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Changes in Distribution of Mercury and Selenium in Soluble Fractions of Rabbit Tissues after Simultaneous Administration

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NAGANUMA, A. AND N. IMURA. *Changes in distribution of mercury and selenium in soluble fractions of rabbit tissues after simultaneous administration.* PHARMAC. BIOCHEM. BEHAV. 13(4) 537–544, 1980.—The existing states of mercury and selenium in the blood and in soluble fractions of perfused rabbit liver and kidney were studied by gel filtration on Sephadex G-200 1 hr or 24 hr after intravenous injection of mercuric chloride and/or sodium selenite. Both mercury and selenium in the plasma and stroma-free hemolysate were found to exist in the high-molecular weight fraction following simultaneous injection of mercuric chloride and sodium selenite. Patterns in gel filtration of the plasma and the stroma-free hemolysate did not show any significant change between 1 hr and 24 hr after the administration. A similar tendency as described above was obtained with the liver-soluble fraction at 24 hr after injection of mercuric chloride and sodium selenite. A possible role of the high-molecular weight complex, which is quickly formed by the interaction of mercury and selenium in blood stream, in decreasing the acute renal toxicity of inorganic mercury is discussed.

Mercuric mercury Selenium Gel filtration Rabbit Plasma Stroma-free hemolysate Liver Kidney Tissue-soluble fraction

MANY studies have been conducted concerning the mechanism of mutual modification of toxicity between selenium and mercury compounds [6, 7, 9, 16, 17]. Several investigations on the interaction between inorganic mercury and selenium indicated that administration of selenite to animals causes remarkable changes in the behaviour of inorganic mercury in the body: in contrast to the results observed after administration of inorganic mercury alone, larger amounts of mercury were found to accumulate in the animal body after simultaneous administration of selenite [3], particularly in the liver, spleen and blood, whereas mercury decreased in the kidney [4, 5, 12, 13, 15, 18]. Selenite accelerated the uptake of inorganic mercury by red blood cells [8,14]. The major portions of mercury and selenium were eluted in a high-molecular weight fraction on gel filtrations of rat plasma [1,19] and rabbit stroma-free hemolysate [8,14] following simultaneous administration of mercuric chloride and selenite. Chen *et al.* [2] reported that mercury in the soluble fractions of the liver, kidney, spleen, and testicles of rats administered mercuric chloride alone was found mainly in the low-molecular weight fraction eluted from the gel filtration column, most of the mercury instead bound to the high-molecular weight fraction by pretreatment with selenite. A similar phenomenon was observed in the organs of a rat continuously fed mercuric chloride with selenite [10]. However, selenium distribution was not clear in these instances.

Chen *et al.* [2] speculated that in the soluble fractions of the organs selenium co-existed with mercury in the high-molecular weight fraction when selenite was administered together with mercury as in the cases of plasma and stroma-free hemolysate described above.

As for the status of selenium and mercury in the soluble fractions of the organs, gel filtrations using Sephadex G-75 or G-100 have been carried out [5,11]. Since a considerable amount of selenium eluted out at the void volume region even when selenite was administered alone, any change in selenium distribution in the high-molecular weight fraction, caused by concurrent administration of mercury in those studies was not clear enough to evaluate the effect of mercury. Thus the need for use of Sephadex of greater G value is emphasized to characterize the complex of mercury and selenium in the high-molecular weight fraction.

Most of the investigations reported so far on the gel filtrations of soluble fractions of organs were conducted without perfusing the organs. However, it has been revealed that both mercury and selenium are retained for a considerably long period in the blood at very high concentrations when mercuric chloride and selenite are administered simultaneously, and that an interaction of mercury and selenium in the blood occurs quite quickly [8]. It is conceivable, therefore, that the observation obtained without perfusion might be different from the real existing state of these two compounds due to contamination of the blood.

The present experiment was undertaken to study the interaction between inorganic mercury and selenite and the time course of the changes in distribution of mercury and selenium after individual and simultaneous intravenous administration of mercuric chloride and selenite to rabbits. The amounts and the existing states of mercury and selenium in

TABLE 1

MERCURY AND SELENIUM CONTENTS IN BLOOD AND PERFUSED ORGANS FROM RABBITS INJECTED WITH MERCURIC CHLORIDE AND/OR SELENITE*

	Hg content				Se content			
	^{203}Hg		^{203}Hg+Se		^{75}Se		^{75}Se+Hg	
	1 hr	24 hr	1 hr	24 hr	1 hr	24 hr	1 hr	24 hr
Blood	2.81 ±0.66	0.53 ±0.07	14.85 ±1.73	9.34 ±0.61	2.74 ±0.40	1.01 ±0.12	15.52 ±2.08	9.96 ±0.77
Liver	7.83 ±1.29	2.64 ±0.09	7.21 ±0.48	10.89 ±2.92	18.59 ±3.70	2.58 ±0.85	8.63 ±0.48	10.39 ±2.59
Kidney	82.52 ±2.74	97.18 ±20.47	4.57 ±0.53	25.53 ±8.93	19.38 ±2.73	5.18 ±2.05	8.16 ±1.77	6.75 ±1.16

*Values are mean ± SD in nmol Hg or Se/g organ or ml blood (average of 3 rabbits). Rabbits were injected IV with $^{203}HgCl_2$, $Na_2{}^{75}SeO_3$, $^{203}HgCl_2$ plus Na_2SeO_3, or $HgCl_2$ plus $Na_2{}^{75}SeO_3$ (1.5 μmol Hg or Se/kg).

the blood and in the soluble fractions of perfused organs have been carefully examined (1 hr and 24 hr after the administration) by gel filtration on Sephadex G-200.

METHOD

Male rabbits weighing about 2.5 kg and fed solid feed (CR-I type available from Nippon CLEA Co. Ltd., Tokyo) and water ad lib were used in the experiment.

Non-radioactive substances dissolved in physiological saline, and radioactive preparations purchased from Radiochemical Center (England) and adjusted the concentrations with the appropriate saline solutions of the cold substances were used for administration.

In the experiment where selenite and mercuric chloride were administered separately, (^{203}Hg)-mercuric chloride (40 μCi/1.5 μmol/kg) or (^{75}Se)-sodium selenite (40 μCi/1.5 μmol/kg) was injected into the auricular veins of the rabbit, whereas in the experiment where these substances were administered together, (^{203}Hg)-mercuric chloride (40 μCi/1.5 μmol/kg) and cold sodium selenite (1.5 μmol/kg), or (^{75}Se)-sodium selenite (40 μCi/1.5 μmol/kg) and cold mercuric chloride (1.5 μmol/kg) were injected to the auricular veins of the different ears of the rabbits at the same time.

One or twenty-four hour after administration, blood samples were taken from the carotid artery of the rabbits under anesthesia with 25 mg/kg of sodium pentobarbital (Nembutal, Abbot Laboratories, North Chicago, IL) in the presence of 1% heparin sodium solution (1,000 units/ml). The liver and kidney were perfused from the portal vein and renal artery by 300 ml and 50 ml of Ringer's solution, respectively. Perfused livers and kidneys were kept at −20°C and used in the experiment within 24 hr.

Immediately after sampling, plasma and stroma-free hemolysate were separated by a method previously reported [8]. Livers and kidneys were homogenized in a 10 mM phosphate buffer solution (pH 7.4) containing 0.25 M sucrose, giving a 20% homogenate, and separated by centrifugation at 4°C for 1 hr at 105,000×g into soluble and insoluble fractions.

One and a half milliliters of plasma, 5.0 ml of stroma-free hemolysate or soluble fractions of the organs were applied on a Sephadex G-200 column (26.4×920 mm). The column was eluted with 9.5 mM phosphate buffer saline (pH 7.4), at a flow rate of about 28 ml/hr, and 5.0 ml of the eluate was pooled in a tube. Yields of ^{203}Hg and ^{75}Se from the column were approximately 77% and 81%, respectively.

The void volume of the column (Vo) and the total elution volume (Vt) were measured by eluting blue dextrane (mol. wt.>2,000,000) and uridine (mol. wt. 244), respectively.

The molecular weight of the substances separated by gel filtration were calculated by comparing the values of (Ve-Vo)/(Vt-Vo) with those of aldolase (mol. wt. 158,000), bovine serum albumin (mol. wt. 68,000), ovalbumin (mol. wt. 45,000), and cytochrome C. (mol. wt. 12,500) as standard substances of known molecular weight (Ve: elution volumes of respective substances).

RESULTS

Table 1 shows the concentrations of mercury and selenium in the blood, liver, and kidney at 1 hr and 24 hr after administration of mercuric chloride and/or sodium selenite.

In comparison with the case of separate administration, the levels of mercury and selenium in the blood markedly increased after the concurrent administration and about 50% of the doses of both elements still remained in the blood even at 24 hr after the injection. The levels of mercury and selenium in the liver of rabbit given mercuric chloride and sodium selenite at the same time were found higher at 24 hr after the administration than those observed 24 hr after the individual injection of these substances. In the kidney, the concentration of mercury was conspicuously lowered by the simultaneous injection. These results seemed to be well coincided with the experimental data reported by other laboratories using rats [5, 12, 13, 18] or mice [4,15].

Distributions of mercury and selenium in the plasma and erythrocytes of rabbit blood as well as the soluble and the insoluble fractions of the liver and kidney are indicated in Table 2. As reported previously [8] both mercury and selenium were uptaken to a greater extent by the erythrocytes of rabbit given mercuric chloride and sodium selenite concurrently than in the case of individual injection. The ratios of mercury and selenium in the insoluble fractions of the liver to those in the soluble fractions were increased to some degree by the concurrent administration.

Figure 1 indicates gel filtration patterns of radioactive mercury and selenium in plasma on Sephadex G-200 at 1 hr after administration. When mercuric chloride and sodium

TABLE 2

MERCURY AND SELENIUM CONTENTS IN SOLUBLE AND INSOLUBLE FRACTIONS OF BLOOD OR PERFUSED ORGANS FROM RABBITS INJECTED WITH MERCURIC CHLORIDE AND/OR SODIUM SELENITE*

		Hg content				Se content			
		^{203}Hg		^{203}Hg+Se		^{75}Se		^{75}Se+Hg	
		1 hr	24 hr	1 hr	24 hr	1 hr	24 hr	1 hr	24 hr
Blood	Plasma	2.03 ±0.45	0.23 ± 0.02	7.44 ±1.07	3.18 ±0.25	2.28 ±0.29	0.65 ±0.76	6.05 ±0.88	3.74 ±0.75
	Erythrocyte	0.78 ±0.27	0.30 ± 0.06	7.41 ±0.98	6.16 ±0.41	0.46 ±0.12	0.36 ±0.04	9.47 ±1.20	6.22 ±0.69
Liver	Sol. fr.†	4.11 ±0.67	1.63 ± 0.05	2.72 ±0.14	3.86 ±1.12	13.53 ±2.59	1.51 ±0.50	4.91 ±0.14	3.49 ±0.91
	Insol. fr.‡	3.72 ±0.67	1.01 ± 0.08	4.49 ±0.41	7.03 ±1.80	5.06 ±1.11	1.07 ±0.35	3.72 ±0.36	6.90 ±1.74
Kidney	Sol fr.†	45.72 ±2.44	70.75 ±15.64	2.84 ±0.41	13.12 ±3.43	11.65 ±1.87	2.02 ±0.94	4.62 ±1.31	2.33 ±1.02
	Insol. fr.‡	36.80 ±2.04	26.43 ± 6.23	1.73 ±0.33	12.41 ±3.56	7.73 ±1.11	3.16 ±1.15	3.54 ±0.49	4.42 ±0.85

*Values are mean ± SD in nmol Hg or Se/g organ or ml blood (average of 3 rabbits).
†soluble fraction, ‡insoluble fraction.

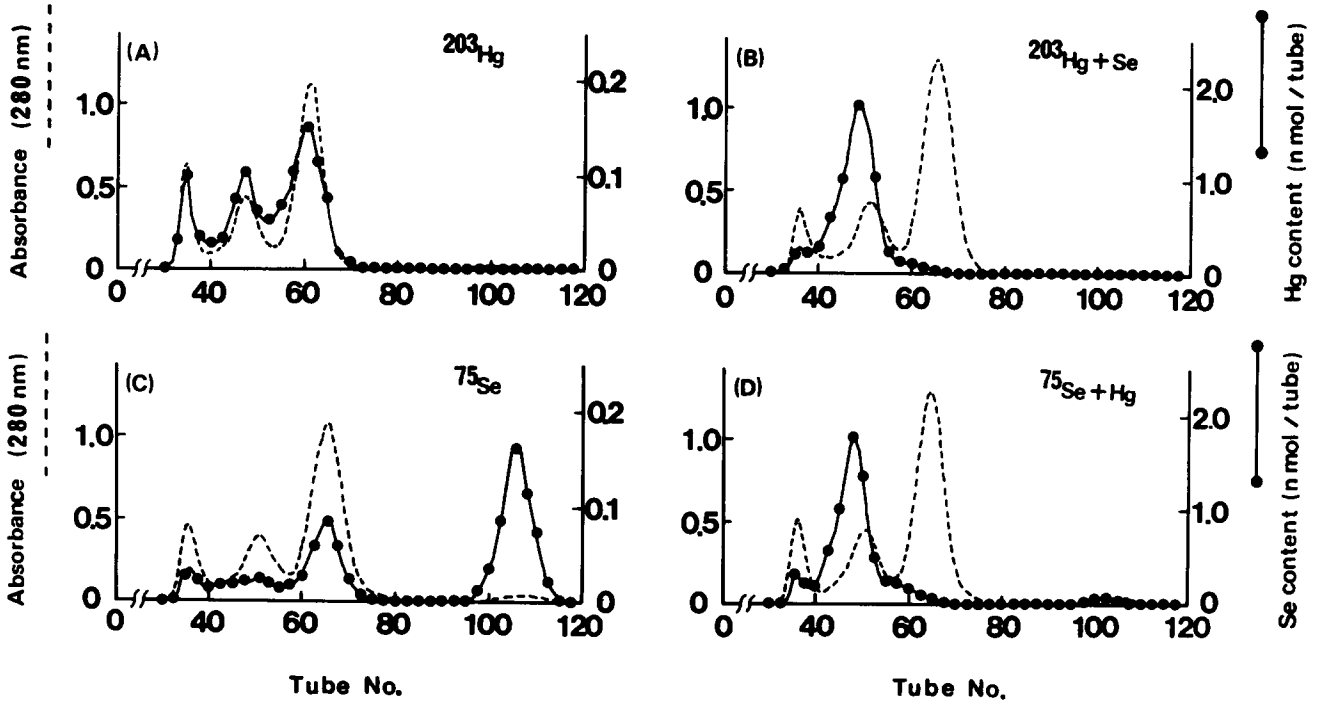

FIG. 1. Sephadex G-200 chromatogram of rabbit plasma 1 hr after IV injection of mercuric chloride and/or sodium selenite. Rabbits were injected with $^{203}HgCl_2$ (A), $^{203}HgCl_2$ and Na_2SeO_3 (B), $Na_2{}^{75}SeO_3$ (C), or $Na_2{}^{75}SeO_3$ and $HgCl_2$ (D). Sephadex G-200 column was eluted with 9.5 mM PBS (pH 7.4) at a flow rate of 28 ml/hr. The eluate was fractionated into 5.0 ml portions.

selenite were administered concurrently, both mercury and selenium showed entirely different elution patterns from those shown after the individual administration. Most of the mercury and selenium were eluted in a high-molecular weight fraction (mol. wt. above 200,000: tube Nos. 40–54). These elution patterns of mercury and selenium in plasma hardly changed through 24 hr after administration (Fig. 2).

One hour after the concurrent administration of mercuric chloride and sodium selenite the stroma-free hemolysate was applied to the Sephadex G-200 column for gel filtration, giving the elution patterns of radioactivity indicated in Fig. 3. Most of the mercury and selenium were found in the high-

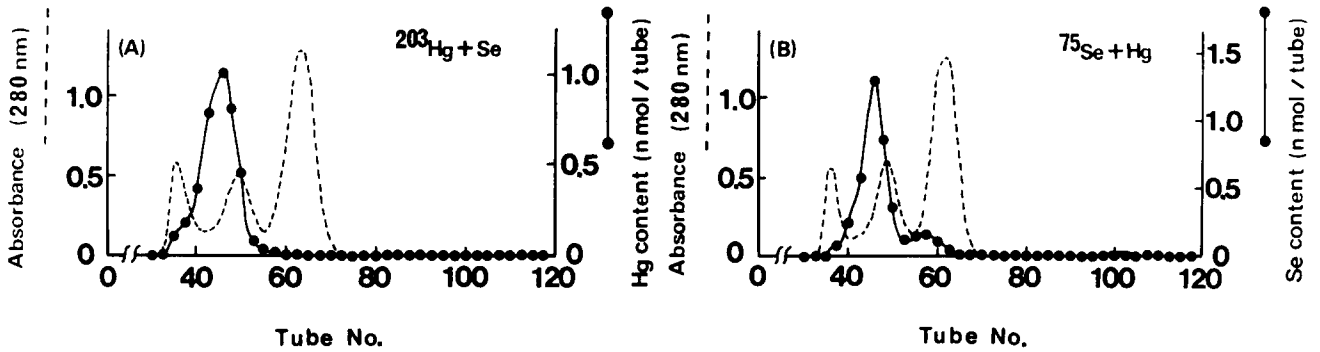

FIG. 2. Sephadex G-200 chromatogram of rabbit plasma 24 hr after IV injection of mercuric chloride and sodium selenite. Rabbits were injected with $^{203}HgCl_2$ and Na_2SeO_3 (A), or $Na_2{}^{75}SeO_3$ and $HgCl_2$ (B).

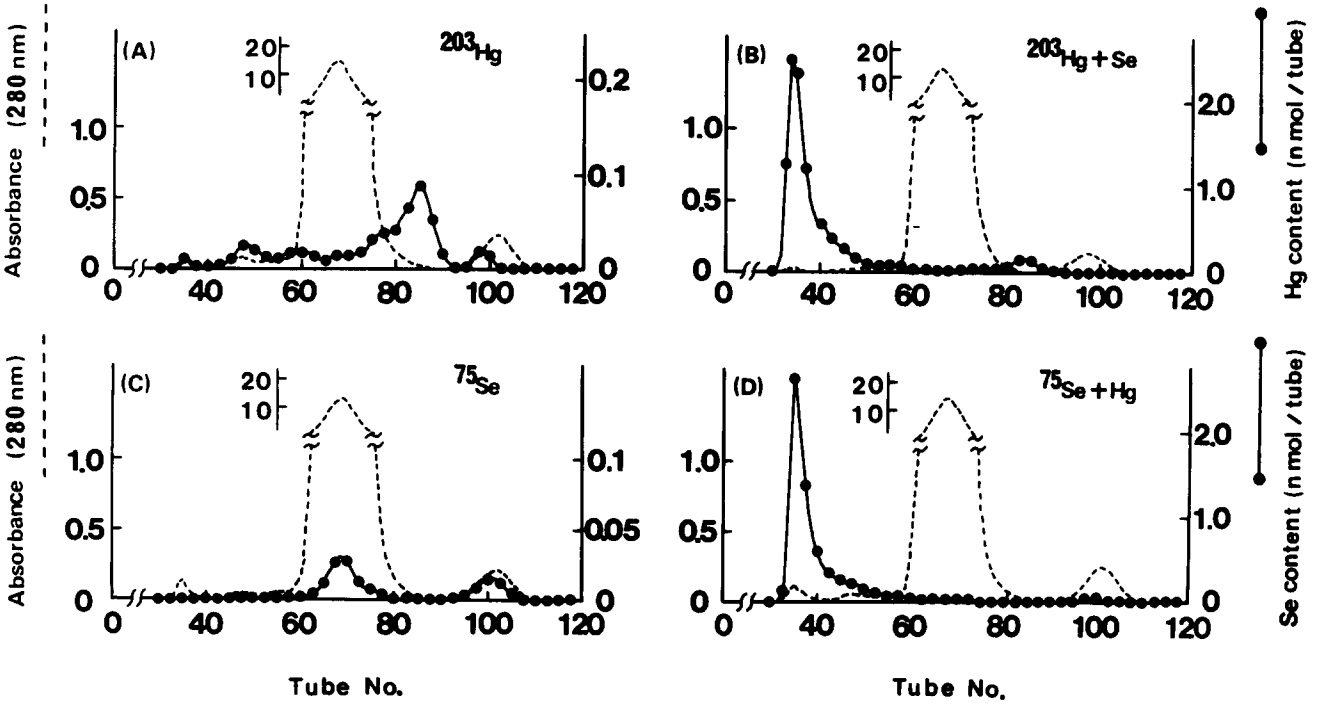

FIG. 3. Sephadex G-200 chromatogram of rabbit stroma-free hemolysate 1 hr after IV injection of mercuric chloride and/or sodium selenite. Rabbits were injected with $^{203}HgCl_2$ (A), $^{203}HgCl_2$ and Na_2SeO_3 (B), $Na_2{}^{75}SeO_3$ (C), or $Na_2{}^{75}SeO_3$ and $HgCl_2$ (D).

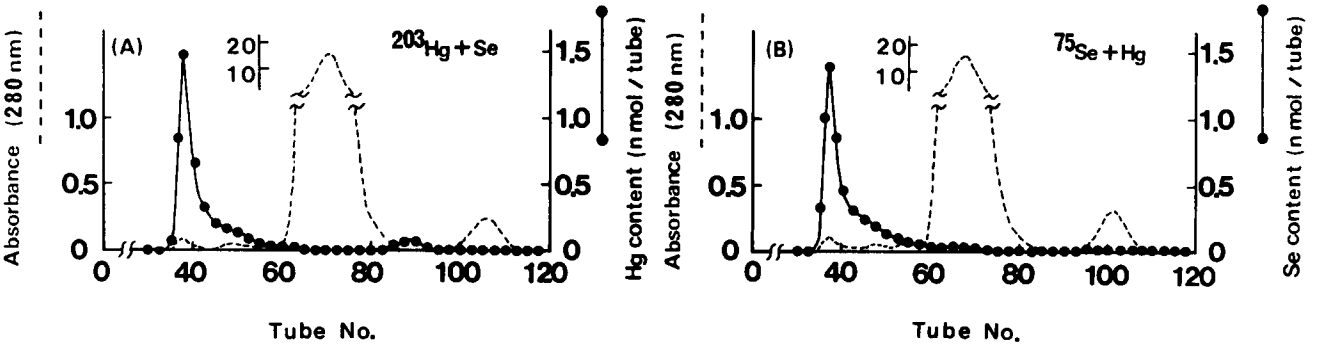

FIG. 4. Sephadex G-200 chromatogram of rabbit stroma-free hemolysate 24 hr after IV injection of mercuric chloride and sodium selenite. Rabbits were injected with $^{203}HgCl_2$ and Na_2SeO_3 (A), or $Na_2{}^{75}SeO_3$ and $HgCl_2$ (B).

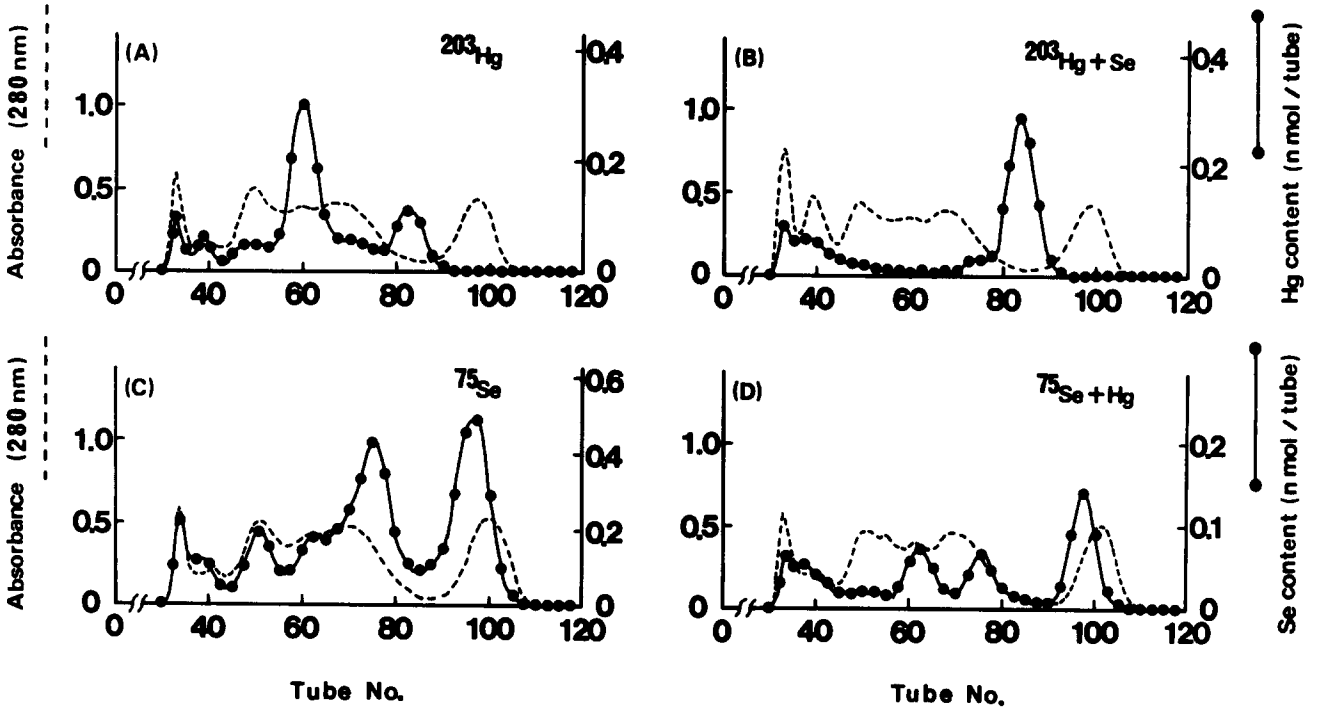

FIG. 5. Sephadex G-200 chromatogram of perfused rabbit liver soluble fraction 1 hr after IV injection of mercuric chloride and/or sodium selenite. Rabbits were injected with $^{203}HgCl_2$ (A), $^{203}HgCl_2$ and Na_2SeO_3 (B), $Na_2{}^{75}SeO_3$ (C), or $Na_2{}^{75}SeO_3$ and $HgCl_2$ (D).

molecular weight fraction (tube Nos. 34–44) eluted at the void volume (Figs. 3B and 3D), whereas neither mercury nor selenium was eluted in this fraction when each of them was administered alone (Figs. 3A and 3C).

The elution patterns of mercury and selenium in stroma-free hemolysate at 24 hr after simultaneous administration were almost the same as those at 1 hr after administration (Fig. 4).

Figure 5 shows the gel filtration pattern of the soluble fraction of the liver at 1 hr after administration. Mercuric mercury, administered alone, existed mainly in the fraction of approximately 65,000 mol. wt. (tube Nos. 56–64) and in the metallothionein-like fraction (tube Nos. 78–88) of approximately 10,500 mol. wt. (Fig. 5A). When sodium selenite was administered concurrently, however, the peak of 65,000 mol. wt. disappeared and most of the mercury was eluted in the metallothionein-like fraction (Fig. 5B). On the other hand, radioactive selenium, administered alone as sodium selenite and distributed in the soluble fraction of the liver, showed the six main peaks on gel filtration indicated in Fig. 5C. When administered simultaneously with mercuric chloride, the ratio of selenium in these fractions changed slightly in comparison with the case of sole administration of sodium selenite, and the elution position of these peaks of selenium hardly changed (Fig. 5D).

Mercury in the soluble fraction of the liver at 24 hr after the administration of mercuric chloride alone mainly existed in the metallothionein-like fraction. When sodium selenite was administered concurrently, the mercury in the metallothionein-like fraction was lowered and the highest peak appeared at the void volume region as shown in Figs. 6A and 6B. Simultaneous administration of mercuric chloride remarkably increased the amount of selenium in the liver. Most of the selenium thus increased in the soluble fraction was also eluted from the column at the void volume (Fig. 6D).

Simultaneous administration of selenite lowered the level of mercury in the kidney to a great degree, but did not affect the relative pattern of mercury on gel filtration (Figs. 7A and 7B). The gel filtration pattern of selenium in the kidney soluble fraction did not show any remarkable change after the simultaneous administration of mercuric chloride as indicated in Figs. 7C and 7D.

Figure 8 displays the gel filtration patterns of the soluble fraction of the kidney prepared at 24 hr after administration. Most of the mercury administered alone as mercuric chloride was found in the metallothionein-like fraction (Fig. 8A). After simultaneous administration of selenite the level of mercury in this fraction markedly decreased as shown in Fig. 8B.

Mercuric chloride concurrently administered with (^{75}Se)-sodium selenite did increase the level of selenium which was eluted at the void volume (tube Nos. 34–44) in gel filtration of the kidney soluble fraction prepared at 24 hr after administration (Figs. 8C and 8D).

All the organ samples for gel filtration were prepared after perfusing the organs with Ringer's solution. As an example of the effect of perfusion on gel filtration patterns, the pattern for the soluble fraction of a kidney prepared without perfusion at 1 hr after administration is illustrated in Fig. 9.

DISCUSSION

We have previously reported that the levels of mercury and selenium in the blood hardly changed between 1 min and 1 hr after intravenous injection of mercuric chloride and sodium selenite to the rabbit [8]. In the present study, the ratio and the levels of mercury and selenium, co-existing in the high-molecular weight fractions in both plasma and stroma-free hemolysate and separated by gel filtration, did not show any significant change between 1 hr and 24 hr after administration. This fact seems to indicate the rapid interac-

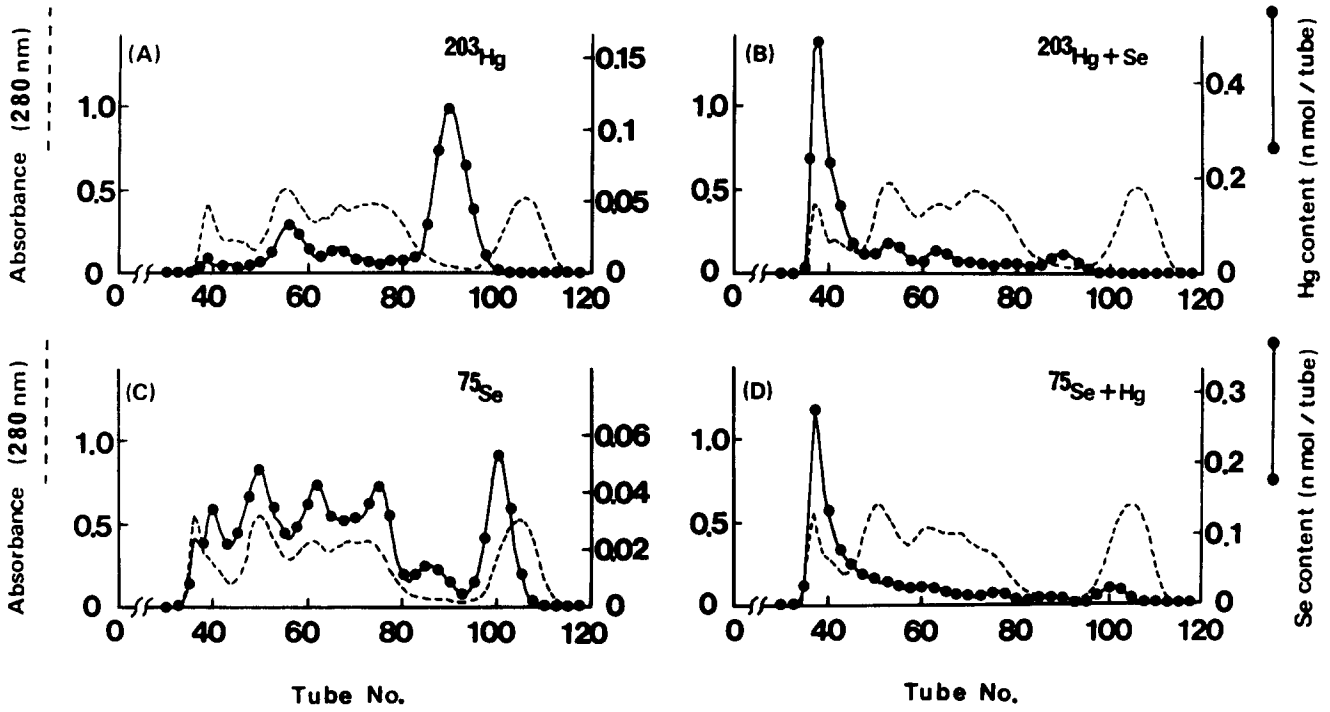

FIG. 6. Sephadex G-200 chromatogram of perfused rabbit liver soluble fraction 24 hr after IV injection of mercuric chloride and/or sodium selenite. Rabbits were injected with $^{203}HgCl_2$ (A), $^{203}HgCl_2$ and Na_2SeO_3 (B), $Na_2{}^{75}SeO_3$ (C), or $Na_2{}^{75}SeO_3$ and $HgCl_2$ (D).

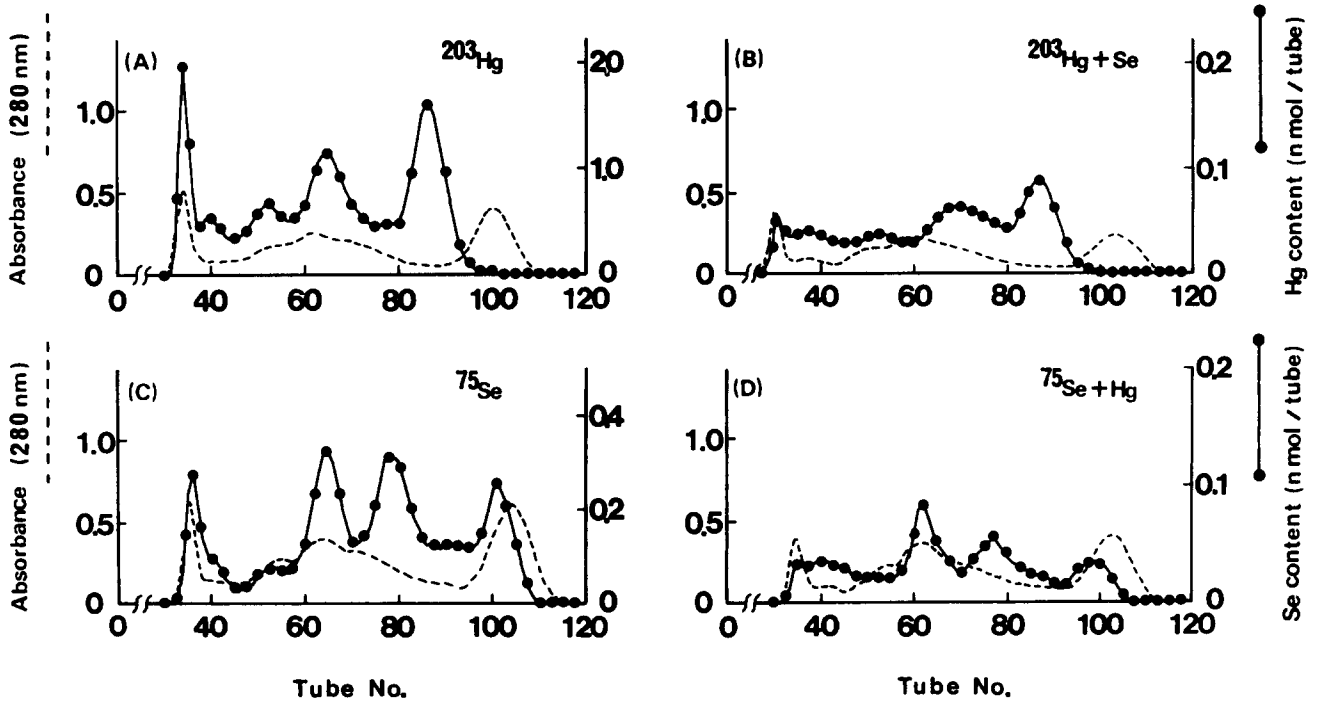

FIG. 7. Sephadex G-200 chromatogram of perfused rabbit kidney soluble fraction 1 hr after IV injection of mercuric chloride and/or sodium selenite. Rabbits were injected with $^{203}HgCl_2$ (A), $^{203}HgCl_2$ and Na_2SeO_3 (B), $Na_2{}^{75}SeO_3$ (C), or $Na_2{}^{75}SeO_3$ and $HgCl_2$ (D).

tion of those two substances as reported previously [8] and the high stability of the products in blood stream (Figs. 1, 2, 3, and 4).

Chen *et al.* [2] reported that administration of selenite modified the distribution of mercury in rat organs and most of the mercury in soluble fraction of the organs was found in high-molecular weight fractions at 1 hr after the administration of mercuric chloride which was in turn given 30 min

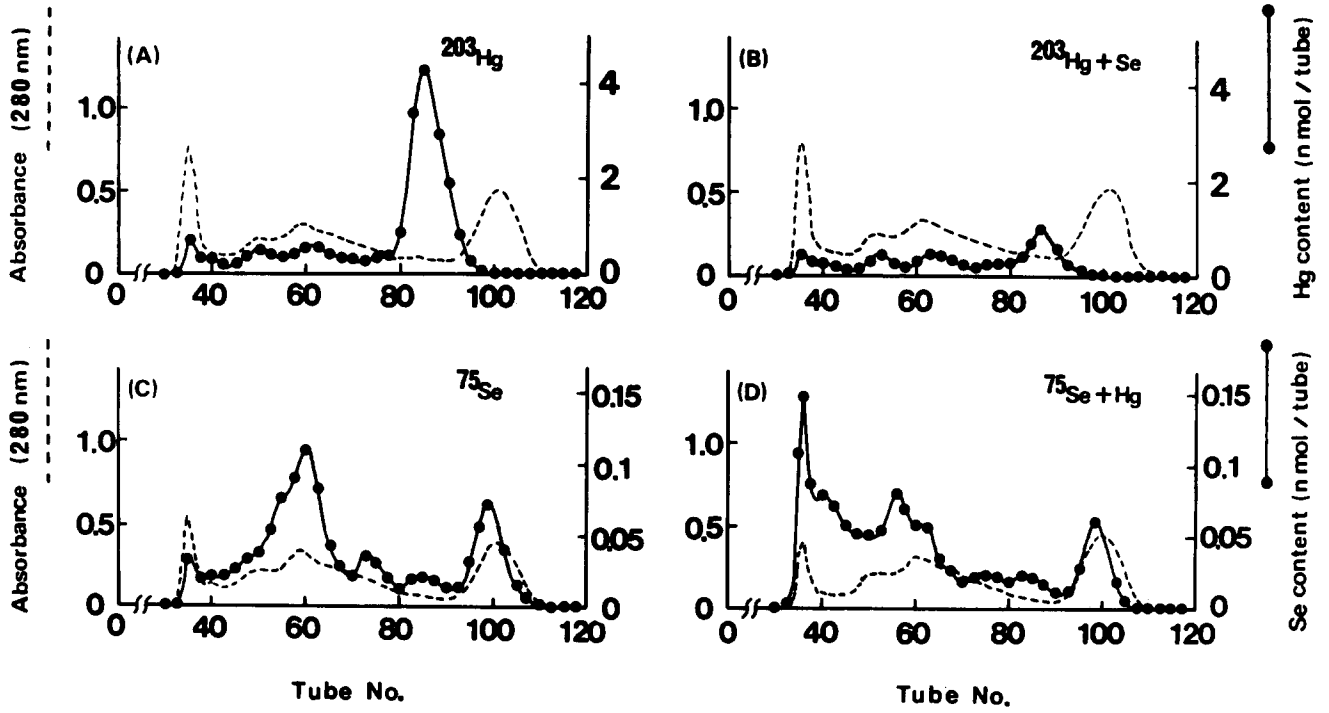

FIG. 8. Sephadex G-200 chromatogram of perfused rabbit kidney soluble fraction 24 hr after IV injection of mercuric chloride and/or sodium selenite. Rabbits were injected with $^{203}HgCl_2$ (A), $^{203}HgCl_2$ and Na_2SeO_3 (B), $Na_2{}^{75}SeO_3$ (C), or $Na_2{}^{75}SeO_3$ and $HgCl_2$ (D).

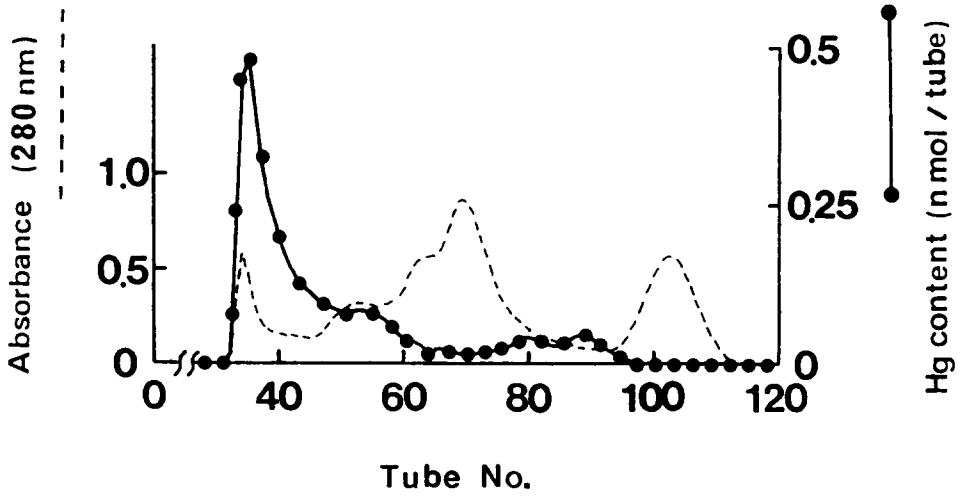

FIG. 9. Sephadex G-200 chromatogram of rabbit kidney soluble fraction prepared without perfusion 1 hr after IV injection of $^{203}HgCl_2$ and Na_2SeO_3.

after the injection of sodium selenite. In the present experiment using rabbits, however, no significant increase of mercury bound to the high-molecular weight substances could be observed in the soluble fractions of the liver and kidney at 1 hr after the administration of mercuric chloride and sodium selenite. Gel filtration of the kidney soluble fraction without perfusion gave similar elution profiles of mercury to those reported by Chen *et al.* [2] (Fig. 9). The gel filtration pattern of the soluble fraction prepared without perfusion, however, was not constant probably because of varying amounts of blood remained in the organs. Blood contained in the organs thus may affect the gel filtration patterns of the samples from animals simultaneously administered mercuric chloride and sodium selenite. Instead of the increase of mercury in the high-molecular weight fraction which was reported by Chen *et al.*, a distinct change in the elution pattern of mercury of the liver soluble fraction was observed 1 hr after the simultaneous administration of selenium, with an increase of the mercury level in the metallothionein-like fraction accompanied by a decrease in the peak of 65,000 mol. wt. (Figs. 5A and 5B). Both mercury and selenium, markedly increased in the liver soluble fraction, were eluted out of the Sephadex

column at the void volume 24 hr after simultaneous administration (Figs. 6B and 6D). Since no complex of high-molecular weight was detectable in the liver 1 hr after the simultaneous injection in spite of considerable accumulation of mercury and selenium, it might not be unreasonable to assume that the interaction of these two substances occurred not in the liver but in the blood and the complex thus formed was uptaken by the liver and accumulated with lapse of time.

In the present experiment using the rabbit, the increase of the mercury level in the high-molecular weight fraction caused by selenite administration was remarkable in the blood and the liver soluble fraction, but not observed in the kidney soluble fraction. These facts are of great interest considering our previously reported experimental results that chemically stabilized mercury existed in the liver, spleen, and blood but not in the kidney and brain of mouse when mercuric chloride and sodium selenite were simultaneously administered [15].

Some papers have mentioned that simultaneous administration of sodium selenite and mercuric chloride decreased the amount of mercury accumulated in the kidney, a target organ in poisoning of inorganic mercury [4, 5, 12, 13, 15, 18]. As shown in Table 1, the mercury concentration in the rabbit kidney at 1 hr after concurrent administration of mercuric chloride and sodium selenite was only about 1/18 of that in the case of sole administration of mercuric chloride. The results mentioned above seems to suggest a mechanism for modifying the toxicity of inorganic mercury by selenium, that is, mercury and selenium administered concurrently are subjected to quick reactions in the blood to form a complex of high-molecular weight. Thereby the complex formation delayed considerably the transfer of mercury from the blood to the kidneys and lowered its accumulation in the kidneys at the early stage of administration, probably because the complex could not pass through the glomerulus membrane as speculated by Parizek *et al.* [19]. Thus, the acute renal toxicity of inorganic mercury is depressed to a considerable extent.

The formation of high-molecular weight complex of mercury and selenium may contribute to depress the toxic action not only of mercury but also of selenium.

Since considerable amounts of the mercury and selenium administered distributed into the insoluble fractions of various tissues as indicated in Table 2, it seems to be necessary to characterize both the substances in these insoluble fractions besides those in the soluble fractions.

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