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Transport pathways for cadmium in the intestine and kidney proximal tubule: Focus on the interaction with essential metals

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ABSTRACT

Cadmium (Cd) is a toxic metal with a propensity to accumulate in the proximal tubules cells (PTC) of the kidney where it can lead to tubular dysfunction and eventually renal failure. Although Cd^{2+}-induced nephrotoxicity has been well described there is still uncertainty about how this metal gains entry into these cells to induce toxicity. As a non-essential metal, specific transport proteins for Cd are unlikely to exist. Rather transport proteins/channels used by essential metals (iron, zinc, calcium) are thought to be responsible. When these dietary essential metals are in short supply and deficiencies develop, Cd absorption and toxicity are enhanced. This is primarily due to increased expression of essential metal transport proteins such as divalent metal transporter 1 (DMT1) which can transport Cd in the intestine and enhance toxicity in the kidney. The zinc/bicarbonate sympoters ZIP8 and 14 are expressed at the apical membrane of enterocytes and PTC, and can transport Cd into cells. TRPV5 and 6 are major transporters for calcium in intestine and kidney and may be involved in Cd transport in these locations. Cd in the circulation is bound to proteins such as metallothioneins (MT) which are readily filtered. Two multiligand receptors, megalin and cubulin, reabsorb filtered proteins including albumin and MT by the process of receptor-mediated endocytosis. This review summarises the transport pathways for Cd in the intestine and kidney proximal tubule focusing in particular at how Cd uses essential metal transport processes to gain entry to the circulation and the kidney.

1. Introduction

Although cadmium (Cd) toxicity has now been shown in nearly every organ and tissue of the body, the kidney is still regarded as critical organ for its accumulation and toxicity. Greater than one-third of body Cd deposits are found in the kidney, the majority being in the S1 and S2 segments of the proximal tubule (PT) within the renal cortex (Dorian et al., 1992; Satarug et al., 2006). These segments of the PT have a large apical membrane surface area due to numerous microvilli and are densely packed with large mitochondria. This enables these cells to efficiently perform an important role in reabsorption of filtered nutrients. About 70% of fluid filtered by the glomeruli is reabsorbed by the PT, including water, proteins, glucose, sodium, amino acids, bicarbonate and some essential metals. Because there is no efficient excretory mechanism for Cd from the body and it is bound with high affinity to the metal binding protein metallothionein (MT) within cells, it accumulates here with a half-life of between 10 and 30 years (Jarup et al., 1998).

Tubule dysfunction may occur if the Cd concentrations in the kidney cortex rise above a critical threshold concentration. Once estimated to be 200 μg/g wet weight of kidney cortex, it is now thought to be in the region of 50 μg/g (Buchet et al., 1990; Roels et al., 1979; Satarug et al., 2006). However, even this may need further revision with the identification of more sensitive biomarkers of toxicity, improved analytical tools and the realisation that certain populations are at increased risk of Cd-induced toxicity (Prozialeck and Edwards, 2010; Satarug et al., 2010). It is estimated that up to 7% of populations exposed to Cd develop tubule dysfunction (Nordberg, 2009; Smith and Thevenod, 2009). This tubule dysfunction, which resembles Fanconi's syndrome, leads to increases in protein, amino acids, bicarbonate, glucose and phosphate in the urine (Gonick et al., 1975). The mechanisms by which Cd is absorbed, transported, and taken up by cells are still not fully understood. As a toxic metal, there is unlikely to be specific transport proteins for Cd. Rather, because Cd has similar chemical and physical properties to essential metals such as iron (Fe), zinc (Zn) and calcium (Ca), it can be transported and taken up by cells by a process referred to as "ionic and molecular mimicry" (Bridges and Zalups, 2005; Clarkson, 1993). As Cd avidly binds to sulfur amino acids and many proteins containing sulfhydryl groups (Cd actually

Abbreviations: Cd, cadmium; DMT1, divalent metal transporter 1; DCYTB, duodenal cytochrome reductase b; FPN1, ferroportin1; MT, metallothioneins; TRPV, transient receptor potential vanilloid; Mn, manganese; ZIP, Zrt-/Irt-like protein; GSH, glutathione; Tf, Transferrin; PT, Proximal tubule.

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has a higher affinity than Zn for these), this is likely to influence how the body handles this toxic metal (Jones and Cherian, 1990).

It is estimated that one-third of all enzymes require metals for their activity. Fe and Zn are often crucial components of metalloenzymes and Ca is commonly required as a cofactor for metal-activated enzymes. Because of their essential roles, and the fact that they in themselves can be toxic when present at higher levels, their concentrations are tightly regulated by the body at the level of absorption, storage and excretion. This is achieved by specialised transporter proteins for these metals which can be hormonally regulated and also binding proteins, such as metallothioneins (MT). The metal transport mechanisms for Fe, Zn and Ca are the ones that have been most closely investigated in connection with Cd uptake and distribution in the body and are considered in this review.

Numerous studies, in both animals and humans, have now demonstrated that dietary restriction of the essential metals Fe, Zn and Ca can lead to greater absorption and tissue accumulation of Cd (Berglund et al., 1994; Brzoska and Moniuszko-Jakoniuk, 2001; Evans et al., 1970; Fox, 1983; Fox et al., 1984; Jacobs et al., 1983; Kello et al., 1979; Kippler et al., 2007, 2009; Koo et al., 1978; Min et al., 2008).

A study by Flanagan et al. (1978) was one of the first to demonstrate that Fe deficiency causes an increase in Cd absorption from the gastrointestinal tract. Mice and humans low in body stores of Fe absorbed enhanced amounts of Cd. Mice accumulated increased levels of Cd in their liver and kidneys. At the time the mechanism of this effect was unclear (Flanagan et al., 1978). Subsequent studies demonstrated that Fe deficiency substantially increases the expression of the main apical intestinal Fe transport protein divalent metal transporter 1 (DMT1) and that DMT1 can also transport other metal ions including Cd (Gunshin et al., 1997). Park et al. (2002) reported that, in Fe deficient rats, a nine-fold increase in duodenal ^{109}Cd was associated with a 15-fold increase in duodenal DMT1 mRNA. In the kidney, there was a three-fold increase in Cd accumulation with a 30% increase in DMT1 mRNA.

Similarly studies have shown that low Zn status favours Cd absorption and accumulation. A study in Japanese quail demonstrated that a diet low in Zn enhanced the absorption of Cd and its accumulation in the duodenum, liver and kidney by 66%, 21% and 11%, respectively (Fox et al., 1984). In apical membrane vesicles from pig intestine it was shown that Cd and Zn compete for a transporter which was not associated with Ca uptake and in Caco-2 cells it was reported that the competition between Cd and Zn was independent of DMT1 (Elisma and Jumarie, 2001; Tacnet et al., 1991). Tanaka et al. (1995) found that rats deficient in Zn exhibited significant kidney proximal tubule injury that was completely prevented by an adequate Zn diet. In other studies, Cd-induced renal damage could be prevented by prior or co-administration of Zn (Jacquillet et al., 2006; Liu et al., 1996).

A study by Larsson and Piscator (1971) found that rats fed a low Ca diet accumulated 60% more Cd in the liver and kidneys than rats fed a diet sufficient in Ca. It was proposed that the activity of an intestinal Ca binding protein was increased by the low Ca diet (Washko and Cousins, 1976). The Ca transporter, transient receptor potential vanilloid 6 (TRVP6, also called CaT1), is increased by more than six-fold by low Ca diets (Bouillon et al., 2003; Min et al., 2008). Studies in fish have shown that diets elevated in Ca reduce Cd uptake and distribution to tissues (Klinck et al., 2009). However, experiments have also demonstrated that Cd actually blocks Ca uptake by TRVP6 (Vennekens et al., 2001).

In a study by Reeves et al., female rats were fed a low Cd-containing rice diet marginal in Fe, Zn and Ca for 5 weeks, and then a meal labelled with ^{109}Cd. It was found that these rats accumulated eight-fold more ^{109}Cd during the next 2 weeks than those fed a normal diet in the first 5 weeks (Reeves and Chaney, 2002). If the original diet was marginal in just Fe or Ca, there was three-fold higher retention of the label. However, in rats where the original diet was marginal in just Zn there was only a slight increase in ^{109}Cd uptake. Not only did deficient rats accumulate more Cd but the rate of Cd loss was much slower. These findings suggest that Cd absorption is mediated by transport mechanisms used by these essential metals, particularly Ca and Fe. Of interest in these studies was the fact that if the diet of the rats was changed from rice to one of sunflower kernels the absorption of Cd was significantly reduced, indicating that dietary constituents greatly impact on the bioavailability of dietary Cd.

Epidemiological studies in humans support these experimental findings at least with regards to Fe status (Berglund et al., 1994; Flanagan et al., 1978; Kippler et al., 2009). The inverse relationship between body Fe status and Cd absorption and accumulation was demonstrated nicely in a study of 57 Swedish women. Low body Fe stores, as measured by serum ferritin concentrations, were associated with increased blood and urinary Cd concentrations (Berglund et al., 1994). Women tend to have a higher body burden of Cd than men. This is because Fe stores in women are generally lower which leads to greater Cd absorption (Vahter et al., 2007). In a recent cohort study of pregnant Bangladeshi women the negative association between Fe status and blood Cd was confirmed. It also revealed a strong positive association between blood Cd and manganese (Mn) that remained after adjustment for Fe status. This indicates the possibility that Cd is absorbed via an undefined Mn transporter as previously reported in MT deficient cells (Himeno et al., 2002). No association between blood Cd levels and Zn status was found and there was a negative association between blood Ca and Cd. A previous study has reported that Mn absorption was highest in young women with low ferritin levels (Finley, 1999).

2. Absorption of zinc, iron, calcium and cadmium by the small intestine

As discussed above a critical determinant of Cd levels in the body, and its accumulation in various organs, is the level of essential metal transporters in the gastrointestinal tract. This is determined by body stores of essential metals and their dietary level. What happens in the gastrointestinal tract with regards Cd absorption is also likely to shed light on mechanisms for Cd uptake by the kidney. The essential metal transporters for Fe, Zn and Ca are located in the duodenum and proximal jejunum and these are the sites where most Cd is absorbed from the diet.

Absorption across epithelia can occur by two distinct processes, termed paracellular and transcellular transport. Paracellular transport occurs by passive diffusion or solvent drag and involves the passage through tight junctions formed where neighbouring cells abut. Transcellular transport involves passage across at least two membranes, is often energy dependent and is facilitated by membrane proteins. Transcellular transport across intestine is envisaged to be a three-step process; binding at the apical membrane, transport across the cytoplasm, and its efflux from the cell into the circulation at the basolateral membrane (Khanal and Nemere, 2008).

2.1. Zinc absorption by the intestine

The majority of Zn is absorbed by the small intestine, primarily the jejunum, by a transcellular mechanism. Zrt-/Irt-like protein 4 (ZIP4, SLC39A4), which is present at the duodenal and jejunum apical membrane, has been identified as the most important route for dietary Zn absorption. Its expression is highly responsive to dietary Zn, being up-regulated under Zn deficiency and down-regulated with increased Zn concentrations. Mutations in the ZIP4 gene leads to the condition acrodermatitis enteropathica with characteristic