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Plasma Membrane Transporters for Lead and Cadmium

Joseph P. Bressler[1,2], Luisa Olivi[2], Yongbae Kim[4], Desmond Bannon[5],
Hong Sook Ko[3] and Jae Hoon Cheong[3,*]

[1]*Department of Environmental Health Sciences, Bloomberg School of Public Health,*
Johns Hopkins University

[2]*Kennedy-Krieger Institute, Baltimore, MD, 21205*

[3]*Department of Pharmacy, Sahmyook University, Seoul, Korea*

[4]*Department of Preventive Medicine, Soonchunhyan University, Chunan City, Korea*

[5]*US Army, Aberdeen Proving Ground, MD 21010*

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Abstract – Lead and cadmium are potent environmental toxicants that affect populations living in Europe, Americas, and Asia. Identifying transporters for lead and cadmium could potentially l help us better understand possible risk factors. The iron transporter, divalent metal transporter 1 (DMT1), mediates intestinal transport of cadmium, and lead in yeast and fibroblasts overexpressing DMT1. In human intestinal cells knocking down expression of DMT1 attenuated uptake of cadmium and iron but not lead. A possible explanation is the expression of a second transporter for lead in intestine. In astrocytes, however, DMT1 appears to transport lead in an extracellular buffer at pH value. At neutral pH, transport was not mediated by DMT1 but rather by a transporter that is stimulated by bicarbonate and inhibited by 4,4'-diisothiocyanatodihydrostilbene-2,2'-disulfonic acid. The identity of this lead transporter will be verified by future study.

Keywords □ divalent metal transporter 1 (DMT1), cadmium, lead,

Lead and cadmium as environmental toxicant

Since the beginning of the industrial revolution, the general population has been exposed to a broad range of environmental toxicants. These toxicants cause a host of health problems including cancer, cardiovascular disease, and motor and cognitive impairment. Our laboratory is mostly concerned with metals, and more specifically, cadmium and lead. Both metals have found uses throughout industry. Cadmium affects a number of organ systems, but the kidney is recognized as the most sensitive(Jarup, *et al.*, 2000). Human and animals studies have revealed higher levels of cadmium in kidney than other soft tissue. The effects of cadmium on kidney physiology are more likely to be observed in adults because cadmium accumulates in the kidney with age. Because of better clinical diagnosis, recent studies have suggested that damage to the kidney occurs at levels of cadmium that were thought to be safe. Accordingly, suggestions have been made for lowering the maximal tolerated cadmium intake (Satarug, *et al.*, 2000). Since the levels of cadmium in the environment continue to rise, large populations of people living in Southeast Asian and Europe have exposure levels that are now considered damaging (Drasch, *et al.*, 1983).

Regarding lead poisoning, our concern has historically been in the health of children. Low-level exposure to lead in children is associated with impaired cognitive development (Bellinger, 1994) and delayed puberty in girls (Selevan, *et al.*, 2003). Even though lead was removed from paint and gasoline (the major sources of lead) in the early 1970's, approximately 5% of the children living in the U.S. in 1994 had blood lead levels greater than 10 μg/dl (Paschal, *et al.*, 2003), which is considered a risk by the Centers for Disease Control and the Environmental Protection Agency. Interestingly, more children are likely at risk when considering a recent study showing a relation between IQ and blood lead levels below 10 μg/dl in three-five year olds (Fig. 1) (Canfield, *et al.*, 2003). What is even more disconcerting is that lead is not excreted but is stored in bone throughout life. In female adults, lead re-enters the bloodstream because of calcium reabsorption during pregnancy and in older age

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*Corresponding author
Tel: 02-3399-3361,3657 Fax: 02-979-5931
E-mail: cheongjh@syu.ac.kr

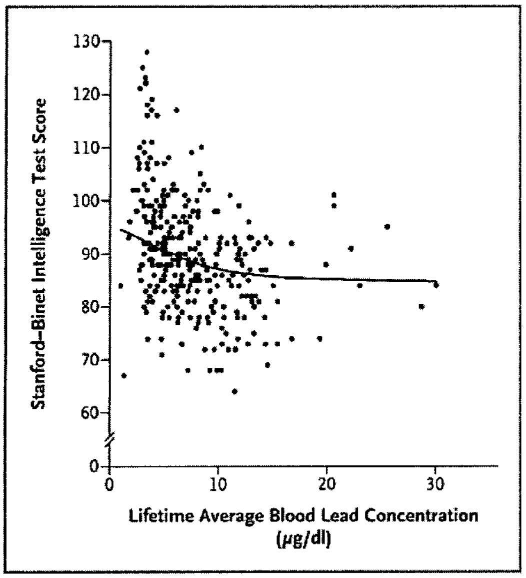

Fig. 1. IQ score as a function of lifetime average blood lead concentration. The line represents the relation between IQ and lifetime average blood lead concentration estimated by the covariate-adjusted penalized-spline mixed model. Individual points are the unadjusted life time average blod lead IQ values. *N. Engl. J. Med. 2003; 348 : 1517-26*

because of osteoporosis. Not surprisingly, increases in body lead burden is also associated with hypertension (Hertz-Picciotto and Croft, 1993; Cheng, *et al.*, 2001) and impaired cognition in adults (Stewart, *et al.*, 1999).

Risk factors have been identified that increase risk to lead and cadmium poisoning. Risk factors include genetic susceptibility and/or socio-economic status, which generally co-relates with living conditions in environments with high exposures. Also families with low-socio economic status suffer from other problems including greater stress (Lupien, *et al.*, 2000) and poor nutrition (Olson, 1999). Stress, for example, increases susceptibility to infection and impairs cognitive development (de Kloet and Oitzl, 2003). The combination of exposure to lead and stress might work synergistically in impairing cognitive development in children.

Uptake of lead and cadmium

Poor nutrition is an additional factor that has been suggested to increase the risk to the toxicity of lead and cadmium. The studies suggesting the involvement of poor nutrition have come from large population studies that have measured body burden of lead and cadmium along with levels of nutrients in the blood. From the many nutrients measured, most noteworthy fact is the inverse relation between iron status and body burden of lead and cadmium. Iron is generally taken from red meat. Women with preference for vegetarian or mixed diets have reduced Fe stores (measured by serum ferritin) and higher levels of cadmium in the blood (Berglund, *et al.*, 1994). Additionally, increased absorption of cadmium from a high shellfish diet was found in women with low body Fe stores (Vahter, *et al.*, 1996). In an experimental study, the average absorption of cadmium was 8.9% in subjects with low body Fe stores, which was significantly greater than the average absorption of 2.3% that was observed in subjects with normal Fe stores (Flanagan, *et al.*, 1978). Animal studies have largely agreed with the conclusions reached in the studies in humans (Ragan, 1977; Valberg, *et al.*, 1976). Fe deficiency also increased the level of cadmium in the kidneys [16]. In considering lead, a recent study found a significant inverse relationship between infants' 6-month and 12-month lead level with their intake of iron. In an experimental study, iron deficiency resulted in higher levels of blood leads in dams and pups fed relatively low levels of lead in drinking water (Crowe and Morgan 1996).

The relation between iron status and body burden of lead and cadmium suggests the possibility that the exposure route for all three metals is identical. Indeed, the exposure route of cadmium and lead in nonsmokers in the general population is the diet. Noteworthy, shellfish, rice, and leafy vegetables contain relatively high levels of cadmium (Satarug, *et al.*, 2000). Cadmium is found in different types of food (Satarug, *et al.*, 2000) either in complex with protein or in an inorganic form. In animals the major cadmium-binding protein is metallothionein (Mt), a similar protein, phytochelatin, occurs in plants (Cobbett, 2000; Klein, *et al.*, 1986). The relative importance of the inorganic form and the protein complex with respect to cadmium toxicity is unclear. Both forms (Sugawara and Sugawara, 1991; Ohta and Cherian, 1991) are absorbed in the gastrointestinal tract, but more inorganic form is taken up. Interestingly, iron inhibits the absorption of both forms (Groten, *et al.*, 1992). In exposures unrelated to occupation, the most significant sources of lead are paint, drinking water, and soil. Lead in soil is particularly important, because children accidentally ingest 50-200 mg of soil per day by hand-to-mouth behavior (Calabrese, *et al.*, 1997; Stanek and Calabrese, 2000). A recent study suggests that lead complexes formed in the small intestine can release free lead, which then can contribute to transport across the intestinal epithelium (Oomen, *et al.*, 2003).

Divalent metal transporter 1 (DMT1)

Intestinal absorption of essential metals occurs through a three-step process (Simpson and Peters, 1986). For iron, the steps are; 1) DMT1 mediates transport of the ferrous form of iron in the lumen (Trinder, *et al.*, 2000; Fleming, *et al.*, 1998) 2) a poorly understood mechanism mediates the serosal transfer to the basolateral side, and 3) and basolateral transfer to the plasma is mediated by ferroportin/Ireg1/MTP1 (Donovan, *et al.*, 2000) and oxidation to the ferric form by hephaestin (Vulpe, *et al.*, 1999) for binding to plasma transferrin (Fig. 2). DMT1 is a hydrogen-coupled divalent-metal transporter that belongs to a large family of metal transporters that have been identified throughout the animal and plant kingdoms (Fig. 3). In mammalian cells, DMT1 is thought to transport a broad range of metals. In Xenopus oocyte model, overexpressing rat DMT1 was found to increase the uptake of copper, manganese, cadmium, zinc and lead (Gunshin, *et al.*, 1997) in a surrogate assay for measuring transport of metals. Direct evidence supporting demonstrating DMT1-mediated lead uptake was shown in yeast and fibroblasts overexpressing DMT1. Uptake of lead was greater at acidic pH, thereby satisfying DMT1's requirement for H^+. Also, uptake was inhibited by iron (Bannon, *et al.*, 2002). To examine DMT1 mediated uptake of metals in intestine, a model of human intestinal absorption was examined by using the Caco-2 cell line (Bannon, *et al.*, 2003a). The uptake of lead and iron was a carrier mediated and temperature-dependent, which suggests the involvement of a transporter (Fig. 4). To specifically examine the involvement of DMT1, knockdown (KD) cells lines expressing low levels of DMT1 was established using ribozyme constructs containing an antisense sequence to the IRE form of DMT1. Control cell lines were established with ribozyme constructs missing the sequence. The KD cell lines displayed lower levels of DMT1 mRNA than controls. The transport of iron and cadmium, but not lead, was lower in the KD cell lines compared to the controls (Bannon, *et al.*, 2003b). It is possible that knocking down DMT1 does not decrease uptake of lead because Caco-2 cells express other transporters for lead. As we will discuss later, zinc transporters might also be candidate lead transporters.

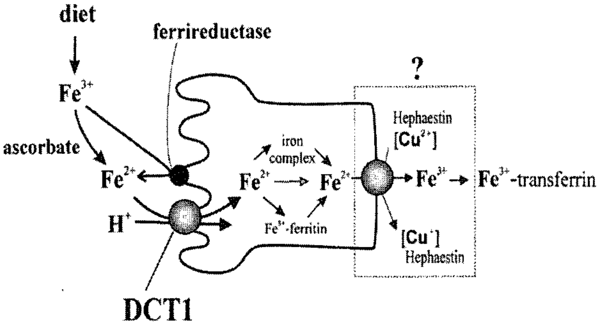

Fig. 2. Iron transporter in lumen of small intestine. Individual cells take up iron bound to transferrin using the transferrin receptor. DCT1 transports also iron into the cell at the apical brush border of the duodenal epithelial cell. Iron export from the epithelial cell also requires a copper-dependent ferroxidase called hephaestin.

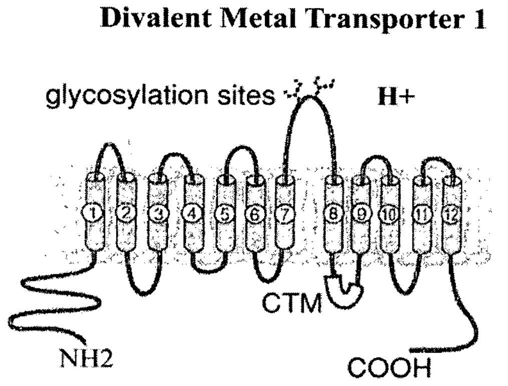

Fig. 3. DMT1. The transporter for nonheme iron at the luminal intestinal surface is DMT1, which is an H^+-coupled and electrogenic membrane transporter that belongs to a large family of integral membrane proteins highly conserved throughout evolution.

DMT1 in astrocytes

In the brain, astrocytes accumulate much of the lead in rats fed lead in their drinking water (Holtzman, *et al.*, 1984). A carrier-mediated temperature dependent transport of lead was shown in cultured astrocytes. Interestingly, transport of lead is likely mediated by at least two transporters in astrocytes and one transporter is likely DMT1 (Cheong, *et al.*, 2004). The evidence supporting the involvement of DMT1 was that increasing expression of DMT1 in astrocytes treated with deferoxamine resulted in increased uptake of lead when the transport assay was conducted at pH 5.5 not at pH 7.4. Furthermore, iron inhibited uptake of lead but only at pH 5.5 (Fig. 4). Acidic conditions favor DMT1-mediated transport of iron.

At pH 7.4, but not at pH 5.5, 4,4'-diisothiocyanatodihydrostilbene-2, 2'-disulfonic acid (DIDS) inhibited the transport of lead. DIDS is a very specific inhibitor of various types of anion transporters including the anion exchanger and organic anion transporters (Markovich and Murer, 2004; Romero, *et al.*, 2004; Hediger, *et al.*, 2004; Mount and Romero, 2004). It is a noncompetitive inhibitor and binds to external lysine groups of

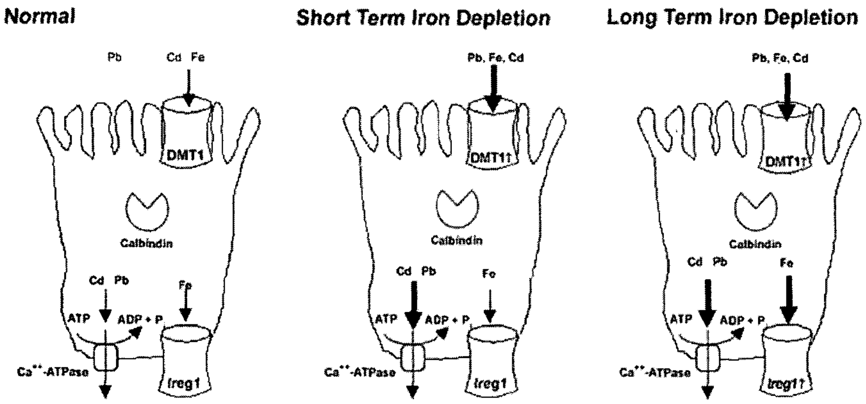

Fig. 4. Transport of lead and cadmium through DMT1. Higher levels of DMT1 could result in increased absorption of Cd and Pb because of calbindin and Ca-ATPase. Longer time on an iron-deplete diet will result in increased levels of Ireg1.

the transporters (Schopfer and Salhany, 1995). In erythrocytes, early studies found that the transport of lead was inhibited by DIDS but the transporter was identified as the anion exchanger (Simons, 1986; Lal, *et al.*, 1996), which mediates the electroneutral exchange of anions (Alper, *et al.*, 2002). No one, to our knowledge, has delineated a mechanism in which an anion exchanger mediates the transport of a divalent cation such as lead even though DIDS was also found to inhibit the transport of cadmium in erythrocytes (Lou, *et al.*, 1991). The anion exchanger mediates the 1:1 exchange of bicarbonate for chloride and enables the erythrocyte to metabolize carbon dioxide. The metabolism of carbon dioxide is a vital function of erythrocytes, which explains why 20% of erythrocyte membrane is the anion exchanger (also referred to as band 3) (Alper, 1998). It is possible for the anion exchanger to mediate the transport of a monovalent cation that forms a complex with carbonate because the complex retains a negative charge. The exchange between the complex and chloride would be electroneutral. A complex of lead (or cadmium) with carbonate would have no net charge and could not participate in anion exchange. On the other hand, the high levels of the anion exchanger might explain how a small amount of exchange is possibly not electroneutral. In addition to that, the large amount of the anion exchanger could also explain why approximately 95% of the blood lead is in erythrocytes.

A member of the family of anion exchangers has been identified in astrocytes but does not constitute 20% of the astrocyte membrane (Bevensee, *et al.*, 1997a; Bevensee, *et al.*, 1997b). Another possibility was that an organic anion transporter mediates the transport of a complex of lead and an organic anion (e.g. lead citrate). The effect of different inhibitors of organic anion transporters was examined but none inhibited uptake of lead in astrocytes. To better understand the mechanism of DIDS-mediated inhibition, we examined astroglial surface proteins that bind DIDS using an antibody against DIDS. Immunoprecipitation and SDS-PAGE revealed three proteins with molecular masses of 220 kDa, 125 kDa, and 70 kDa in astrocytes treated with 5 and 25 µM DIDS. We also found that the anion bicarbonate stimulated the uptake of lead in astrocytes (Alper, 1998). We suggest that stimulation by bicarbonate, and inhibition by DIDS, are important clues in uncovering the transporter for lead in astrocytes (Fig. 5).

In searching for transporters for lead in astrocytes, our laboratory has begun studying a family of transporters, SLC39 (also referred as ZIP) that mediates the cell surface acquisition of zinc and has members throughout the plant and animal kingdom (Eide, 2004; Gaither and Eide, 2000). We were interested in this family because of previous studies demonstrating

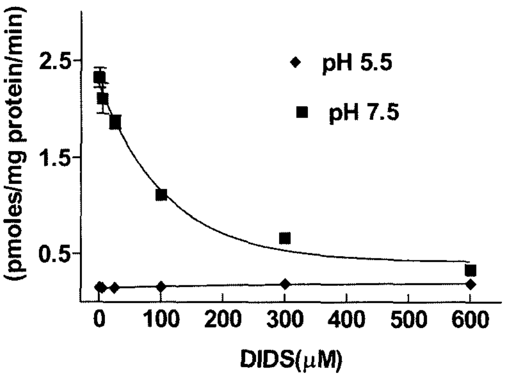

Fig. 5. The uptake of Pb in cells treated with DIDS. Glial cell cultures were washed with phosphate buffered saline and treated with different concentrations of DIDS. The uptake of 10 µM Pb in buffer at pH 5.5 and pH 7.4 was measured. Data points represent the mean ±S.E. of three replicates.

increases in lead uptake in rats fed diets deficient in zinc (Bebe and Panemangalore, 1996; Cerklewski and Forbes, 1976) and also because ZIP2-mediated transport of zinc is stimulated by bicarbonate (Gaither and Eide, 2000). So far, four members, ZIP1, 2,3, and 4, have been identified in mammals (Guerinot, 2000). It is possible that other members of the ZIP family are stimulated by bicarbonate because extensive characterization of ZIP 1,3, and 4-mediated transport of zinc has not, to our knowledge been published. Because of our interests in lead transport in the brain, we have been examining family member ZIP1 because it is found in brain and other tissues except pancreas. ZIP2 is moderately rare and is found in skin, liver, ovary and visceral yolk sak, and zip3 mRNA is mostly in testes (Eide, 2004). ZIP4 is exclusively in intestine (Dufner-Beattie, *et al.*, 2003). In situ hybridization studies reveal, however, that ZIP1 mRNA is not expressed by astrocytes in vivo though it is expressed cultures of astrocytes. Interestingly, neurons and choroid plexus epithelial cells express ZIP1 in vivo (not published). Whether members of the ZIP family mediate the transport of lead is a question for future studies.

In summary, cadmium and lead are potent toxicants that are absorbed in the gastrointestinal tract. The iron transporter DMT1 clearly mediates the transport of cadmium but whether it also mediates the transport of lead is unclear. The involvement of DMT1 in transporting cadmium and possibly lead helps explain why iron status is inversely associated with body burden of lead and cadmium. In astrocytes, DMT1 and yet an unidentified transporter mediates uptake of lead. Because of the associations between zinc status and lead burden, zinc transporters are likely candidates in transporting lead.

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