

Factors Influencing Susceptibility to Metals

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Although the long-neglected field of human susceptibility to environmental toxicants is currently receiving renewed attention, there is only scant literature on factors influencing susceptibility to heavy metals. Genetic factors may influence the availability of sulfhydryl-containing compounds such as glutathione and metallothionein, which modify the distribution and toxicity of certain metals. Age and gender play a role in modifying uptake and distribution, although the mechanisms are often obscure. Concurrent exposure to divalent cations may enhance or reduce the toxicity of certain metals through competition for receptor-mediated transport or targets. Increasing use of biomarkers of exposure should greatly increase our understanding of the underlying distribution of susceptibility to various environmental agents. — *Environ Health Perspect* 105(Suppl 4):817–822 (1997)

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Introduction

Susceptibility can be viewed in terms of both individuals and populations; and it can be quantified as the likelihood or probability that there will be a response, given a particular event or exposure. Within a population the susceptibility to an agent—whether chemical or biological—can be represented by a distribution, but the shape of that distribution is rarely known. Susceptibility to any agent results from the interaction between genetics (enzyme polymorphisms, for example) and

environment (fitness, nutrition, past or concurrent exposures, etc.). Although there have been many publications on risk factors for disease, as well as on the phenotypic variation of various hematologic or biochemical markers in populations, relatively few studies have combined these studies to focus on susceptibility per se (1).

Whether genetic or epigenetic in origin, it is the phenotype, and specifically the phenotypic or constitutional condition at the time of exposure, that determines whether individuals will get sick or how sick they will get. Most studies focus on phenotype since phenotypic variation can be studied much more easily than the underlying genotype (2).

In humans most susceptibility studies have focused on infectious diseases or risk factors for cardiovascular disease or cancer. Very little attention has been devoted to susceptibility to metal toxicity (0 of 239 references; Medline, 1986). Even works with broader coverage of the genetics of susceptibility and resistance in an evolutionary framework ignore metal toxicity (3–5).

Toxicologic study designs in animals can address susceptibility since to some degree different strains, species, and genders can be incorporated into bioassays. Some rodent strains have been bred specifically for their heightened susceptibility or resistance to certain conditions or agents.

Yet in these inbred strains, the underlying genetic variation has been deliberately narrowed; thus the use of several highly inbred strains may not be an appropriate model of susceptibility for human populations or even for wild rodent populations.

One reason for the paucity of literature on susceptibility is the difficulty of measuring it in isolation; it cannot be separated from exposures, and controlled exposures are seldom used in humans. Most often we are forced to estimate the likelihood of response from the proportion of organisms responding to a known or estimated dose or from the severity of response in the individual.

Genetic Variability

Humans have enormous genetic heterogeneity (6). Evolutionary processes tend to lead to fixation of one or another allele at a locus, thereby enhancing the adaptive integrity of the genome, promoting developmental canalization. The relationship among genetic variation, natural selection, and fitness is the domain of population genetics, in which there is an extensive theoretical and applied literature to which clinicians and risk assessors seldom refer (7). Human breeding patterns and artificial environments have mitigated much of the selective pressure towards population homozygosity. At the same time one can point to heterozygosity as a hedge against changing environments; and humans, indeed, accelerate the changes in their own environment.

Some of the genetic diversity occurs between populations of humans (for example, in the frequency of the various blood groups). However, the within-population genetic variability is generally greater than that between populations (6).

For more than 50 years medical anthropologists have measured the frequency and variability of various biological markers in populations throughout the world. Much of this work has been concerned with studies of population genetics, human migration, and evolution. In 1901 Landsteiner characterized the A, B, O blood group system (8), and subsequently there has been extensive study of the distribution of these antigens in different populations and the differential frequency with which blood groups are represented in different disease states.

As early as 1922 Pearl (8) argued that heritability was an important determinant of longevity because it influences disease

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Abbreviations used: AAT, α_1 -antitrypsin; Cd, cadmium; GSH, glutathione; MT, metallothionein(s); Zn, zinc.

susceptibility. Kalow (9) defined pharmacogenetics in terms of idiosyncratic drug responses with a heritable basis; Nebert (10) identified more than 60 pharmacogenetic differences in humans, at least three of which were associated with cancer.

Genetic Screening for Hypersusceptibility

Understanding susceptibility can be important in enhancing resistance or reducing exposures. In occupational health, there is a long-standing controversy regarding genetic screening that might identify workers who are at unusually great risk (hypersusceptible) from some workplace exposure.

In 1938 Haldane (11) suggested that if individuals susceptible to "Potter's Asthma" could be identified prospectively, they could be shifted to jobs where they would not be placed at risk. Brieger (12) reviewed the genetic basis of susceptibility to toxic agents for occupational physicians, and Mountain (13) provided suggestions for detecting hypersusceptible individuals. Since that time the issue has resurfaced at about 10-year intervals as new and promising genetic markers of susceptibility are reported and then found wanting. The next recommendation for identifying hypersusceptible workers came from Stokinger (14) who was enamored of α_1 -antitrypsin (AAT) deficiency as a risk factor for emphysema in workers exposed to pulmonary irritants. Omenn (15) suggested how genetic screening might be implemented without violating workers' rights. To date, however, there has been no successful application of predictive genetic screening for hypersusceptible workers. Moreover, these ethical concerns are not even mentioned in most works on the ethical issues raised by new genetic technologies (16).

Susceptibility to Metal Toxicity

In one of the early publications on hypersusceptibility, Mountain (13) identified an interaction between vanadium (V) and copper (Cu), where exposure to V reduced circulating Cu levels and therefore the seriousness of the Wilson's disease. This observation notwithstanding, none of the genetic markers proposed relate to heavy metals. Despite the fact that heavy metals such as lead (Pb), mercury (Hg), cadmium (Cd), manganese (Mn), nickel (Ni), chromium (Cr), and tin (Sn) and the metalloids arsenic (As) and selenium (Se) are toxic to humans, the risk factors that might render some people more susceptible

than others remain mostly obscure. Some of these elements are essential trace elements (Mn, Cr, Se), while others have no known beneficial function in humans (Pb, Cd, Hg, As).

In this article I examine some aspects of human susceptibility to metal toxicity or factors modifying metal effects, but not the converse role of how metals influence susceptibility to other agents. There are numerous papers on how exposure to metals affects other disease processes or renders individuals more susceptible to other agents. There are fewer papers on the interactions among metals: how exposure to one metal influences response to another metal introduced concurrently or subsequently. Unlike information on P450 variants or debrisoquine sensitivity, there is negligible information on how genetic variation or genetic polymorphisms influence susceptibility to any metal. Much of the following information, therefore, must be inferred from other studies.

In the following discussion it is important to distinguish heritable genetic factors from environmental/epigenetic factors. Factors influencing susceptibility may act at the site of exposure (usually by increasing or decreasing uptake), may effect the toxicodynamics of a metal (usually by complexing or covalent binding), may influence the transport to a target organ, or (theoretically at least) may influence some immunologic, biochemical, or cytologic functional response at the target organ.

Since metals are not themselves metabolized, the opportunities for influencing toxicity are more restricted than for many organics, in which the availability of alternative metabolic pathways may profoundly influence an organism's response.

Effect Modifiers

Age

As a general rule immature animals, including humans, are more susceptible to metal toxicity than mature animals, and elderly or senescent animals likewise often show heightened susceptibility. Immature animals often have much greater uptake (e.g., 50% for lead in the immature intestine vs 10% for adults), and their organs may be more vulnerable as well. This is especially true of neurotoxic chemicals that can produce significant impairment in the developing nervous system.

However, in the rat embryo, metallothionein (MT) levels rise late in gestation and remain elevated for about 7 weeks

postpartum, even in the absence of exogenous zinc (Zn) or Cd (17).

Older rats, 24 to 30 months old, showed greater dopamine depletion after Mn administration than 2- to 3-month-old rats (18). Using measures of liver enzymes, P450 content and activity, and histology, Rikans (19) found that 15- and 25-month-old rats were more sensitive to the hepatotoxic effects of some chemicals but not others; however, she did not test any metal compounds. Kopp et al. (20) did not find increasing sensitivity of cardiac muscle to cadmium with age in rats; toxicity increased with exposure duration.

Metallothionein levels vary with age. Most organs in rat neonates have high MT levels that decrease to adult levels by about 1 month of age (21); however, their brain MT is low at birth and does not rise to adult levels until age 21 days. Lead levels also vary with age, infants having higher levels than older children in the same family and community (22). Whether MT is protective or not, it may influence the response of any organ to a heavy metal.

Gender

Post hoc studies of metal exposure show that women often have higher blood levels of metals than men in the same families or communities. The mechanisms are not clear. Nor are such data typically corrected for hematocrit or albumin level. If the higher blood levels influence body burden or half-life, they would reflect susceptibility, but at present I found no studies to clarify this. In some studies women have higher levels of metals in hair, but this is as likely to reflect a protective mechanism (increased excretion) as a susceptibility (increased absorption). Bosque et al. (23) found that girls in Spain had higher hair levels of Cd than boys in the same community. Sturaro et al. (24) report that females have elevated levels; but except for Ni, their data show essentially no difference for Cu, Zn, or Mn.

For Pb, intellectual development in boys has a stronger negative relationship to lead level than in girls (25).

Many studies show that metals behave differently in males and females of various animals. For example, given an equal dose of Se, male rats had higher concentrations in kidney but lower concentrations in liver than females (26). Female rabbits showed an earlier and higher rise in Zn protoporphyrin after lead exposure than males, but there was no difference in hemoglobin or hematocrit (27).

Gochfeld and Burger (28) examined nine metals in livers of males and females of three species of ducks. Of the 18 comparisons with sufficient sample size, only 5 were significantly different with males higher in three (Cu, Zn, and Mn in black duck, *Anas rubripes*) and females higher in two (Pb and Mn in greater scaup, *Aythya marila*). These differences may have reflected differential feeding areas of males and females, or different metal dynamics.

Burger (29) reviewed nine studies that examined gender differences in metal levels in bird feathers. In most cases there was no significant difference, but in some studies males had higher feather Hg and in other studies females did. Pb and Cd were higher in females. Female herring gulls (*Larus argentatus*) had higher Pb levels in feathers than males, but there was no significant difference for Hg, Cd, Cr, Mn, or Se (30). Even black skimmers (*Rynchops niger*), with their great sexual size dimorphism and a tendency for males and females to eat different sized foods (31), had no significant gender difference for most metals (32).

Exercise

Exercise significantly affects metabolism and cardiovascular dynamics in both the short- and the long-term. Short-term effects on the distribution of metals and on blood levels of Cu (decreased) and Zn (increased) have been reported (33), but the levels reverted almost to normal within 30 min.

Socioeconomic Status

Lead poisoning is much more common in urban populations of low socioeconomic status than in other urban or nonurban groups (25). To a large extent this reflects greater opportunity for exposure, but there are other factors that modify the effects of Pb exposure. Familial and social stresses often result in poorer learning aptitude and poorer adjustment, end points that are also attributed to Pb poisoning. Nutritional deficiencies, particularly of calcium (Ca) and iron (Fe) as well as phosphate or protein, enhance the absorption of Pb from the intestine. Also, nutritionally deprived and emotionally deprived children may have significant pica and mouthing activity that greatly increase their exposure.

Chronic Diseases

Certain chronic neoplastic or metabolic diseases produce changes in one or more body systems which should, indirectly at least, render those systems more susceptible to metal toxicity. Diabetics, for example,

develop a variety of kidney lesions (including diffuse and nodular glomerulosclerosis, but also interstitial tubular disease. This would alter the substrate on which nephrotoxic heavy metals such as Hg and Pb act. Diabetics who already have significant reduction in renal function will clearly be at increased risk from the added nephrotoxic effects of any heavy metal. In one study diabetics had significantly lower serum Ni concentrations than healthy controls (34).

Similarly, diabetics often develop hypertension secondary to their kidney disease, as do people with chronic Pb exposure. Each condition enhances the vulnerability of the individual to clinically significant disease.

Although Pb and other heavy metals usually inhibit enzymes by binding -SH groups and distorting structure, Pb enhances gluconeogenesis at several enzymatic steps. Lead-exposed animals are less tolerant of a glucose load (35), from which one might infer that diabetics with high blood glucose are more vulnerable to the effects of Pb, or vice versa.

Renal insufficiency or metabolic disorders associated with osteoporosis may enhance the release of Pb or other metals from bone, thereby increasing exposure to the nervous system (36). A similar effect can be accomplished with chelating agents.

Other Factors

Lack of parental supervision during infancy (independent of socioeconomic status) has been associated with increased exposure to Pb. This places a subpopulation at high risk, making them vulnerable to Pb but not necessarily more susceptible to its toxic effects once the Pb has entered the body.

Nicotine alters the distribution and ratios of trace elements in various tissues. Nicotine and presumably therefore, smoking, depress the concentration of glutathione (GSH) in liver, leading to elevated Zn and Cu levels (37).

Metal Exposure Lead Levels and Toxicity

Lead

There is a relative abundance of books on Pb toxicity (38,39), yet they offer remarkably little attention to risk factors or susceptibility.

Lead has many effects in the body. One of the best studied is the impact on hemoglobin synthesis. Lead inhibits several of the enzymes in the heme formation pathway, including δ -aminolevulinic acid

dehydratase, coproporphyrinogen oxidase, and ferrochelatase. The result is anemia, sometimes profound. Females, by virtue of their lower average hemoglobin counts, would be more likely to show clinical effects from Pb-induced anemia, but there is no evidence that their synthetic pathway is more susceptible.

Lead is toxic to developing chickens, but chicks treated with an antioxidant (ethoxyquin) show significantly lower growth inhibition from Pb (40). This suggests that intrinsic antioxidant levels may influence susceptibility to some of the effects of Pb. Additional factors affecting exposure and susceptibility to the neurodevelopmental effects of Pb (25) have been mentioned above.

Any study of Pb levels in a population shows substantial variation due in part to variation in exposure and partly to underlying genetic and phenotypic differences. For example, Romieu's recent study of Pb in Mexican children found a high overall coefficient of variation (standard deviation/mean) of 58%, while six carefully measured exposure variables explained only 23% of the variance in blood Pb (41). The remainder must be ascribed both to unsuspected exposure variables and to variations influencing absorption, excretion, and distribution to the blood.

Cadmium

C3H mice are highly susceptible to the hepatotoxic effects of Cd, while Swiss strain mice are not. Two studies (42,43) proposed that this was likely to reflect impairment of MT synthesis or function. Quaife et al. (44) found that there was no difference in either gene expression or MT protein accumulation in the two strains after exposure to Cd, despite the fact that liver lesions were present at the light microscope level in the C3H. Electron microscopy revealed endothelial lesions in the C3H, suggesting that the susceptibility operates through endothelial cells with subsequent ischemic damage.

Cadmium has well-established nephrotoxic effects on the proximal renal tubule. Administration of Zn or Se with Cd enhanced the toxicity as evidenced by the release of tubular enzymes (45). Co-administration of GSH and *N*-acetylcysteine with Cd did not inhibit its toxicity to cultured intestinal epithelial cells (46).

Mercury

Co-administration of GSH with inorganic Hg in rats reduced the concentration of

Hg in blood and increased the relative fraction in the plasma. The GSH-Hg complex enhanced the clearance of Hg from blood and apparently reduced its uptake by erythrocytes (47). In the same animals there was a temporary increase of Hg in the kidney as well as increased urinary excretion. Thus deficiencies of GSH would presumably increase the toxicity of Hg by extending its half-life in blood and enhancing its distribution to target organs. They also found a similar effect injecting cysteine with Hg (48). However, administration of GSH with Hg did not reduce its toxicity to cultured intestinal epithelial cells, while a different chelating agent, *N*-acetylcysteine, did (46).

The kidney is a target organ for inorganic mercury which damages the proximal tubular cells and the basement membrane of the glomerulus. Although the latter involves the formation of immune complexes, it is not clear how this is influenced by genetic or acquired factors.

Mercury produces a renal autoimmune response in brown Norway, (BN) but not in Lewis, rats. The former show a decrease of RT6.2 ± T lymphocytes while the latter do not. Using adrenalectomized animals, Kosuda et al. (49) showed that this was not simply a general stress response. They depleted the same lymphocyte fraction in the Lewis rats without producing the autoimmune response, even after administration of Hg. Thus the lymphocyte depletion is not a necessary step in the toxicity but may be linked to the genetic loci causing the BN strain to be susceptible.

Methylmercury

Methylmercury (MeHg) is a potent neurotoxin exerting its greatest effect on the developing nervous system. Even among immature animals, the developmental stage influences the susceptibility of different brain regions to MeHg (50). Since MeHg interferes with the establishment of connections between regions of the developing brain, its subsequent clinical manifestations depend on when in development exposure occurs. However, this begs the question of what factors might alter susceptibility of the developing region to interference by MeHg.

Selenium

Various inorganic and organic species of Se induce glutathione peroxidase (GPX). Using human lymphoblast cell lines deficient in trans-sulfuration enzymes, Beilstein and Whanger (51) showed that the induction of GPX by selenomethionine

was significantly reduced, while there was no change in induction by selenite or selenocysteine. Thus the metabolism of selenomethionine was clearly altered, although the impact on the toxicity of Se remains to be studied.

Cesium

Nonradioactive cesium chloride induces chromosomal aberrations in mouse bone marrow; the frequency of aberrations is significantly reduced by pre- or concurrent treatment of mice with calcium (52).

Interactions among Metals

Most of the heavy metals occur, at least partially, in the 2⁺ state, and divalent cations may compete for common transport sites or other receptors. Some of the interactions, whether protective or enhancing, are mentioned briefly below.

Calcium and Lead

The protective effect of Ca in Pb-exposed people has been known for decades, and in Britain, leadworkers were given free milk each morning, long before the specific protective effect of Ca was understood (53). Calcium inhibits the absorption of Pb in the gastrointestinal (GI) tract but also inhibits the storage of Pb in bone. This may enhance both its excretion and its transport to sensitive target organs such as the brain. Women with higher Ca intake tend to have lower blood Pb (54).

Strontium (Sr) behaves similarly to Ca in the intestine, in bone deposition and in the kidney, but there is evidence that the body preferentially absorbs Ca in the GI tract and preferentially excretes Sr in the renal tubule, when both Ca and Sr are present. However, this function is subject to maturation, and the rat kidney develops this discrimination between age 10 and 21 days (55).

Mercury and Selenium

Selenium apparently has a protective effect against some aspects of Hg toxicity. In lactating animals selenite treatment increases the concentrations of Hg in milk, presumably because blood levels are increased (56).

Cadmium and Zinc

Adequate levels of Zn or pretreatment of experimental animals blocks several toxic effects of Cd, including its teratogenicity (57). Cadmium and also Cu interfere with Zn transport in the proximal renal tubule. These cations enter the tubule with a

common carrier-mediated process that is saturable, hence competitive (58).

Other Interactions

Manganese and Zn compete with Fe²⁺ for transport binding sites on cell membranes, and this process can be saturated. There is also competition with Fe³⁺ (59). Mercury or As inhibits coproporphyrinogen oxidase in rats, and can cause porphyria. Exposure to either reduces enzyme activity and can increase susceptibility to the other (60). However, the cytotoxicity of Hg and Cd on intestinal epithelial cells in culture was neither additive nor synergistic (46).

Bone can be an important reservoir for divalent cations, and there is a complex interaction of Ca and phosphorus intake with heavy metals, which deserves more extensive research (61).

Metallothionein

Metallothioneins are a family of low molecular weight, inducible proteins rich in sulfhydryl groups, some of which are believed to have evolved to modulate the effects of Zn. In rats the mRNA's responsible for MT production peak about 6 to 9 hr after administration of a Zn dose, and remain elevated for at least 36 hr (62). Different MTs are synthesized and degraded at different rates (62), affording the opportunity for variations in MT levels and thereby in susceptibility. Quafe et al. (44) examined the highly susceptible C3H and the resistant Swiss strains of mice, and found no difference in the expression of the MT gene, either in mRNA or in the actual measurement of MT levels or the amount of Cd bound to MT. However, the C3H strain is deficient in a metalloproteinase that degrades MT (63). Is the MT actually enhancing Cd toxicity?

Cadmium, much more than other divalent cations, binds to MT, and it may prove to enhance the body's elimination of Cd. However, pretreatment of rats with Cu, Hg, and silver significantly reduced Cd-MT binding (64). It seems reasonable that different alleles at an MT locus might result in proteins with different binding affinities and different efficiencies.

Pretreatment of renal tubular cells in culture with a low dose of Zn induced MT formation sufficient to inhibit the nephrotoxicity of Cd as measured by the release of tubular enzymes (45). Although Zn is the natural inducer and Cd is a potent inducer, other metals, such as Hg and Cu, also induce MT in various tissues, including brain (65).

Inorganic Hg likewise induces MT formation, even in the brain, and this in turn can alter the blood levels of other cations such as Cu and Zn (65).

DNA Repair

Variation in DNA repair is a well-established factor in varying susceptibility to ionizing radiation. Exposure to clastogenic metallic compounds or radionuclides could, therefore, be influenced by DNA

repair efficiency. A population living close to a uranium-mining operation experienced both cytogenetic abnormalities, and subsequent exposure of their lymphocytes to a radiation source revealed abnormal DNA repair (66).

Summary

Among studies of variation in susceptibility to xenobiotics, studies of susceptibility to metals are notably few. However, this

paper outlines a variety of effect modifiers, including those intrinsic to the individual (age, gender), and those related to other exposures. Genetic factors modifying the structure or function of enzymes, must alter susceptibility to metal toxicity, but in general this remains an area for future study. It is worthwhile to distinguish susceptibility (the response to an exposure) from vulnerability, which includes risk factors affecting exposure.

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