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The preferential accumulation of cadmium ions among various tissues in mice

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ABSTRACT

Cadmium (Cd) is hazardous to human health because of its toxicity and long half-life of clearance. Many studies have explored the relationship between chronic Cd exposure and different human diseases. However, most of the studies limited the study targets of Cd toxicity to two or three organ systems. The goal of this study was to establish a mouse model of Cd accumulation in most organ systems and to particularly investigate the potential toxic effects of Cd to the cardiovascular system. Mice were divided into three groups: the control group, Cd-100 group, and Cd-200 group. In the control group, Cd was detected in the kidney, lung, liver, heart and urine but was undetectable in the aorta, intestine, thigh bone, spinal bone and serum. Upon chronic exposure in the Cd-100 and Cd-200 groups, Cd accumulated in all tissues, with a dramatic increase in concentration. We confirmed that Cd could accumulate significantly in the heart and aorta upon chronic exposure. This finding might help to explain the potential toxic effects of Cd on these organs. In addition, the calcium concentration in the bones and kidney declined when the exposure to Cd increased. This finding aligned with the negative effects of Cd on bony mineralization and the potential direct toxic effects of Cd on bones. The impacts of Cd on the cardiovascular system were explored. Histologically, chronic Cd exposure led to myocytes hypertrophy and myocardial architecture disarray in the Cd-100 group compared to those in the control group. Our research confirms that Cd can accumulate in all of the organs studied upon chronic exposure, and suggests that the toxicity of Cd accumulation may play important roles in mediating the pathophysiologic effects in these target organs, especially the bone and heart.

1. Introduction

As technology advances, many poisonous chemicals have been used in agriculture and industry. Cadmium (Cd), a well-known toxic heavy metal, has large negative impacts on human health. Cd is harmful to both the environment and creatures. It exists in the air, water, and soils [1,2]. Exposure to Cd occurs through tobacco smoking [3,4], contaminated water or food [5,6], polluted air from fossil fuel combustion [7], or occupational contamination. One of the largest origins of Cd exposure to the human body is via the food chain [8], such as in crops, rice, seafood [9,10], and vegetables [11]. Moreover, there is no efficient excretory mechanism for Cd in the body, and it accumulates throughout life, with a clearance half-life of twenty-five years [12]. This indicates that Cd accumulation in humans will increase with age and sustain damage to the human body for a long time. Therefore, the risk of Cd to human health is a critical issue and merits attention and investigation.

Cd exposure is considered a severe problem. Although acute Cd intoxication is currently rare, chronic low-level exposure may still be harmful to human health. Cd is recognized as a human carcinogen by the International Agency for Research on Cancer because of ample proof of its carcinogenicity in humans, including its promotion of lung cancer [13–15] and kidney cancer [16,17]. Cd exposure can also increase the risk of bone fractures and osteoporosis [18–26]. Recent studies have demonstrated the association of chronic Cd exposure with an increased

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risk of heart failure [27–29] and atherosclerotic diseases, including coronary artery disease [30–35], peripheral artery disease [35–37], stroke and carotid artery disease [27,33,35,38–40].

Several mechanisms have been reported to be involved in Cd induced tissue damage. Cd induces cell apoptosis in several organs via affecting transcription factors and regulation of their target genes [41,42]. Cd induces oxidative stress and leads to oxidation and damage of proteins, DNA, lipids and cellular membrane phospholipids [43–45]. Cd may damage mitochondria by blocking mitochondrial electron-transfer chain [43]. Cd also causes accumulation of mitochondrial reactive oxygen species (ROS) [46], decrease of mitochondrial membrane potential and increase of ion permeability in the inner membrane, which further leads to cell apoptosis [43]. Other postulated mechanisms of Cd toxicity include ER stress-mediated apoptosis caused by Cd [47], inhibition of some DNA repair enzymes and damage of DNA [48], and epigenetic changes leading to altered gene expression [49,50].

Although Cd is very harmful to human health, few studies (see Table 1) have investigated the accumulation profile of Cd in most organs. The purpose of our study was to expose mice to chronic nontoxic, relatively low concentration of Cd via drinking water. We explored the Cd content in various organs, including the spinal bone, thigh bone, aorta, heart, kidney, lung, liver, and intestine. In addition, the concentration of Cd in serum and urine was also studied. We also studied the effects of Cd exposure on some aspects of the cardiovascular system. Compared to previous studies, we tried to build a broader profile of Cd accumulation in mice. This research may help to explain the harmful effects of Cd on various organs, especially those for which the Cd concentration upon chronic exposure has not been previously well established.

2. Experimental section

2.1. Chemical reagents

Acetic acid (CH_3COOH), cadmium chloride ($CdCl_2$), Schiff's reagent and paraformaldehyde were purchased from Alfa Aesar (Ward Hill, MA, USA). Absolute ethanol (C_2H_6O), eosin, hematoxylin, nitric acid (HNO_3), potassium dichromate ($K_2Cr_2O_7$) and xylene (C_8H_{10}) were purchased from Sigma Aldrich (St. Louis, MO, USA). Sodium carbonate (Na_2CO_3) was purchased from Showa (Chemical Co., Japan). Dithiothreitol (DTT) was purchased from Across Organics. Periodic acid and sulfurous acid were purchased from J. T. Baker (Phillipsburg, NJ, USA).

2.2. Ethics statement and experimental protocol

All procedures followed the standards for care and use of animal subjects as stated in the ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines; the procedures were also approved by the Institutional Animal Care and Use Committee of Chang Gung Memorial Hospital (Permit Number: 2019071201 and 2020031301). Thirsty-night C57BL/6 male mice (25−30 g) were housed at the animal facility of the Chang Gung Memorial Hospital, Taiwan. The animals had a standard diet ad libitum and free access to water, and were kept on a 12-h light/dark cycle, in accordance with the Lab guidelines and regulations of Chang Gung Memorial Hospital. After sufficient acclimation period (1 week) for the animals to be stabilized in the new surroundings, the eight-week-old male mice were divided into 3 groups: group 1, the control group, received normal water (control group, n = 11); group 2, the low-dose Cd exposure group, received 100 mg/L $CdCl_2$ in drinking water (Cd-100 group, n = 18); and group 3, the high-dose Cd exposure group, received 200 mg/L $CdCl_2$ in drinking water (Cd-200 group, n = 10). Blood pressure and heart rate were measured every 4 weeks, and body weight was measured every 2 weeks. Urine samples were collected for study in the 12th week. After 12 weeks of treatment, the mice were sacrificed for further experiments. The organs and tissues collected for investigation included the spinal bone, thigh bone, aorta, heart, kidney, lung, liver, intestine, serum and urine. All surgical procedures of animals were performed under anesthesia with intraperitoneal Zoletil, and all efforts were made to minimize animal suffering.

Table 1
Comparison of various analytical methods for the determination of Cd concentration.

Method	Cadmium sources	Detection locations	Reference
ICP-MS	rice, wheat, vegetables	kidney and urine	[51]
UPLC-QTOF-MS	chow	kidney and urine	[52]
Atomic absorption spectroscopy	food	liver, kidney and intestine	[53]
High-performance liquid chromatography (fluorescence method)	injection	liver and kidney	[54]
ICP-MS	water	liver	[55]
ICP-MS	water	spinal bone, thigh bone, aorta, heart, kidney, lung, liver, intestine, serum and urine	This work

2.3. Measurement of the concentration of Cd and other metal elements (calcium and lead) in blood and tissues

The concentrations of Cd, calcium, and lead in blood and tissues including the spinal bone, thigh bone, aorta, heart, kidney, lung, liver, intestine, serum and urine were analyzed by ICP-MS. Various tissue samples (sampling weight were shown in Supplement Table 1), 1 mL serum or 1mL urine were predigested with 68 % HNO_3 in 2 mL and reacted in a 15 mL centrifuge tube for one week, respectively. After the tissues were digested completely, the samples were diluted with deionized water to 10 mL. These samples were analyzed with a 7500ce ICP-MS instrument (Agilent Instruments, Japan). The instrument conditions are detail in Table 2. High-purity (1000 ppm) metal element standard solutions were diluted to 0.8 ppb, 4 ppb, 20 ppb, 50 ppb, and 100 ppb standard solutions with 1% HNO_3, and calibration curves were produced. After that, the samples were analyzed by ICP-MS for the detection of these metal elements.

2.4. Measurement of blood pressure

Mice were first acclimatized to a blood pressure apparatus to reduce stress-related blood pressure variability. The animals were placed in restraining units (2.5 × 10 cm) mounted on a warmed (27-28 °C) surface, and the mouse tails were passed through a cuff attached to a custom-built indirect mouse tail pressure monitoring system. Blood flow was detected photoelectrically (Harvard Apparatus; Holliston, MA, USA) and sampled digitally at 200 Hz. The tail cuff was manually inflated to 200 mmHg and released; the first onset of the pulse was recorded as the systolic blood pressure.

2.5. Tissue preparation and histopathology assessment

All animals were anesthetized by intraperitoneal Zoletil, and tissues were perfusion-fixed by direct intracardiac injection of heparinized (10

Table 2
Operating parameters for the 7500ce ICP-MS instrument.

Parameters	Setting
ICP ratio frequency power	1.5 kW
Reflected power	< 5 W
Plasma gas flow rate	15 L/min
Auxiliary flow rate	0.8 L/min
Nebulizer flow rate	0.95 L/min

U/mL) phosphate-buffered saline, followed by injection of phosphate-buffered 2% paraformaldehyde (pH 7.4) for 10 min. For heart morphometry, hearts were arrested with KCl, fixed with 10 % buffered formalin, and embedded in paraffin. The baseline sections of the left ventricles were stained with hematoxylin and eosin (H&E). We also used Verhoeff–Van Gieson (V.V.G.) stain for elastic fibers, silver stain for reticular fibers and periodic acid-Schiff (PAS) stain for carbohydrates.

2.6. Statistical analysis

Results are expressed as the mean ± standard error. Student's *t* test and the Mann–Whitney *U* test were used to determine the significance of variable differences among the two groups. The $\chi 2$ test or Fisher's exact test was used to compare categorical data as appropriate. Significance was established at $P < 0.05$. All statistical analyses were performed using SPSS 16.0 for Windows (SPSS, Chicago, IL, USA).

3. Results and discussion

3.1. Accumulation of Cd in different tissues

In this study, the average amount of water intake for one mouse was 36 ± 9 mL and 39 ± 6 mL per week in the Cd-100, and Cd-200 groups. The average dose of Cd intake, calculated according to water consumption, was 131 ± 27 mg and 239 ± 36 mg per kilogram body weight per week in the Cd-100 and Cd-200 groups (Supplemental Fig. 1). The mineral composition in different tissues of mice was detected by ICP-MS, including the spinal bone, thigh bone, aorta, heart, kidney, lung, liver, intestine, serum and urine. Fig. 1 shows the Cd levels in different tissues. To compare with and without the urine and the serum, we used two representations. As shown in Fig. 1A, the Cd concentrations of the solution was investigated. In the control group, the order of Cd concentration in tissues was kidney (0.06465 ppm)> lung (0.02483 ppm)> liver (0.01081 ppm)> urine (0.00295 ppm) > heart (0.0007936 ppm). Cd ions were undetectable in the aorta, intestine, thigh bone, spinal bone and serum (0 ppm). In the Cd-100 group, the order of Cd concentration was kidney (25.3975 ppm)> liver (15.98 ppm)> intestine (1.6199 ppm)> heart (0.74817 ppm)> lung (0.53253 ppm) > aorta (0.38977 ppm)> urine (0.2216 ppm) > thigh bone (0.20637 ppm)> spinal bone (0.18077 ppm)> serum (0.00924 ppm). In the Cd-200 group, the order of Cd concentration was liver (34.73333 ppm)> kidney (25.27333 ppm)> intestine (7.131 ppm)> heart (1.71267 ppm)> lung (1.25766 ppm) > thigh bone (0.55476 ppm)> aorta (0.47475 ppm)> spinal bone (0.38204 ppm)> urine (0.24373 ppm) > serum (0.02271 ppm). Compared to that in the control group, the Cd concentration in all tissues increased significantly in the Cd-100 and Cd-200 groups. It was verified that Cd can also accumulate in thin and long bones, the aorta and the heart, in addition to the previously known kidney, lung and liver. When the Cd concentration in drinking water increased from 100 mg/dL to 200 mg/dL, the accumulation of Cd was further enhanced more than twofold in the liver (15.98 to 34.73333 ppm), intestine (1.6199–7.131 ppm), heart (0.74817–1.71267 ppm), lung (0.53253–1.25766 ppm), thigh bones (0.20637 to 0.55476 ppm) and spinal bones (0.18077 to 0.38204 ppm), but the accumulation only slightly changed in the kidney (25.3975 to 25.27333 ppm) and aorta (0.38977 to 0.47475 ppm).

On the other hand, the results for Cd content in mg/kg organ wet weight was presented in Fig. 1B. This expression was more general than previous expression. In the control group, the order of Cd concentration in tissues was lung (1.03975 mg/kg organ weight) > kidney (0.32838 mg/kg) > heart (0.08063 mg/kg) > liver (0.02153 mg/kg). The Cd concentration in urine was 0.00295 mg/L. Cd ions were undetectable in the aorta, intestine, thigh bone, spinal bone and serum. In the Cd-100 group, the order of Cd concentration was kidney (164.255 mg/kg) > aorta (43.5135 mg/kg) > liver (29.3407 mg/kg) > heart (17.9017 mg/kg) > lung (7.4843 mg/kg) > intestine (6.4271 mg/kg) > thigh bone (1.81326 mg/kg) > spinal bone (0.79625 mg/kg). The Cd concentration in serum and urine was 0.00924 mg/L and 0.2216 mg/L, respectively. In the Cd-200 group, the order of Cd concentration was kidney (139.09019 mg/kg) > heart (59.16301 mg/kg) > liver (49.72359 mg/kg) > aorta (41.66676 mg/kg) > lung (17.09849 mg/kg) > intestine (14.09108 mg/kg) > thigh bone (5.16957 mg/kg) > spinal bone (1.82952 mg/kg). The Cd concentration in serum and urine was 0.02271 mg/L and 0.24373 mg/L, respectively. Compared to that in the control group, the Cd concentration in all tissues increased significantly in the Cd-100 and Cd-200 groups. It was verified that Cd can also accumulate in thin and long bones, the aorta and the heart, in addition to the previously known kidney, lung and liver. When the Cd concentration in drinking water increased from 100 mg/dL to 200 mg/dL, the accumulation of Cd was further enhanced 1.7 times to three-fold in the liver (29.3407–49.72359 mg/kg), intestine (6.4271–14.09108 mg/kg), heart (17.9017–59.16301 mg/kg), lung (7.4843–17.09849 mg/kg), thigh bones (1.81326–5.16957 mg/kg), spinal bones (0.79625–1.82952 mg/kg) and serum (0.00924 to 0.02271 mg/L), but the accumulation did not increase in the kidney (164.255 to 139.09019 mg/kg) and aorta

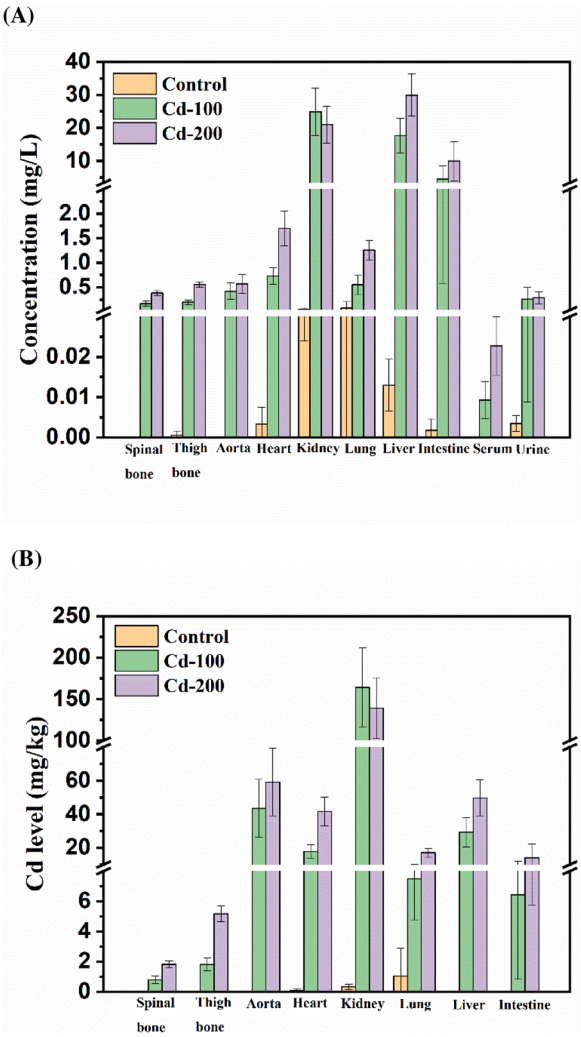

Fig. 1. The solution presentation (A) and the weight presentation (B) of the accumulation of cadmium ions in the spinal bone, thigh bone, aorta, heart, kidney, lung, liver, intestine, serum and urine of three different feeding groups of mice. Orange, control group, receiving normal water; green, Cd-100 group, 100 mg/dL $CdCl_2$ in drinking water; purple, Cd-200 group, 200 mg/dL $CdCl_2$ in drinking water. N = 11, 18, 10 for the control, Cd-100 and Cd-200 groups, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

(43.5135 to 41.66676 mg/kg).

We speculated that the accumulation of Cd in kidney and aorta tissues was nearly saturated in the Cd-100 group and that chronic exposure to higher dose of Cd in the Cd-200 group did not lead to a higher concentration, even a lower concentration in the kidney. Thijssen et al. suggested that kidney Cd content is a reliable indicator of chronic exposure [56]. They found a linear relationship between the total Cd ingested and Cd found in the kidney cortex of mice. However, the concentration of $CdCl_2$ in drinking water that they used was between 0 and 100 mg/L. Based on the results of our study, further research is needed to confirm whether this correlation is still sustained when the mice are exposed to higher doses of Cd.

3.2. Accumulation of Cd in the cardiovascular systems

In this study, we clarified the profiles of Cd accumulation in the cardiovascular system (heart and aorta) of mice exposed to a chronic Cd dose. When mice were fed normal water, the heart and aorta contained little or no Cd, in contrast to the kidney and lung which contained 0.32838 to 1.03975 mg/kg of Cd. When mice were exposed to a chronic Cd dose, Cd accumulated prominently in the heart and aorta. Epidemiologically, chronic Cd exposure is well known to be associated with an increased risk of heart failure [27–29] or cardiovascular disease, such as coronary artery disease [30–34], peripheral artery disease [36,37], carotid artery disease and stroke [27,33,38–40]. Animal studies have also demonstrated potential toxic effects of Cd on the heart [57] or aorta [58–60]. However, little is known about the accumulation profiles of Cd in these two organs. Our study confirmed that Cd could accumulate significantly in the heart and aorta upon chronic exposure, and bridged the gap between exposure and the potential toxic effects on these organs.

3.3. Influences of Cd on other cations

The addition of Cd ions may influence the metabolism of other ions. In this study, the possible interaction between Cd and calcium ions was explored. As shown in Fig. 2, the Cd and calcium concentrations in the spinal bone, thigh bone, and kidney were analyzed. When the Cd concentration in these tissues increased, as the $CdCl_2$ level in the drinking water increased, the calcium concentration decreased significantly. The inverse correlation between Cd and calcium concentrations was similar in the kidney, spinal bone and thigh bone.

Previous epidemiological studies have clarified that increased Cd exposure correlates significantly with decreased bone mineral density and increased risk of fracture [20–26,61]. Furthermore, Cd might have direct toxic effects on bones [23,62]. Cd has been shown to inhibit the differentiation of bone marrow mesenchymal stem cells into osteoblasts, activate osteoclases, promote bone resorption, and induce osteoblast injury and apoptosis [62]. Other possible mechanisms have also been proposed, including Cd-induced renal tubular damage [61] with hypercalciuria [63] and demineralization of bones, and reduced generation of active vitamin D in renal tubular cells [64,65] with resultant decreased calcium uptake in the duodenum [66]. These potential mechanisms lead to a negative calcium balance, and might accelerate bone turnover and resorption [19]. Our finding that increased Cd exposure would cause its direct accumulation in the spine bone and thigh bone of mice, as well as the depletion of calcium content in these bones, further confirmed the negative effects of Cd on bony mineralization and potential direct toxic effects of Cd on bones.

Furthermore, to confirm the observation of our study oncardiovascular diseases would not interfere with other ions, the concentration of lead ions in different Cd concentration groups was explored. As shown in Fig. 3, the lead concentration in the intestine did not increase as the Cd exposure and concentration in the intestine increased. This result indicated that the water we used was not polluted by lead. This finding means that the results of our research were credible and not due to the effect of lead.

3.4. Body weight, blood pressure and heart rate

During the experiment all mice increased in weight (Fig. 4A). Exposure to either 100 mg/L or 200 mg/L $CdCl_2$ in drinking water did not significantly affect the rate of body weight increase.

The influence of Cd exposure on blood pressure and heart rate is shown in Fig. 4B and C. As the duration of exposure to Cd increased from 0 to 12 weeks in the Cd-100 and Cd-200 groups, the blood pressure did not change significantly. Heart rate increased slightly as the mice aged

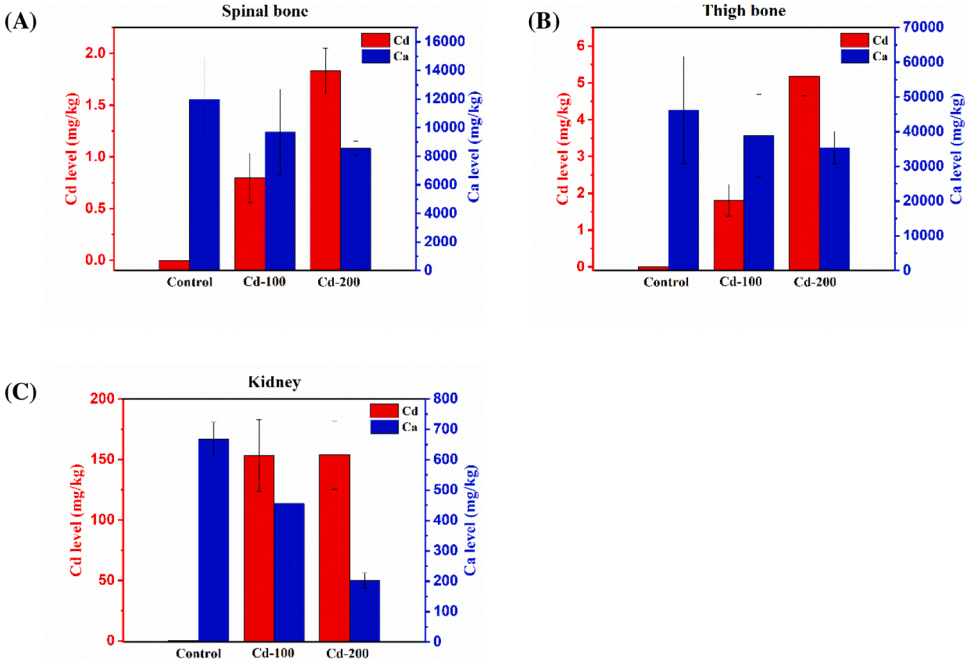

Fig. 2. The relationship between concentration of cadmium ions and calcium ions in the (A) spinal bone, (B) thigh bone, and (C) kidney in the control, Cd-100 and Cd-200 groups.

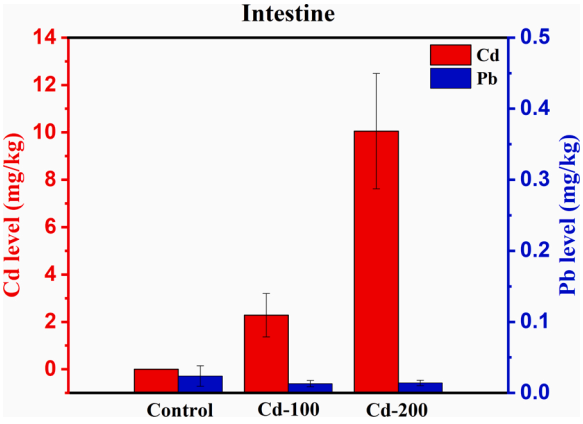

Fig. 3. The relationship between concentration of cadmium and lead ions in the intestine in the control, Cd-100 and Cd-200 groups.

in the control and Cd groups. Compared to that in the control group, blood pressure was significantly higher in the $CdCl_2$ 200 mg/L group in the 4th and 8th weeks, but this result could be due to sample bias because of a difference in initial blood pressure. The heart rate in both the Cd-100 and Cd-200 groups was not significantly different from that in the control group at any time point.

3.5. Histologic sections of the heart

H&E staining of the heart is shown in Fig. 5A and B. In a high-power view, compared to those in the control group, the myocytes were more hypertrophic in the Cd-100 group, with reduced interstitial space between myocytes. This result was confirmed by semiquantification of the myocyte size in silver stain images (Supplemental Fig. 2). Compared to those in the control group, more myocytes in the Cd-100 group were counted as medium or large in size.

Silver staining also showed prominent structural changes in myocytes and myocardial fascicles in the Cd-100 group (Fig. 5C, D). In the control group, reticular fibers were seen as parallel bundles of myocardial fascicles, but the myocardial architecture was disarrayed in

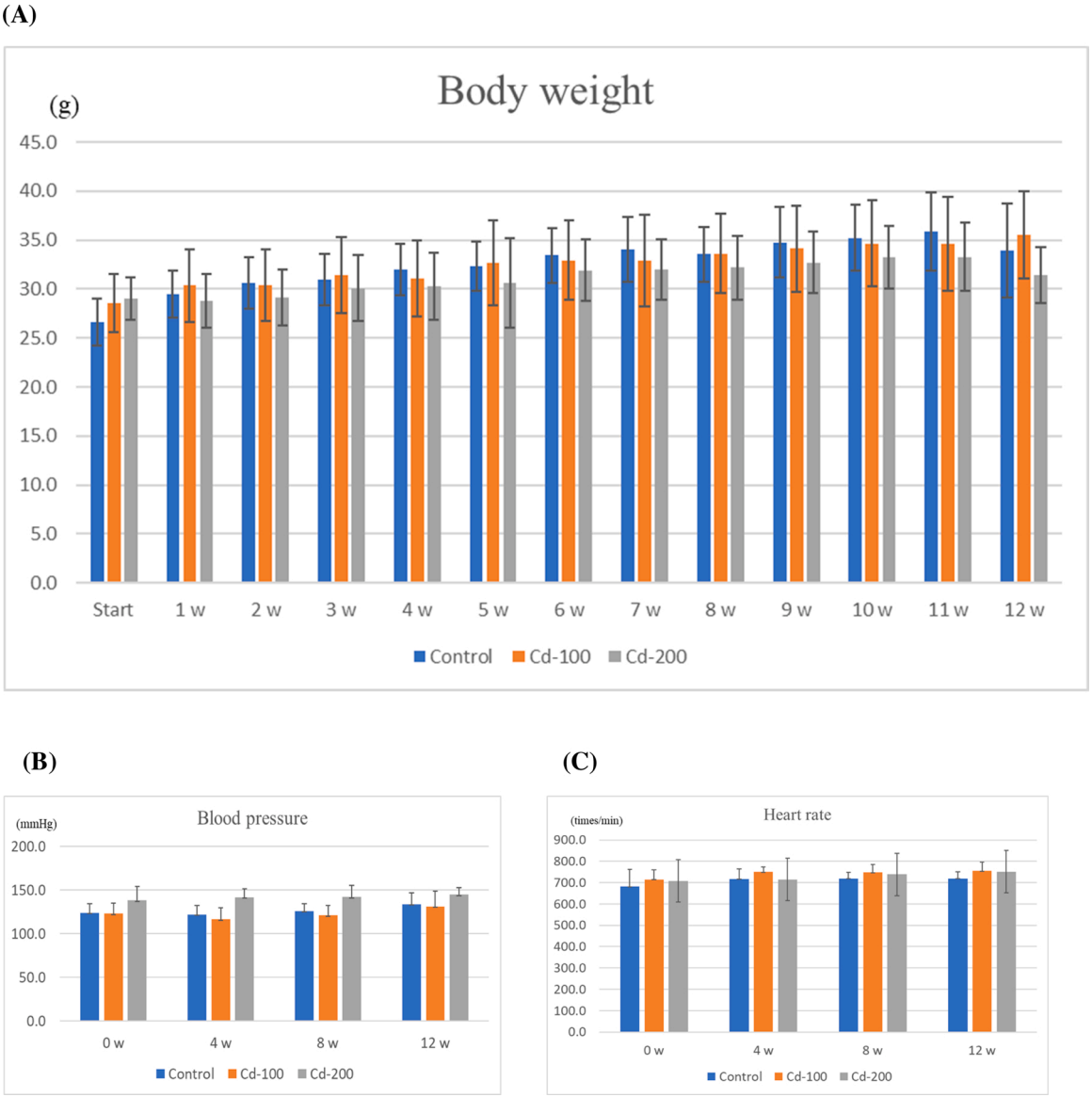

Fig. 4. Chronic Cd exposure does not significantly influence body weight (A), blood pressure (B) or heart rate (C). N = 11, 18 and 10 in control, Cd-100 and Cd-200 groups in A; N = 7, 11 and 5 in control, Cd-100 and Cd-200 groups in B and C.

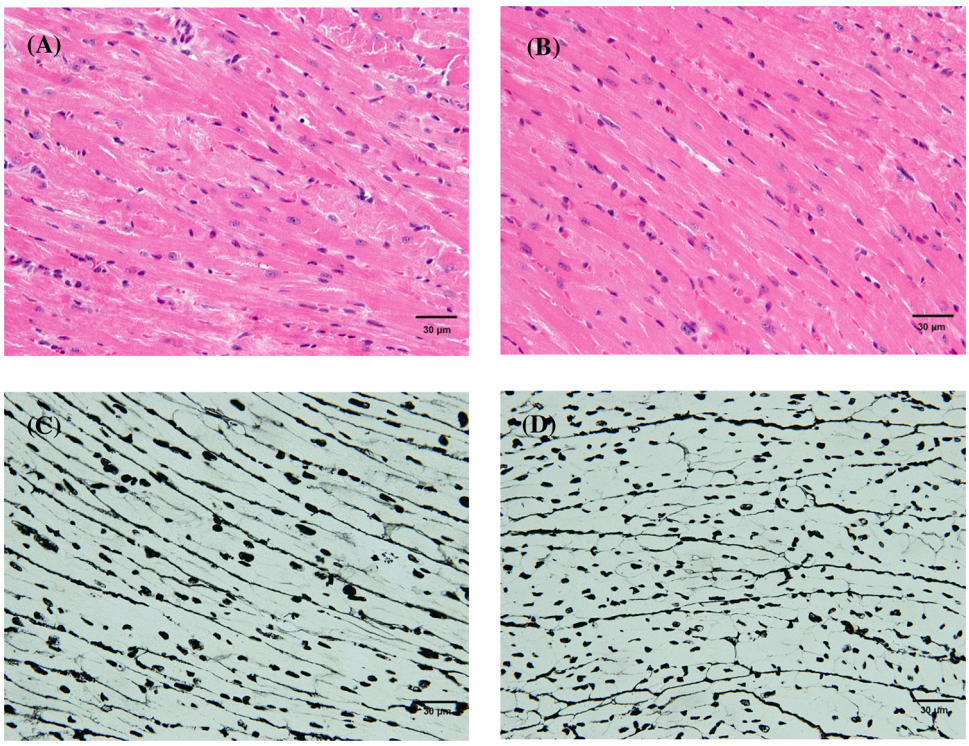

Fig. 5. Histological sections of the heart. Images of H&E staining of hearts in the control (A) and Cd-100 groups (B) under a high-power view. Hypertrophy of myocytes and reduced interstitial space were noted in the Cd-100 group. Images of silver staining of the heart in the control (C) and Cd-100 groups (D) under a high-power view. Prominent structural changes in the myocytes and myocardial fascicles were observed in the Cd-100 group.

the Cd-100 group. Furthermore, the reticular fibers in the perimysium of myocardial fascicles in the control group were homogeneous in thickness, but became heterogeneous in thickness with multiple small breaks in the Cd-100 group. In addition, the reticular fibers in the endomysium of myocytes in the control group were clearly observed in most of the myocytes but disappeared in a large portion of the myocytes in the Cd-100 group.

One possible mechanism of Cd induced toxicity is cell apoptosis. The apoptotic DNA fragmentation of cardiomyocytes was identified by TUNEL assay. Prominently increased TUNEL positive cells in myocardial section were noted in the Cd-200 group, whereas there were scarce TUNEL positive cells in the control group (data unpublished). Previous animal studies revealed that Cd induces apoptosis in kidney [42,67], testes [68] and bone [69]. Cd may induce cell apoptosis through affecting transcription factors [41,42], damage to mitochondrial due to accumulation of ROS [46] or increased permeability of mitochondrial inner membrane [43], or increased ER stress [47]. In rat proximal tubular NRK-52E cells, Cd decreases inhibitor of apoptosis protein 1 (IAP1) and IAP2 via suppression of nuclear factor-kappa B (NF-κB) [70]. IAP1 and IAP2 bind to caspases and inhibit apoptosis [71]. Therefore, Cd exposure leads to the activation of caspases 3, 7 and 9 and induced caspase-dependent apoptosis via suppression of NF-κB, IAP1 and IAP2 [70]. Further research is required to investigate the possible role of these mechanisms in the toxicity of Cd exposure to the heart.

3.6. *Biologically active compounds against Cd toxicity*

In addition to causing cell apoptosis, mitochondrial damage and increased ER stress, Cd also induces oxidative stress and causes oxidation and damage of proteins and DNA [43–45]. Biologically active compounds, such as nutraceuticals, antioxidants and anti-inflammatory agents, may provide beneficial effects and counteract Cd toxicity through targeting these molecular pathways. Some promising examples among these compounds are polyphenolic substances [43,72,73], myo-inositols [67,74], resveratrol [75] and flavonoids [76,77]. Giovanni et al. reported that treatment with myo-inositol protected against Cd-induced damages in mice kidney, significantly lowered TUNEL positive cells number, and increased glutathione content and glutathione peroxidase activity in kidney. They suggested a strong anti-oxidant role of this nutraceutical against Cd harmful effects on kidney [67]. The protective effects of flavonoids against Cd toxicity are attributable to their functions to clear ROS, chelate Cd and thus lower the accumulation of Cd in *vivo*, reduce DNA damage and inhibit apoptosis [77]. Further research will benefit from evaluating the potentially protective effects of these compounds against Cd toxicity in the heart.

4. Conclusions

In summary, the establishment of a mouse model of Cd accumulation was demonstrated comprehensively. Various tissue samples, including the spinal bone, thigh bone, aorta, heart, kidney, lung, liver, intestine, serum and urine were investigated. We proved that the Cd would accumulate in all samples studied after chronic exposure. This research might help to explain the potential toxic effects of Cd on these organs, especially because the accumulation profiles have not been well studied previously. Compared with that of the Cd-100 group, the Cd concentration of the Cd-200 group in the kidney and aorta did not increase further. We speculated that the accumulation of Cd in these tissues was nearly saturated in the Cd-100 group. The calcium concentration in the bones and kidney declined when the exposure to Cd increased. This finding supported the negative and possibly direct toxic effects of Cd on bones. Although the body weight, blood pressure and heart rate did not change significantly upon Cd exposure, histologically significant structural changes were found in the heart. Our study suggests that the toxicity of Cd accumulation may play important roles in mediating the pathophysiological effects in these organs especially the bone and heart.

Author contributions

Yu-Ting Tai, Shing-Hsien Chou, Chien-Te Ho, Fu-Hsiang Ko, and Pao-Hsien Chu conceived and planned the experiments. Shing-Hsien Chou and Pao-Hsien Chu carried out the formal analysis. Yu-Ting Tai, Shing-Hsien Chou, Chien-Te Ho, Fu-Hsiang Ko, and Pao-Hsien Chu planned and carried out the methology. Shing-Hsien Chou, Chien-Te Ho, Hung-Chen Lin, and Shih-Ming Jung contributed to visualization. Yu-Ting Tai and Chia-Yun Cheng contributed to ICP-MS sample preparation and analysis. Yu-Ting Tai and Shing-Hsien Chou took the lead in writing the manuscript. Fu-Hsiang Ko and Pao-Hsien Chu provided critical feedback and helped shape the research, analysis and manuscript.

Authorship conformation form

All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version.

Conflict of interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

All foci coordinates, activation probability maps, in addition to the supplemental information will be available on ANIMA: a data-sharing initiative for neuro-imaging meta-analyses:anima.fz-juelich.de.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.toxrep.2022.01.002.

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