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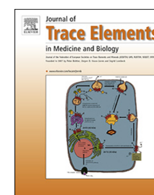

Bioavailability

Effect of administration route and dose on metabolism of nine bioselenocompounds

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ABSTRACT

The nutritional availability of selenium (Se) is highly dependent on its chemical form because chemical form affects absorption, distribution, metabolism, and excretion. We evaluated the effects of administration route and dose on the bioavailability of nine Se compounds found in biota, the so-called bioselenocompounds, such as selenite, selenate, selenocyanate (SeCN), *Se*-methylselenocysteine (MeSeCys), selenomethionine (SeMet), selenohomolanthionine (SeHLan), selenocystine (SeCys2), 1β-methylseleno-*N*-acetyl-D-galactosamine (SeSug1), and trimethylselenonium ion (TMSe). We determined the bioavailability of bioselenocompounds recovered as urinary selenometabolites and serum selenoproteins from urine and serum of Se-deficient rats after the administration of bioselenocompounds by speciation analysis. Urinary Se was more easily recovered than serum selenoproteins, suggesting that the speciation of urinary Se is a better tool to indicate Se status in the body. The intravenous administration of bioselenocompounds showed different Se bioavailability from the oral administration. Intestinal microflora might be involved in the bioavailability of some bioselenocompounds, such as SeCN, MeSeCys, and SeSug1.

1. Introduction

Selenium (Se) is an essential micronutrient in animals. It functions in the body as selenoproteins, which contain Se in their primary structures in the form of selenocysteine (SeCys) [1]. Although animals and human ingest Se from feeds and foods, the feeds and foods contain various chemical forms of Se. Many naturally occurring Se species have been reported. *Se*-methylselenocysteine (MeSeCys) and its derivatives, such as γ-glutamyl-*Se*-methylselenocysteine, are the major Se metabolites in plant [2–4]. Selenomethionine (SeMet) is produced in yeast and grains from inorganic Se species [5,6]. Selenohomolanthionine (SeHLan) is also detected in some Se-accumulating plants and yeasts [7–9]. Animals metabolize ingested Se into SeCys in selenoproteins and 1β-methylseleno-*N*-acetyl-D-galactosamine (SeSug1), which is excreted into urine [10,11]. When rats ingested an excessive amount of Se, trimethylselenonium ion (TMSe) is also detected in urine [12]. In addition, selenocyanate (SeCN) is detected as a metabolite in animal cells [13]. As animals can utilize the selenocompounds mentioned above, those selenocompounds are named bioselenocompounds [14].

Se is biologically ambivalent, i.e., it is essential but highly toxic. Indeed, ethnic diseases owing to Se toxicosis and deficiency have been reported [15,16]. In addition, Se deficiency is often reported in patients who take total parenteral nutrition (TPN) and special milk for specific metabolic diseases [17–19]. We had reported that orally administered bioselenocompounds except TMSe were equally utilized to biosynthesize serum selenoproteins, such as extracellular glutathione peroxidase (GPX3) and selenoprotein P (SELENOP) [14]. However, the effects of intravenously administered bioselenocompounds have not been compared although TPN is used in clinical practice.

In this study, the metabolism of the nine bioselenocompounds shown in Fig. 1 was compared depending on the administration route and the dose to clarify their specific activities.

2. Materials and methods

2.1. Materials

Sodium selenate and potassium selenocyanate (SeCN) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Sodium selenite and seleno-L-methionine (SeMet) were purchased from Nacalai Tesque (Kyoto, Japan). *Se*-Methylseleno-L-cysteine (MeSeCys) and L-selenocystine (SeCys2) were purchased from Acros Organics (Waltham, MA, USA) and Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan), respectively. Trimethylselenonium iodide (TMSe) was

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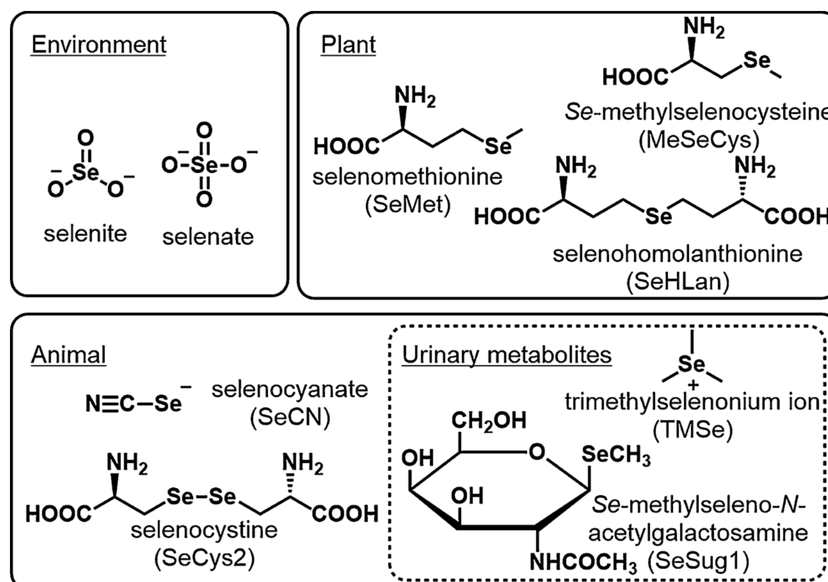

Fig. 1. Structures of bioselenocompounds used in this study. SeCN: selenocyanate, SeMet: L-selenomethionine, MeSeCys: Se-methylseleno-L-cysteine, SeHLan: L-selenohomolanthionine, SeCys2: selenocystine, SeSug1: Se-methylseleno-*N*-acetylgalactosamine, TMSe: trimethylselenonium ion.

purchased from Tri Chemical (Uenohara, Japan). L-Selenohomolanthionine (SeHLan) and *Se*-methylseleno-*N*-acetylgalactosamine (SeSug1) were synthesized in our laboratory in accordance with our previous work [7,11]. The chemical structures of these bioselenocompounds are shown in Fig. 1. Nitric acid was purchased from Wako. Ammonium acetate was purchased from Nacalai. Trizma® hydrochloride solution (1 M, pH 7.4) was purchased from Sigma Aldrich (Tokyo).

2.2. Animal care

All animal experiments were conducted according to 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 (MF, Oriental Yeast Co., Ltd., Tokyo, Japan) (ca. 600 μg Se/kg) and tap water ad libitum. After a one-week acclimation period, the diet and water were changed to a Se-deficient diet (Oriental Yeast) (< 20 μg Se/kg) 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 used as a Se-deficient rat. The rats continuously fed the commercial diet and tap water were used as positive control.

2.3. Speciation of Se in urine of Se-deficient and -recovered rats

The Se-deficient rats were orally administered each Se compound dissolved in saline at the dose of 2 μg Se/0.5 mL/rat or intravenously 2 μg Se/0.2 mL/rat or 10 μg Se/0.2 mL/rat. The saline-administered rats served as negative control. Urine samples were collected for 24 h before and 24 h after administration. The collected urine was stored at −30 °C until analyses. A 400 μL aliquot of the collected urine 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 solution became colorless. Se concentration in the samples was determined with an ICP-MS (Agilent 7700cx, Agilent Technologies, Hachiouji, Japan). Creatinine concentration in urine was determined using Labassay™ Creatinine (Wako) according to the manufacturer’s instructions, and Se concentration in each urine sample was compensated with the creatinine concentration.

A 20 μL aliquot of the same urine as above was applied to an HPLC coupled with an ICP-MS (LC-ICP-MS) to analyze Se species in the urine. 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-320HQ, exclusion size > 40,000 Da, 7.5 i.d. × 300 mm with a guard column; Showa Denko, Tokyo, Japan). The column was eluted with 50 mM ammonium acetate, pH 6.5, at the flow rate of 0.6 mL/min. The eluate was introduced directly into the nebulizer tube of the ICP-MS to detect Se at *m/z* 77 and 82. In addition, the urine of Se-deficient rat was also analyzed by an HPLC coupled with an ICP-MS/MS (Agilent 8800, Agilent) (LC-ICP-MS/MS) to confirm the Se peaks detected ICP-single MS because some ghost peaks of Se in urine matrix was detected by ICP-MS. For the LC-ICP-MS/MS, the same LC conditions was used as the LC-ICP-MS. Se was analyzed in the O_2 mass shift mode, which enabled us to detect ^{80}Se by selecting *m/z* 80 as the target for Q1 and *m/z* 96 representing ^{80}Se^{16}O as the target for Q3. The ICP-MS/MS operating conditions were follows; He gas flow rate, 1 mL/min; O_2 gas flow rate, 0.3 mL/min.

2.4. Speciation of Se in Serum of Se-deficient and -recovered rats

The Se-deficient rats were intravenously administered each Se compound in saline at the dose of 2 μg Se/rat once or 10 μg Se/rat once a day for two consecutive days and each delivered volume was 0.2 mL. To obtain a certain increase in the serum selenoproteins, the dose was increased from the preceding experiment described in 2.3. All the rats were sacrificed 24 h after the administration by exsanguination under anesthesia. Non-heparinized blood was collected and centrifuged at 1600 × *g* for 10 min to obtain serum. A 20 μL aliquot of the serum was applied to LC-ICP-MS equipped with another 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) to analyze the distribution of Se in the serum. 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 tube of the ICP-MS to detect Se at *m/z* 77 and 82.

2.5. Statistical analysis

All determinations were performed in three replicates and the results are shown as means ± SD. Statistical analysis was conducted by applying the Student’s *t*-test or one-way analysis of variance (ANOVA) with the Tukey test. A probability of $p < 0.05$ was considered statistically significant.

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