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Invited Review

Kidney Dysfunction and Hypertension: Role for Cadmium, P450 and Heme Oxygenases?

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SATARUG, S., NISHIJO, M., LASKER, J.M., EDWARDS, R.J. and MOORE, M.R. *Kidney Dysfunction and Hypertension: Role for Cadmium, P450 and Heme Oxygenases?* Tohoku J. Exp. Med., 2006, **208** (3), 179-202 —— Cadmium (Cd) is a metal toxin of continuing worldwide concern. Daily intake of Cd, albeit in small quantities, is associated with a number of adverse health effects which are attributable to distinct pathological changes in a variety of tissues and organs. In the present review, we focus on its renal tubular effects in people who have been exposed environmentally to Cd at levels below the provisional tolerable intake level set for the toxin. We highlight the data linking such low-level Cd intake with tubular injury, altered abundance of cytochromes P450 (CYPs) in the kidney and an expression of a hypertensive phenotype. We provide updated knowledge on renal and vascular effects of the eicosanoids 20-hydroxyeicosatetraenoic acid (20-HETE) and eicosatrienoic acids (EETs), which are biologically active metabolites from arachidonate metabolism mediated by certain CYPs in the kidney. We note the ability of Cd to elicit "oxidative stress" and to alter metal homeostasis notably of zinc which may lead to augmentation of the defense mechanisms involving induction of the antioxidant enzyme heme oxygenase-1 (HO-1) and the metal binding protein metallothionein (MT) in the kidney. We hypothesize that renal Cd accumulation triggers the host responses mediated by HO-1 and MT in an attempt to protect the kidney against injurious oxidative stress and to resist a rise in blood pressure levels. This hypothesis predicts that individuals with less active HO-1 (caused by the HO-1 genetic polymorphisms) are more likely to have renal injury and express a hypertensive phenotype following chronic ingestion of low-level Cd, compared with those having more active HO-1. Future analytical and molecular epidemiologic research should pave the way to the utility of induction of heme oxygenases together with dietary antioxidants in reducing the risk of kidney injury and hypertension in susceptible people. ———— cadmium; kidney; cytochromes P450; heme oxygenases; 20-hydroxyeicosatetraenoic acid

The metal toxin cadmium(Cd) is found in low abundance in the earth crust and most surface soils (International Programme on Chemical Safety 1992; Waalkes et al. 1992; Järup et al. 1998). High concentrations of Cd can be found in soils in an area rich in zinc ores in which the toxin Cd occurs naturally in high abundance together with lead and copper (Järup 2003). This makes Cd a by-product or a waste product of industrial production of zinc, lead and copper. Increasing levels of Cd in agricultural soils is attributable to the use of Cd-containing phosphatic fertilizers and environmental pollution associated with industrial zinc production activities (McLaughlin and Singh 1999; Järup 2003; Simmons et al. 2005). Cd exhibits higher rates of soil to plant transference than do other metal toxins such as lead and mercury. In consequence, it enters the food chain and it is present in most human foodstuffs albeit in varying quantities (Galal-Gorchev 1993; Australia New Zealand Food Authority 1998; Kikuchi et al. 2002). Large quantities of Cd are found in offal notably liver and kidney and in certain bivalve molluscs and crustaceans because of their ability to concentrate Cd from aquatic environment (Kikuchi et al. 2002; Kruzynski 2004; Prankel et al. 2004). Cd is an integral constituent of tobacco because of the propensity of the *Nicotiana* species to concentrate Cd independent of soil-Cd content. Tobacco Cd content varies widely, but a typical range is 1-2 μg/g dry weight, equivalent to 0.5-1 μg/cigarette (Elinder et al. 1983). Cd oxide generated during the burning of cigarettes is highly bioavailable. Approximately a 10% of the inhaled Cd oxide is deposited in lung tissues, and another 30-40% is

absorbed into systemic blood circulation of smokers. Smokers have 4-5 times higher Cd levels in blood and 2-3 times higher Cd levels in their kidneys than do non-smokers (WHO 1989; International Programme on Chemical Safety 1992; Järup et al. 1998). We have shown that normal Thai men who on average smoked 9 cigarettes per day for 9 years had approximately 2-fold greater body Cd load than did non-smoking men of same age (Satarug et al. 2004a). In another study on men older than 50 years of age in northern Taiwan, smokers were 2.5 times more likely to excrete higher urinary Cd levels than nonsmokers (Chen et al. 2001). Cigarette smoking thus constitutes a source of non-workplace exposure to Cd other than exposure from consumption of food crops grown on Cd-contaminated soils or on soils naturally rich in this metal.

A safe intake level, known as the provisional tolerable weekly intake (PTWI), has been established for Cd since 1989 by the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA, WHO 1989). The PTWI for Cd was set at 7 μg/kg body weight/week, corresponding to 1 μg/kg body weight/day or 70 μg/day for a 70-kg person. This PTWI for Cd was derived from the assumption that enteral Cd uptake rate is about 5% with a daily excretion rate of 0.005% of body burden, two-third of which is in the liver and kidney. The toxicokinetic model, developed using the similar assumptions predicts that a Cd level of 50 μg/g kidney cortex ww, corresponding to urinary Cd excretion of 2-4 μg/day, may be attained after 50 years of intake of about 1 μg Cd/kg body weight/day (Elinder et al. 1976; Buchet et al. 1990). This figure is equivalent to the current guideline for safe intake levels of dietary Cd. In this connection, it should be noted however that Cd uptake rates vary widely among people (Horiguchi et al. 2004). It can be as high as 20-30% in individuals with low iron stores and iron deficiency (Flanagan et al. 1978; Bergland et al. 1994; Olsson et al. 2002; Kikuchi et al. 2003). Our study has revealed that normal Thai women with average age of 30 years who had serum ferritin < 20 μg/L, suggestive of low body iron stores, showed 3.4-fold greater Cd accumulation than did women with normal iron status (Satarug et al. 2004a). Our observation thus explains increased Cd accumulation in women to be caused by elevated Cd uptake rates associated with low-body iron stores.

Chronic Cd exposure is associated with a number of distinct pathological changes in a variety of tissues and organs, reflecting the multiplicity of Cd targets and toxicities (Satarug and Moore 2004b). We provide a list of Cd targets and toxicities in Table 1 together with references in which further information can be found. The different targets and toxicity outcomes observed among people are a function of Cd doses, duration and routes of exposure, gender, dietary, nutritional factors, coupled with genetic susceptibility (polymorphisms) and the presence of other disease. Emphysema arising in the workers exposed to Cd in dust and fumes suggests lung is a critical target organ for high-dose, inhalation exposure. Increased risk of renal stone was reported for another group of Cd-exposed workers (Järup et al. 1998). Severe damages to the kidney and bone occur concurrently following chronic ingestion of extremely high-dose Cd as reported for Japanese Itai-itai disease patients who accumulated large quantities of Cd in livers and kidneys and excreted Cd in extremely high levels (> 20 μg/g creatinine) in urine (Takebayashi et al. 2000). Recent data show that a fall in bone density mass equivalent to a 1.7-year increase in age associated with a 2-fold rise in Cd burden in a group of adult Japanese women with mean urinary Cd of 2.87 μg/g creatinine (Honda et al. 2003a). In another study (Schwartz et al. 2003), risk of having diabetes was increased in people with urinary Cd levels between 1 and 1.99 μg/g creatinine (odds ratio [OR] = 1.48, confidence interval [CI] 1.21 to 1.82). Such risk was further increased in people with urinary Cd > 2 μg/g creatinine (OR = 2.05, CI 1.42 to 2.95). Increased risk of having atherosclerosis has been noted in a representative sample of the general U.S. population with average urinary Cd excretion of 0.36 μg/L and the urinary Cd excretion at 25th and 90th percentile of 0.19 μg/L and

TABLE 1. *Multiplicity of cadmium targets and toxicities in human subjects*

Cadmium targets	Toxicities	References
Kidney	Tubular and glomerular dysfunction, chronic renal failure, stone, hypertension, depressed renal synthesis of active vitamin D, cancer	Buchet et al. (1990); Hayano et al. (1996); Yamanaka et al. (1998); Pesch et al. (2000); Hellstrom et al. (2001); Cai et al. (2001); Satarug et al. (2003, 2004b, c, d, e); Baker et al. (2005); Akesson et al. (2005)
Bone	Osteoporosis	Staessen et al. (1999); Alfven et al. (2000, 2002); Honda et al. (2003a); Aoshima et al. (2003); Jin et al. (2004)
Peripheral vascular tissues	Atherosclerosis	Navas-Acien et al. (2005)
Unknown	Increased risk of diabetes	Schwartz et al. (2003)
Liver	Increased risk of deranged drug metabolism and liver cancer associated with environmental exposure to procarcinogens attributable to cadmium induction of CYP2A6, CYP2E1 and CYP2C9 in liver	Baker et al. (2001, 2002, 2003, 2005); Satarug et al. (2004b, c, e)
Mammary gland	Reduction in calcium secretion in milk	Nishijo et al. (2002); Honda et al. (2003b)
Placenta	Impaired placental metal transport function, increased risk of preterm delivery	Nishijo et al. (2002)
Prostate, breast, colon, pancreas	Malignant disease	Ekman (1999); Schwartz and Reis (2000); Coyle (2004)

1.16 μg/L, respectively. On average, the subjects with atherosclerosis excreted 36% higher urinary Cd levels than those without atherosclerosis (Navas-Acien et al. 2005).

In this review we highlight the results of our investigations that uncover a plausible link between Cd-induced tubular dysfunction and high blood pressure in adult populations exposed to Cd in normal diet at the levels within the internationally accepted "safe" intake limit set for this metal (Satarug et al. 2000a). We present the results of our investigations on renal Cd accumulation and concurrent alteration in abundance of cytochromes P450 (CYPs) in the kidney, conducted using postmortem kidney samples from Australian Caucasian subjects who had no history of exposure to metals in the workplace. We summarize the results of our analytical epidemiologic investigations conducted on samples of normal adults, considered to be the representative of the general Thai population whom pressor effects of chronic, low-dose Cd was detected for the first time in non-smoking men. A diagram has been depicted to show sources of Cd deposited in kidney and Cd-induced nephropathy leading to an expression of a hypertensive phenotype (Fig. 1). In addition, a hypothetical model (Fig. 2) has been constructed to show some Cd targets in a proximal tubular cell together with defense mechanisms that determine the differences among people in their susceptibility to kidney dysfunction and hypertension following chronic intake of low-level Cd.

1. The kidney as a critical target in non-occupationally exposed populations

1.1 Sources and the half-life of Cd deposited in the human kidney

Previously, it was viewed that Cd of the dietary origin was deposited in liver prior to its release into blood circulation and renal uptake producing higher Cd levels in liver than kidney. It was later clarified that such hepatic deposition prior to renal uptake was observed only in rats fed with Cd in high doses. In contrast, rats fed with the diet containing Cd at the levels close to those found in human foodstuffs (0.03-3 mg/kg), showed higher levels of Cd in kidney than liver (Scheuhammer 1988; Elsenhans et al. 1992, 1997). Likewise, rats fed with contaminated rice consisting of Cd in the range of 0.1-1.0 mg/kg for 1, 4 and 8 months all showed higher levels of Cd in kidney than liver (Hiratsuka et al. 1999). There is also evidence suggesting that Cd of dietary origin can deposit directly in kidney when it is absorbed in a complex with metallothionein (MT) induced by low-level Cd found in most normal diets (Elsenhans et al. 1992, 1997). Data on Cd contents in liver and kidney cortex samples from non-occupationally exposed people follows tissue distributions similar to those in rats chronically fed with low-dose Cd (Orlowski et al. 1998; Satarug et al. 2001, 2002).

In the medulla of the kidney, Cd is present in low concentrations. The largest amount of Cd is found in the cortex, particularly in proximal tubular cells (PTCs) where most filtered Cd is reabsorbed (IPCS 1992; Jarup et al. 1998). Renal cortical Cd load increases with age and usually it reaches a plateau at 50 years of age, consonant with an age-related decline in renal function notably tubular reabsorption function (Satarug et al. 2002). Cd in the kidney accounts for one-third of the total Cd quantity in the body of which a 0.005% is excreted per day mostly in urine. For these reasons, urinary Cd excretion is considered to be a reliable indicator of cumulative lifetime or long-term exposure (Lauwerys et al. 1994; Mueller et al. 1998). The half-life of Cd in the kidney is estimated to be 20-30 years using human autopsy data (Elinder et al. 1976), indicating a long residence time of Cd in this organ. This is because of tubular reabsorption coupled with an extremely slow excretion rate of Cd attributable to a lack of an active biochemical mechanism for elimination of Cd from the body. The persistence of Cd in the kidney provides an opportunity for nephrotoxicity with no additional exposure. This may occur during infection and sepsis, when the levels of cellular nitric oxide are increased with the attendant release of the Cd previously bound to MT in the proximal tubular cells (Satarug et al. 2000b). This may explain a rise in mortality risk by 40-100% in individuals with signs of Cd-linked nephropathy discussed below. A lack of therapeutically effective chelating agents for elimination of Cd from the kidney is an additional insidious feature of this metal.

1.2 Renal Cd toxicities and adverse health outcomes

The manifestations of Cd nephropathy (low-molecular-weight proteinuria, calciuria, aminoaciduria, glycosuria, and tubular necrosis) share some similarities to those of the Fanconi syndrome, a genetic disorder characteristic of impaired renal tubular function (Thevenod 2003). The results from our epidemiologic investigations on two groups of 197 and 200 normal adult Thai men and women aged 19-60 years indicated a 10% to 15% increase in the probability of having tubular injury in those excreting urinary Cd between 1.4 and 3.8 μg/g creatinine (Satarug et al. 2004c, d, e, 2005). These results agree with the previous epidemiological studies conducted in Belgium (Buchet et al. 1990; Staessen et al. 1996), China (Jin et al. 2004), Japan (Ikeda et al. 2000; Oo et al. 2000; Suwazono et al. 2000), the United States (Noonan et al. 2002), Sweden (Järup et al. 2000). In a recent study, concurrent renal tubular and glomerular toxicities have been detected in a group of women aged 50 to 59 years with average urinary Cd excretion rate of 0.8 μg/g creatinine (Akesson et al. 2005).

It has been argued that Cd toxicities detectable in those people exposed environmentally to Cd is benign and is probably reversible. However, a parallel may be made with diabetic patients who

show increased urinary excretion of microalbumin, which is a symptom of abnormal capillary leakage. This is, in fact, an early warning of renal complications, subclinical or clinical morbidity and mortality. More importantly, recent data indeed link "benign" tubular dysfunction with urinary calcium loss, causing osteoporosis and increased risk of fracture. In a cross-sectional study in Belgium, it was noted that urinary calcium excretion rose by 10 mg/day for every 2-fold increment in urinary Cd excretion (Buchet et al. 1990) whereas a study in Sweden reported that urinary Ca excretion was increased by 90% in women 50-70 years of age whose urinary Cd excretion exceeded 1 μg/g creatinine (Järup et al. 1998). In a prospective study (median follow-up of 6.6 years) of a Belgian population, a 2-fold increase in urinary Cd correlated with a 0.01 g/cm^2 decrease in bone density ($p < 0.02$) in postmenopausal women (Staessen et al. 1999). The risks associated with doubled urinary Cd were 1.73 ($p = 0.007$) for fractures in women and 1.60 ($p = 0.08$) for height loss in men. Thus, chronic exposure to low-level Cd increases bone fragility and risk of fractures in women, despite the non-significant change in men. These female-linked effects are consistent with the previously described studies linking Cd absorption with reduced Fe stores mentioned earlier. In a Chinese population including residents from low- and high-exposure areas based on Cd concentrations in rice, the prevalence of calciuria was increased by 10% in subjects whose urinary Cd excretion of greater than 2 μg/g creatinine (Wu et al. 2001).

Previously, increased urinary excretion of the low molecular weight protein namely β2-microglobulin was implicated in long-term life prognosis. Mortality risk was increased by 40-80 % in people with signs of Cd-linked tubular injury (Iwata et al. 1992; Nakagawa et al. 1993, 1999; Nakagawa and Nishijo 1996). Urinary excretion levels of Cd and β2-microglobulin were associated with mortality risk in a dose-dependent manner (Nishijo et al. 1999). These data show such sign of Cd-linked renal nephropathy to be an early warning of complications, sub-clinical or clinical morbidity and mortality (Nakagawa and Nishijo 1996). Additionally, microalbuminuria has been linked to risk of having cardiovascular disease, renal failure, stroke, and high blood pressure (Mueller et al. 1995; Murtaugh et al. 2003; Lane 2004), but Cd exposures of subjects were not considered in these studies. A potential link between hypertension and mild renal dysfunction was suggested by an observation that subjects with mild hypertension who had microalbuminuria also excreted elevated N-acetyl-β-D-glucosaminidase (NAG) in the urine (Mueller et al. 1995).

1.3 Molecular mechanisms underlying renal Cd toxicity

The molecular pathogenesis of the nephropathy following chronic low-dose Cd exposure has not been fully elucidated (Thevenod 2003). It is suggested that Cd in the liver is released into the blood circulation in a complex with the low-molecular-weight metal binding protein, named metallothionein (MT). By virtue of its small mass of 6 kDa, the Cd-MT complex is filtered through the glomerulus. The filtered Cd-MT complexes are reabsorbed into the proximal tubular cells via the apical membrane by receptor-mediated endocytosis whereas the Cd-MT in the blood circulation is absorbed into the PTCs via the basolateral membrane (Erfurt et al. 2003). In addition to these two routes of entry, passive uptake may occur. Cd-MT complexes are degraded in the lysosome with a concomitant release of unbound Cd into the cytosol to cause toxicity. It is conceivable that such unbound Cd is a form causing toxicity.

Cd does not undergo valency changes, but its ability to cause "oxidative stress" has consistently been demonstrated using a number of in vivo and in vitro systems (Ercal et al. 2001). Cd was found to induce the generation of hydroxyl radicals in the presence of MT and damaged mitochondria (O'Brien and Salacinski 1998). This can be a result of Cd displacement of the redox active metal copper (Cu) previously bound to the MT. We have previously shown in rats that Cd and nitric oxide both could displace copper and zinc, sequestered in renal MT (Satarug et al. 2000b).

Cd binds strongly to thiol, which depletes cellular sulfhydryl pool and changes cellular redox (Nigam et al. 1999). Pretreatment of cells with the sulfhydryl donor N-acetylcysteine prevents in part Cd-linked oxidative damage. Cd-induced "oxidative stress" has been shown to cause damage to a variety of kidney proteins notably Na^+/K^+-ATPase (Thevenod and Friedmann 1999). The abnormally oxidised Na^+/K^+-ATPase is subject to degradation prematurely resulting a fall in its cellular concentrations. In one study in rats, a fall of kidney Na^+/K^+-ATPase activity by 13, 20 and 32% was recorded at 1, 2 and 3 weeks after repeated injection of Cd at the dose of 1 mg/kg (i.p.) for 1, 2 and 4 weeks, respectively (Lall et al. 1997). Interestingly, such fall in the Na^+/K^+-ATPase enzyme activity after Cd treatments occurred concomitant with a rise in blood pressure of 44, 84 and 75 mmHg.

In addition to oxidative stress, Cd causes a disruption of mitochondrial membrane potential and mitochondrial swelling with the release of cytochrome c and apoptosis (Robertson and Orrenius 2000; Erfurt et al. 2003). However, activation of caspases and apoptosis was independent of the Cd-induced release of cytochrome c since treatment with caspase inhibitors was unable to rescue cells from apoptosis after Cd exposure. The nature of mitochondrial involvement in Cd-induced apoptosis is not known. In summary, it has been proposed that toxicity of Cd is a result of injurious effects of reactive oxygen species, lipid peroxidation, protein crosslinking, DNA damage, and alteration of intracellular calcium levels.

Cd has also the ability to alter expression levels of a variety of genes and their corresponding proteins in the renal PTCs possibly via the pathways linked to specific transcriptional activators and repressors, notably the nuclear factor-kappa B, Nrf2, Bach1 (Thevenod et al. 2000; Stewart et al. 2003; Suzuki et al. 2003). The Cd responsive genes include c-fos, c-jun, MT, heme-oxygenase 1(HO-1), glutathione *S*-transferase, the detoxifying pump multi-drug resistance P-glycoprotein, and the sodium-dependent glucose transporters. Cd at a concentration of 5 μM induces mostly MT synthesis, and it induces mostly HO-1 at concentrations between 10 μM and 20 μM (Garrett et al. 1998; Klaassen et al. 1999; Hill-Kapturczak et al. 2003). Cd induces the specific subtype of sodium-dependent glucose transporter while it suppresses two other subtypes (Tabatabai et al. 2001). Some of these Cd inducible proteins are known to participate in defense mechanism that provides protection against injury. For instance, MT protects the tubular cells by sequestering "toxic" unbound Cd and whereas HO-1 protects the tubular cells against oxidative injury (Sato and Kondoh 2002) and an increase in blood pressure levels as detailed in section 3.4. The documented beneficial effects of enhanced HO-1 activity include depression of cellular levels of a toxic prooxidant heme, generation of the substances notably bilirubin and carbon monoxide exhibiting antioxidant, antiapoptotic and anti-inflammatory properties. The molecular basis for induction of the HO-1 gene expression is provided in section 5.5.

2. Cd nephropathy and hypertension: Are they linked?

2.1 Experimental induction of hypertension with low-dose Cd

Chronic low-dose Cd administrations raise the levels of blood pressure in dogs, rabbits, monkeys, and various strains of rats. However, the mechanism by which Cd induces a hypertensive phenotype in these animals is unknown. In chronic feeding studies, male and female rats of the Long-Evans strain were provided with Cd, lead, or chromium (III) in drinking water (5 ppm) from the time of weaning throughout life (Schroeder and Vinton 1962; Schroeder 1964, 1965). Hypertension developed in Cd-exposed rats and it occurred more frequently in females than in males and in those receiving both Cd and sodium chloride (0.1% NaCl). Females exposed to Cd alone and those exposed to Cd plus sodium chloride ingested 65% and 75% more Cd, respectively, compared to males. The greater intake of fluids and Cd by female rats may account for the higher incidence of hypertension. In another chronic feeding study, Cd concentrations in the kidney of hypertensive rats ranged between 5 and

50 μg/g wet weight (Perry and Erlanger 1974; Perry et al. 1977, 1978). These renal Cd levels were in the same range that found in the kidneys from Australian subjects environmentally exposed to Cd (Satarug et al. 2001, 2002) and most environmentally exposed populations. Cd-exposed hypertensive rats showed increased mortality and marked renal vascular changes (Schroeder 1964). In addition, they showed aortic atherosclerosis (Revis et al. 1981), increased retention of radioactively labelled sodium administered by intraperitoneal injection (Perry and Erlanger 1981) and reduced urinary volume and sodium excretion (Pena and Iturri 1993). These signs overlap those seen in some forms of human essential hypertension.

It should also be noted that Cd effects on blood pressure vary among species and strains of animals and Cd dose levels (Nomiyama and Nomiyama 2000). For example, the inherited hypertensive Dahl rats showed increased sensitivity to pressor effects of Cd and thus only low Cd concentrations between 1 ppm and 2.5 ppm in drinking water was sufficient to raise blood pressure in these rats (Ohanian et al. 1978; Ohanian and Iwai 1979). In sharp contrast, however, in the spontaneously hypertensive rats of the Wistar-Kyoto strain and of the Munster strain, Cd produced depressor effects attributable to increased activity of heme oxygenase caused by Cd (Zumkley et al. 1985). Of note, hypertension is not always evident after high-dose Cd exposure. A lack of pressor effects of high and very high-dose Cd in experimental animals is consistent with human data where hypertension was rarely found among highly exposed subjects. Indeed, in an early report, occupationally exposed subjects tended to have lowered blood pressure when Cd exposure levels were very high. Hypertension was never found among the Japanese itai-itai disease patients who ingested Cd in very high doses (Nakagawa and Nishijo 1996). We therefore consider that evidence for pressor effects of Cd thus should be sought from the general population exposed to Cd at levels lower than or closes to the PTWI.

2.2 High blood pressure arising in men with signs of Cd-linked tubular injury and dysfunction

In an effort to link mild tubular Cd toxicity with an adverse health outcome, we undertook an in-depth analysis of the relationship between blood pressure levels and signs of tubular injury in people environmentally exposed to Cd (Satarug et al. 2005). Our study included 200 normal Thai subjects, 16 and 60 years of age (100 female nonsmokers, 53 male nonsmokers, and 47 male smokers). None of these subjects had been exposed to Cd or Pb in the workplace. Urinary Cd excretion rate was used to reflect renal load and a cumulative lifetime exposure. Urinary excretion of plasma derived low-molecular weight proteins, notably β2-microglobulin (β2-MG) were used to assess tubular re-absorption capacity. Urinary excretion of the enzyme NAG was used to reflect an injury to tubular cells resulting in abnormal release of the enzyme in the urine. We found that Cd exposure levels experienced by the subjects in this study are associated with increases in prevalence of high blood pressure and signs of renal tubular damage. Subjects with average urinary Cd concentration of 10 nM (1.16 μg/L) face a 11% increase in the probability of having high blood pressure whereas subjects with Cd-linked NAG-uria (excreting > 8 NAG enzyme units/g creatinine) face a 20% increase in the probability of having of high blood pressure. Urinary excretion rates for the plasma derived β2-MG and for the renal enzyme NAG increase by 61% and 32%, respectively as urinary Cd concentration rose from 3.5 nM to 10 nM (0.39 μg/L to 1.12 μg/L). Thus, environmental Cd exposure levels experienced by the subjects in the present study may increase risks of high blood pressure. This study provides the first evidence linking tubular damage and dysfunction caused by low-dose Cd exposure with increased risk of high blood pressure.

2.3 Putative pathophysiologic mechanisms linking Cd nephropathy with expression of a hypertensive phenotype

As displayed in Fig. 1, Cd deposited in kidney includes those originated from the diet and

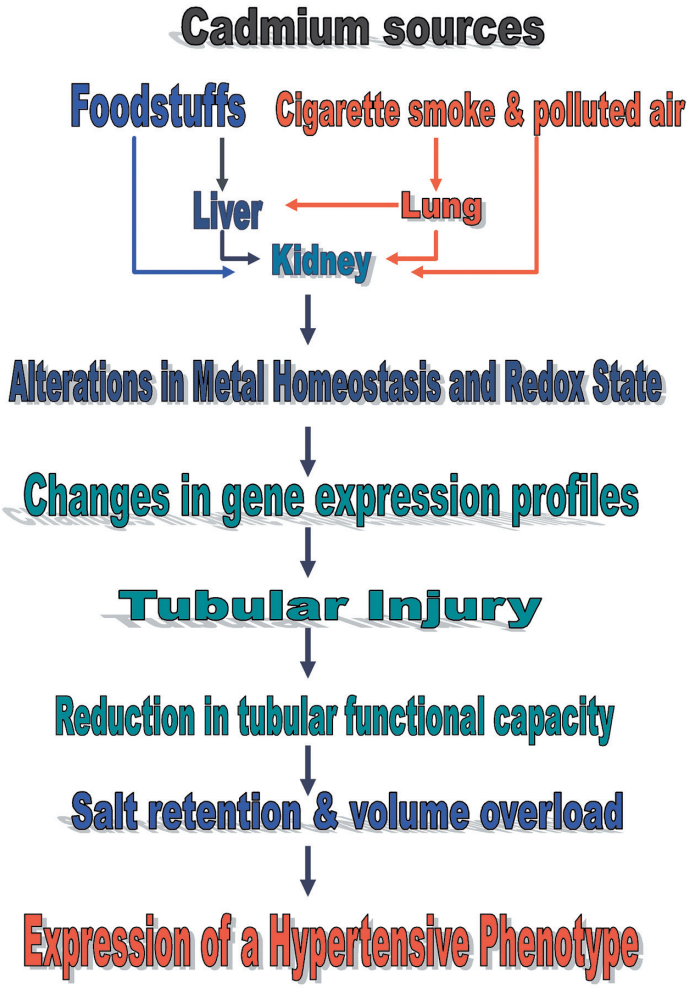

Fig. 1. A schematic representation of sources of cadmium deposited in human kidney and cadmium-induced nephropathy leading to an expression of a hypertensive phenotype.
Deposition of Cd, originated from dietary sources, cigarette smoke and polluted air, in the proximal tubular cells of the kidney cortex causes changes in redox state in conjunction with increased synthesis of the metal binding protein metallohionein (MT), which alters metal homeostasis and gene expression profile. As Cd intake continues, the host's metal binding and antioxidant capacities are exceeded, tubular injury ensues with attendant functional impairment. Prolonged renal dysfunction causes volume overload and salt retention that resets pressure natriuretic response and hypertension.

inhaled air firstly deposited in liver and lung prior to its release into blood circulation and renal uptake. It also includes those derived directly from the diet. The deposition of Cd proximal tubular cell increases the synthesis of MT and causes alterations in redox state and cellular essential metal homeostasis. These inturn cause changes in gene expression profile notably of the heme oxgenase-1 gene and certain CYP forms to normalize cellular physiologic state. As Cd intake continues, renal Cd accumulation exceeds the capacity of the host defense, leading to tubular injury reflected by a release into the filtrate and urine of enzymes originated from the lysosome of the tubular cell such as NAG. This follows by impaired tubular function, salt retention and volume overload. Prolonged tubular functional impairment results in resetting of pressure natriuresis and expression of hypertensive phenotype. These proposed mechanisms are consistent with

recent data that expand early observations on a critical role of kidney in determining long-term blood pressure levels, discussed in the next section.

3. The kidney as a regulator of long-term blood pressure levels

A role for the kidney in blood pressure control was evidenced in 1970s when the transplant of a kidney from a hypertensive rat into a normotensive host raised blood pressure while the transplant of a normal kidney to hypertensive host lowered blood pressure (Dahl et al. 1972, 1974; Dahl and Heine 1975). Later work has revealed a close relationship between renal perfusion pressures, urine flow and sodium excretion (Guyton 1991) which has led to the prediction that hypertension develops when pressure-natriuresis response is shifted to higher pressures. The pressure-natriuresis mechanism is a feedback system for long-term control of arterial pressure whereby a rise in renal perfusion pressure reduces sodium reabsorption with an increase in urinary sodium excretion. A number of studies with various hypertensive models in rats provide data supporting of the pressure-natriuretic response theory (Garbers and Dubois 1991; Lifton 1996; Lifton et al. 2001; Roman 2002). A few studies are summarised here to illustrate complexity of renal control of blood pressure and mechanistic heterogeneity among various hypertensive rat models used. In Lyon hypertensive rats, an elevated renal vascular tone that lowers glomerular filtration rate is attained via resetting of the pressure-natriuresis relationship. In spontaneously hypertensive (SHR) rats, an elevated vascular tone that reduces renal blood flow and interstitial pressure creates blunted pressure-natriuresis response. In the Dahl salt-sensitive (Dahl S) rats, a blunted pressure-natriuresis is due to increased sodium uptake in the thick ascending loop of Henle (Roman 1986). Collectively, these observations link renal handling of sodium and water with an expression of high blood pressure levels (Rossier et al. 2002; Firsov 2004; Morrison and Mindel 2004). We thus summarize below an update of the knowledge on renal specific transporters responsible for sodium reabsorption and excretion.

The kidney reabsorbs 95% - 98% of Na^+ ion from the filtrate under normal physiologic conditions (Hamilton and Butt 2000; Granger et al. 2002; Schild 2004). Of these, approximately 70% of filtered Na^+ is reabsorbed in the proximal tubule. The remainder is reabsorbed in the thick ascending limb of the loop of Henle (TALH), the distal convoluted tubule and in the aldosterone-sensitive distal nephron, which includes the late distal convoluted tubule, the connecting tubule, and the cortical collecting duct. Several sodium transporters involving in the entry and exit of Na^+ in these segments of renal tubule have now been identified and characterised. These are Na^+/K^+-ATPase, the epithelial sodium channel (ENaC) and Na^+-K^+-Cl co-transporter (Matsubara 2000; Morrison and Mindel 2004). The ENaC is mainly responsible for Na^+ reabsorption in the connecting tubule, which retains sodium in response to a fall in daily salt intake. It is suggested that the endothelial nitric oxide synthase and nicotinamide adenine dinucleotide (phosphate) oxidase of the tubular epithelial cells within the renal medulla could also be involved (Evans and Fitzgerald 2005). These proteins collectively underlie the ability of the kidney to control the volume and osmolarity of the extracellular body fluids, the blood volume and the blood pressure. In support of this notion, the ENaC with increased activities via gain-of-function mutations was found to cause volume expansion and hypertension (Rossier et al. 2002; Schild 2004). Research on the functional consequences of mutations in the renal sodium transporters can indeed provide us an insight on pathogenesis of human hypertension.

Of relevance, evidence has now accumulated to suggest another group of proteins which are members of the cytochrome P450 (CYP) superfamily, notably those of CYP4 family, underlie in part the capacity of the kidney to regulate blood pressure levels. These enzymes produce biologically active metabolites, known collectively as eicosanoids, from the unsaturated fatty acid arachidonic acid (5,8,11,14-eicosatetraenoic acid). Examples of the eicosanoinds are eicosatrienoic

acids (EETs), dihydroxyeicosatrienoic acids (DHET) and 20-hydroxyeicosatetraenoic (20-HETEs). These eicosanoids have local vasoactive properties and regulate vascular tone, tubular reabsorption of Na^+ (Roman 2002; Sarkis and Roman 2004; Sarkis et al. 2004). As with sodium transporters, the ecicosanoid-producing CYPs in the kidney are currently under intensive investigation worldwide in the search for better understanding of the pathogenesis of hypertension (Capdevila et al. 2000; Imig and Zhao 2003; Sarkis et al. 2004; Kroetz and Xu 2005).

3.1 Cytochrome P450 (CYP) superfamily and their quantitation

Cytochrome P450 is a mixture of enzymes present in human and animal tissues, and indeed in all eukaryotes and prokaryotes (http://drnelson.utmem.edu/cytochromeP450.html). These enzymes have an absolutely conserved cysteine residue in the protein primary amino acid sequence. The cysteine thiolate group allows for binding the heme prosthetic group of these enzymes and this determines also the particular characteristic of the proteins's absorbance spectrum with a peak at 450 nm and hence the term cytochrome P450. These enzymes can catalyse

TABLE 2. *Multiplicity of substrates and expression organs for selected human CYP enzymes*

CYP forms	Expression Organs*	Substrates	
		Endobiotics	Drugs and other xenobiotics
CYP1A2	Liver, lung, esophagus, stomach, colon	Unknown	Caffeine, theophylline, phenacetin, ethoxyresorufin, clozapine, olanzapine, tacrine, heterocyclic amines
CYP2A6	Liver, nasal mucosa, trachea, lung	Unknown	Methoxyflurane, halothane, losigamone, valproic acid, letrozole, fadrozole, disulfiram, tegafur, dimethylxanthine, coumarin, nicotine, tobacco-specific nitrosamines
CYP2B6	Liver, kidney, nasal mucosa, trachea, lung	Fatty acids	Cyclophosphamide, bupropion, various nitrosamines
CYP2C9	Liver, small intestine	5-hydroxytryptamine, fatty acids (linoleic acid, arachidonic acid)	Phenytoin, diclofenac, tolbutamide, warfarin, losartan, torsemide, cyclophosphamide
CYP2E1	Liver, lung, esophagus, small intestine	Acetone	Acetaminophen, ethanol, chlorzoxazone, dimethylnitrosamine, benzene, carbon tetrachloride, halogenated alkane, halothane
CYP3A4	Liver, lung, stomach, small intestine, colon	Steroid hormones such as testosterone, cortisol	Erythromycin, midazolam, nifedipine, dapsone, lidocaine, alfentanil, carbamazepin, cyclosporine, tacrolimus, calcium-channel blockers, vinca alkaloid
CYP4A11	Liver, kidney	Lauric acid, oleic acid arachidonic acid, leukotriene B4	Unknown
CYP4F2	Liver, kidney	Arachidonic acid, leukotriene B4, vitamin E	Unknown

* Expression assessment based on mRNA and/or protein.

the monooxygenase reaction of a wide variety of substrates having dissimilar structures, including xenobiotic and endobiotic substrates. The multiplicity of substrates and expression organs for selected CYPs are shown in Table 2. Individual CYP enzymes could not be named after their substrates, in the way normal enzymes of intermediary metabolism are named.

Instead, a system of nomenclature was developed based on the primary amino acid sequences of these proteins (http://drnelson.utmem.edu/cytochromeP450.html). The system is based on identification of homology between sequences of amino acids in different proteins. All proteins with the conserved cysteine thiolate ligand to the prosthetic heme are called CYP, which defines the superfamily. Proteins with more than 40% overall primary amino acid sequence homology are classed in the same family which is given an arabic numeral (CYP**1**, CYP**2**, CYP**3** etc). Proteins within a family which have more than about 55-60% primary amino acid sequence homology are assigned an alphabetical letter which identifies the subfamily (CYP1**A**, CYP1**B**). Individual proteins within a subfamily are given an arabic numeral to identify them and there may be members showing more than 98% primary amino acid sequence homology (CYP1**A1**, CYP1**A2**). There are 58 CYP forms in humans. The CYPs of families 1, 2 and 3 are mainly present in liver and are mainly responsible for xenobiotic metabolism and they show the remarkable diversity of substrate selectivity. CYPs in other families (i.e., CYP4 family) are much more selective for their substrates which are mainly endobiotics and they are expressed in specific tissues, catalysing reactions which are characteristic of those tissues. Most CYPs are localized in the endoplasmic reticulum while some forms are present in the mitochondria.

Quantitation of the abundance of a particular CYP form in tissue samples of interest is often not possible by measuring catalytic activity because of a lack of substrate selectivity. Furthermore, as the substrates of CYPs are extremely lipophilic, only low aqueous concentrations are achievable. In consequences, measurement of catalytic activity at saturating substrate concentrations is only possible in the presence of organic reagents used to solubilise the substrates; with the attendant problems that these organic solvents are also inhibitors of the CYPs. For these reasons, we detected the abundance of CYPs in the kidney of humans by immunochemical detection. This method uses antibodies raised against a purified protein or against unique peptides in particular enzymes that allows highly selective detection; taking advantage of the differences in primary amino acid sequences to design antigens that will generate antibodies that will not cross react with other, even quite closely related forms (Edwards et al. 1998).

3.2 Emerging role of the eicosanoids derived from renal CYP-mediated lipid metabolism in the control of tubular function and systemic blood pressure

In the kidney of rats, a number of CYPs are found. Some of these are capable of producing various eicosanoids from the substrate arachinodate. CYP2C11, CYP2C12, CYP2C23, CYP2C24, CYP2J3, CYP2J4 and CYP2J10 catalyse an epoxygenase reaction from which EETs are generated. CYP4A1, CYP4A2, CYP4A3, CYP4A8, and certain CYP4F forms catalyse ω-hydroxylation reaction from which 20-HETE is generated (Wang et al. 1999; Roman 2002; Sarkis et al. 2004; Kalsotra et al. 2005). Recent data showed CYP4F1, 4F4 and 4F5 mRNA expression in the cortex of rat kidneys and CYP4F6 mRNA expression in the medulla (Kalsotra et al. 2005). CYP4A2 and CYP4A3 are predominantly expressed in renal arterioles, glomeruli, proximal tubules, and the thick ascending loop of Henle (TALH). CYP4A8 is expressed in the cortical proximal tubules, cortical thick ascending loop of Henle, and the collecting duct, but it is not expressed in the medulla. Also CYP4A is expressed in renal vascular smooth muscle cells. CYP4A12 and CYP4A14 are found in the kidney of mice (Holla et al. 2001).

Evidence for a role for CYP4A and 20-HETE in the pathogenesis of hypertension comes mostly from studies with normal rats and the hereditary

hypertensive rats. A rise in blood pressure of 46 and 57 mmHg was observed in normal male and female rats, respectively, following an administration of the androgen 5-α dihydrotestosterone that has the ability to induce renal expression of CYP4A8 and increase the synthesis of 20-HETE (Nakagawa et al. 2003). Elevated renal expression of CYP4A2 and synthesis of 20-HETE coincide with the development of hypertension in the SHR rats (Omata et al. 1992a, b). Diminution of 20-HETE synthesis by tin (SnCl2) and heme arginate treatments prevented the development of hypertension in these rats (Escalate et al. 1989, 1991; Sacerdoti et al. 1989; Levere et al. 1990; Da Siva et al. 1994). Inhibition of CYP-mediated arachidonate metabolism improved renal function in Lyon rats (Messer-Letienne et al. 1999a, b). Selective inhibition of 20-HETE production reduced blood pressure in SHRs and attenuated the vasoconstrictor response of renal interlobar arteries to angiotensin II in vitro (Xu et al. 2002). Induction of renal CYP4A in the Dahl S rats prevented the development of hypertension possibly via restoration of the blunted pressure-natriuresis attributable to increased sodium uptake in TALH. Such renal CYP4A induction also reduced glomerular injury and proteinuria (Ma et al. 1994; Alonso-Galicia et al. 1998). In the CYP4A14 knockout mice showing a hypertensive phenotype, expression of renal CYP4A12 was increased together with renal synthesis and urinary excretion of 20-HETE (Holla et al. 2001). Knocking down of renal CYP4A1 or CYP4A2 expression with antisense oligonucleotides caused a 16 mmHg fall in blood pressure in normal rats and inherited spontaneous hypertensive rats (Wang et al. 1999). Likewise, changes in renal expression of CYP4A with administration of the expression vector pcDNA3.1 containing sense or antisense CYP4A1 cDNA caused a 13 mmHg rise or fall in blood pressure in Sprague-Dawley rats (Zhang et al. 2002). These latter two experiments provide data supporting a role for specific renal CYP forms in blood pressure control in rats. Certain CYP4A enzymes are induced by the lipid-lowering drug clofibrate that was shown to have also blood-pressure lowering effects in rats (Roman 2002). These effects of clofibrate are mediated by the peroxisome proliferator-activated receptor (PPAR) in a complex with retinoid X receptor (Issemann et al. 1993).

3.3 Renal and vascular effects of eicosanoids

In the proximal tubule, 20-HETE inhibits Na/K-ATPase activity and sodium transport (Schwartzman et al. 1985; Omitnato et al. 1996; Nowicksi et al. 1997; Kroetz and Xu 2005). In addition, 20-HETE acts as a second messenger for parathyroid hormone, dopamine and angiotensin II (Roman 2002; Imig and Zhao 2003). In the TALH, 20-HETE serves as a second messenger controlling potassium recycling and sodium uptake from the filtrate. It inhibits sodium reuptake by inhibition of Na^+/K^+-Cl co-transport. In addition, 20-HETE reduces the lumen-positive transepithelial potential, essential for passive uptake of Na^+, K^+, Ca^{2+}, and Mg^{2+}. Also in the TALH cells, 20-HETE mediates the inhibitory effects of angiotensin II and bradykinin. In small arteries and arterioles (< 100 μm), 20-HETE is a vasoconstrictor, but it has no effect on larger arteries or the aorta. In summary, 20-HETE has both prohypertensive and antihypertensive properties. It reduces blood volume and opposes hypertension development via inhibition of sodium transport. Prohypertensive effects stem from its capacity to increase the renal and peripheral vascular tone. It also magnifies the actions of pressor hormones notably of the angiotensin II which has been shown to cause oxidative stress and hypertension in rats (Ishizaka et al. 1997; Haugen et al. 2000).

EETs regulate the glomerular filtration rate via activation of the Na/K exchanger in the glomerular mesangial cells (Sarkis and Roman 2004; Spector et al. 2004). EETs serve as second messenger for natriuretic effects of angiotensin II, probably through potentiation of the release of intracellular Ca^{2+} and inhibition of the Na/K exchanger translocation. In the collecting ducts, EET and DiHET inhibit the hydrosmotic effects of vasopressin, sodium transport and reduce transepithelial voltage. EETs cause hyperpolarisation in the vascular smooth muscle cells by increasing

the activity of large-conductance, Ca^{2+}-activated K^+ channels. EETs increase levels of intracellular Ca^{2+} in endothelial cells leading to enhanced synthesis and release of endothelial factors such as nitric oxide (NO), prostraglandin I (PGI), PGE2, PGF2α and thromboxane that can modulate vascular effects of EETs. As with 20-HETE, EETs produce both pressor and depressor effects. An example of depressor effects is their ability of cause vasodilatation (Sarkis et al. 2004).

3.4 Expression of CYPs in the human kidney in relation to Cd content, urinary 20-HETE excretion and a hypertensive phenotype

In comparison with rodents, much less is known about the CYPs in human kidney and their capacity to produce eicosanoids. However, production of 20-HETE from arachidonate in human kidney and urinary excretion of this eicosanoid has been reported (Schwartzman et al. 1990; Prakash et al. 1992). Thus, as a first step in defining the role of human renal CYPs in Cd-induced hypertension, we examined the CYP forms that are expressed in this extrahepatic organ by Western blotting with a panel of specific CYP antibodies (Baker et al. 2001, 2002, 2003). Our immunochemical data suggested that CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2D6, CYP2E1 and CYP3A4 proteins were not expressed in the human kidney microsomes while CYP2C and CYP2J were present in trace quantities. In contrast, CYP2B6, CYP4A11, CYP4F2, and CYP4F3b proteins were present in relatively large quantities in microsomes derived from human renal cortical tissue. Of these latter CYPs, CYP2J2 exhibits epoxygenase activity and thus may underlie renal production of EETs (Roman 2002; Kroetz and Xu 2005). Studies with human kidney microsomes have revealed that CYP4A11 underlies renal ω-hydroxylation of medium- and long-chain fatty acids including lauric acid and arachidonic acid (Powell et al. 1996, 1998; Lasker et al. 2000). CYP4F2 and CYP4F3b were found to metabolize arachidonic acid but not lauric acid, and to ω-hydroxylate the potent inflammatory agent leukotriene B4, thereby inactivating this agent (Jin et al. 1998; Lasker et al. 2000). Thus, these CYP enzymes may also be involved in fatty acid homeostasis and/or tissue inflammatory processes. CYP4F2 and CYP4A11 both have been shown to produce 20-HETE from arachidonate. In vitro studies with renal microsomes suggest that 67% of the 20-HETE produced is from CYP4F2 activity while a reminder is CYP4A11-mediated (Lasker et al. 2000). The contribution of CYP4F3b to renal 20-HETE production has not yet been determined, nor have the relationships among CYP4A11, CYP4F2 and CYP4F3b levels in the kidney and their role in renal tubular ion transport and/or vascular tone.

We next analysed the relationship between CYP abundance and Cd contents in kidney cortex samples and found that the levels of CYP4A11 inversely correlated with renal Cd loads (Baker et al. 2002, 2003). In another study (Baker et al. 2005), we examined CYP4F2 protein abundance where we found that kidney Cd loads between 2 and 63 g/g wet weight positively correlated with age ($r = 0.41$, $p = 0.02$) and with CYP4F2 levels ($r = 0.44$, $p = 0.01$). Controlling for age did not affect the strength of correlation between renal CYP4F2 and Cd levels. These observations suggest the potential for involvement of Cd as a mediator of CYP4A11 and CYP4F2 expression in kidney, and indicate that elevations in kidney Cd loads may result in altered renal 20-HETE production and 20-HETE-linked hypertension via the changes in the expression of these particular CYP forms.

Several studies have investigated the role of 20-HETE in essential hypertension in humans. Laffer et al. (2003a) examined the change in urinary 20-HETE excretion following salt loading and depletion in salt-resistant hypertensive and salt-sensitive hypertensive subjects and found urinary excretion of 20-HETE was increased in both groups of subjects following saline loading. A correlation between elevated urinary 20-HETE excretion and increased sodium excretion was seen only in salt-resistant hypertensive patients. It was concluded that a lack of inhibition of sodium transport by 20-HETE might contribute to an increase in blood pressure in salt-sensitive patients following salt loading. In another study,

an expected increase in urinary 20-HETE excretion following furosemide administration was found in normal subjects but not in salt-sensitive hypertensive subjects. Laffers and colleagues (2003b) concluded that impaired synthesis or actions of renal 20-HETE might contribute to the expression of salt-sensitive hypertension. These features are similar to hose seen in the salt-sensitive Dahl rats (Ma et al. 1994; Alonso-Galicia et al. 1998). In this connection, it should also be noted that the defects other than 20-HETE has also been noted in causing changes in renal function and salt sensitivity in the Dahl rats. These may include changes in the synthesis of nitric oxide (Manning et al. 2001) and the activity of 11 β-steroidhydroxylase (CYP11B2) that catalyzes the conversion of cortisol to cortisone (Morgan et al. 1990). Indeed, a certain genetic variant of *CYP11B2* has been linked to some forms of human essential hypertension (Matsubara 2000).

3.5 Emerging role of heme oxygenase as a renal protector and a depressor

Heme oxygenase -1 (HO-1) is one of the two reported functional isozymes of heme oxygenases that oxidise heme producing ferrous iron, carbon monoxide and biliverdin which is converted to biliurubin (Hill-Kapturczak et al. 2002; Shibahara et al. 2002; Shibahara 2003; Wagener et al. 2003; Sikorski et al. 2004). As with CYPs, HO-1 is localised in the endoplasmic reticulum. Expression of HO-1 is increased following exposure to a wide variety of cellular stressors. A renal protector role of HO-1 is evident from severe damage in the kidney of a human case and mice with HO-1-deficiency (Poss and Tonegawa 1997a,b; Yachie et al. 1999; Ohta et al. 2000). Kidney sections of the HO-1-deficient patient contained iron deposition in the proximal tubular cells. Likewise, kidneys of HO-1 knockout mice showed iron deposition in renal proximal tubular epithelium and occasional glomerulonephritis. In addition, embryonic fibroblasts from the HO-1-deficient mice were more sensitive to Cd (Poss and Tonegawa 1997a, b). Renal protector effects of HO-1 in vivo was evidenced in a rat model of rhabdomyolysis where HO-1 mRNA was induced 3-6 h after injury, and administration of an HO-1 inhibitor, tin protoporphyrin, worsened renal damage, while prior induction of HO-1 decreased mortality (Nath et al. 1992, 2000).

Renal protection of the HO-1 expression was seen also in ischemia-reperfusion injury, cisplatin exposure, glomerulonephritis and renal transplant (Mains et al. 1993; Agarwal et al. 1995; Aizawa et al. 2000; Shimizu et al. 2000; Shiraishi et al. 2000; Baan et al. 2004). In the glycerol model of acute renal injury, more severe renal dysfunction and tubular injury with 100% mortality was seen in the HO-1 (–/–) mice compared with HO-1 (+/+) mice (Nath et al. 2000). HO-1 (–/–) mice treated with cisplatin developed more severe renal failure with increased apoptosis and necrosis, compared with cisplatin-treated wild type or heterozygote mice (Agarwal and Nick 2000; Shiraishi et al. 2000). The proposed mechanisms for protector effects of HO-1 include its ability to degrade pro-oxidant heme with the release of biliverdin and subsequent conversion to bilirubin, both of which have antioxidant properties. Based on these findings, the renal protector role has been firmly established for HO-1. An investigation into clinical relevance and the protective effects of HO-1 in Cd-induced nephropathy is worthwhile.

As with renal CYPs, evidence for depressor effects of HO-1 comes from studies with hereditary hypertensive and normal rats. Administration of HO-1 inducer such as stannous chloride restored high blood pressure to normal pressure levels in spontaneously hypertensive (SH) rats (Escalante et al. 1991) whereas other inducers of HO-1 or HO substrates decrease BP in hypertensive SH rats (Levere et al. 1990; Martasek et al. 1991; Johnson et al. 1996). Treatment of normal rats with inhibitors of HO (metalloporphyrins) raises blood pressure. In another study, an increase in renal heme oxygenase activity resulting from over-expression caused a decrease in blood pressure in the SH rats (Sabaawy et al. 2001). Hypertension induced by one kidney-one clip procedure was more severe in HO-1-null mice (Wiesel et al. 2001). However, there was no difference in systolic blood pressure between

HO-1 (+/+), HO-1 (+/–), and HO-1 (–/–) mice. This was attributed to a compensatory role for HO-2 to resist an increase in blood pressure. There is now evidence to suggest the inducibility properties also for HO-2 (Han et al. 2005). Overall data are consistent with depressor properties of HO-1 and possibly HO-2. The proposed mechanisms for depressor effects of HO-1 is attributable the ability of HO-1 to generate CO which has vasodepressor properties (reviewed by Chen et al. 2001). Based on the hypothesis that HO-1 participates in the defense mechanism providing protection against Cd-induced nephropathy and resistance to a rise in blood pressure, it can be predicted that people with reduced HO-1 activities will be more susceptible Cd-induced nephropathy and experience more severe hypertension, compared with those with normal HO-1 activity. Such reduced HO-1 activity can possibly be caused by non-synonymous mutations in the coding regions of the gene critical in catalytic activity. Several single nucleotide polymorphisms (SNPs) have been found for both the HO-1 and HO-2 genes of human. However, the relationships between any of these SNPs in the coding regions of these genes and the susceptibility to Cd renal toxicity have not been investigated.

3.6 Induction of the renal HO-1 gene expression by Cd

The *cis*-acting elements essential for Cd induction of the HO-1 gene expression identified to-date include the Stress Responsive Element (StRE), known also as *Maf recognition Antioxidant Response Element* (*MARE*), *Cd Response Element* (*CdRE*) and internal enhancers. The *MARE* contains binding site for the activator protein 1 (AP-1) transcription factors and 12-O-tetradecanoylphorbol-13-acetate-responsive element. The *trans*-acting elements involved in Cd induction of the HO-1 gene are the transcription repressor Bach1 and the transcription activator named the nuclear-related erythroid factor 2 (Nrf2) (Alam et al. 2000, 2003; Suzuki et al. 2003). It is suggested that Cd causes the nuclear export of Bach1 which relieves the repression of the HO-1 gene. This allows subsequent transactivation by the Nrf2 in a pair with the small musculoaponeurotic fibrosarcoma (Maf). Cd also increases cellular levels of (Nrf2) by diminishing its degradation thereby increasing its biological half-life (Stewart et al. 2003). These Bach1- and Nrf2- dependent Cd effects are linked to the activation of the p38 mitogen-activated protein kinase (p38 MARK) and the extracellular signal-regulated protein kinase-1/2 (ERK 1/2) (Stewart et al. 2003; Susuki et al. 2003). Cd induction of the HO-1 gene through the *CdRE* and enhancer elements is less clear. The (*CdRE*) consisting of 10 base pairs (T**GC**TA**G**ATTT) is located at approximately -4.0 kb in the human HO-1 promoter (Takeda et al. 1994, 1995; Hill-Kapturczak et al. 2003). The *CdRE* confers the ability for Cd to induce the HO-1 gene in HeLa cells. The **GC** dinucleotides and the **G** residue in the CdRE are essential for such Cd induction. However, the protein that binds to the human CdRE is yet to be identified. The *CdRE* of the human HO-1 gene is unresponsive to other HO-1 inducers, including heme, sodium arsenite, cobalt protoporphyrin, and zinc. The CdRE is distinct from the metal response element (*MRE*) located in the human metallothionein gene, which is responsive to both Cd and zinc (Yoshida et al. 1988; Takeda et al. 1995). Cd enhancer elements have recently been found in the human HO-1 gene (Hill-Kapturczak et al. 2003). These elements together with the *CdRE* confer a 30-fold increase in HO-1 levels in the kidney following Cd exposure. Because of a critical role played by the nucleotide sequences in conferring Cd induction of the HO-1, it can be predicted that different sequences in the HO-1 gene and/or in the gene encoding for the *CdRE* binding protein will influence HO-1 expression levels. Such genetic polymorphisms in the HO-1 and some other critical protein components of the HO-1 induction pathway therefore can contribute in part to the variation among people in their susceptibility to Cd-induced nephropathy and hypertension. In one epidemiologic study, a certain variant of the HO-1 promoter was associated with hypertension in postmenopausal Japanese women (Ono et al.

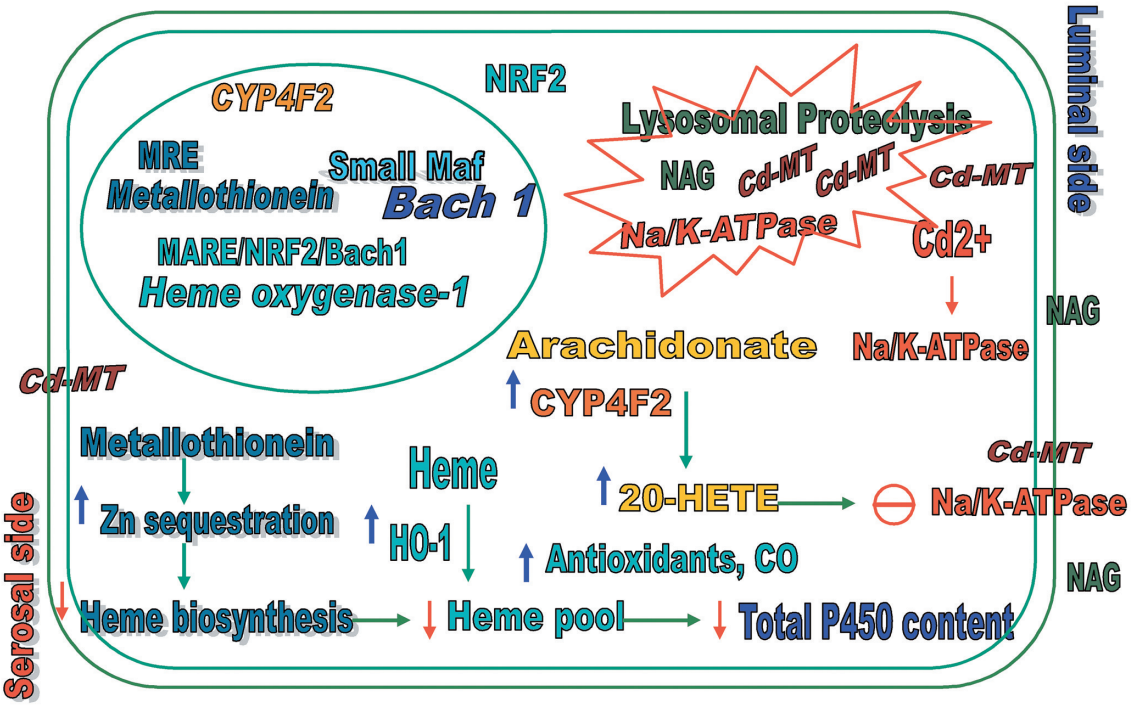

Fig. 2. A hypothetical model showing molecular targets for cadmium together with defense mechanisms in a proximal tubular cell, involving the metal binding protein metallothionein and antioxidant enzyme heme oxygenase-1.

In a proximal tubular cell, internalized Cd-MT complexes undergo degradation in the lysosome with liberation of unbound Cd which causes oxidative stress and transcriptional activation of the MT and HO-1 genes possibly via the signaling pathways involving *MRE*, *MARE*, Nrf2, small Maf and Bach1. Cd-linked oxidative stress enhances lysosomal degradation of oxidatively damaged Na/K-ATPase and a fall in cellular Na/K-ATPase levels while induction of MT by Cd increases sequestration of zinc in newly synthesized MT with attendant reductions in the rate of heme synthesis and total P450 content. Induction of HO-1 by Cd generates antioxidants that reverse some of the Cd-induced oxidative stress. It also generates carbon monoxide which depresses activity of certain CYP forms, especially the EET generators. Induction of the 20-HETE generators (notably CYP4F2) by Cd causes the levels of 20-HETE to rise with attendant renovascular constriction and magnification of the hormone angiotensin II. The combination of these changes causes changes in pressure-natriuretic response which is followed by hypertension.

2003).

4. A hypothetical model showing Cd molecular targets and defense mechanisms in proximal tubular cells in response to Cd load

From the results of our research and the literature reports available to date, a hypothetical model can be constructed (Fig. 2) to show the molecular targets for Cd together with defense mechanisms in a proximal tubular cell. In the model, uptake of Cd-MT complexes from the filtrate and blood circulation into the proximal tubular cells occurs via the luminal and serosal sides of cell membranes. The internalization of Cd-MT complexes is followed by degradation in the lysosome and releasing the toxic unbound Cd (Cd^{2+}) into the cytoplasm where it causes oxidative injurious to lipids (lipid peroxidation) and proteins in the membrane and in the cytoplasm. The unbound Cd also causes transcriptional activation of the MT and HO-1 genes, possibly via the metal response elements (*MRE*), Maf recognition antioxidant response element (*MARE*). In the absence of Cd and other cellular stressors, the binding of

the repressor Bach1 to the *MARE* prevents an expression of the HO-1 gene. In the presence of Cd, Bach1 is exported to the cytoplasm. This allows transactivation of the HO-1 gene by the activator Nrf2 in a complex with small Maf. Increased levels of antioxidants (bilirubin and biliverdin) together with the antiapoptotic and anti-inflammatory agent (CO) from heme degradation catalysed by induced HO-1 can reduce renal injury and degradation rates of damaged proteins, including the Na^+/K^+-ATPase, leading to normalization of cellular redox state with a concomitant fall in cellular heme concentrations. Increased MT expression levels by Cd leads to sequestration of zinc with attendant reduction in the heme biosynthetic rate because of limited availability of zinc, a co-factor required in heme biosynthesis. Such diminution of intracellular heme by HO-1 and MT markedly depresses total P450 content and expression levels of most CYPs notably those with epoxygenase activity leading to a fall in renal synthesis of EETs. Elevated levels of carbon monoxide (CO) from Cd induction of HO-1 depress also epoxygenase activities of EET-generating CYPs. In contrast to these CYPs, expression of certain 20-HETE generators (notably CYP4F2) in the proximal tubular cells are increased, causing the levels of 20-HETE to rise with attendant renovascular constriction and magnification of pressor effects of angiotensin II. There is also a concurrent fall in cellular levels of Na^+/K^+-ATPase due to enhanced degradation of oxidatively damaged Na^+/K^+-ATPase caused by unbound Cd. The combination of these changes gradually leads to salt retention and volume overload, causing natriuretic response to shift to higher pressures. Concurrent peripheral vascular effects of Cd cause vascular resistance to rise. Prolonged volume overload, increased sodium retention in conjunction with increased vascular resistance thus contribute to lasting hypertension.

Concluding Remarks

Substantial dietary Cd intake and renal Cd loads in the non-occupationally exposed population is evidenced from published data on renal Cd concentrations and urinary Cd excretion rates for non-smoking subjects who have not been exposed to Cd in the workplace. This could in part be attributable to continuing mobilization of small amounts of the metal toxin from nonbioavailable geologic matrices into biologically accessible situations coupled with high rates of soil-to-plant transference of Cd. More importantly, we have detected occurrence of substantial renal effects at the renal Cd loads and urinary Cd levels, which are well below values commonly associated with causing extensive kidney damage. These findings thus suggest that the current PTWI is set too high and it is not sufficiently restrictive to protect the general population. A revision of the current PTWI for Cd is needed. The potential role played by chronic low-level Cd in the development of high blood pressure calls for a concern as high blood pressure has already affected 25-35% of the adult population and 60-70% of the elderly in most economically developed countries. This common disorder is associated with significant morbidity and mortality. Multiple genetic and environmental factors have long been aetiologically implicated. It is yet to be seen whether Cd is an additional risk factor or a relevant environmental factor in the aetiology of human essential hypertension. Future population-based research is required to quantify the risk of hypertension associated with chronic intake of low-level Cd in people with differing genetic variants of HO-1 and CYPs. In the absence of effective chelation therapy for Cd, such research will lead to discovery of potential targets for the therapeutic intervention in Cd-linked hypertension.

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