, we observed that oral nano-Fe_3O_4 didn't cause obvious hepatotoxicity. However, oral $CdCl_2$ caused obvious oxidative injury in the liver, as indicated by the liver dysfunction and histopathological abnormalities. Co-administration of nano-Fe_3O_4 with $CdCl_2$ significantly attenuated $CdCl_2$-induced damage in liver.

Interestingly, a negative cooperative effect on the uptake of Fe and Cd in the liver was observed after co-administration of nano-Fe_3O_4 with $CdCl_2$. After oral administration, nano-Fe_3O_4 and $CdCl_2$ entered the blood by the uptake of gastrointestinal tract and further distributed into different organs. Cd in the liver is believed to be taken up via divalent metal transporter 1 (DMT1), a transmembrane proton-coupled Fe^{2+} transporter[16]. DMT1 transports not only Fe^{2+}, but also other cations including Cd^{2+}. The negative cooperative effects of nano-Fe_3O_4 and $CdCl_2$ on the biodistributions of Fe and Cd in the mice suggested that Fe and Cd mutually inhibited the uptake of each other in a competitive manner since they shared the same uptake pathway *via* DMT1. Kwong et al.[17] also showed that Fe^{2+} and Cd^{2+} competitively inhibited the uptake of each other in fish enterocytes.

The protection of $CdCl_2$-induced hepatotoxicity in mice by nano-Fe_3O_4 may be partially attributed to the reduction of Cd accumulation in the liver by nano-Fe_3O_4. Fig. 3(a) showed that oral administration of $CdCl_2$ significantly decreased the Fe level in the liver. Cd not only inhibited the uptake of Fe in the liver, but also replaced Fe in Fe-dependent enzymes and proteins[18], which caused Fe deficiency and disturbances of the Fe metabolism. Cd-induced Fe deficiency in mice is considered as a major aspect of Cd toxicity[18-20]. The Fe level dramatically increases in the liver of the mice after co-administration of nano-Fe_3O_4 with $CdCl_2$ being higher than that of the $CdCl_2$ group (Fig. 3(a)). The increase in Fe uptake and decrease in the replacement of Fe in Fe-dependent proteins by Cd after co-administration should be considered as another key mechanism underlying the nano-Fe_3O_4-mediated protection of Cd toxicity.

Cd^{2+} is reported to induce oxidative stress in the liver, which causes lipid peroxidation. The activities of antioxidant enzymes such as GPx, SOD are important indicators of oxidative stress. Yalin et al.[21] reported that the activities of SOD decreased after a single-dose injection of Cd to rats. We also observed that the activities of SOD and GPx in the liver decreased after oral administration of $CdCl_2$. SOD contains Zn and Cu in its active site. The Cd-induced decrease in SOD activity should be a consequence of the replacement of the Zn in SOD by Cd[22]. GPx contains a Se-Cys residue at its active site. The reduction in GPx activity might be due to the interaction of the Se at the active site of GPx with Cd[23]. Co-administration of nano-Fe_3O_4 with $CdCl_2$ significantly increased the SOD and GPx activities compared with the $CdCl_2$ group, which is attributed to the reduction of Cd accumulation in the liver by nano-Fe_3O_4.

4 Conclusion

Nano-Fe_3O_4 has an antagonistic effect on Cd-induced hepatotoxicity in mice. Co-administration of nano-Fe_3O_4 with $CdCl_2$ has negative cooperative effects on the biodistributions of Fe and Cd in the liver. The inhibition of Cd-induced deprivation of tissue Fe and reduction of Cd accumulation in tissues after co-administration of nano-Fe_3O_4 with $CdCl_2$ may play two key roles in the protective effect of nano-Fe_3O_4 on $CdCl_2$-induced oxidative damage in mice. Nano-Fe_3O_4 may be used as a perfect MRI contrast agent and drug carrier for

patients with Cd poisoning, since it not only acts as an MRI contrast agent or drug carrier, but also simultaneously attenuates Cd-induced toxicity.

References

[1] NEL A, XIA T, MADLER L, et al. Toxic potential of materials at the nanolevel[J]. Science, 2006, 311(5761): 622-627.

[2] ZHU X J, ZHOU J, CHEN M, et al. Core-shell Fe_3O_4@$NaLuF_4$: Yb, Er/Tm nanostructure for MRI, CT and upconversion luminescence tri-modality imaging[J]. Biomaterials, 2012, 33(18): 4618-4627.

[3] PARK E J, KIM H, KIM Y, et al. Inflammatory responses may be induced by a single intratracheal instillation of iron nanoparticles in mice [J]. Toxicology, 2010, 275: 65-71.

[4] GALAZYN-SIDORCZUK M, BRZOSKA M M, JURCZUK M, et al. Oxidative damage to proteins and DNA in rats exposed to cadmium and/or ethanol[J]. Chemico-Biological Interactions, 2009, 180(1): 31-38.

[5] KLAASSEN C D, LIU J, DIWAN B A. Metallothionein protection of cadmium toxicity [J]. Toxicology and Applied Pharmacology, 2009, 238(3): 215-220.

[6] LEE B K, KIM Y. Iron deficiency is associated with increased levels of blood cadmium in the Korean general population: Analysis of 2008-2009 Korean National Health and Nutrition Examination Survey data [J]. Environmental Research, 2012, 112:155-163.

[7] HABEEBU S S M, LIU J, KLAASSEN C D. Cadmium-induced apoptosis in mouse liver [J]. Toxicology and Applied Pharmacology, 1998, 149(2): 203-209.

[8] CUYPERS A, PLUSQUIN M, REMANS T, et al. Cadmium stress: An oxidative challenge [J]. Biometals, 2010, 23(5): 927-940.

[9] WLOSTOWSKI T, KRASOWSKA A, BONDA E. An iron-rich diet protects the liver and kidneys against cadmium-induced injury in the bank vole (Clethrionomys glareolus) [J]. Ecotoxicology and Environmental Safety, 2003, 54(2): 194-198.

[10] CHARGUI A, ZEKRI S, JACQUILLET G, et al. Cadmium-induced autophagy in rat kidney: An early biomarker of subtoxic exposure [J]. Toxicological Sciences, 2011, 121(1): 31-42.

[11] HAHN P F, STARK D D, LEWIS J M, et al. First clinical trial of a new superparamagnetic iron oxide for use as an oral gastrointestinal contrast agent in MR imaging[J]. Radiology, 1990, 175(3): 695-700.

[12] JURCZUK M, BRZOSKA M M, MONIUSZKO-JAKONIUK J, et al. Antioxidant enzymes activity and lipid peroxidation in liver and kidney of rats exposed to cadmium and ethanol [J]. Food and Chemical Toxicology, 2004, 42(3): 429-438.

[13] JIN Y, ZHANG S, TAO R, et al. Oral exposure of mice to cadmium (II), chromium (VI) and their mixture induce oxidative- and endoplasmic reticulum-stress mediated apoptosis in the livers [J]. Environmental Toxicology, 2016, 31(6): 693-705.

[14] SIREERATAWONG S, JAIJOY K, KHONSUNG P, et al. Acute and chronic toxicities of Bacopa monnieri extract in Sprague-Dawley rats [J]. BMC Complementary and Alternative Medicine, 2016, 16: 249.

[15] GUO M, XU X, YAN X, et al. In vivo biodistribution and synergistic toxicity of silica nanoparticles and cadmium chloride in mice[J]. Journal of Hazardous Materials, 2013, 260: 780-788.

[16] RAJA K B, JAFRI S E, PETERS T J, et al. Iron and cadmium uptake by duodenum of hypotransferrinaemic mice[J]. Biometals, 2006, 19(5): 547-553.

[17] KWONG R W, NIYOGI S. Cadmium transport in isolated enterocytes of freshwater rainbow trout: Interactions with zinc and iron, effects of complexation with cysteine, and an ATPase-coupled efflux [J]. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology, 2012, 155(2): 238-246.

[18] DJUKIĆ-COSIĆ D, JOVANOVIĆ M C, BULAT Z P, et al. Relation between lipid peroxidation and iron concentration in mouse liver after acute and subacute cadmium intoxication[J]. Journal of Trace Elements in Medicine and Biology, 2008, 22(1): 66-72.

[19] CHMIELNICKA J, CHERIAN M G. Environmental exposure to cadmium and factors affecting trace-element metabolism and metal toxicity[J]. Biological Trace Element Research, 1986, 10(3): 243-262.

[20] GROTEN J P, SINKELDAM E J, MUYS T, et al. Interaction of dietary Ca, P, Mg, Mn, Cu, Fe, Zn and Se with the accumulation and oral toxicity of cadmium in rats[J]. Food and Chemical Toxicology, 1991, 29(4): 249-258.

[21] YALIN S, COMELEKOGLU U, BAGIS S, et al. Acute effect of single-dose cadmium treatment on lipid peroxidation and antioxidant enzymes in ovariectomized rats [J]. Ecotoxicology and Environmental Safety, 2006, 65(1): 140-144.

[22] BAUER R, DEMETER I, HASEMANN V, et al. Structural properties of the zinc site in Cu, Zn-superoxide dismutase; Perturbed angular correlation of gamma ray spectroscopy on the Cu, ^{111}Cd-superoxide dismutase derivative[J]. Biochemical and Biophysical Research Communications, 1980, 94(4): 1296-1302.

[23] JIHEN EL H, FATIMA H, NOUHA A, et al. Cadmium retention increase: A probable key mechanism of the protective effect of zinc on cadmium-induced toxicity in the kidney[J]. Toxicology Letters, 2010, 196(2): 104-109.