

EFFECTS OF METALS ON THE NERVOUS SYSTEM OF HUMANS AND ANIMALS

DAVID O. CARPENTER

School of Public Health
University at Albany
Rensselaer, NY, USA

Abstract. Several metals have toxic actions on nerve cells and neurobehavioral functioning. These toxic actions can be expressed either as developmental effects or as an increased risk of neurodegenerative diseases in old age. The major metals causing neurobehavioral effects after developmental exposure are lead and methylmercury. Lead exposure in young children results in a permanent loss of IQ of approximately 5 to 7 IQ points, and also results in a shortened attention span and expression of anti-social behaviors. There is a critical time period (<2 years of age) for development of these effects, after which the effects do not appear to be reversible even if blood lead levels are lowered with chelation. Methylmercury has also been found to have effects on cognition at low doses, and prenatal exposure at higher levels can disrupt brain development. Metals have also been implicated in neurodegenerative diseases, although it is unlikely that they are the sole cause for any of them. Elevated aluminum levels in blood, usually resulting from kidney dialysis at home with well water containing high aluminum, result in dementia that is similar to but probably different from that of Alzheimer's disease. However, there is some epidemiological evidence for elevated risk of Alzheimer's in areas where there is high concentration of aluminum in drinking water. Other metals, especially lead, mercury, manganese and copper, have been implicated in amyotrophic lateral sclerosis and Parkinson's disease.

Key words:

IQ, Attention span, Alzheimer's disease, Parkinson's disease, Lead, Methylmercury

INTRODUCTION

It has been alleged that the decline of the Roman empire was because of lead poisoning, secondary to storing and drinking wine from lead goblets [1]. At high levels, lead causes encephalopathy, coma and death. But since the work of Needleman and colleagues [2] it is clear that lead also has adverse neurobehavioral effects at much lower levels. However, other metals also influence neuronal function, including mercury and especially methylmercury, aluminum, nickel, tin, bismuth, cobalt, iron, thorium and various heavy metals. The goal of this overview is to summarize the effects of metals on neurobehavioral development, the mechanisms of neurotoxicity and the possible

role of metals in neurodegenerative diseases. We will first review the evidence from human studies, and then summarize what has been done in animal investigations to both confirm the toxic actions and, in some cases, actually approach mechanistic explanations for the toxicity.

There are many sources of human exposure to metals. Since metals are natural elements, some exposure occurs simply from soils and rocks. This is particularly true for aluminum, which is the third most common element on the face of the earth. So every unwashed carrot will result in human exposure to aluminum. Fortunately, aluminum is poorly absorbed from the human gastrointestinal tract. Lead exposure comes from multiple sources, because lead has been used for many centuries for many purposes.

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Address reprint requests to Dr D.O. Carpenter, University at Albany, SUNY, School of Public Health, One University Place, Room B242, Rensselaer, NY 12144, USA.

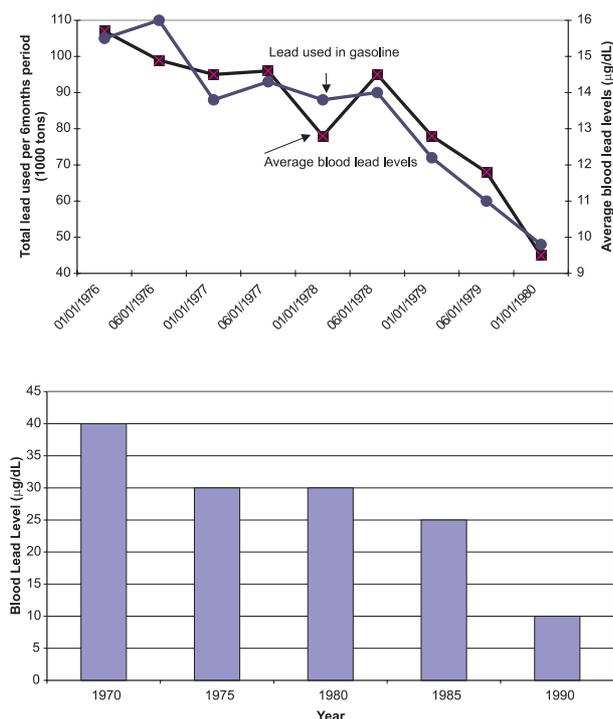


Fig. 1. Upper: Changes in average blood levels in the US population in relationship to the decline in use of lead in gasoline over time. Data derived by Annett [4] from CDC (1991).

Lower: Blood lead levels considered to be dangerous to human health by CDC. Data from CDC (1991).

Worldwide, the major source of exposure is from the use of leaded gasoline. While it is organolead that is added to gasoline to improve combustion efficiency, when it is burned it is elemental lead that is emitted with the exhaust. The dust settles in the street, blows into the homes and is consumed or inhaled by people. There has been a striking decline in the average blood lead level in children in the USA following the elimination of leaded gasoline (Fig. 1, top). Unfortunately, leaded gasoline is still used in much of the developing world. There has been an increased awareness of the dangers of lead exposure. Figure 1 (bottom) shows the lowering over the past 30 years in the blood lead levels considered by the US Centers for Disease Control (CDC) to constitute a human health hazards [3].

Organometals, regardless of which metal base it is, are in general more toxic to humans than the inorganic form, primarily because they are lipid soluble and therefore penetrate the body more easily, especially the brain.

In the United States (but fortunately not in most of the rest of the world) a major source of exposure to lead is from white paint, to which for many years lead was added to make the white whiter. This is a particular problem in old homes in center cities that are poorly maintained, where children eat the paint chips. Mercury exposure also comes from many sources, including broken mercury thermometers, mercury used in religious ceremonies in some cultures, and especially, in the case of methylmercury, from consumption of fish. Mercury comes from incineration, burning of coal and other fuel sources. Mercury is also leached from rock, especially in the presence of acid rain. When mercury washes into rivers, streams or lakes, it is converted to methylmercury by bacteria. While the methylmercury is probably not inherently more toxic than mercury because it is lipophilic, it accumulates in biologic tissues, and then bioaccumulates within the food chain and is persistent. These facts result in a magnification of the toxic actions of mercury. Most of the other forms of metal toxicity result from occupational or accidental exposure or access to mine tailings or other soils with excess concentrations.

STUDIES OF LOWER LEVELS OF LEAD ON NEUROBEHAVIOR, ESPECIALLY DURING DEVELOPMENT

Needleman et al. [2] first reported that exposure of young children to moderate amounts of lead resulted in the reduced IQ. They obtained deciduous teeth from children in Boston, from which they determined lead concentrations. Since lead behaves physiologically like calcium, it is stored in bones and teeth, although it can also be easily measured in blood. However, tooth lead is a good indicator of overall lifetime exposure, and particularly the exposure during the period of time when the tooth is forming. When children with high dentine lead (greater than 24 ppm) were compared to children with low dentine lead (less than 6 ppm), the high lead children were found to have a 4.5 point deficit in full-scale IQ, 4.6 point deficit in verbal IQ and a 3.8 point deficit in performance IQ. The blood lead levels in these populations were $35.5 \pm 10.1 \mu\text{g/dl}$

for the high and 23.8 ± 6.0 $\mu\text{g}/\text{dl}$ for the low exposure group. Thus even the low exposure group had high lead levels by today's standards.

There have been a number of studies from around the world that have confirmed the observations of Needleman et al. These are summarized in two meta-analyses [5,6], and a recent review by Banks et al. [7]. While not all investigators report as strong a relationship as the early study of Needleman et al. [2], most have found at least some cognitive decline with exposure that could not be explained by socio-economic status or other confounders. In a later follow-up of the same children from the 1979 study, Needleman et al. [8] found that the effects of lead on IQ do not recover with time. When studied 11 years later, this cohort of children still showed the same relative decrement in IQ, strongly suggesting that the effects of lead on intelligence are not reversible. Moreover, recent investigations have demonstrated that even when children at the age of about 2 or more are chelated to lower elevated lead levels the effects on cognition and behavior are not reversible [9]. Thus exposure of young children to lead is a very serious public health issue.

Even in the earliest study by Needleman et al. [2] it was apparent that not only IQ was reduced, but also there were a number of behavioral abnormalities more common in lead-exposed kids. When dentine lead was considered at six levels, there was a rough dose-response relationship for a number of behaviors which are not conducive to learning. These include distractibility, lack of persistence, dependent behavior, lack of being organized, hyperactivity, impulsiveness, being easily frustrated and showing a low overall functioning (Fig. 2, bottom). Effects of lead exposure on behavior and attention have also been noted in most other studies. Bellinger et al. [10] essentially replicated the Needleman observation in a study of teacher reports of student behavior correlated with bone lead concentrations. The major deficit appears to be in attention span [11]. Minder et al. [12] studied a group of boys with learning problems, and found that high lead in hair was correlated with a significantly slower reaction time, and less flexibility in changing focus of attention. Sciarillo et al. [13] found that children with high lead levels were

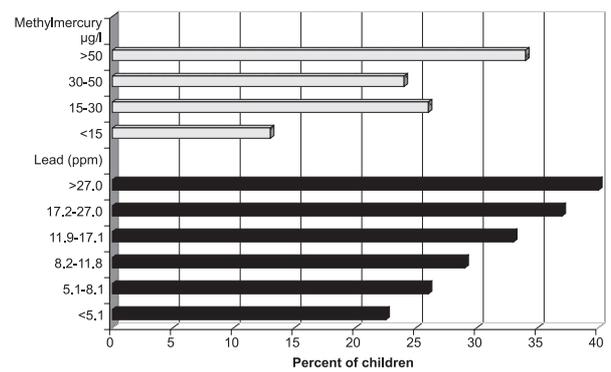


Fig. 2. Effects of methylmercury and lead on measures of attention. Upper panel: Effects of methylmercury in blood on attention in Faroese children. Attention was measured by reaction time on the NES2 Continued Performance Test. Data derived from Grandjean et al. [15]. Lower panel: Effects of dentine lead concentration on school teachers' evaluation of the ease with which children were distractible. Data derived from Needleman et al. [2].

rated higher by parents on a Child Behavior Checklist for negative behaviors, with aggression and hyperactivity being particularly elevated. This does not indicate that lead effects on behavior have been reported in every study. In their 1988 study of lead-exposed children in New Zealand, which showed a weak but causal association between lead levels and attention and activity, Fergusson et al. [14] list seven previous studies showing such a relationship and another seven that did not. However, in total the human studies (and animal studies discussed below) strongly suggest that there is at least a weak association. One interesting question in this regard is which comes first – the decrement in IQ or the short attention span. It is clearly difficult to learn if one cannot pay attention.

With a few exceptions, similar cognitive declines in lead exposed individuals have not been reported in adults. However, Schwartz et al. [16] studied cognitive function of former lead workers related to tibial lead levels, and found that those with high lead performed worse on three tests of visuo-constructive ability, verbal memory and learning. Meyer-Baron and Seeber [17] have reported a meta-analysis for neurobehavioral effects of occupational exposure to lead at levels greater than 70 $\mu\text{g}/\text{dl}$, and find a small but consistent decrement. Muldoon et al. [18] studied blood lead levels in old women in a nursing home and related levels to cognitive function. They found that blood

lead levels as low as 8 $\mu\text{g}/\text{dl}$ were associated with poorer cognitive function. Payton et al. [19] examined cognitive function in elderly men, and reported that men with higher blood and tibial lead levels recalled and defined fewer words, identified fewer line-drawn objects and required more time to attain the same level of accuracy on a perceptual comparison test. In neither of these studies were the lead levels exceptionally high. These observations suggest that the adverse effects of lead are not limited to the developing brain, and that they can be detected at the other end of the life span when general cognitive functioning is reduced or upon a greater exposure in otherwise healthy adults. On the other hand, cognitive decrements can be detected in healthy adults only at relatively high lead levels.

Recently, there has been speculation of a possible role of lead exposure in anti-social behavior in adults, possibly as a result of irreversible effects of lead on the brain during development. There is ample evidence that lead-exposed children exhibit a shortened attention span and disruptive behaviors similar to that seen in attention deficit hyperactivity disorder [7]. Nevin [20] has hypothesized that one reason violent crime in the US is declining is the reduction in lead poisoning secondary to removing lead from gasoline and paint.

There have also been extensive animal behavior studies after exposure to lead. Rice [21] studied cynomolgus monkeys dosed with lead from birth, and demonstrated impaired learning and attentional deficits. She found slower acquisition and less stability of responses to a fixed interval reinforcement schedule, with animals producing more responses during time out periods when reinforcements were not forthcoming, an effect that persisted for three years [22]. Discrimination reversal tasks were more affected than simple visual discrimination reversal tasks [23]. In rats, Winneke et al. [24] showed deficits in a visual discrimination task at 250 ppm (18 $\mu\text{g}/\text{dl}$), but with no deficit at the same concentration in a two-way active avoidance task. Others have shown deficits after lead exposure in fixed-interval responding [25] and with a variable inertial delay, a task that requires a flexible response strategy [26]. Kuhlmann et al. [27] showed significant

impairment of rats' performance in a water maze after being exposed to lead during gestation and lactation, but none in rats exposed only after weaning. However, the same laboratory has shown significant impairment in the Morris water maze following injection of lead directly into the hippocampus [28]. They conclude that lead can both disrupt the developing hippocampus, but can also interfere pharmacologically with specific brain sites important in the cognitive processes. These and many other behavioral studies of lead-exposed animals have been reviewed by Banks et al. [7], who conclude that some behaviors are more affected by lead than others, that the animal studies are congruent with lead-induced deficits in attention in children, and that simple learning is less affected than more complex tasks.

POSSIBLE MECHANISMS OF LEAD ACTION

While the molecular and physiologic mechanisms of learning and attention are not understood, tetanus-induced long-term potentiation (LTP) is one of the best available animal model systems for electrophysiological and biochemical study of cognitive processes. LTP is a prolonged alteration in synaptic plasticity which occurs following a patterned stimulation. LTP is found only at certain synapses in the brain, for the most part in areas known to be involved in higher nervous functions [29]. LTP is reduced in aging [30] and in animals that show an inborn low learning capacity [31]. Mutant mice that do not express calcium-calmodulin kinase II show impaired spatial learning, and do not express LTP [32,33]. Moreover, LTP in piriform cortex [34] and the CA1 [35,36] and dentate [37] regions of the hippocampus is blocked by lead, consistent with the hypothesis that LTP is an appropriate model system for investigating the mechanisms of lead neurotoxicity. In her doctoral dissertation in my laboratory, Hussain [38] has demonstrated, using brain slices of 30 day old rats, that two pharmacologically different forms of LTP (studied in the CA1 and CA3 regions of rat hippocampus) are blocked by lead. Figure 3 shows the results from this study. The upper traces show a plot of the peak population response obtained when the mossy fiber path-

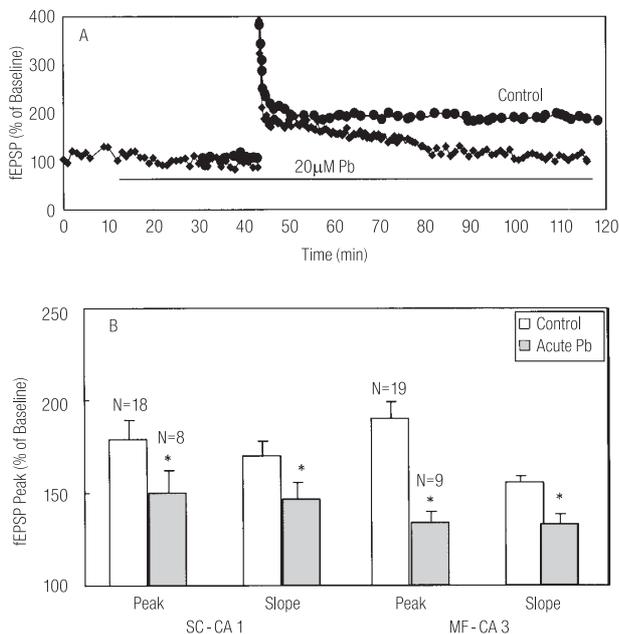


Fig. 3. Upper record: Acute *in vitro* lead exposure inhibits LTP in CA1 and CA3 when studied to isolated brain slices from animals at 30 days of age. The duration of lead application (a saturated solution) is indicated by the line. The fast excitatory postsynaptic potential (fEPSP) was recorded in area CA3 upon stimulation at a frequency of 0.2 Hz of the mossy fiber pathway. LTP was induced at time of 45 min by application of 2 one second stimulations at 100 Hz, then the stimulation frequency was again reduced to 0.2 Hz. Note that in the control there is a persistent increase (following the transient responses) in response after induction of LTP relative to control, but during lead perfusion this long-lasting increase is blocked.

Lower record: Acute perfusion of lead blocks LTP in both CA1 and CA3 in 30-day old animals whether the response is measured as the peak fEPSP or as the slope of the rising fEPSP response. The bars show the mean \pm SE in control (open bars) and after acute lead exposure (hatched bars). Asterisks indicate statistically significant decreases in LTP ($p < 0.05$).

way to area CA3 is activated in control 30-day animal slices. If lead is acutely perfused over the slice preparation for 30 min prior to eliciting the LTP, the same stimulus parameters as used in the control, there is a transient increase in the response but the LTP is blocked in that the response returns to the baseline value within about 30 min. She also demonstrated that chronic lead exposure during gestation and lactation, administered by added lead to the dam's drinking water, resulted in blockade of LTP in both sites at this age.

There are several possible mechanisms whereby lead might block LTP. LTP in CA1 and piriform cortex is

dependent upon entry of calcium into the cell, and this can occur both through voltage-activated calcium channels (VACCs) and through a subtype of excitatory amino acid receptor, the N-methyl-D-aspartic acid (NMDA) activated ion channel. Lead blocks VACCs [39–41] and NMDA responses [42,43]. However, these effects on VACCs and NMDA currents occur only at concentrations that are higher than those that block LTP [34]. If lead blockade is not via action at either VACCs or NMDA responses, it might be at one of the multiple biochemical steps involved, such as protein kinase C (PKC). PKC activation is necessary but not sufficient for producing LTP [44], and in CA1 there is a persistent PKC activation in the maintenance phase of LTP [45]. A variety of other kinases are also involved in LTP and could be targets of lead action [46]. There remains some confusion over what exactly lead does to PKC activity, since there are conflicting reports of activation at very low concentrations [47,48] or inhibition [49,50] of PKC by lead. The recent studies of effects of lead on LTP in CA1 as compared to CA3 [38] provide evidence that PKC is a target for lead action, but that different PKC isoforms may be affected differently. There is clear evidence for developmental changes in the PKC isoforms, and this may explain the changes in sensitivity of LTP to lead exposure in some brain areas.

METHYLMERCURY NEUROTOXICITY

Methylmercury also causes neurobehavioral decrements, especially when exposure occurs prenatally [51]. Much of what is known of methylmercury toxicity comes from an accidental poisoning episode in Iraq where methylmercury treated grain, meant as seed, was used in making bread. Mothers who ate such bread gave birth to infants with dose-dependent deficits on developmental and general IQ tests [52]. It is believed that much of the nervous system damage results from abnormalities in neuronal migration during development secondary to binding of methylmercury to sulfhydryl groups.

Because methylmercury contaminates and bioaccumulates in fish and marine mammals there is considerable concern about the effects of maternal consumption of fish and resulting damage to the fetus. This is the basis of recent advisories against eating certain ocean fish, such as shark, by the US Food and Drug Administration (FDA). However, the evidence that methylmercury at the levels of exposure found in most human populations is mixed. Grandjean et al. [15,53] studied Faroe Islanders who consume significant amounts of pilot whales, and reported decrements in language, attention and memory in 7-year olds which correlated with maternal reports of pilot whale consumption, and mercury levels in umbilical cord blood and hair. There were also decrements in visuospatial and motor functions. The authors also determined serum PCB concentrations, since PCBs also cause neurobehavioral decrement, but found that the PCB levels did not explain the cognitive deficits. As shown in Fig. 2 (top), these decrements were rather similar to those reported for lead in the original Needleman et al. [2] study. Mergler et al [54] studied people who ate fish from the upper St. Lawrence River lakes, and found that they both had higher mercury levels and did more poorly on tests requiring cognitive flexibility, word naming, auditory recall and on more complex motor tasks. However, study of another major fish-eating population with significantly elevated methylmercury exposure in the Seychellois Islands has not demonstrated any significant cognitive decrement [55,56]. In this study exposed children actually performed better on some tests, which the authors attribute to the dietary benefits of fish consumption.

There have been many studies of the effects of mercury and methylmercury in animals and isolated neurons. Rice [57] has reviewed the behavioral effects of methylmercury exposure in monkeys and rodents and reports that impairments of visual, auditory and somatosensory systems have been demonstrated in monkeys. In addition, there appear to be late effects where years after dosing the monkeys show overall clumsiness and slowness in reaching for objects. However, the effects of cognitive performance in monkeys are less clear. In rodents, prenatal exposure results in retarded development and impaired motor func-

tion. Again effects of cognition are less consistent. The studies of Watanabe et al. [58] in mice suggest that selenium deficiency may significantly increase the effects of methylmercury. This is of interest since selenium is known to be protective against mercury poisoning.

As with lead, methylmercury has a number of subcellular actions, including blocking of evoked neurotransmitter release [59], probably secondary to blockade of calcium channel currents [60], and interference with transport of amino acids and ions [61], probably secondary to binding to sulfhydryl groups [62]. Protein synthesis is also inhibited by methylmercury [63], so the picture of toxicity may result from multiple causes. There are, however, several features of methylmercury poisoning in humans which are difficult to explain. The damage is limited almost exclusively to the nervous system, and is highly localized, especially to the visual cortex and the granular layer of the cerebellum, where there is neuronal death. The earliest symptoms are non-specific subjective complaints including paraesthesia, blurred vision and malaise [64].

ROLE OF METALS IN NEURODEGENERATIVE DISEASES

Several metals have been implicated in neurodegenerative diseases [65], although probably none is the sole cause. One exception to this generalization is aluminum in the case of dialysis dementia. Individuals undergoing dialysis for kidney failure, if dialyzed with water containing high levels of aluminum, develop a severe dementia [66]. The end result is often similar to, but not identical to, Alzheimer's disease in both symptomology and pathology [67]. A similar but less severe neurologic impairment has been seen in infants receiving intravenous feeding with solutions containing aluminum [68]. Furthermore, aluminum workers may also show neurobehavioral impairment [69,70]. Numerous animal studies have documented that aluminum is toxic to certain neurons, especially motoneurons and some brain stem neurons [71,72]. Before cell death the neurons develop inclusions of neurofilaments. Aluminum has also been suggested to be an etiologic agent in Alzheimer's disease [73] since some of

the neurofibrillary tangles seen in Alzheimer's brains have been found to contain high levels of aluminum [74] and there is some epidemiological evidence that areas with elevated aluminum in the drinking water have higher levels of Alzheimer's [75]. Interestingly, Shin et al. [76] have demonstrated that aluminum promotes the hyperphosphorylation of tau protein, the major precipitated protein of the tangles, and this may be at least a contributing factor to the cause of the disease.

There is also evidence suggestive of an involvement of other metals in the neurodegeneration seen in Alzheimer's disease [77], amyotrophic lateral sclerosis (ALS) and Parkinson's disease, the other major types of neurodegenerative disorders. Copper, iron, mercury and zinc have all been reported to be elevated in Alzheimer's senile plaques [78,79], and copper, manganese and zinc were elevated in serum and CSF of ALS patients as compared to age-matched controls [80]. Manganese [81] and iron [82] have been implicated in Parkinson's disease, probably because both induce the production of reactive oxygen species which cause neuronal damage. Thus while none of the neurodegenerative diseases appears to be due solely to actions of metals, there is at least some adverse influence of different metals in the development of these diseases.

CONCLUSIONS

While many metals are essential to life, but toxic at higher concentrations, others are only toxic. The nervous system is a major site of metal toxicity. At moderate levels of exposure the very young and the old appear to be most vulnerable to these actions. However, much remains poorly understood regarding the mechanisms of metal neurotoxicity.

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