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Effect of Age and Diet on Renal Cadmium Retention in Rats

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The results of our previous and recent work on cadmium metabolism in relation to age and diet are presented. Experiments were performed on albino rats aged 1–26 weeks. In some experiments rats were given different foods (milk, meat, bread) instead of standard rat diet. Some animals received trisodium calcium salt of diethylenetriaminepentaacetate (DTPA) intraperitoneally to decrease cadmium retention. Radioactive cadmium (^{115m}Cd) was administered orally and intraperitoneally. Whole body (WB), carcass (C) and organ (kidney, liver and brain) retentions were determined 1 and 2 weeks after a single radioisotope administration. The results are expressed as percentages of the administered dose (% D) and as percentages of whole body (% WB) and carcass (% C) radioactivities.

After oral administration whole-body cadmium retention was higher in sucklings than in weaned animals, primarily due to increased gut retention. The kidney retention of orally administered cadmium was about 5–7 times higher in sucklings than in older rats. Cadmium distribution (% C) was similar after oral and intraperitoneal administration. In sucklings, kidney retention made a lower fraction of the carcass radioactivity one week after ^{115m}Cd administration but reached adult values a week later. Liver retention in sucklings was a slightly lower fraction of the carcass radioactivity than in older rats at both time intervals. Brain retention (% C) was about 10 times higher in sucklings than in older rats throughout the experiment.

Preliminary data on the influence of dietary treatments and treatment with DTPA indicate that some treatments which influence cadmium retention also influence cadmium distribution. Our results confirm previous findings that sucklings are at a higher risk than adults at the same level of environmental exposure to cadmium.

Introduction

The kidney is known to be the critical organ for the effects of cadmium in the body (*1*). Data on kidney retention are therefore relevant for establishing criteria for environmental cadmium exposure.

For this purpose, our previous and new results on cadmium toxicokinetics in rats after a single oral or intraperitoneal ^{115m}Cd administration are presented in terms of kidney and other organ (liver and brain) retentions and distribution in relation to age. Data on the effect of some dietary treatments and treatment with chelating agents are also included.

Methods

Experiments were performed on random-bred albino rats aged 1–26 weeks. They were fed a stock laboratory diet (1.2% Ca and 0.8% P). Animals fed on other foods (milk, meat, bread) received the relevant dietary treatment 3 days before the beginning and until the end of the toxicokinetic studies. In some experiments, the trisodium calcium salt of diethylenetriaminepentaacetate (DTPA) (600 μmole/kg body weight) was administered intraperitoneally immediately and 24 hr after intraperitoneal administration of radioactive cadmium.

Radioactive cadmium (^{115m}Cd) was supplied by the Radiochemical Centre, Amersham, England (specific activity of about 0.5 μCi/mg). It was given orally, to sucklings by artificial feeding (*2*) and to older animals by gastric intubation, or intraperitoneally.

The retention in the whole body (WB), carcass (C) (whole body after removal of the total gastrointestinal tract) and gut (G) (total gastrointestinal tract contents included) was determined in a

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two-crystal scintillation crystal scintillation counter 1 and 2 weeks after a single radioisotope administration. The radioactivity in the kidney (K), liver (L) and brain (B) was determined at the same time intervals in an automatic gamma scintillation counter. The results were corrected for radioactive decay and geometry of the samples. The retentions were expressed as percentages of the dose (%D) and also as percentages of the whole body (%WB), and carcass retention (%C). Results given in the tables present only essential data from each experiment (arithmetic means and number of animals in parentheses). References are given whenever available where more details, including statistical treatment of data for each experiment, can be found.

Results

Effect of Age on Cadmium Retention and Distribution after Intraperitoneal and Oral Administration

Data presented in Tables 1 and 2 are expressed as percentage of the administered dose and those in Table 3 as percentages of the whole body and carcass retentions.

After intraperitoneal administration, cadmium retention in the whole body and carcass was very high in all animals, regardless of age, at both time intervals after administration (Table 1). Kidney retention was lower in sucklings than in older animals 1 week after cadmium administration but reached adult levels 1 week later. Liver retention was a slightly lower fraction of the administered dose in sucklings than in older rats at both time intervals. Brain retention in sucklings was about ten times that in older rats throughout the experiment.

Cadmium whole body retention after oral administration was much higher in sucklings than in older rats (Table 2). This high body retention decreased with time due to the short half life of the cadmium retention in the gut. Carcass values were maintained at almost the same level throughout the observation period. This level in sucklings was about seven times that in older rats. Kidney retention in sucklings was about five times that in older rats 1 week after cadmium administration. A further increase in kidney retention was observed at the later time interval, but no comparison with kidney retention in older rats could be made since these data were not available. Liver retention in sucklings was also about 7 and brain retention about 60 times that in older rats.

Data in Table 3 were calculated from mean values in Tables 1 and 2 and present cadmium distribution in various organs in relation to whole

Table 1. Effect of age on body and organ retention of ^{115m}Cd 1 and 2 weeks after intraperitoneal administration (per cent dose).

	Age, weeks[b]	Weeks after adm.	^{115m}Cd, % of dose[a]						Ref.
			WB	C	K	L	B	G	
Sucklings	1 (9)	1	85	74	2.1	37	—	10	(3)
	1 (18)	1	81	67	1.6	33	0.38	14	(4)
	1 (18)	1	89	76	2.8	44	0.36	13	(5)
	1 (18)	1	97	82	2.2	45	—	15	(6)
	Mean	1	88	75	2.2	40	0.37	13	
	1 (22)	2	89	—	6.1	46	—	—	(7)
	1 (18)	2	76	71	3.0	35	—	5.5	(3)
	1 (18)	2	80	73	4.1	45	0.37	6.7	(5)
	Mean	2	82	72	4.4	42	0.37	6.1	
Older rats	8 (10)	1	83	77	3.1	48	0.04	11	(8)
	18 (12)	1	83	80	3.4	66	—	3	(3)
	26 (8)	1	87	78	3.2	53	0.03	13	(8)
	Mean	1	84	78	3.2	56	0.04	9	
	3 (10)	2	81	—	4.8	53	—	—	(6)
	6 (9)	2	78	—	4.8	56	—	—	(6)
	26 (11)	2	93	83	4.5	69	0.04	—	(5)
	Mean	2	84	83	4.7	59	0.04	—	

[a]Whole body (WB), carcass (C) (WB after removal of the total gastrointestinal tract) kidney (K); liver (L); brain (B); gut (G) (total gastrointestinal tract contents included).

[b]Number of animals in parentheses.

Table 2. Effect of age on body and organ retention of ^{115m}Cd 1 and 2 weeks after oral administration (per cent dose).

	Age, weeks[b]	Weeks after adm.	^{115m}Cd, % of dose[a]						
			WB	C	K	L	B	G	Ref.
Sucklings	1 (53)	1	30	9.3	0.4	6.2	0.05	20	(*4*)
	1 (18)	1	35	13	0.5	5.5	—	21	(*9*)
	1 (11)	1	20	9.1	0.4	5.3	—	11	(*3*)
	1 (16)	1	21	9.8	0.4	5.3	—	13	—
	1 (9)	1	18	7.8	0.4	5.0	10	10	—
	Mean	1	25	10	0.4	5.5	0.05	15	
	1 (10)	2	12	9.8	0.5	6.0	—	2.6	(*3*)
	1 (13)	2	12	9.5	0.7	6.0	—	2.8	—
	Mean	2	12	9.7	0.6	6.0	—	2.7	
Older rats	6 (12)	1	1.5	1.3	0.09	0.8	0.0008	0.22	(*4*)
	6 (18)	1	1.8	1.5	0.07	0.8	—	0.23	—
	Mean	1	1.7	1.4	0.08	0.8	0.0008	0.23	

[a]Whole body (WB); carcass (C) (WB after removal of the total gastrointestinal tract); kidney (K); liver (L); brain (B); gut (G) (total gastrointestinal tract contents included).
[b]Number of animals in parentheses.

body and carcass radioactivity. Organ retentions expressed as percentages of the carcass radioactivity seem to show best the effect of age and route of cadmium administration on its distribution. These results show that the cadmium distribution in various organs is similar after intraperitoneal and oral administration.

Effect of Various Foods on Cadmium Retention and Distribution

We noticed previously that various foods influence the bioavailability of cadmium in short-term feeding experiments (*10*). Cadmium distribution in the kidney and liver in the same animals is presented here (Table 4). All "human" foods caused an increased whole-body retention of orally administered cadmium which was partly due to increased gut retention. All "human" foods also caused a higher increase in kidney than in liver retention, indicating that cadmium distribution in the body can be influenced by dietary treatment.

Effect of Age and DTPA Therapy on Cadmium Retention and Distribution

DTPA treatment was less efficient in reducing the body burden of intraperitoneally administered cadmium in sucklings than in weaned rats (Table 5). These results will be presented in detail elsewhere (*8*). In treated rats, kidney and liver retentions represent almost the same fraction of the whole body and carcass radioactivities, in contrast to controls in which liver retention greatly exceeds kidney retention. This finding applies both to suckling and weaned rats and is the result of a higher efficiency of DTPA in removing cadmium from the liver than from the kidney. These results indicate that some treatments could selectively influence cadmium burden in various organs.

Table 3. Effect of age on organ distribution of ^{115m}Cd 1 and 2 weeks after intraperitoneal or oral ^{115m}Cd administration (% WB; % C).[a]

		^{115m}Cd at various times after administration, %							
		1 week				2 weeks			
		Sucklings		Older rats		Sucklings		Older rats	
Organ		IP	PO	IP	PO	IP	PO	IP	PO
Kidney	% WB	2.5	1.6	3.8	4.7	5.4	5.0	5.6	—
	% C	2.9	4.0	4.1	5.7	6.1	6.2	5.4	5.7
Liver	% WB	45	22	67	47	51	50	70	—
	% C	53	55	72	57	58	62	71	—
Brain	% WB	0.42	0.20	0.04	0.05	0.45	—	0.05	—
	% C	0.49	0.50	0.05	0.06	0.51	—	0.05	—

[a]Results calculated from the means in Tables 1 and 2; whole body (WB); carcass (C) (WB after removal of the total gastrointestinal tract).

Table 4. Effect of various foods on ^{115m}Cd retention and distribution 6 days after oral administration.[a]

		^{115m}Cd retention, % of dose[b]				
		WB	C	K	L	G
Rats chow	% D	1.8	1.5	0.07	0.8	0.23
(18)	% WB	—	83	3.8	44	13
	% C	—	—	4.7	53	—
Milk	% D	7.8	5.2	0.51	2.0	2.6
(18)	% WB	—	67	6.5	26	33
	% C	—	—	9.8	39	—
Meat	% D	8.3	5.1	0.48	1.6	3.1
(10)	% WB	—	61	5.8	19	37
	% C	—	—	9.4	31	—
Bread	% D	7.3	5.1	0.33	1.5	2.3
(10)	% WB	—	70	4.5	21	32
	% C	—	—	6.4	29	—

[a]Number of animals in parentheses. Milk, meat, bread given to rats 3 days before ^{115m}Cd administration and till the end of the experiment.

[b]Whole body (WB); carcass (C) (WB after removal of the total gastrointestinal tract); kidney (K); liver (L); brain (B); gut (G) (total gastrointestinal tract contents included); percent of administered dose (% D). WB values from Rabar and Kostial (*10*).

Discussion

We tried to evaluate the effect of age on cadmium retention in the kidney from seven different experiments not specially designed for this purpose. However, our data are in general agreement with the results of more detailed studies on cadmium retention and distribution recently published by several authors (*11–15*). A detailed comparison of the results is very difficult to make because of different experimental conditions (time, frequency, dose, route of cadmium administration, etc.) and different ways in which various authors expressed their results. A good example of the possible ways of expressing toxicokinetic results in growing animals is given by Wong and Klaassen (*14*).

Like several other authors (*14–16*), we found lower kidney retention in immature animals at the earlier time. However, kidney retention in sucklings soon reached adult levels by redistribution from other parts of the body. This might indicate a higher rate of kidney accumulation in sucklings than in older rats at later time intervals after cadmium administration. Sasser and Jarboe (*17*) obtained comparable results. Wong and Klaassen (*15*), however, found a similar kidney accumulation rate in sucklings and adult rats.

The retention in the liver was slightly lower in sucklings than in older rats. This supports the conclusions made by several authors that the higher liver metallothionein concentration (*18,19*) does not influence cadmium distribution

Table 5. Effect of age and DTPA therapy on ^{115m}Cd retention and distribution: % D, % WB, % C 6 days after intraperitoneal administration.[a]

		Controls[b]			Treated			Controls/treated		
		% D	% WB	% C	% D	% WB	% C	% D	% WB	% C
Sucklings[c]	WB	81	—	—	7.7	—	—	11	—	—
(18)	C	67	83	—	6.5	84	—	10	—	—
	K	1.6	2.0	2.4	0.78	10	12	2.1	0.2	0.2
	L	33	41	49	1.2	16	19	28	2.6	2.6
	B	0.38	0.5	0.6	0.18	2.3	2.7	2.1	0.2	0.2
Older rats[d]	WB	83	—	—	2.0	—	—	42	—	—
(10)	C	77	93	—	1.5	75	—	51	1.2	—
	K	3.1	3.7	4.0	0.33	17	23	9.4	0.2	0.2
	L	48	58	62	0.41	21	28	117	2.8	2.2
	B	0.04	0.05	0.05	0.007	0.4	0.5	5.7	0.1	0.1

[a]Trisodium calcium salt of diethylenetriamine pentaacetate (DTPA) (600 μmole/kg body weight) administered IP immediately and 24 hr after ^{115m}Cd administration.

[b]Whole body (WB); carcass (C) (WB after removal of the total gastrointestinal tract); kidney (K); liver (L); brain (B); gut (G) (total gastrointestinal tract content included). Percent of administered dose (% D) values from Kostial and co-workers (*8*).

[c]One week old.

[d]Eight weeks old.

(*15,20,21*). The higher brain retention found in sucklings is in agreement with several previously published results (*11,22*).

Our results also show that sucklings retain a higher fraction of cadmium in other parts of the body since liver and kidney retentions together represent a lower fraction of the body retention in sucklings than in adult rats. The higher fraction of cadmium might be in the hair (*23,24*) or in other organs which are also known to accumulate cadmium like the spleen (*16*) or the adrenals (*25*).

When expressing data as percentages of the carcass retention, we found a similar retention and distribution of cadmium after oral and intraperitoneal administration. A similar conclusion was arrived at earlier by Moore and co-workers (*26*). However, these data do not include gut retention, which might be important in conditions of oral exposure. A much higher gut retention of orally administered cadmium in sucklings than in older rats was also found by other authors (*17,27*). A very high gut retention was also observed in adult monkeys in which the largest fraction of cadmium was found in the intestine 3 weeks after oral administration (*28*).

Dietary factors are known to be important in cadmium metabolism, especially in determining absorption from the gastrointestinal tract (*29,30*). Our preliminary data indicate that dietary factors not only influence absorption but may also influence distribution of cadmium in the body. This finding is in agreement with some previous results by Omori and Muto (*31*) on the influence of calcium, phosphorus and dietary fibers on cadmium metabolism. Further studies are necessary to confirm these results. Some physiological states, such as pregnancy and lactation, were also found to influence not only cadmium absorption but also cadmium distribution and especially the retention in the kidney (*34,35*).

The administration of DTPA was less efficient in removing cadmium from the body of sucklings than from older animals. However, in both age groups DTPA caused a higher reduction of cadmium retention in the liver than in the kidney. This is in agreement with some previous results (*32*). However, in different experimental conditions (chronic subcutaneous cadmium administration) it was found that DTPA removed cadmium only from the kidney and testes without affecting liver retention (*33*).

Differences in cadmium metabolism in relation to age, including a lower efficiency of the chelating agent in reducing cadmium retention in neonates, are most probably the result of the age-related functional immaturity. The term immaturity is not well defined and is especially difficult to use in interspecies comparisons of cadmium metabolism (*27,36*). The term is usually related to the immaturity of the intestinal barrier but also to blood–brain, blood–kidney, blood–testes, etc., barriers. Immaturity obviously influences uptake from blood to organs as well as elimination and perhaps age-related differences in the binding affinities and/or content of metal carrier proteins. These and other possibilities are discussed in detail elsewhere (*21,37–39*).

More studies performed under conditions of prolonged low level oral exposure (the most likely way of human exposure to cadmium) are needed before definite conclusions on the effect of age, diet and other treatments on kidney retention of cadmium can be reached. However, it may be concluded that sucklings are likely to accumulate a higher burden of cadmium in the kidney and other organs than adults at the same level of oral exposure. Other factors which influence cadmium absorption or enhance cadmium elimination are also likely to influence cadmium distribution in the body and especially kidney retention.

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