Original Article

Effect of cerium oxide on iron metabolism in mice

Yuki Kanome,[1] Shunki Ohtomo,[1] Masaharu Nakatsu,[2] Masahiro Kohno,[1] and Koji Fukui[1,*]

[1]Molecular Cell Biology Laboratory, Department of Systems Engineering and Science, Graduate School of Engineering and Science, Shibaura Institute of Technology, Fukasaku 307, Minuma-ku, Saitama 337-8570, Japan
[2]applause Company Limited, Biko building 4F, Shinkawa 2-24-2, Chuo-ku, Tokyo 104-0033, Japan

(Received 4 March, 2024; Accepted 27 April, 2024; Released online in J-STAGE as advance publication 27 August, 2024)

The use of metal nanoparticles such as cerium oxide nanoparticles (nanoceria) in living organisms is attracting increasing attention. We administered nanoceria to chronic kidney disease model rats, including a 5/6 nephrectomy model and adenine administration model rats, and reported high phosphorus adsorption capacity and renal function improvement effects of nanoceria. However, the iron ion concentration in the serum fluctuated significantly after administration. Therefore, we investigated changes in proteins related to iron metabolism following administration of nanoceria to normal mice without chronic kidney disease over different periods of time. Nanoceria were administered to 10-week-old C57BL/6 mice for 4 or 12 weeks. Another group was administrated lanthanum carbonate, which is currently used as a phosphorus adsorbent. The amount of iron in the serum and the concentration of transferrin in the liver were significantly increased following nanoceria administration, and the amount of iron in the liver was significantly decreased. There were no changes in serum hepcidin, ferroportin, cholesterol, or low-density lipoprotein levels. These results indicate that nanoceria administration can affect iron metabolism in mice. Although the detailed mechanism remains unknown, caution is warranted when considering biological utilization in the future.

***Key Words*: nanoceria, iron, kidney, CKD, mice**

Cerium oxide (CeO_2), an oxide of cerium (Ce), a lanthanide with atomic number 58, is the most abundant rare earth element in the Earth's crust. Cerium exists primarily as cerium oxide, cerium carbonate, cerium nitrate, and cerium hydroxide. Among cerium species, cerium oxide is most commonly used as a polishing agent for glass, and it is also added to automobile windshields due to its ability to absorb ultraviolet rays.[1,2] Cerium hydroxide and cerium carbonate reportedly exhibit high ion-adsorption properties; cerium hydroxide has been put to practical use as an adsorbent for phosphorus in water.[3] Cerium-based compounds are primarily used industrially.

However, in recent years, cerium has also been used in some biological applications. Cerium is also used as a cosmetic material due to its ability to absorb ultraviolet rays,[4] and cerium oxide nanoparticles (nanoceria) reportedly exhibit antioxidant effects.[5,6] We previously focused on the high phosphorus-adsorption capacity of cerium and investigated whether it could be used to treat hyperphosphatemia in chronic kidney disease (CKD).[7,8] The primary agent for treating hyperphosphatemia lanthanum is carbonate hydrate.[9] However, lanthanum carbonate hydrate has been associated with digestive system side effects such as vomiting and diarrhea.[10]

Therefore, we investigated the potential medical application of nanoceria by administering them to 5/6 nephrectomy model rats as a candidate substance to replace lanthanum carbonate hydrate for the treatment of hyperphosphatemia in CKD. *In vitro*, nanoceria showed a high capacity for phosphorus adsorption, equivalent to or greater than that of lanthanum carbonate; *in vivo*, serum urea nitrogen and creatinine values were significantly improved following nanoceria administration.[6] The detailed mechanism of the effectiveness of nanoceria remains unclear, however, one possible mechanism involves anion exchange between phosphate and the surface of the nanoceria particles.[11] The trivalent to tetravalent surface ratio seems to be important for the antioxidant activity of cerium oxide.[4] However, in this case, serum free iron concentrations were significantly lower (5-folds) in 5/6 nephrectomized rats treated with nanoceria than in untreated rats (data not shown). These results suggest that nanoceria are suitable for the treatment of extreme hyperphosphatemia in CKD, but the data suggest that it may also affect iron homeostasis *in vivo*. Iron is an essential mineral involved in oxygen transport in red blood cells.[12] Low serum iron leads to anemia, and the presence of iron ions is also closely related to ferroptosis, a type of cell death.[13,14] In this study, therefore, we investigated the effect of cerium oxide administration via nanoceria on iron metabolism in mice.

Methods

Animals. All animal experiments were performed with approval from the Animal Protection and Ethics Committee of Shibaura Institute of Technology, Tokyo, Japan (approval number #21005, permission obtained August 16, 2021). Ten-weeks-old C57BL6J male mice were purchased from Japan SLC, Inc. (Shizuoka, Japan) and housed under controlled conditions (22 ± 2°C, 12-h light/dark cycle). All mice were provided *ad libitum* access to food and water. After 1 week of habituation and feeding of Labo MR Stock (Nosan Corp., Kanagawa, Japan), the mice were fed a control diet (Ctrl; AIN93G, Funabashi Farm Co., Ltd., Chiba, Japan) or diet supplemented with either 0.5% lanthanum carbonate (NIKKI Corp., Saitama, Japan) (La) or 1.31% cerium oxide (Ce) for 4 or 12 weeks. Body weight as well as food and water intake were measured once per week. Following assessments, mice were euthanized, and blood, liver, kidney, heart and spleen samples were obtained for analysis.

Biochemical analysis. Blood was stored at room temperature (RT) for 1 h and centrifuged at 7,000 rpm for 20 min to separate serum. Blood urea nitrogen (BUN), creatinine (CRE), uric acid (UA), inorganic phosphate (IP), triglyceride (TG), total-cholesterol (T-CHO), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), iron (Fe), and unsaturated iron binding capacity (UIBC) were measured by an animal inspection service (Oriental Yeast Co., Ltd., Tokyo, Japan). Total iron binding capacity (TIBC) and transferrin saturation (TSAT) were calculated as Fe + UIBC and (Fe/TIBC) × 100, respectively.

*To whom correspondence should be addressed.
E-mail: koji@sic.shibaura-it.ac.jp

doi: 10.3164/jcbn.24-38

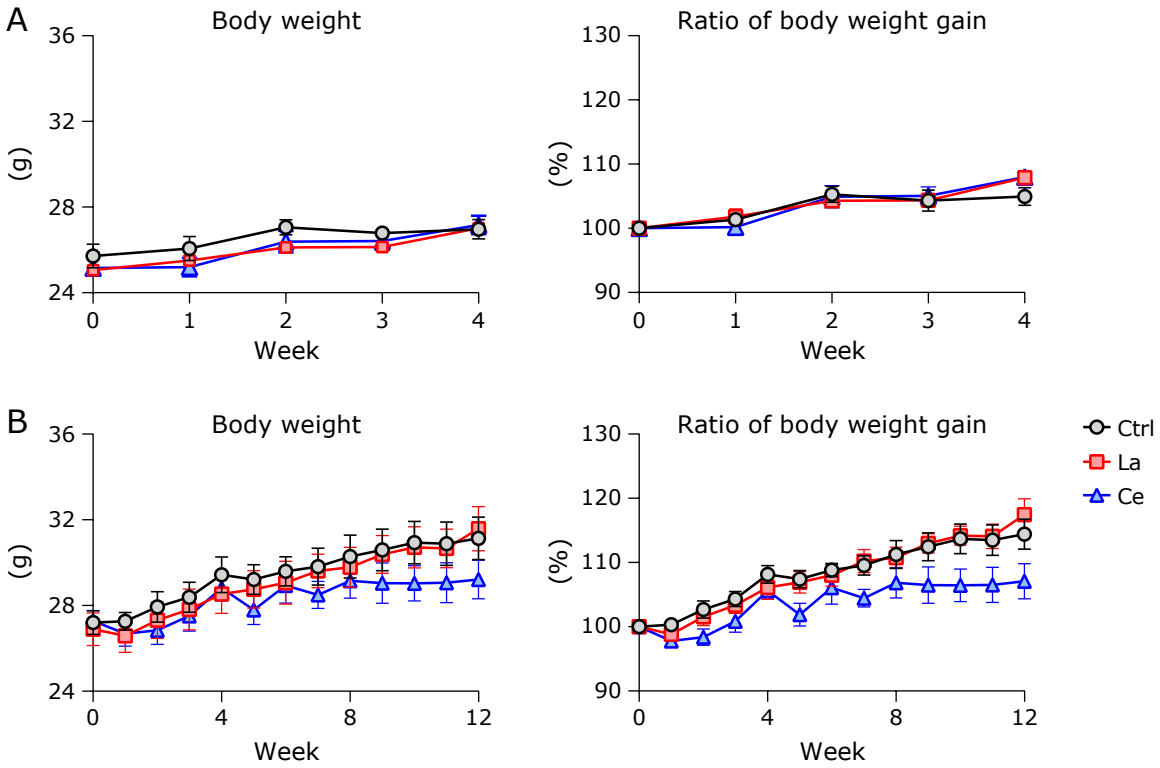

Fig. 1. Changes in the body weight and the ratio of body weight gain. Graphs show data for 4 (A) or 12 weeks (B) of treatment. Data are shown as mean ± SE. Statistical analyses were performed using two-way analysis of variance (ANOVA) and Tukey–Kramer test for post-hoc comparisons. $^{\#}p<0.05$ compared to the age matched La group. Ctrl, control diet, $n = 6$; La, lanthanum-added diet, $n = 6$; Ce, cerium-added diet, $n = 6$.

Western blotting. Twenty micrograms of sample protein were separated on 15% sodium dodecyl sulfate polyacrylamide gels. The proteins on the gels were then transferred on nitrocellulose membranes (Clear trans, 0.2 µm, #030-25643; FUJIFILM Wako Pure Chemical Corp., Osaka, Japan). The membranes were stained using Ponceau S solution (Sigma Aldrich Corp., St. Louis, MO). The membrane were blocked with 2% skim milk and incubated for 1 h at RT. After blocking, the membranes were reacted with anti-transferrin receptor (TfR) antibody (1:1,000, #ab84036; abcam plc., Cambridge, UK), anti-SLC40A1 (ferroportin; FPN) antibody (1:1,000, #ab78066; abcam plc.) and anti-hepcidin-25 (Hep) antibody (1:1,000, #ab30760; abcam plc.) overnight at 4°C. Anti-rabbit IgG HRP (Promega Co., Madison, WI) or anti-mouse IgG HRP (Promega Co.) antibodies were used as the secondary antibody at 1:4,000 dilution. After washing the membranes, chemiluminescent signals were detected using a LAS-3000 system (FUJIFILM Corp., Tokyo, Japan). Relative band intensities were measured using Image Quant TL software, ver. 8.2 (Cytiva, Tokyo, Japan).

Measurement of iron concentration. Sample homogenate was mixed with 1 M HCl, incubated at RT for 30 min, and centrifuged at 7,500 rpm and 4°C for 10 min. The iron level was measured using an Iron Assay kit (#FE02M; Metallogenics Co., Ltd., Chiba, Japan), according to the manufacturer's instructions. Samples were analyzed using a microplate reader at a wavelength of 750 nm.

Statistical analysis. All data are presented as means ± SE, and differences were analyzed using the Tukey–Kramer method with GraphPad Prism 9.2.0 (GraphPad Software Inc., San Diego, CA). $P<0.05$ was considered statistically significant.

Results

Treatment with nanoceria significantly decreased body weight. Mice were fed three different diets for 4 and 12 weeks, respectively, and body weight was measured weekly (Fig. 1). The body weight of mouse group gradually increased. The lanthanum-treated and control-diet groups did not differ at any time point, but in the nanoceria-treated group, the difference in body weight gradually increased relative to the other two groups. The body weight of the nanoceria-treated group tended to decrease relative to the other two groups. However, the difference was not significant differences in any weeks in either treatment period.

Long-term treatment with nanoceria increased serum iron levels. After completion of the two different feeding periods for each diet, serum was collected and used to analyze iron-related parameters. After 4 weeks of treatment, TIBC was significantly increased in the nanoceria-treated group compared with the controls (Fig. 2). Irons levels and the iron parameters UIBC and TIBC were significantly increased after 12 weeks of treatment with nanoceria compared with the age-matched controls. TIBC scores were significantly higher after with 12 weeks of treatment with nanoceria compared with the other two groups.

Nanoceria treatment did not affect other serum indices, regardless of administration period. There were no significant differences between any of the serum indices in any mouse group or treatment period (Table 1).

Nanoceria treatment did not affect tissue weight during any administration period. The weight of the kidney, liver, spleen, and heart was measured for the mice in each group (Fig. 3). There were no significant differences in the weight of any of the tissues between any group or treatment period.

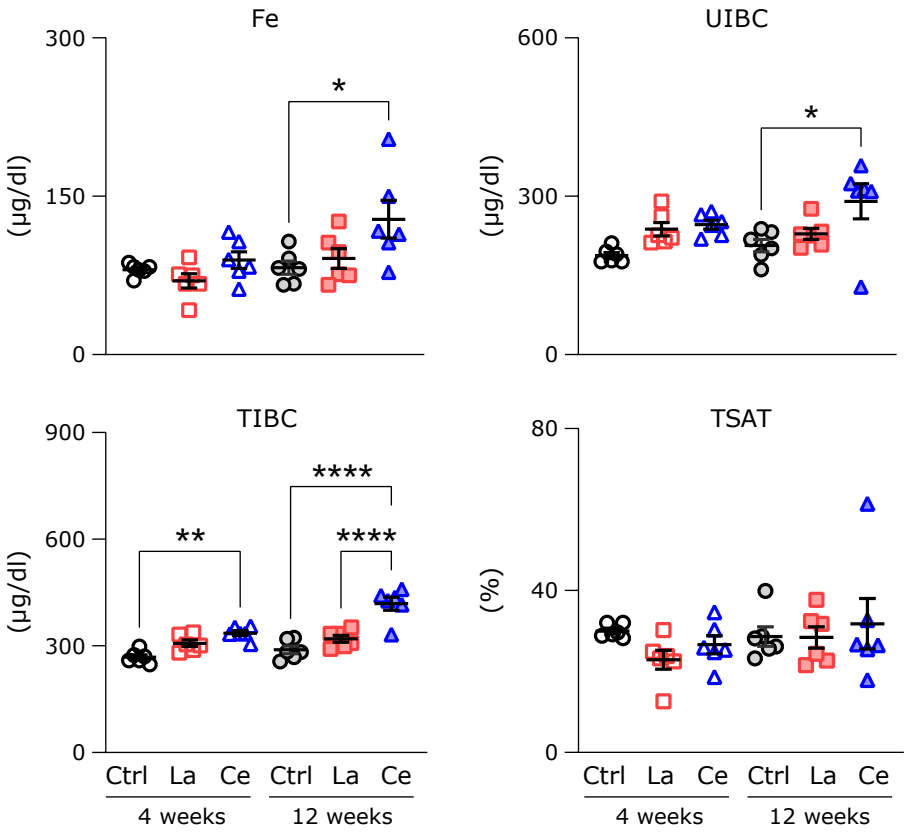

Fig. 2. Changes in iron-related serum indices in each group. Iron (Fe) and unsaturated iron-binding capacity (UIBC) were measured. Total iron-binding capacity (TIBC) and transferrin saturation (TSAT) were calculated according to Fe + UIBC and (Fe/TIBC) × 100, respectively. Ctrl, control diet, $n = 6$; La, lanthanum-added diet, $n = 6$; Ce, cerium added diet, $n = 6$. Each diet was administrated for 4 and 12 weeks. Data are shown as mean ± SE. Statistical analyses were performed using the Tukey–Kramer method. *p<0.05, **p<0.01, ****p<0.0001.

Table 1. Serum parameters in each mouse

	Weeks	Ctrl	La	Ce
BUN (mg/dl)	4	31.0 ± 2.49	30.3 ± 4.08	26.2 ± 1.77
	12	31.9 ± 1.45	37.9 ± 3.91	32.7 ± 3.88
CRE (mg/dl)	4	0.12 ± 0.01	0.12 ± 0.01	0.11 ± 0.00
	12	0.13 ± 0.01	0.14 ± 0.01	0.13 ± 0.01
UA (mg/dl)	4	1.75 ± 0.27	1.70 ± 0.20	1.73 ± 0.23
	12	2.13 ± 0.34	2.40 ± 0.22	2.14 ± 0.23
IP (mg/dl)	4	9.05 ± 0.45	8.67 ± 0.44	8.60 ± 0.25
	12	7.60 ± 0.42	9.37 ± 0.43	8.20 ± 0.54
TG (mg/dl)	4	120.0 ± 7.84	129.3 ± 13.21	128.7 ± 6.82
	12	53.2 ± 4.53	64.2 ± 6.80	66.8 ± 6.09
T-CHO (mg/dl)	4	120.2 ± 3.27	104.3 ± 8.55	114.3 ± 8.93
	12	100.3 ± 8.06	101.3 ± 7.64	98.8 ± 6.29
LDL-C (mg/dl)	4	5.17 ± 0.31	5.00 ± 0.37	4.33 ± 0.42
	12	3.17 ± 0.65	2.83 ± 0.31	2.50 ± 0.34
HDL-C (mg/dl)	4	71.0 ± 2.00	58.3 ± 5.54	67.0 ± 6.00
	12	58.3 ± 5.40	61.2 ± 6.26	62.3 ± 5.26
AST (IU/L)	4	58.3 ± 2.01	66.0 ± 6.24	63.0 ± 6.72
	12	68.8 ± 7.12	62.5 ± 5.12	76.5 ± 7.35
ALT (IU/L)	4	17.3 ± 1.28	17.7 ± 2.92	17.8 ± 1.42
	12	20.7 ± 1.86	16.2 ± 0.87	20.5 ± 3.97

doi: 10.3164/jcbn.24-38

		4 weeks		12 weeks	
		(g)	(g/100 g b.w.)	(g)	(g/100 g b.w.)
Liver	Ctrl	0.85 ± 0.02	3.16 ± 0.06	0.88 ± 0.05	2.81 ± 0.13
	La	0.77 ± 0.04	2.86 ± 0.15	0.86 ± 0.04	2.73 ± 0.12
	Ce	0.80 ± 0.06	2.96 ± 0.20	0.82 ± 0.02	2.83 ± 0.10
Kidney	Ctrl	0.28 ± 0.01	1.03 ± 0.02	0.34 ± 0.01	1.09 ± 0.05
	La	0.29 ± 0.01	1.09 ± 0.03	0.34 ± 0.02	1.06 ± 0.04
	Ce	0.29 ± 0.01	1.07 ± 0.02	0.33 ± 0.02	1.14 ± 0.04
Heart	Ctrl	0.11 ± 0.00	0.40 ± 0.01	0.15 ± 0.01	0.47 ± 0.03
	La	0.12 ± 0.01	0.43 ± 0.03	0.14 ± 0.01	0.44 ± 0.02
	Ce	0.11 ± 0.00	0.41 ± 0.01	0.13 ± 0.01	0.46 ± 0.02
Spleen	Ctrl	0.06 ± 0.00	0.22 ± 0.02	0.07 ± 0.00	0.23 ± 0.01
	La	0.06 ± 0.00	0.23 ± 0.02	0.07 ± 0.00	0.21 ± 0.01
	Ce	0.06 ± 0.00	0.20 ± 0.01	0.06 ± 0.01	0.21 ± 0.02

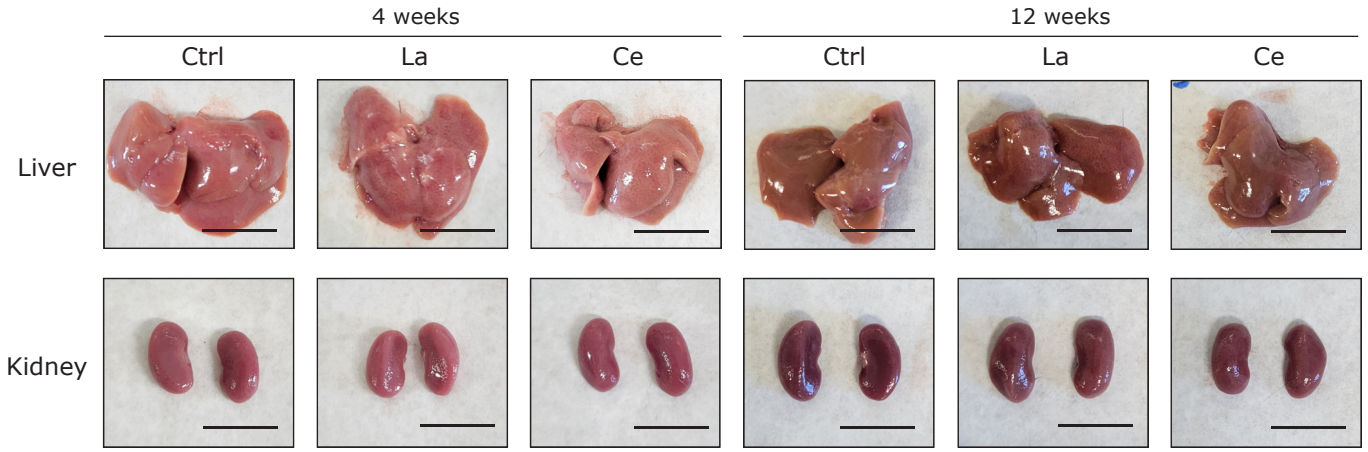

Fig. 3. Tissue weight and representative images of liver and kidney in each mouse group. The weight of the liver, kidney, heart, and spleen were determined in each mouse group (A). Representative photographs of liver and kidney from each group (B). Ctrl, control diet, $n = 6$; La, lanthanum-added diet, $n = 6$; Ce, cerium-added diet, $n = 6$. Treatment periods for each diet were 4 and 12 weeks. Data are shown as mean ± SE. Statistical analyses were performed using the Tukey–Kramer method. Scale bars are 1 cm.

Transferrin receptor protein expression significantly increased in mice treated with long-term nanoceria administration. Levels of iron-related proteins in the liver were compared using Western blotting. The expression level of TfR, a receptor that takes up iron from the blood, was significantly increased in the nanoceria-treated group compared with the other two groups. However, there were no differences between the groups in the expression levels of FPN, which releases iron from organs into the blood, and there were no differences in the levels of Hep.

Organ iron content was significantly lower after treatment with nanoceria. The amount of iron in the liver and spleen was measured using a metalloassay kit. After 4 and 12 weeks of treatment with nanoceria, the level of iron in liver and spleen was significantly reduced compared with the other two groups. In the spleen, the iron level 4 weeks after initiation of treatment with nanoceria was significantly lower than that in the lanthanum-treated group, and the iron content 12 weeks after initiation of treatment with nanoceria was significantly lower than that of the other two groups.

Discussion

Long-term treatment with nanoceria tended to decrease body weight in mice. Iron is normally involved in oxygen transport and DNA synthesis as hemoglobin, but it has been reported that excessive iron induces the Fenton reaction and puts cells and tissues in a state of oxidative stress.[12,15] When dietary heme iron and non-heme iron are absorbed from the small intestine, non-heme iron is reduced to divalent iron via duodenal cytochrome B reductase in the membrane of intestinal epithelial cells. It is then taken up into cells via divalent metal transporter 1 and transported into the blood by FPN within the blood vessel lumen. After being absorbed, iron is bounded by transferrin in the blood and transported to various tissues. Iron is stored in the liver and spleen as ferritin.[16–18] Almost no iron is excreted from the body; only trace amounts are excreted through the sloughing of gastrointestinal epithelial cells and through the urine and sweat.[19,20] Therefore, to investigate the effect of nanoceria administration on iron metabolism, nanoceria were mixed into the mouse feed and administered for short and long terms. These mice were compared to a control group of mice treated with

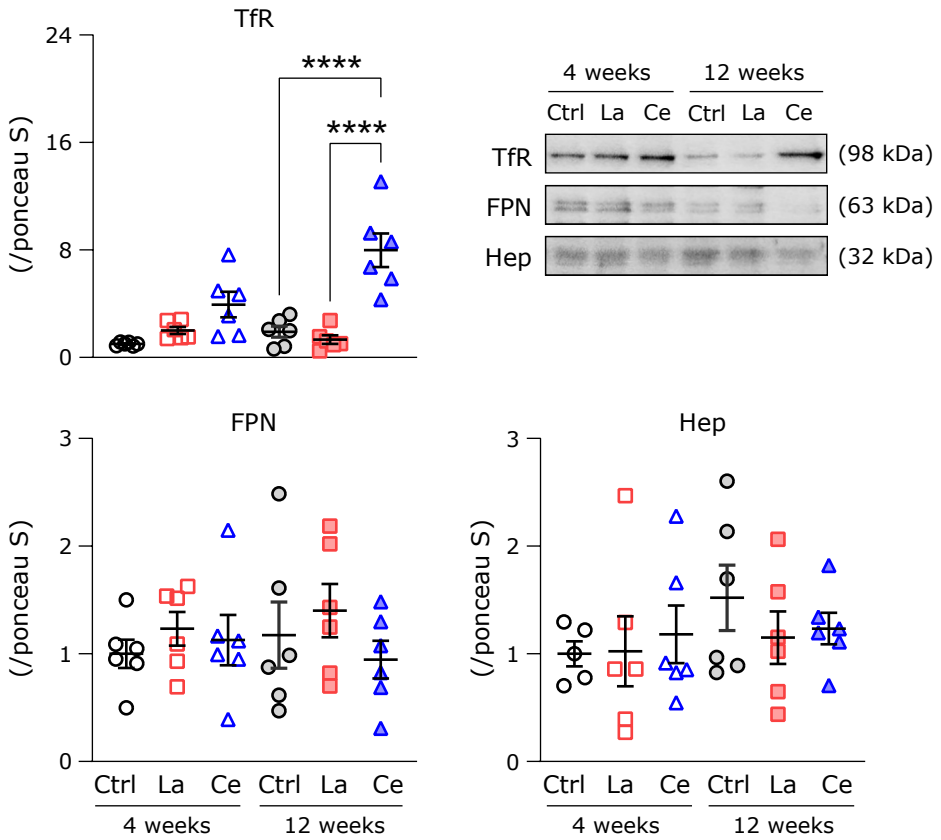

Fig. 4. Western blotting analysis of TfR, FPN, and Hep expression of mouse liver. Ctrl, control diet, $n = 6$; La, lanthanum-added diet, $n = 6$; Ce, cerium-added diet, $n = 6$. Treatment periods for each diet were 4 and 12 weeks. Data are shown as mean ± SE. Statistical analyses were performed using the Tukey–Kramer method. ****$p<0.0001$.

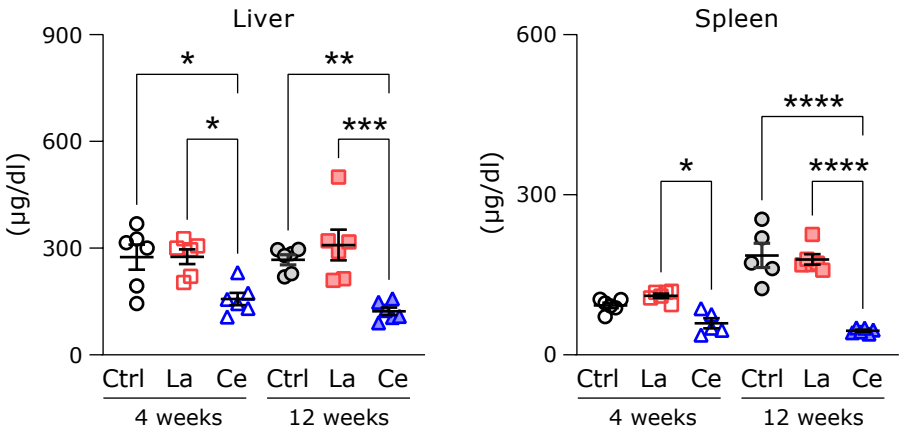

Fig. 5. Iron concentration in each liver and spleen. Ctrl, control diet, $n = 6$; La, lanthanum-added diet, $n = 6$; Ce, cerium added diet, $n = 6$. Treatment periods for each diet were 4 and 12 weeks. Data are shown as mean ± SE. Statistical analyses were performed using the Tukey–Kramer method. *$p<0.05$, **$p<0.01$, ***$p<0.001$, ****$p<0.0001$.

lanthanum carbonate, which is currently used as a phosphorus adsorbent.

After short-term administration of nanoceria, there was no significant difference in body weight between any of the groups. However, with long-term treatment, mice treated with nanoceria tended to lose weight, but the difference was not significant compared with the other two groups (Fig. 1). There was no significant difference in food intake between the two groups after short-term treatment, but food intake in the long-term nanoceria-treated group declined significantly compared with the other two groups. There were no significant differences in water intake with either treatment period or diet. There was no difference in organ weight between any of the groups (Fig. 3).

Rocca *et al.*[21] conducted an experiment in which 3T3-L1 cells (mouse fibroblasts) were treated with nanoceria at 20 μg/ml. The mRNA expression levels of the adipogenesis-related genes *Glycerol-3-phosphate dehydrogenase 1*, *Lipoprotein lipase*, and *Peroxisome proliferator-activated receptor gamma* decreased, and

doi: 10.3164/jcbn.24-38

glyceraldehyde-3-phosphate dehydrogenase activity decreased. Furthermore, intraperitoneal administration of nanoceria (0.5 mg/kg) once every 2 weeks for 6 weeks to Wistar rats suppressed weight gain. The authors reported that administration of nanoceria reduced the level of triglyceride synthesis in rats and suppressed weight gain.[21] Furthermore, Lopez-Pascual *et al.*[22] proposed that treatment of inflamed 3T3-L1 cells with nanoceria reduced extracellular reactive oxygen species, suggesting that nanoceria may have an insulin-sensitizing effect. However, in our present study, although weight gain was suppressed, no differences were observed in serum cholesterol or triglyceride concentrations. Therefore, whether nanoceria exert an anti-obesity effect remains to be determined.

Possibility of interaction between nanoceria and iron. Mice were fed the lanthanoids lanthanum carbonate and nanoceria for 4 or 12 weeks, and levels of various iron-related proteins were measured in serum and organs. Serum levels of iron and proteins related to iron metabolism did not change during either treatment period in the lanthanum carbonate treatment group compared with the control group (Fig. 2). However, in the nanoceria-treated group, blood Fe, UIBC, and TIBC concentrations increased significantly compared with the control group 12 weeks after initiation of treatment. In the nanoceria-treated group, the TfR level tended to increase compared with the other groups with short-term treatment, and its expression level increased significantly compared with other groups following long-term administration (Fig. 4). Furthermore, the level of iron in the liver and spleen of the nanoceria group was significantly reduced compared with the other two groups, regardless of the treatment period (Fig. 5).

We did not anticipate that treatment with nanoceria would significantly reduce the level of iron in the organs. This is because when similar experiments were previously performed in rats, the level of iron in the organs increased significantly. The reason for this discrepancy is unknown, but it may be that mice absorb more nanoceria from the diet than rats. In previous experiments, nanoceria were studied as a candidate phosphorus adsorbent, and inductively coupled plasma mass spectrometry analysis confirmed the presence of trace amounts of nanoceria in organs.[8]

Experiments conducted by others have compared mouse strains. When nanoceria were administered to C57BL/6 and BALB/C mice, tissue cerium levels increased more in C57BL/6 mice.[23] Furthermore, it has been suggested that the level of nanoceria in the organs may vary greatly depending on the size of the nanoceria and the method of administration.[24] Fernandez-Varo *et al.*[25] reported that as a result of a single administration of nanoceria (5.7 mg/kg body weight), a large amount of nanoceria accumulated in the liver and spleen by the 100th day of administration. This suggests that nanoceria are taken up into the bloodstream and accumulate in the liver and spleen, inhibiting iron absorption in these organs. It is thought that as a result of the difficulty of storing iron in the liver and spleen, the iron concentration in the blood increases, and the expression level of TfR in the liver increases, promoting absorption. However, the absorption mechanism of nanoceria is unknown. Additonally, we did not measure the level of nanoceria in the liver or spleen in this experiment. Our previous preliminary tests detected small amounts of cerium in the liver and kidneys of rats. We fed 4-week-old Wistar rats a diet supplemented with 1.31% nanoceria for 4 weeks. Cerium was detected at concentrations of 0.67 μg/g tissue in the liver and 0.27 μg/g tissue in the kidneys, but below the detection limit in the blood. This suggests that nanoceria can be absorbed by rodents even in small amounts. Further studies are thus required to evaluate this hypothesis. Another possibility involves an interaction between nanoceria and iron oxide. Several reports have mentioned the possibility of mutual bonding between nanoceria and iron oxide.[26] Furthermore, it has been reported that transferrin itself causes abnormal iron metabolism by binding to nanoceria.[27]

Due to antioxidant activity, nanoceria are thought to be effective for treating hepatitis.[28] Our previous research also suggests that nanoceria may be effective in treating kidney failure.[7,8] However, nanoceria are metal nanoparticles, and many details regarding their effects on living organisms remain unknown. Our results suggest that nanoceria administration can affect iron metabolism, although our data only pertain mice. However, it is highly possible that this problem can be improved by varying the administration period, dosage, administration method, and/or nanoparticle manufacturing method. Further research is needed to clarify the effectiveness of nanoceria.

Author Contributions

Conceptualization, KF; Data curation, YK, SO, and KF; Formal analysis, YK and KF; Investigation, KF; Resources, MN; Project administration, KF; Supervision, MK and KF; Writing-review and editing, KF; All other contributions to the research, KF. All authors have read and agreed to the published version of the manuscript.

Funding

This research was conducted under a joint research agreement between Shibaura Institute of Technology and applause Co. Ltd. The research funding was provided by applause Co. Ltd.

Conflict of Interest

MN is an employee of applause Co., Ltd., which sells a nanoceria product with a similar, but not identical formulation as the one used in this study. The nanoceria used in the study were not the commercially available product but rather one produced by applause Co., Ltd. For research use. The sponsor had no role in the data interpretation, writing, or publication of this work. The other authors declare no conflicts of interest.

References

1 Stanek CR, Tan AHH, Owens SL, Grimes RW. Atomistic simulation of CeO_2 surface hydroxylation: implications for glass polishing. *J Mater Sci* 2008; **43**: 4157–4162.
2 Álvarez-Asencio R, Corkery RW, Ahniyaz A. Solventless synthesis of cerium oxide nanoparticles and their application in UV protective clear coatings. *RSC Adv* 2020; **10**: 14818–14825.
3 Ogata F, Tominaga H, Yabutani H, Kawasaki N. Phosphate adsorption ability of granular gibbsite and cerium hydroxide. *J Oleo Sci* 2011; **60**: 133–138.
4 Zambon A, Malavasi G, Pallini A, Fraulini F, Lusvardi G. Cerium containing bioactive glasses: a review. *ACS Biomater Sci Eng* 2021; **7**: 4388–4401.
5 Barker E, Shepherd J, Asencio IO. The use of cerium compounds as antimicrobials for biomedical applications. *Molecules* 2022; **27**: 2678.
6 Li C, Shi X, Shen Q, Guo C, Hou Z, Zhang J. Hot topics and challenges of regenerative nanoceria in application of antioxidant therapy. *J Nanomater* 2018; 4857461. DOI: 10.1155/2018/4857461
7 Hashimoto A, Gao J, Kanome Y, *et al*. Evaluation of cerium oxide as a phosphate binder using 5/6 nephrectomy model rat. *BMC Nephrol* 2022; **23**: 277.
8 Kanome Y, Gao J, Hashimoto A, *et al*. Effects of cerium oxide nanoparticles on adenine-induced chronic kidney disease model rats. *Geriatr Gerontol Int* 2024; **24 Suppl 1**: 88–95.
9 Hutchison AJ, Maes B, Vanwalleghem J, *et al*. Efficacy, tolerability, and safety of lanthanum carbonate in hyperphosphatemia: a 6-month, randomized,

comparative trial versus calcium carbonate. *Nephron Clin Pract* 2005; **100**: c8–c19.
10 Xu J, Zhang YX, Yu XQ, *et al*. Lanthanum carbonate for the treatment of hyperphosphatemia in CKD5D: multicenter, double blind, randomized, controlled trial in mainland China. *BMC Nephrol* 2013; **14**: 29.
11 Römer I, Briffa SM, Arroyo Rojas Dasilva Y, *et al*. Impact of particle size, oxidation state and capping agent of different cerium dioxide nanoparticles on the phosphate-induced transformations at different pH and concentration. *PLoS One* 2019; **14**: e0217483.
12 Zeidan RS, Han SM, Leeuwenburgh C, Xiao R. Iron homeostasis and organismal aging. *Ageing Res Rev* 2021; **72**: 101510.
13 Elstrott B, Khan L, Olson S, Raghunathan V, DeLoughery T, Shatzel JJ. The role of iron repletion in adult iron deficiency anemia and other diseases. *Eur J Hematol* 2020; **104**: 153–161.
14 Li Z, Jiang L, Chew SH, Hirayama T, Sekido Y, Toyokuni S. Carbonic anhydrase 9 confers resistance to ferroptosis/apoptosis in malignant mesothelioma under hypoxia. *Redox Biol* 2019; **26**: 101297.
15 Abe C, Miyazawa T, Miyazawa T. Current use of Fenton reaction in drugs and food. *Molcules* 2022; **27**: 5451.
16 Camaschella C, Nai A, Silvestri L. Iron metabolism and iron disorders revisited in the hepcidin era. *Haematologica* 2020; **105**: 260–272.
17 Roemhid K, von Maltzahn F, Weiskirchen R, Knüchel R, von Stillfried S, Lammers T. Iron metabolism: pathophysiology and pharmacology. *Trends Pharmacol Sci* 2021; **42**: 640–656.
18 Abbasi U, Abbina S, Gill A, Takuechi LE, Kizhakkedathu JN. Role of iron in the molecular pathogenesis of diseases and therapeutic opportunities. *ACS Chem Biol* 2021; **16**: 945–972.
19 Chifman J, Laubenbacher R, Torti SV. A systems biology approach to iron metabolism. *Adv Exp Med Biol* 2014; **844**: 201–225.
20 Nakatani S, Nakatani A, Ishimura E, *et al*. Urinary iron excretion is associated with urinary full-length megalin and renal oxidative stress in chronic kidney disease. *Kidney Blood Press Res* 2018; **43**: 458–470.
21 Rocca A, Moscato S, Ronca F, *et al*. Pilot *in vivo* investigation of cerium oxide nanoparticles as a novel anti-obesity pharmaceutical formulation. *Nanomedicine* 2015; **11**: 1725–1734.
22 Lopez-Pascual A, Urrutia-Sarratea A, Lorente-Cebrián S, Martinez JA, González-Muniesa P. Cerium oxide nanoparticles regulate insulin sensitivity and oxidative markers in 3T3-L1 adipocytes and C2C12 myotubes. *Oxid Med Cell Longev* 2019; **2019;** 2695289.
23 Yokel RA, Tseng MT, Butterfield DA, *et al*. Nanoceria distribution and effects are mouse-strain dependent. *Nanotoxicology* 2020; **14**: 827–846.
24 Carlander U, Moto TP, Desalegn AA, Yokel RA, Johanson G. Physiologically based pharmacokinetic modeling of nanoceria systemic distribution in rats suggests dose- and route-dependent biokinetics. *Int J Nanomedicine* 2018; **13**: 2631–2646.
25 Fernandez-Varo G, Perramon M, Carvajal S, *et al*. Bespoken nanoceria: an effective treatment in experimental hepatocellular carcinoma. *Hepatology* 2020; **72**: 1267–1282.
26 Turin-Moleavin IA, Fifere A, Lungoci AL, *et al*. *In vitro* and *in vivo* antioxidant activity of the new magnetic-cerium oxide nanoconjugates. *Nanomaterials (Basel)* 2019; **9**: 1565.
27 Butterfield AD, Wang B, Wu P, *et al*. Plasma and serum proteins bound to nanoceria: insights into pathways by which nanoceria may exert its beneficial and deleterious effects *in vivo*. *J Nanomed Nanotechnol* 2020; **11**: 546.
28 Córdoba-Jover B, Arce-Cerezo A, Ribera J, *et al*. Cerium oxide nanoparticles improve liver regeneration after acetaminophen-induced liver injury and partial hepatectomy in rats. *J Nanobiotechnology* 2019; **17**: 112.

doi: 10.3164/jcbn.24-38