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Differential Zinc Transport Into Testis and Brain of Cadmium-Sensitive and -Resistant Murine Strains

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ABSTRACT: Recently, we showed that murine strain differences to the testicular toxicity of cadmium (Cd) are the result of variable transport of Cd across the blood-testis barrier. Because Cd is a nonessential trace element, it must be using the transporter for an endogenous substance. The objectives for this study were to determine the natural ligand for the transport system used by Cd to enter testis and brain, and to determine whether the transport of that natural ligand also differs among Cd-sensitive and -resistant murine strains. Because zinc (Zn) and Cd are cations of similar size and charge, and because Cd has been shown to inhibit Zn uptake in a variety of systems, we hypothesized that Cd was using Zn transporters to enter tissues. In this study we characterized Zn transport into the testis and brain of Cd-sensitive and -resistant murine strains. We found that the transport of ^{65}Zn into testis and brain of Cd-resistant A/J mice was significantly reduced compared with that in Cd-sensitive 129/J mice. In 129/J mice, unlabeled $CdCl_2$ significantly reduced ^{65}Zn transport by 56% in testes and by 47% in brain. Pretreatment with Zn had no significant effect on ^{109}Cd transport rates into testes or brain of 129/J or A/J mice, but did reduce the percentage of the injected ^{109}Cd dose in testes of 129/J mice by 44% within 60 minutes. From these results we can conclude that Cd is using transport systems that normally function to regulate Zn levels in testes and brain. Murine strain resistance to the testicular effects of Cd is associated with a concomitant attenuation of the Zn transport system in testis.

Key words: Blood-testis barrier, blood-brain barrier, ion transport.
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Vascular barriers present in certain tissues regulate the exchange of substances between the blood and those tissues. In testis, the blood-testis barrier serves to provide a specialized environment for spermatogenesis; to regulate the access of hormones, metabolites, and antibodies to the germinal cells; and to ensure that the body's immunological system does not encounter the immunologically foreign haploid cells and mount an immune response to them (Setchell, 1994). The blood-testis barrier was characterized by electron microscopy in the rat in 1970 (Dym and Fawcett, 1970; Fawcett et al, 1970), and it has recently been suggested that there are actually 3 barriers in the testis of most species: 1) the endothelial cells lining the blood vessels and the lymphatic spaces, 2) the peritubular layer of myoid cells, and 3) the tight junctions between Sertoli cells (Plöen and Setchell, 1992). If a substance is able to cross the endothelial cell barrier of the testis, there is still a large interstitial space that includes Leydig cells, macrophages, and the lymphatic space, which must be traversed prior to encountering either the peritubular myoid cells or the Sertoli cell barrier.

In brain, the blood-brain barrier regulates the exchange of nutrients, hormones, toxins, and therapeutic agents between the central nervous system and blood (Rapoport, 1976). The blood-brain barrier is composed of specialized endothelial cells without clefts connected by tight junctions, which serve to restrict the passage of substances from the vasculature into the cerebral interstitium (Brightman and Reese, 1969).

Several trace metals have been shown to cross the blood-brain barrier quite readily, including lead (Bradbury and Deane, 1986), calcium (Smith, 1990), iron (Banks et al, 1988; Bradbury, 1997), and manganese (Aschner and Aschner, 1990). The very slow penetration of administered Zn into the brain suggests a low permeability of the blood-brain barrier to Zn; however, Zn influx into tissues is under homeostatic control, with net Zn uptake increasing during dietary deficiency (Kasarkis, 1984). This suggests that special means exist for essential trace metal entry into the brain, such as ion channels or transport proteins. The use of these transport systems by nonessential or toxic metals such as Hg or Cd may explain the toxicity of these metals. Methyl mercury enters the brain through an amino acid carrier-mediated process (Aschner and Clarkson, 1989). Cadmium has been shown to accumulate in the brain and induce cerebral edema and blood-brain barrier dysfunction (Webster and Valois, 1981; Shukla et al, 1996).

Murine strains that differ in their testicular sensitivity

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to Cd have been shown to have significant differences in cadmium uptake into reproductive organs (Gunn and Gould, 1970; Hata et al, 1980; Chellman et al, 1984). Acute Cd exposure results in complete testicular hemorrhagic necrosis in Cd-sensitive strains. Cd appears to cross the endothelial cell layer of the blood-testis barrier and to drastically increase the vascular permeability of testis. This increased permeability causes fluid to rush into the testis, which overwhelms the draining function of the lymphatic system, resulting in hemorrhage, ischemia, and finally, necrosis. However, Zn pretreatment has been found to prevent Cd-induced testicular toxicity by diverting Cd away from testes and into the liver (Chen et al, 1974, King et al, 1998). We have recently shown that ^{109}Cd transport (administered as $^{109}CdCl_2$) differs significantly in 2 murine strains that vary in their testicular response to acute Cd exposure. Mice of strain 129/J, which are sensitive to acute Cd-induced testicular toxicity, have a significantly increased transport of ^{109}Cd into testes and brain compared with that of Cd-resistant A/J mice (King et al, 1999).

In the light of the significant differences in Cd transport seen in these 2 murine strains, we sought to determine the natural ligand for the transporter that Cd uses to enter tissues. Cd has a similar size as that of the cations, Zn and Ca, and the 3 ions have many common properties. In addition, Cd has been shown to inhibit Zn and Ca uptake in many different tissues. However, whereas Cd transport in testis was competitively inhibited by Zn, it was not affected by Ca (King et al, 1999). Similarly, Cd influx across the corneal epithelium is not competitively inhibited by Ca (Weidner and Sillman, 1997). Therefore, the transport system used by Cd in these systems may be selective and not used by nonspecific divalent cations. In the light of these findings, we hypothesized that Zn was the natural ligand for the transporters Cd was using to enter tissues. To test this hypothesis, we characterized the transport of ^{65}Zn (administered as $^{65}ZnCl_2$) in testis and brain of Cd-sensitive 129/J and Cd-resistant A/J mice to determine if differential Zn transport occurs in these murine strains.

Materials and Methods

Chemicals

Cadmium chloride ($CdCl_2$), zinc acetate (ZnAc), and bovine serum albumin (BSA) fraction V were purchased from Sigma Chemical Company (St Louis, Mo). Laboratory grade (type II) water was prepared using a Life Scientific Inc water purification system (St Louis, Mo). Lactated Ringer's solution was purchased from McGaw Inc, (Irvine, Calif). The radiolabels $^{109}CdCl_2$, $Na^{125}I$, and $^{65}ZnCl_2$ were obtained from NEN Life Science Products (Boston, Mass). ^{125}I-labeled albumin (I-alb) was prepared by the chloramine-T method (Greenwood et al, 1963).

Animals

Male mice (8–12 weeks of age) were purchased from Jackson Laboratories (Bar Harbor, Maine). Mice of the 129/J strain are sensitive to the testicular effects of Cd, whereas those of strain A/J are resistant (Gunn and Gould, 1970; Hata et al, 1980; Chellman et al, 1984). Mice were housed in a vivarium at the Tulane University Center for Bioenvironmental Research, which is approved by the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC International). Animals were housed under conditions of controlled light (12 hours light/12 hours dark), air, and temperature (23°C). Animals had free access to food and water at all times.

Measurement of Zinc and Cadmium Entry Rates

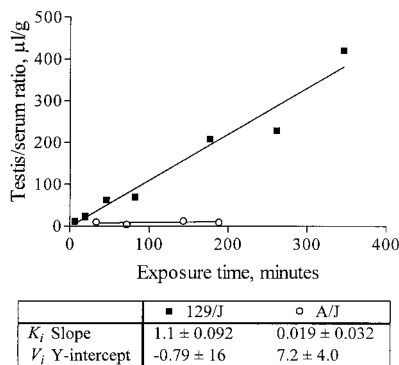
Measurement was carried out essentially as described by Banks and Kastin (1992) and Banks et al (1993). Briefly, mice were anesthetized with intraperitoneal (IP) urethane (2 g/kg of body weight), and the right carotid artery and left jugular vein were exposed. An injection of 0.2 mL of lactated Ringer's solution containing 1% BSA, 1×10^6 cpm $^{109}CdCl_2$, and 1×10^6 cpm ^{125}I-alb was made into the jugular vein. For Zn entry rate studies, 1×10^6 cpm $^{65}ZnCl_2$ was used in lieu of $^{109}CdCl_2$. Arterial blood was collected at regular time intervals after intravenous (IV) injection from an incision in the carotid artery. The mice were decapitated immediately after the collection of arterial blood. Serum was obtained by centrifugation at $3000 \times g$ for 10 minutes at 4°C. Testis, epididymis, and brain were removed, weighed, and counted in a gamma counter with the serum. The specific activity of the $^{109}CdCl_2$ used in all studies was 1.12 mCi/mg, and that for the $^{65}ZnCl_2$ was 0.89 mCi/mg.

The unidirectional influx constant (K_i in μL/g-minute) from blood into tissue was determined by the multiple-time regression analysis method (Patlak et al, 1983) as applied to the testicular influx of cytokines (Banks and Kastin, 1992). Briefly, this was determined by plotting the tissue/serum ratio (in μL/g) against exposure time (minutes). Exposure time is the integral value for cpm/μL arterial serum versus time (from 0 minutes to time t) divided by cpm/μL at t (Gjedde, 1981; Blasberg et al, 1983; Patlak et al, 1983). Exposure time is increased over real time, and reflects a constant plasma isotope concentration. The slope of the linear portion of the curve correlates the tissue ratio and exposure time, thus estimating K_i. The Y axis intercept of the line estimates V_i, the distribution volume of the compartments that rapidly and reversibly exchange with the plasma. Several animals were used per each experimental period, but because exposure time differs from real time, the values for exposure times differ between animals. The exact number of animals used in each experiment is indicated in the Figure and Table legends.

The percentage of the injection dose entering the testes (C_t) was determined after correction for the albumin space by the equation:

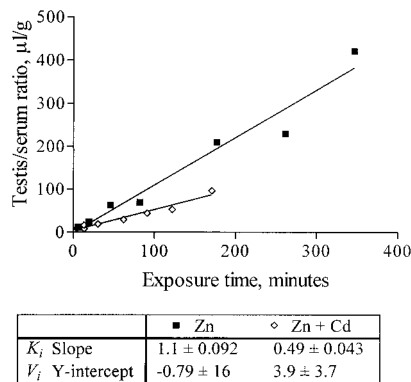
$$C_t = 100(R_i - R_a)(S_i)/I$$

where R_i is the testis/serum ratio for ^{109}Cd or ^{65}Zn, R_a is the testis/serum ratio for ^{125}I-alb, S_i is the cpm of ^{109}Cd or ^{65}Zn per mL of serum, and I is the cpm of ^{109}Cd or ^{65}Zn injected per mouse.



	▪ 129/J	○ A/J
K_i Slope	1.1 ± 0.092	0.019 ± 0.032
V_i Y-intercept	-0.79 ± 16	7.2 ± 4.0

Figure 1. Transport of ^{65}Zn in testis of 129/J and A/J mice 1 to 60 minutes after an IV injection of 2 µCi $^{65}ZnCl_2$. Exposure time is increased over real time, and is used to reflect a constant plasma ^{65}Zn concentration. Each symbol represents 1 animal; 129/J, n = 8; A/J, n = 4.



	▪ Zn	◇ Zn + Cd
K_i Slope	1.1 ± 0.092	0.49 ± 0.043
V_i Y-intercept	-0.79 ± 16	3.9 ± 3.7

Figure 3. Transport of ^{65}Zn in testis of 129/J mice after concurrent IV administration of 20 µmol/kg $CdCl_2$and 2 µCi $^{65}ZnCl_2$ (Zn + Cd) or 2 µCi $^{65}ZnCl_2$ alone (Zn). Each symbol represents 1 animal; Zn, n = 8; Zn + Cd, n = 8.

Zinc Pretreatment

Mice were injected with 250 µmol/kg ZnAc subcutaneously (sc) in the subscapular region 24 hours prior to $^{109}CdCl_2$ influx rate measurements.

Statistics

Regression lines were computed by the least squares method. Serum clearance was quantified by fitting the data to an equation for 1-phase exponential decay. Departure of lines from linearity was determined by the runs test, and statistical significance of the lines was determined by comparison of the slopes and intercepts using the Prism program (GraphPad Software Inc, San Diego, Calif).

Results

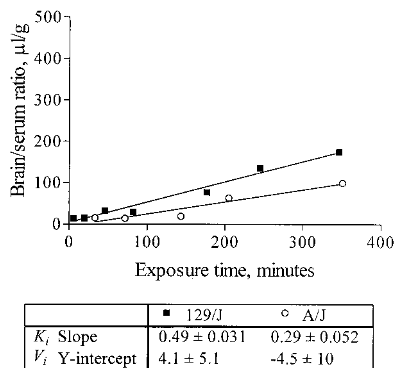
^{65}Zinc Transport

Influx of ^{65}Zinc Into Testis and Brain—In order to characterize the nature of Zn transport, multiple-time regression analysis was conducted 1 to 60 minutes after injection of $^{65}ZnCl_2$ and ^{125}I-alb. I-alb was used to verify that the ^{65}Zn treatment did not alter the integrity of the vascular barrier.

^{65}Zn transport in testis (Figure 1) and brain (Figure 2) was significantly greater in 129/J mice than in A/J mice (testis, P = .0002; brain, P = .006). No consistent entry of I-alb into tissues occurred during this time period, and the tissue/serum ratios for albumin were not significantly different between strains for either tissue, with tissue/serum ratios in testis of 29.73 ± 2.98 g/µL for 129/J mice (n = 22) and 18.58 ± 5.37 g/µL for A/J mice (n = 10). In brain, the tissue/serum ratios were 14.3 ± 0.6 g/µL for 129/J mice (n = 19) and 12.68 ± 0.96 g/µL for A/J mice (n = 9).

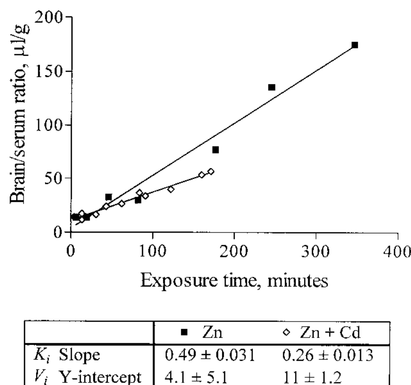
Characterization of ^{65}Zn Transport

Competition With Cd—To determine whether Cd and Zn use the same transport mechanism, $CdCl_2$ (20 µmol/kg) was given concurrently with ^{65}Zn. In 129/J mice, the concurrent administration of $CdCl_2$ significantly (P = .0018) inhibited the transport of ^{65}Zn in testes, resulting in a 56% reduction in transport (Figure 3). A similar effect occurred in brain, with concurrent $CdCl_2$ administration significantly (P < .0001) inhibiting the transport of ^{65}Zn by 47% (Figure 4).



	▪ 129/J	○ A/J
K_i Slope	0.49 ± 0.031	0.29 ± 0.052
V_i Y-intercept	4.1 ± 5.1	-4.5 ± 10

Figure 2. Transport of ^{65}Zn in brain of 129/J and A/J mice 1 to 60 minutes after an IV injection of 2 µCi $^{65}ZnCl_2$. Exposure time is increased over real time, and is used to reflect a constant plasma ^{65}Zn concentration. Each symbol represents 1 animal; 129/J, n = 8; A/J, n = 5.



	▪ Zn	◇ Zn + Cd
K_i Slope	0.49 ± 0.031	0.26 ± 0.013
V_i Y-intercept	4.1 ± 5.1	11 ± 1.2

Figure 4. Transport of ^{65}Zn in brain of 129/J mice after concurrent IV administration of 20 µmol/kg $CdCl_2$ and 2 µCi $^{65}ZnCl_2$ alone (Zn). Each symbol represents 1 animal; Zn, n = 8; Zn + Cd, n = 11.

Table 1. *Effect of Cd on ^{65}Zn transport in A/J mice**

	Testis		Brain	
	^{65}Zn	Cd + ^{65}Zn	^{65}Zn	Cd + ^{65}Zn
K_i	0.019 ± 0.032	0.0074 ± 0.028	0.291 ± 0.052	0.095 ± 0.054
V_i	7.235 ± 4.002	1.801 ± 3.514	−4.535 ± 10.20	8.520 ± 6.718
r^2	0.1542	0.7744	0.9124	0.6068
n	4	4	5	4

* Values expressed as mean ± SD. An IV administration of 2 μCi $^{65}ZnCl_2$ was given either alone (^{65}Zn) or concurrently with 20 μmol/kg $CdCl_2$ (Cd + ^{65}Zn). These values are not significantly different ($P > .05$).

In A/J mice, transport of Zn into both testis and brain was so negligible that concurrent administration of $CdCl_2$ had no statistically significant effect (Table 1).

Comparison of ^{109}Cd and ^{65}Zn Transport—To quantify the transport rates of the 2 cations, the influx of ^{109}Cd and ^{65}Zn were compared within the same tissue and strain. Within the same strain, there was no significant difference between ^{109}Cd and ^{65}Zn transport into testis (Table 2); however, there was a significantly increased ($P < .0001$) transport of ^{65}Zn compared with ^{109}Cd into brains of both 129/J and A/J mice (Figure 5). Neither the serum clearance of ^{109}Cd (Figure 6) nor ^{65}Zn (Figure 7) was significantly different between the strains.

Zinc Pretreatment

Effect on Influx of ^{109}Cd Into Testis and Brain—The entry of ^{109}Cd into testis and brain was significantly greater in the Cd-sensitive 129/J mice than in the Cd-resistant A/J mice. Pretreatment with Zn 24 hours prior to transport experiments had no significant effect on the influx of ^{109}Cd into testis or brain of either 129/J or A/J mice (Table 3).

Effect on Percentage of ^{109}Cd Injection Reaching the 129/J Testis—Zinc pretreatment 24 hours prior to transport experiments decreased the percentage of an injected ^{109}Cd dose reaching the testis of 129/J mice by 44% (from 2.02% to 1.14%) and reduced the area under the curve by 48% (107.5%-minutes to 56.3%-minutes; Figure 8). Peak values were seen at 15 to 30 minutes in both the control and Zn-pretreated groups.

Effect on the Clearance of ^{109}Cd From Serum in 129/J Mice—Because the percent uptake of an administered dose is a function of entry rate and blood levels, the serum clearance rates of ^{109}Cd were examined in Zn-pretreated 129/J mice and compared with untreated mice of the same strain. As shown in Figure 9, Zn-pretreatment 24 hours prior to transport experiments significantly increased ($P < .0001$) the serum clearance of ^{109}Cd in 129/J mice.

Discussion

Although the competition between Zn and Cd has been well-documented in many tissues, Cd transport rates in whole animals have only recently been reported (King et al, 1999). Cd transport was significantly different in 2 murine strains that differ in their susceptibility to the testicular toxicity of Cd. The murine strain that is resistant to testicular effects of Cd was found to have a lower rate of Cd transport, not only in testis, but also in brain (King et al, 1999). The current study measured the ^{65}Zn transport rate in whole animals to determine whether similar murine strain differences exist in the transport of this essential element as has been shown for ^{109}Cd. We found that the Cd-resistant murine strain, A/J, had a significantly lower ^{65}Zn influx into both testis and brain compared with the Cd-sensitive, 129/J strain. The influx rate (K_i) for ^{65}Zn transport into brain of 129/J mice is similar to what has been reported in rats (Pullen et al, 1990; Franklin et al, 1992). The transport rate in the 129/J strain is, therefore, more likely to represent the wild-type state, whereas the low rate of transport in the A/J strain may represent a protective mutation.

Table 2. *^{109}Cd and ^{65}Zn transport in testis of 129/J and A/J mice**

	129/J		A/J	
	^{109}Cd	^{65}Zn	^{109}Cd	^{65}Zn
K_i	1.174 ± 0.037	1.107 ± 0.092	0.019 ± 0.009	0.019 ± 0.032
V_i	5.455 ± 3.183	−0.795 ± 15.54	8.032 ± 0.753	7.235 ± 4.002
r^2	0.9763	0.9603	0.2688	0.1542
n	26	8	14	4

* Values expressed as mean ± SD. An IV administration of 2 μCi $^{109}CdCl_2$ or 2 μCi $^{65}ZnCl_2$ was given. These values were not significantly different when compared within the same strain ($P > .05$). Cadmium transport parameters were previously published in King et al (1999).

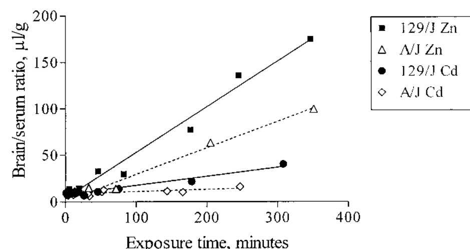


Figure 5. Transport of ^{109}Cd and ^{65}Zn in brain of 129/J and A/J mice 1 to 60 minutes after an IV injection of 2 µCi $^{109}CdCl_2$ (Cd) or $^{65}ZnCl_2$ (Zn). Each symbol represents 1 animal, n = 5–18.

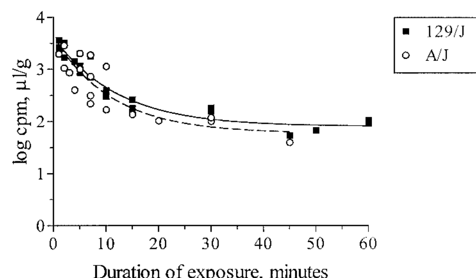


Figure 6. Clearance of ^{109}Cd in serum of 129/J and A/J mice given an IV injection of 2 µCi $^{109}CdCl_2$. Each symbol represents 1 animal; 129/J, n = 23; A/J, n = 19.

The competition between Cd and Zn was demonstrated by cadmium's inhibition of ^{65}Zn influx into both testis and brain of 129/J mice. In a similar manner, Zn significantly inhibited ^{109}Cd transport into these same organs. Zn transport in rat brain has previously been shown to be specific, saturable, and significantly inhibited by Cd (Buxani-Rice et al, 1994). Zn uptake has also been shown to be inhibited by Cd in isolated rat hepatocytes (Failla and Cousins, 1978; Stacey and Klaassen, 1981; Pattison and Cousins, 1986), and in bovine pulmonary aortic endothelial cells (Bobilya et al, 1992). These studies indicate that Cd is able to inhibit Zn transport in a variety of cell systems, and suggest that Cd is using transport mechanisms that exist to regulate Zn levels. Because Cd is a nonessential toxic metal, an endogenous transport mechanism for this cation would not be expected to exist. Therefore, it would appear that the transport mechanism described in our studies is one normally utilized by Zn; Cd is using a Zn-transport system to enter testis and brain.

In the current studies, we found no significant difference in testicular influx rates of ^{109}Cd or ^{65}Zn within the same murine strain; the transport of ^{109}Cd and ^{65}Zn were similar in testis. There was, however, a significantly increased transport of ^{65}Zn compared with ^{109}Cd in brain. The metal transport system in brain exhibited an increased transport rate for the natural ligand, Zn, compared to Cd. This may indicate that the Zn transport system in brain is more specific than that in testis. The testicular influx rates of both ^{109}Cd and ^{65}Zn were much higher than those in brain, which is reflective of the increased permeability of the blood-testis barrier compared with the blood-brain barrier. It may also indicate that testis has an increased requirement for Zn and may have an increased number or type of transport proteins.

Several Zn transporter proteins have recently been described, including ZRT1 and ZRT2 in yeast; ZnT-1 in kidney plasma membrane (Palmiter and Findley, 1995); ZnT-2 in kidney endosomal vesicles (Palmiter et al, 1996a); ZnT-3 in brain and testis (Palmiter et al, 1996b); a Zn transporter in human prostate cell lines (Costello et al, 1999) and in plasma membrane vesicles from rat brain (Colvin, 1998); and a proton-coupled metal-ion transporter, mainly expressed in the duodenum (Gunshin et al, 1997). These studies indicate that several different proteins exist for the transport of Zn, and Zn transport may be regulated in a tissue- or species-specific manner, which is consistent with our findings.

The use of Zn pretreatment to study the transport of Cd is based on the described protective effect of Zn pretreatment on subsequent Cd toxicity (Gunn and Gould, 1970). In the current study, Zn pretreatment was found to have no significant effect on influx rates of ^{109}Cd into testis or brain of Cd-sensitive 129/J or Cd-resistant A/J mice. However, Zn pretreatment did significantly reduce the percentage of an injected ^{109}Cd dose reaching the testis of 129/J mice by increasing the serum clearance of ^{109}Cd. Thus, less ^{109}Cd was available to enter the testis. Zn pretreatment has been shown to induce the formation of the metallothionein (MT) protein in the liver (Webb, 1972; Wahba et al, 1994). This induction presumably increases the clearance of ^{109}Cd from the serum and redistributes it to the liver. In fact, Zn pretreatment has been shown to increase hepatic levels of Cd after 24 hours (King et al, 1998).

Although Zn has been shown to induce MT, MT does not appear to play a role in the differential transport of Zn and Cd as a mechanism of strain resistance to the

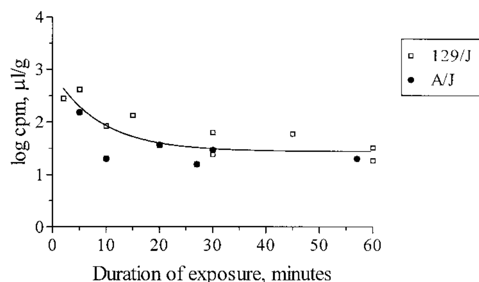


Figure 7. Clearance of ^{65}Zn in serum of 129/J and A/J mice given an IV injection of 2 µCi $^{65}ZnCl_2$. Each symbol represents 1 animal; 129/J, n = 10; A/J, n = 6.

Table 3. *Effect of Zn pretreatment on ^{109}Cd transport parameters in testis and brain of 129/J and A/J mice**

	129/J		A/J	
	^{109}Cd only	Zn + ^{109}Cd	^{109}Cd only	Zn + ^{109}Cd
Testis				
K_i	1.174 ± 0.037	1.0159 ± 0.056	0.019 ± 0.009*	0.008 ± 0.013*
V_i	5.455 ± 3.183	8.781 ± 1.679	8.032 ± 0.753	6.279 ± 0.425
r^2	0.9763	0.9785	0.2688	0.0340
n	26	10	14	12
Brain				
K_i	0.096 ± 0.006	0.100 ± 1.007	0.024 ± 0.007*	0.004 ± 0.015†
V_i	8.059 ± 0.630	8.396 ± 1.496	8.813 ± 0.580	8.030 ± 0.483
r^2	0.9498	0.9499	0.4370	0.006
n	14	13	17	13

* Values expressed as mean ± SD. Exposure to 250 μmol/kg ZnAc was given subcutaneously 24 hours prior to IV administration of 2 μCi $^{109}CdCl_2$ (Zn + ^{109}Cd). Cadmium transport parameters were previously published in King et al (1999).

† $P < .0001$ when compared to corresponding 129/J values.

testicular toxicity of Cd. For example, no differences in testicular MT concentration have been reported in the murine strains used in our studies (Nolan and Shaikh, 1986). In addition, testicular MT does not appear to be inducible (for example, Durnam and Palmiter, 1981; Onosaka et al, 1984; Shaikh et al, 1993). In studies with MT-null mice (ie, no MT expression) or MT-I transgenic mice (ie, MT-I overexpression), no differences were found in Cd distribution to tissues compared with controls (Liu and Klaassen, 1996; Liu et al, 1996). Similarly, no differences were found in Zn transport between MT-null mice and controls (Coyle et al, 1999). In the current study, there were no significant differences between the serum clearances of ^{109}Cd or ^{65}Zn in the 2 strains, which demonstrates that there are no innate differences in metal binding proteins such as MT in the serum of these strains. Therefore, it does not appear that MT plays a role in the initial transport of Cd or Zn, and thus cannot explain the differential transport of Cd and Zn between these 2 murine strains and the subsequent resistance to Cd testicular toxicity.

In summary, our findings indicate that Cd and Zn share a similar transport mechanism in murine testis and brain, and that murine strain resistance to the testicular toxicity of Cd is due in part to an attenuated transport of Zn and Cd because the transport rates of both ^{65}Zn and ^{109}Cd in testis and brain were decreased in the Cd-resistant murine strain, A/J, compared with the Cd-sensitive murine strain, 129/J. This suggests that the Cd-resistant mice have a decrease in the number of Zn-transport proteins or a mutation in the transport proteins that makes them less active. Because Cd and Zn were shown to compete for transport, alterations in the Zn transport system will affect Cd entry. Thus, a decrease in Zn transport in Cd-resistant mice will also manifest as a decrease in Cd transport. And a decrease in the amount of Cd reaching the testis renders A/J mice resistant to the testicular toxicity of Cd. The nature of murine strain resistance to the testicular effects of Cd may be related to the absence or mutation of the Zn transport system.

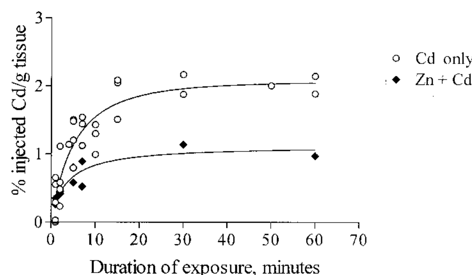


Figure 8. Percentage of ^{109}Cd reaching the testis of 129/J mice given an IV injection of 2 μCi$^{109}CdCl_2$ (Cd only) or 250 μmol ZnAc/kg sc 24 hours prior to 2 μCi $^{109}CdCl_2$ (Zn + Cd). Each symbol represents 1 animal; Cd only, n = 28; Zn + Cd, n = 11.

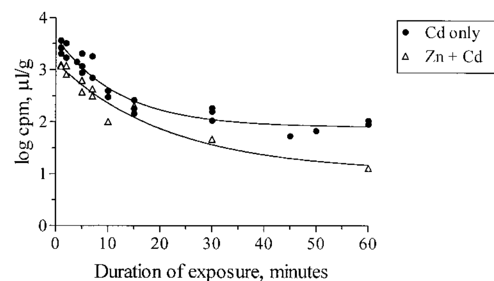


Figure 9. Clearance of ^{109}Cd in serum of 129/J mice given an IV injection of 2 μCi $^{109}CdCl_2$ (Cd only) or 250 μmol ZnAc/kg sc 24 hours prior to 2 μCi $^{109}CdCl_2$ (Zn + Cd). Each symbol represents 1 animal; Cd only, n = 23; Zn + Cd, n = 12.

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