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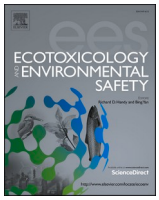

Distributions of mercury and selenium in rats ingesting mercury selenide nanoparticles

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ABSTRACT

Mercury (Hg) is one of the most toxic environmental pollutants, and is biocondensed via the food chain. Selenium (Se) is an essential element that possesses an antagonistic property towards Hg in vivo. The antagonistic property is explained by the assumption that Hg and Se directly interact to form HgSe nanoparticles (HgSe NPs) in organs. It is presumed that the toxic effects of HgSe NPs are lower than that of ionic Hg; however, no precise evaluation has been conducted so far. In the present study, we evaluated the distribution of HgSe NPs ingested in Se-deficient rats. The recovery of serum selenoproteins from a deficient level was not observed in rats orally administered HgSe NPs. In addition, the excretion of Hg and Se via urine was not observed. Interestingly, the biosynthesis of selenoproteins and urinary selenometabolites would have required the production of selenide through the degradation of HgSe NPs. Therefore, it seems that selenide and Hg are not released from HgSe NPs in vivo. The administration of HgSe NPs did not increase Hg and Se concentrations in organs, and almost all HgSe NPs were recovered in feces, indicating no or low bioaccessibility of HgSe NPs even in Se-deficient rats. These results suggest that HgSe NPs are biologically inert and do not become a secondary environmental pollutant of Hg.

1. Introduction

Mercury (Hg) is a highly toxic heavy metal that acts as an environmental toxicant by cycling through soil, water, and atmosphere in various chemical forms. Hg is released to the environment by both natural and anthropogenic processes. Oceans are considered remarkable pools of Hg in the environment because two-thirds of anthropogenic Hg is deposited in the ocean at less than 1000 m depth where much edible fish live (Lamborg et al., 2014). In this regard, fish and shellfish are the main route of Hg exposure for ichthyophagous people. There are several Hg species in ocean, such as volatile Hg (Hg^0) and inorganic Hg (Hg^+/Hg^{2+}), and these species are converted into methylmercury (MeHg) by redox reactions and methylation in the marine environment (Batrakova et al., 2014). MeHg is considered a more potent toxicant than inorganic Hg species because differences in their physicochemical properties result in the unique distribution of MeHg in the body (Yang et al., 2020). In fact, MeHg produces various toxicities, such as neurological, renal, and immunological damage as well as developmental retardation (Li et al., 2010).

In marine animals, Hg is accumulated via the food web, i.e., Hg bioconcentration in predators more severely and rapidly progresses than that in prey. Specific mechanisms to ameliorate Hg toxicity in marine animals have been reported. The biotransformation of MeHg into inorganic Hg, namely, demethylation, is the initial mechanism of such amelioration. Because MeHg is more efficiently absorbed from gut than inorganic Hg, the biotransformation of MeHg into inorganic Hg leads to reduced toxicity. Intestinal microflora has been suggested to play a role in the biotransformation to avoid MeHg ingestion (Guo et al., 2018; Liu et al., 2019). However, MeHg is still efficiently absorbed from gut even though a part of MeHg is demethylated. Marine animals have another mechanism to reduce Hg toxicity, which is antagonism between Hg and selenium (Se) (Azad et al., 2019). Se, an essential element, exerts a variety of effects on Hg toxicity (Azad et al., 2019). It was reported that the simultaneous injection of lethal doses of mercury chloride and sodium selenite did not result in death in the experimental animals. The most acceptable explanation is that Se directly interacts with inorganic Hg to

Abbreviations: CV-AAS, Cold vapor atomic absorption spectrophotometry; GPX3, Glutathione peroxidase 3; HPLC, High-performance liquid chromatography; ICP-MS, Inductively coupled plasma mass spectrometry; NPs, Nanoparticles; SELENOP, Selenoprotein P.

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form an insoluble complex, mercury selenide (HgSe) (Orr et al., 2020). Indeed, HgSe nanoparticles (NPs) were detected in the liver of marine mammals ranked in a high trophic level of the food web (Nakazawa et al., 2011) and in the liver, kidney and muscle in giant petrels (Manceau et al., 2021). Although the formation of HgSe NPs is actually speculated to reduce the toxicity of Hg, the toxicity of HgSe NPs itself have not been evaluated. Because ionic forms of Hg and Se are more toxic than HgSe NPs, decomposition of HgSe NPs is particularly a key reaction for the onset of HgSe NPs toxicity. On the other hand, there are many literatures to addressing the toxicity of metallic NPs. In this case, Hg and Se of HgSe NPs must be distributed together in a body. In addition, Hg and Se transportations in the form of HgSe NPs from prey to predator via a food chain have not been also investigated.

Taken together all concerns mentioned above, in this study, we focused on the distributions of Hg and Se in the major organs and excreta of experimental animals orally administered with HgSe NPs. The distributions of Hg and Se could lead us to the discussion for the toxicity of HgSe NPs. In particular, the data could give us the clue whether HgSe NPs are distributed after the decomposition of HgSe NPs in an animal body or without the decomposition.

2. Materials and methods

2.1. Materials

Sodium selenite and methylmercury chloride were purchased from Nacalai Tesque (Kyoto, Japan) and Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan), respectively. HgSe NPs were synthesized in our laboratory in accordance with previous work (Bouzas-Ramos et al., 2016; Cid-Barrio et al., 2020). Nitric acid was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Sulfuric acid and tin(II) chloride dihydrate were purchased from Kanto Chemical Co., Inc. (Tokyo, Japan). Trizma® hydrochloride solution (1 M, pH 7.4) was purchased from Sigma Aldrich (Tokyo, Japan).

2.2. Animal care

All animal experiments were conducted in accordance with the "Principles of Laboratory Animal Care" (NIH version, revised 1996) and the Guidelines of the Animal Investigation Committee, Chiba University, Japan. Specific pathogen free (SPF) male Wistar rats (4 weeks of age) were purchased from Japan SLC (Shizuoka, Japan) and housed in a humidity-controlled room maintained at 25 ± 2 °C with a 12 h light-dark cycle. The rats were fed a commercial diet containing an adequate amount of Se (MF, Oriental Yeast Co., Ltd., Tokyo, Japan) and tap water ad libitum for acclimation. After a one-week acclimation period, the diet and water were changed to a Se-deficient diet (Oriental Yeast) and Milli-Q water (18.3 MΩ cm), respectively. The rat fed the Se-deficient diet and the Milli-Q water for 3 weeks was defined as a Se-deficient rat. The rats continuously fed the commercial diet and tap water were used as positive control for the evaluation of Se nutritional availability.

2.3. Speciation of Se in rat serum

The Se-deficient rats were orally administered selenite and/or MeHg or HgSe NPs dissolved or suspended in saline at the dose of 10 μg Se/rat once or 25 μg Hg/rat once a day for two consecutive days. The saline-administered rats served as negative control (neg). The experimental groups including the control consisted of 3 rats. The administered rats were sacrificed 24 h after the second administration by exsanguination under anesthesia. Non-heparinized blood was collected from the rats and then centrifuged at 1600×*g* for 10 min to obtain serum. The serum was stored at − 30 °C in a freezer until the following analysis, and a 20 μL aliquot of the serum was applied to an HPLC coupled with an ICP-MS (LC-ICP-MS) to analyze Se species in the serum. A tandem-type ICP-MS (Agilent 8800; Agilent Technologies, Hachioji, Japan) was used. The HPLC system (Prominence, Shimadzu, Kyoto, Japan) consisted of an on-line degasser, an HPLC pump, a Rheodyne six-port injector, and a multi-mode size exclusion column (Shodex GS-520HQ, exclusion size > 300,000 Da, 7.5 i.d. × 300 mm with a guard column; Showa Denko, Tokyo, Japan). The column was eluted with 50 mM Tris-HCl, pH 7.4, at the flow rate of 0.6 mL/min. The eluate was introduced directly into the nebulizer and analyzed with ICP-MS using the O_2 mass shift mode (ICP-MS/MS), where *m/z* 80 and 96 were selected as the Q1 and Q3 targets, representing ^{80}Se and $^{80}Se^{16}O$, respectively. The operating conditions of ICP-MS/MS were follows: He gas flow rate, 1 mL/min; and O_2 gas flow rate, 0.3 mL/min.

2.4. Quantification of Se and Hg in rat organs

Brain, liver, kidney, spleen, testis, and small and large intestines were collected from the rats mentioned above. The collected organs were stored at − 30 °C in a freezer until the following analysis. A 1 g portion of collected liver and other intact organs were homogenized with the same weight volume of 50 mM Tris-HCl, pH 7.4. For Se quantification, a 500 mg aliquot of the 50 w/w% homogenate was mixed with 1000 μL of concentrated nitric acid (ca. 60%) in a glass test tube, and the mixture was ashed at 130 °C for a few days until the precipitate disappeared. Se concentration in the samples was determined with ICP-MS. For Hg quantification, a 200 mg aliquot of 50 w/w % homogenate was mixed with 500 μL of concentrated nitric acid and 500 μL of sulfuric acid, and the mixture was ashed at 230 °C for 2 h. The amount of Hg in the samples was determined by cold vapor atomic absorption spectrophotometry (CV-AAS) (RA-5A; Nippon Instruments Corporation, Tokyo, Japan). We daily checked the validation of our analytical techniques according to the manufacture's instruction.

2.5. Quantification of Se and Hg in rat urine and feces

A rat was housed in a metabolic cage, and urine and feces were collected every 24 h from 24 h before the first administration to 24 h after the second administration. The collected urine was stored at − 30 °C prior to use. The collected feces were lyophilized and then stored at − 30 °C prior to use. For Se quantification, a 400 μL aliquot of the collected urine or a 50 mg portion of the lyophilized feces was mixed with 500 μL of concentrated nitric acid in a test tube, and the mixture was ashed at 130 °C for several days until the precipitate in the test tube disappeared. Se concentration in the samples was determined with an ICP-MS. For Hg quantification, a 400 μL aliquot of the collected urine or a 10 mg portion of the lyophilized feces was mixed with 500 μL of concentrated nitric acid and 500 μL of sulfuric acid in a test tube, and the mixture was ashed at 230 °C for 2 h. The amount of Hg in the samples was determined by CV-AAS.

2.6. Statistical analysis

All determinations were performed in triplicate and the results are shown as means ± SD. Statistical analysis was conducted by applying the one-way or two-way analysis of variance (ANOVA) with the Tukey test. A probability of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Nutritional availability of HgSe NPs as Se source

To determine the nutritional availability of selenite with or without MeHg, and HgSe NPs, two serum selenoproteins, glutathione peroxidase 3 (GPX3) and selenoprotein P (SELENOP), were measured by LC-ICP-MS. Each serum selenoprotein was eluted from the multi-mode column at the retention time of 11.0 and 13.5 min, respectively (Fig. 1).

The concentrations of the two selenoproteins in the serum of Se-deficient rats significantly decreased relative to those in normal rats

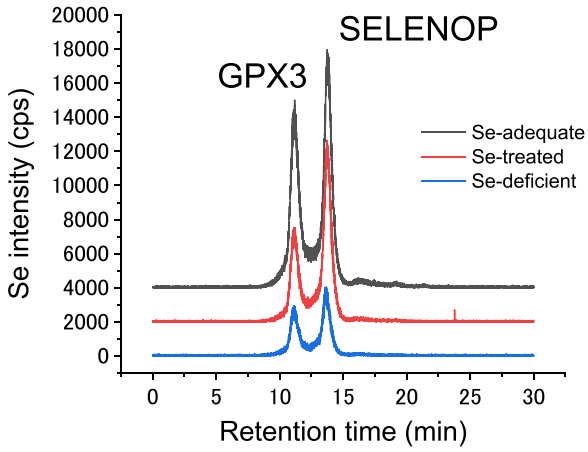

Fig. 1. LC-ICP-MS elution profiles of Se in rat serum.

fed commercial diet; thus, the recovery of selenoproteins in Se-deficient rats treated with Se compounds would be a good index of the nutritional availability of Se compounds (Takahashi et al., 2017). As can be clearly seen in Fig. 2, selenite was significantly recovered the amounts of both selenoprotein levels (GPX3: 49.4 ± 2.07%, SELENOP: 81.3 ± 2.68%), and the recovery in the rats administered selenite and MeHg was comparable to the rats administered selenite alone (GPX3: 51.8 ± 6.60%, SELENOP: 81.4 ± 8.56%) suggesting that the co-administration of MeHg and selenite did not have any effects on the nutritional availability of selenite. The administration of MeHg alone resulted in no significant recoveries of the serum selenoproteins (GPX3: 28.4 ± 1.51%, SELENOP: 30.8 ± 4.37%). Similarly, the administration of HgSe NPs resulted in no significant recoveries of the serum selenoproteins (GPX3: 26.6 ± 0.837%, SELENOP: 34.5 ± 0.566%).

3.2. Distribution of Se and Hg in rat organs

The accumulation of Se and Hg in organs of rats administered Se and Hg compounds was evaluated as well, and the results are shown in Figs. 3 and 4, respectively. The administration of selenite alone induced the significant accumulation of Se the liver (671 ± 21 ng Se/g), kidney (2146 ± 139 ng Se/g), and spleen (360 ± 24 ng Se/g) (Fig. 3a–c), whereas the small intestine (239 ± 44 ng Se/g) and the large intestine (147 ± 20 ng Se/g) showed a tendency for Se accumulation with the selenite administration (Fig. 3f and g). No significant accumulation of Se in the testis (1350 ± 158 ng Se/g) and brain (235 ± 51 ng Se/g) was observed (Fig. 3d and e). The co-administration of selenite and MeHg induced the significant accumulation of Se in the liver (902 ± 168 ng Se/g), kidney (2579 ± 152 ng Se/g), spleen (333 ± 32 ng Se/g), small intestine (277 ± 62 ng Se/g), and large intestine (170 ± 44 ng Se/g) (Fig. 3a–c, f, and g). The administration of MeHg alone led to the significant accumulation of Se in the kidney (1948 ± 262 ng Se/g) and spleen (298 ± 1.2 ng Se/g) (Fig. 3b and c). Significant accumulation of Se by HgSe NP administration was observed in the kidney (1683 ± 141 ng Se/g), spleen (264 ± 2.4 ng Se/g), and large intestine (173 ± 15 ng Se/g), whereas the small intestine (185 ± 31 ng Se/g) showed a tendency for Se accumulation with the HgSe NP administration.

The administration of MeHg alone or in combination with selenite caused significant Hg accumulation in all organs except the large intestine (Fig. 4). The brain of rats co-administered selenite and MeHg showed greater accumulation (70 ± 12 ng Hg/g) than that of rats administered MeHg alone (32 ± 2.0 ng Hg/g) (Fig. 4e). The testis of rats administered MeHg alone showed greater accumulation (63 ± 1.6 ng Hg/g) than that of rats co-administered selenite and MeHg (59 ± 2.0 ng Hg/g) (Fig. 4d). No significant Hg accumulation was observed in the liver (2.0 ± 0.5 ng Hg/g), kidney (21 ± 1.5 ng Hg/g), spleen (2.4 ± 0.4 ng Hg/g), testis (0.3 ± 0.1 ng Hg/g), and small intestine (36 ± 25 ng Hg/g) of rats administered HgSe NPs. However, Hg was significantly accumulated in the large intestine of rats administered HgSe NPs (100 ± 29 ng Hg/g) (Fig. 4g).

3.3. Excretion of Se and Hg

As shown in Fig. 5, the urinary excretion of Se and Hg was significantly increased by the administration of selenite (1st day: 2720 ± 482 ng Se, 2nd day: 4006 ± 52 ng Se) and MeHg (1st day: 51 ± 14 ng Hg, 2nd day: 88 ± 39 ng Hg), respectively (Fig. 5). In contrast, there were no significant differences in the urinary excretion of Se and Hg between rats co-administered and solely administered (1st day: 2132 ± 868 ng Se and 56 ± 16 ng Hg, 2nd day: 3578 ± 1436 ng Se and 136 ± 64 ng Hg). Finally, no significant increase in the urinary excretion of Se and Hg was observed in rats administered HgSe NPs (1st day: 60 ± 26 ng Se and 20 ± 7.6 ng Hg, 2nd day: 43 ± 14 ng Se and 18 ± 11 ng Hg).

As shown in Fig. 6, the fecal excretion of Se and Hg was showed the tendency to be increased by the administration of selenite (1st day: 0.998 ± 0.247 μg Se/g, 2nd day: 2.34 ± 0.46 μg Se/g) and MeHg (1st day: 1.93 ± 0.27 μg Hg/g, 2nd day: 2.83 ± 0.39 μg Hg/g), respectively. In addition, the fecal excretion of Se and Hg showed the tendency to be increased in rats co-administered selenite and MeHg, except the fecal

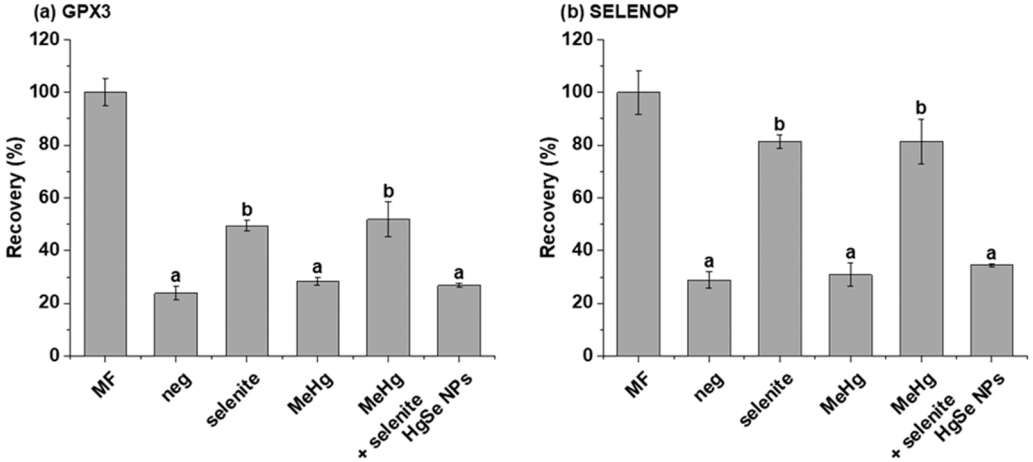

Fig. 2. Recovery of serum selenoproteins GPX3 (a) and SELENOP (b) in rats. Values and bars correspond to means ± SD of three rats. Different letters indicate significant difference ($p \leqq 0.05$).

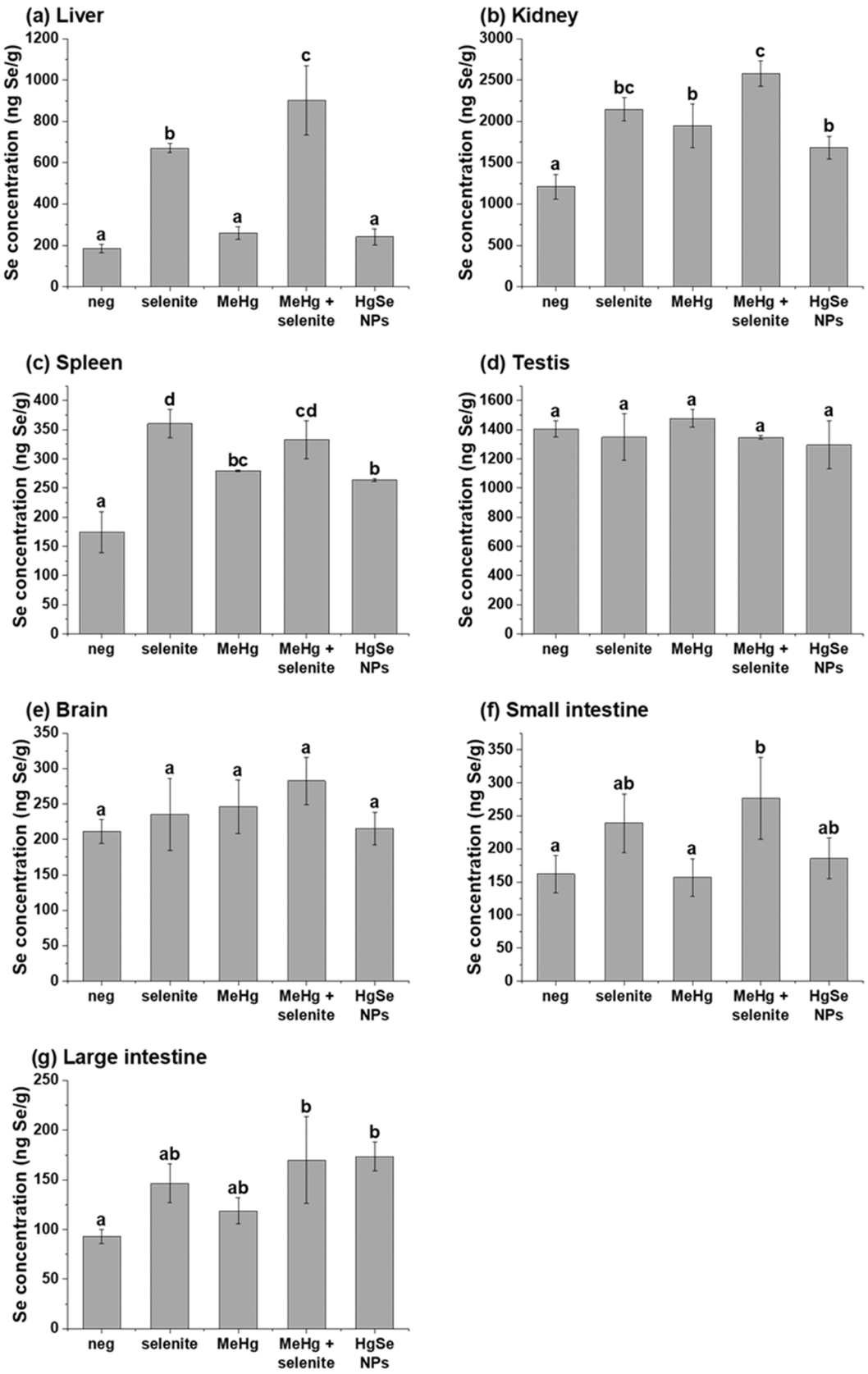

Fig. 3. Se concentrations in liver (a), kidney (b), spleen (c), testis (d), brain (e), small intestine (f), and large intestine (g) in rats administered selenite, MeHg, MeHg and selenite, HgSe NPs, or saline. The concentrations are expressed in ng Se/g wet tissue. Values and bars correspond to means ± SD of three rats. Different letters indicate significant difference ($p \leqq 0.05$).

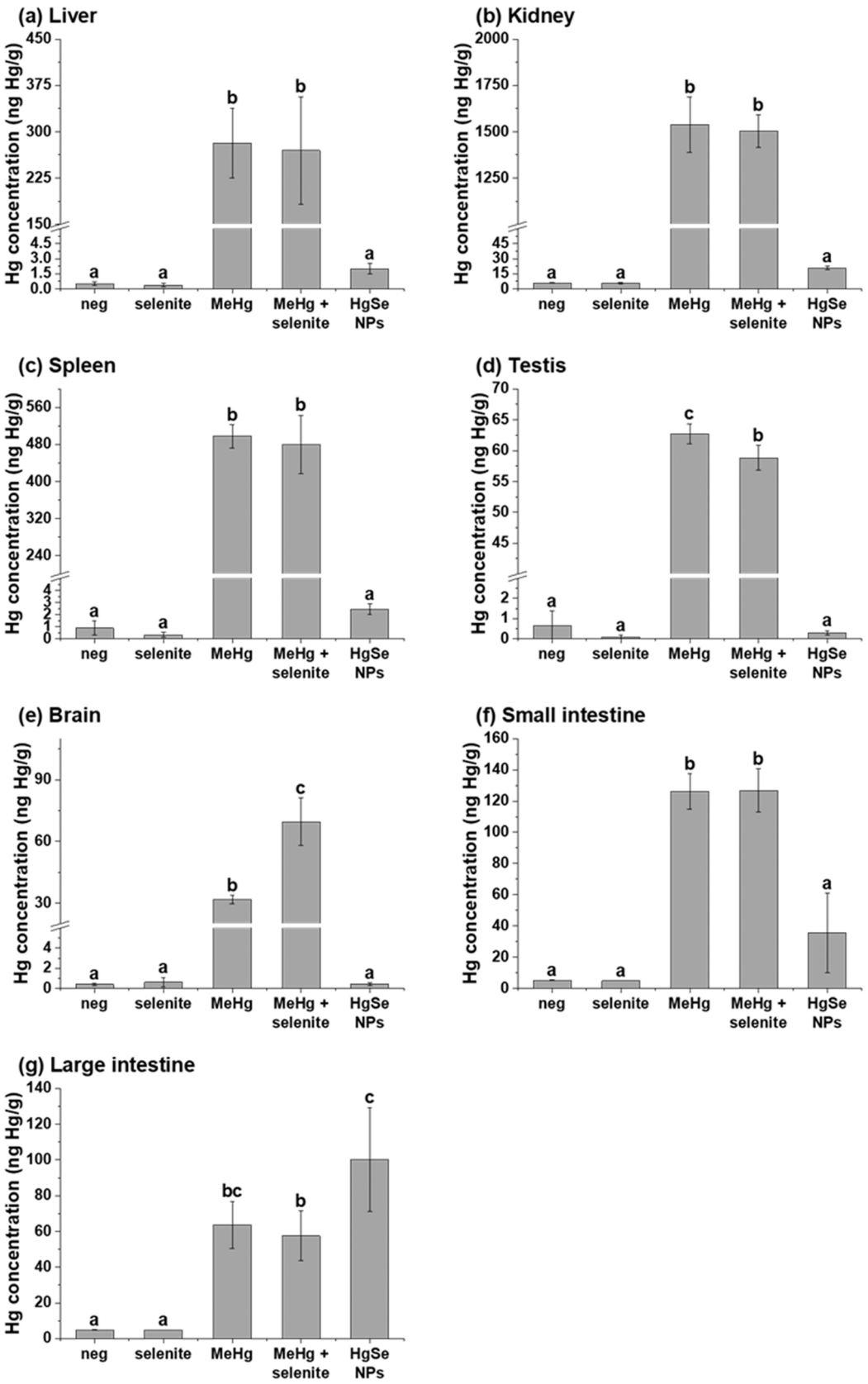

Fig. 4. Hg concentrations in liver (a), kidney (b), spleen (c), testis (d), brain (e), small intestine (f), and large intestine (g) in rats administered selenite, MeHg, MeHg and selenite, HgSe NPs, or saline. The concentrations are expressed in ng Hg/g wet tissue. Values and bars correspond to means ± SD of three rats. Different letters indicate significant difference ($p \leqq 0.05$).

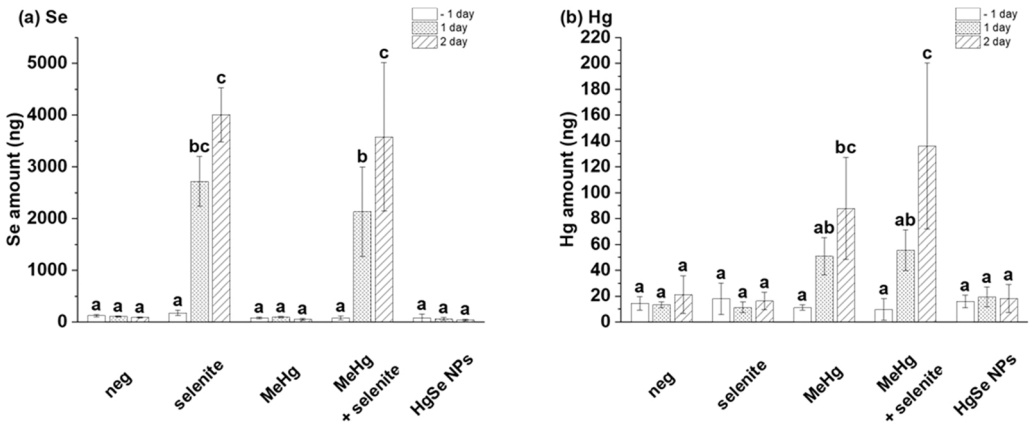

Fig. 5. Amounts of Se (a) and Hg (b) in urine collected from rats 24 h before administration and 24 h after the first administration and the second administration of selenite, MeHg, MeHg and selenite, HgSe NPs, or saline. Values and bars correspond to means ± SD of three rats. Different letters indicate significant difference ($p < 0.05$).

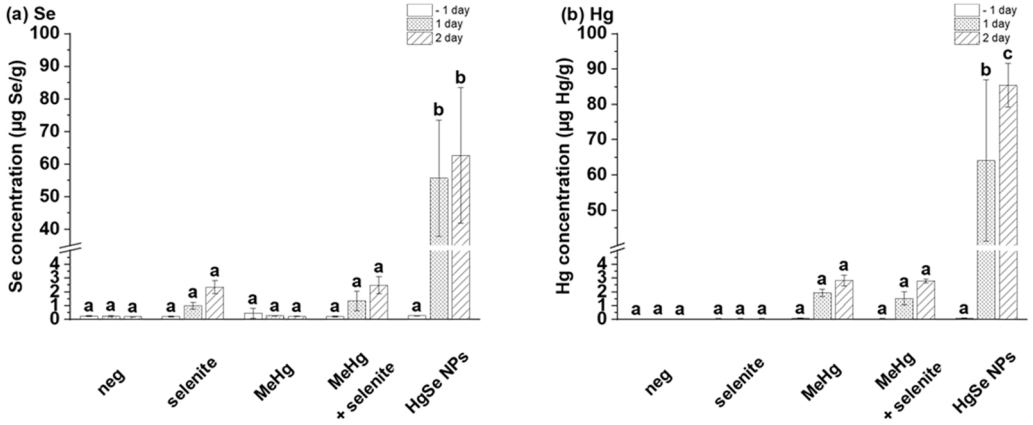

Fig. 6. Se (a) and Hg (b) concentrations in feces collected from rats 24 h before administration and 24 h after the first administration and the second administration of selenite, MeHg, MeHg and selenite, HgSe NPs, or saline. Values and bars correspond to means ± SD of three rats. Different letters indicate significant difference ($p < 0.05$).

excretion of Se on the first day (1st day: 1.33 ± 0.71 μg Se/g and 1.53 ± 0.49 μg Hg/g, 2nd day: 2.47 ± 0.62 μg Se/g and 2.78 ± 0.13 μg Hg/g) (Fig. 6). On the other hand, whereas no significant increase in the amounts of Se and Hg in urine was observed with the administration of HgSe NPs, Se and Hg in feces were significantly increased by the HgSe NP administration (1st day: 56 ± 18 μg Se/g and 64 ± 23 μg Hg/g, 2nd day: 63 ± 21 μg Se/g and 85 ± 6.2 μg Hg/g). In fact, the rats administered HgSe NPs excreted significantly more Se and Hg into feces than those administered selenite or/and MeHg.

4. Discussion

According to the aim of this study, it seemed to be better to use biologically synthesized HgSe NPs. There were no experimental evidences to characterize biologically synthesized HgSe NPs, and there was technical difficulty to extract and partially purify HgSe NPs from tissues. In addition, diameter is one of the important characteristics of NPs. Hence, in this study, we used chemically synthesized HgSe NPs which had comparative diameter of biologically synthesized HgSe NPs.

Selenite administered alone and co-administered with MeHg was utilized in the biosynthesis of two serum selenoproteins with the same efficiency (Figs. 1 and 2). The determination of the recoveries of serum selenoproteins by LC-ICP-MS after the administration of different Se compounds is a very useful strategy to evaluate the nutritional availability of Se (Takahashi et al., 2020, 2018, 2017). As shown in Figs. 1 and 2, HgSe NPs are not utilized in selenoprotein biosynthesis, suggesting that HgSe NPs are biologically inert, and selenide, a necessary metabolic intermediate to produce selenoproteins, is not released by HgSe during its metabolism even though HgSe is administered as nanoparticles. In addition, it is known that biologically utilized Se compounds are excreted into urine (Suzuki, 2005). However, significant increases in urinary Se and Hg excretion were not observed (Fig. 5) on HgSe NP administration. This finding corroborates the idea that HgSe is inert in the body.

Se concentrations in brain and testis were not altered significantly by the administration of selenite (Fig. 3). This can be explained by the fact that the brain and the testis are unable to respond to the Se supplementation because these organs are tolerant to Se deficiency. These findings agree well with the literature (Akahoshi et al., 2019; Behne et al., 1988; Li et al., 2012). In fact, as clearly shown in Figs. 2 and 3, serum selenoproteins and organs sensitive to Se deficiency exhibited increases in Se level as a result of selenite administration.

The co-administration of selenite and MeHg led to an increase in Se accumulation in all organs including the brain (Fig. 3). It is known that the co-administration of selenite and MeHg induces a direct reaction between Se and Hg to form mercury selenide (HgSe) (Orr et al., 2020), which is chemically and biologically inert and can be deposited in the organs. However, Se deposited as HgSe does not seem to be utilized as Se nutritional source, and Hg deposited as HgSe does not seem to induce Hg toxicity.

Se and Hg present in administered HgSe NPs were not distributed in any organs except the large intestine (Fig. 4). Almost all Se and Hg were excreted into feces (Fig. 6). These results indicate that the bioaccessibility of HgSe NPs is considerably low.

The bioaccessibility of organic Hg such as MeHg is very high, and MeHg is easily biocondensed via the food chain. Contrary to biocondensation, it is well known that animals belonging to higher trophic levels accumulate Se and Hg as HgSe in their organs. The biological conversion of highly bioaccessible metabolites into poorly bioaccessible ones is used to reduce the biocondensation of Hg from preys to predators in the food chain. Therefore, it is speculated that the production of HgSe in the body effectively reduces the toxicity of Hg not only in the body, but also in the ecosystem.

The amount of Se in feces increased with the administration of selenite (Fig. 6). Se is mainly excreted into urine as selenosugar and trimethylselenonium ion within metabolic capacity (Byard, 1969; Kobayashi et al., 2002). In our previous study, we found that Se is secreted into bile as selenodiglutathione (Takahashi and Ogra, 2020). Since the dose was within the metabolic capacity of Se, Se could be excreted into feces via bile.

In future studies, chronal effects of biogenic HgSe NPs should be evaluated. In particular, their toxicological effects in a large intestine seem to be notable. In addition, although the chemically synthesized HgSe NPs were used in this study, the biogenic HgSe NPs will be used to more precisely evaluate the ecotoxicity of HgSe NPs.

5. Conclusions

HgSe NPs were not metabolized into selenoproteins and urinary selenometabolites, and were not accumulated in organs due to their biological inertness. In addition, the low bioaccessibility of HgSe NPs observed in this study suggests that Hg transport in the form of HgSe NPs from preys to predators reduces the risk of biocondensation in the ecosystem. Therefore, HgSe NPs produced from environmental pollutants in preys do not become a secondary environmental pollutant for predators.

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CRediT authorship contribution statement

Kazuaki Takahashi: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Jorge Ruiz Encinar:** Conceptualization, Writing – review & editing. **José M. Costa-Fernández:** Conceptualization, Writing – review & editing. **Yasumitsu Ogra:** Conceptualization, Writing – original draft, Writing – review & editing, Funding acquisition, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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