

Neurotoxic effects of selected metals

by Arne Wennberg, MD¹

WENNBERG A. Neurotoxic effects of selected metals. *Scand J Work Environ Health* 1994;20 special issue:65—71. A chemical is considered to be neurotoxic if it is capable of inducing a consistent pattern of neural dysfunction or lesion in the nervous system. Several metals are known as neurotoxic. Among them, four have been selected as being especially important from the occupational point of view, lead, manganese, aluminum, and mercury. All four have proved to be neurotoxic even though the toxic mechanisms may be unclear or unknown. This paper reviews the recently published documentation on the neurotoxic properties of these metals, from the general as well the occupational point of view.

KEY TERMS — aluminum, lead, manganese, mercury, review.

Since the beginning of industrialization in Western countries at the end of the last century, certain metals have been known to be toxic in different ways, and some of them with specificity to the nervous system (ie, neurotoxic).

The meaning of the concept “neurotoxic” can be debated. Damage to the nervous system has often severer consequences than toxic effects to other systems because of the special properties of the nervous system. It is well known that the basic functional unit of that system, the nerve cell or the neuron, cannot multiply itself during a lifetime. Thereby it differs from most cells in the body. The number of nerve cells, estimated to be around 100 billion at the time of birth, declines slowly during one’s life. The reserve capacity of the system is, however, large and the nervous system can, in normal subjects, perform adequately for normal social demands until the end of life. Figure 1 offers a schematic presentation of this process, and it can be assumed that toxic damage in early life can have consequences much later, when a critical level could be reached.

The function of the neuron is complicated and shown schematically in figure 2. A toxic compound could afflict one or several parts of the functional system and thereby cause dysfunction of the whole cell. To understand the clinical picture of a toxic effect, knowledge of the basic mechanisms is important on the cellular level.

In order to determine whether a compound is neurotoxic, it is important to have rules for judging neurotoxicity (ie, how can neurotoxicity be demonstrated).

In 1992 a Nordic expert group published guidelines for evaluating neurotoxicity (1). Neurotoxicity was defined in the following way: A chemical is considered to be neurotoxic if it is capable of inducing a consistent pattern of neural dysfunction or lesion in the nervous system. In the assessment of neurotoxicity, the following six levels were suggested for consideration: (i) reversible subjective symptoms, (ii) irreversible subjective symptoms, (iii) biochemical changes, (iv) physiological or behavioral changes, (v) neurological changes, and (vi) morphological changes. Observations on levels 4—6 were suggested to give sufficient evidence for neurotoxicity, while levels 1—3 could indicate limited evidence. It should be stressed that biochemical changes alone could never give sufficient, but only limited, evidence for neurotoxicity.

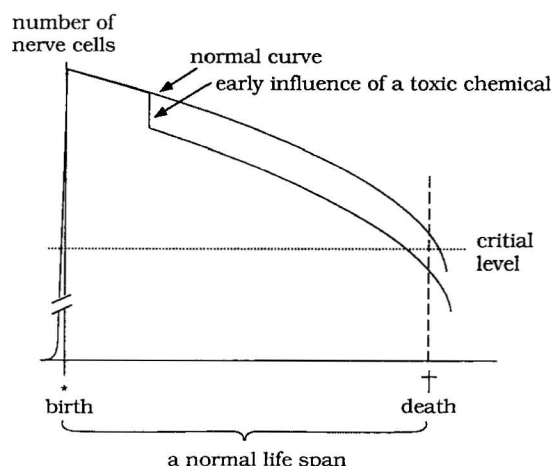


Figure 1. Number of nerve cells during a normal life-span. Critical level indicates the limits for reserve capacity of the nervous system with respect to “normal” behavior during life. Number of nerve cells reaches its maximum (100×10^9) at birth and decreases continuously thereafter.

¹ Department of Neuromedicine, National Institute of Occupational Health, Solna, Sweden

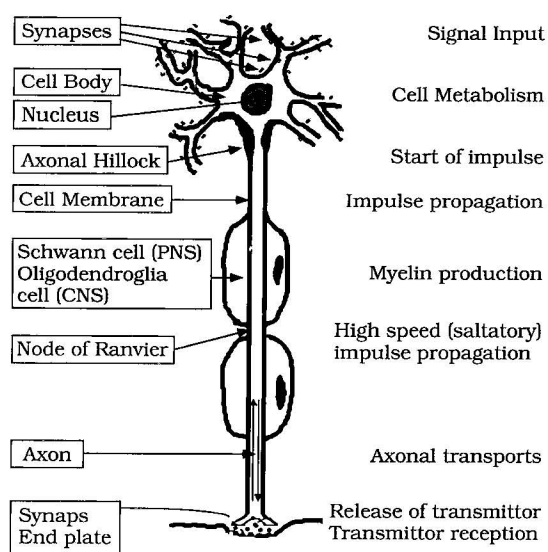


Figure 2. Schematic presentation of a nerve cell. Framed on the left side of the figure are the functional structures, and the corresponding functions are shown on the right side of the figure. (CNS = central nervous system; PNS = peripheral nervous system)

Certain metals or metal compounds have long been known as neurotoxic. For some of them, the neurotoxic effect is regarded as critical (ie, the effect that appears at the lowest concentration compared with other effects). This is the case for aluminum, lead, manganese, and mercury. For mercury and lead, renal effects are also considered critical. These four metals have played an important role in occupational health already for a long time. The neurotoxicity of aluminum and manganese has been much debated recently, while the neurotoxicity of lead is well established and the exposure levels often well under control on the individual level.

Lead

Lead has long been known as neurotoxic (2). Its toxicity was described already in antiquity (3) and has even been discussed as an important factor in the devastation of the Roman empire. The nervous symptoms following lead exposure are multiple, involving the peripheral nervous system with paresis and sensory disturbances and the central nervous system with encephalopathy with ataxia, coma, and convulsions.

Nerve cells

The intracellular calcium ion concentration has been found to be elevated by lead exposure (4), and this phenomenon provides evidence for the role of calcium in mediating the neurotoxicity of lead.

Lead also destroys microtubules and microtubular formation within the nerve cells (5).

Nerve transmission

Nerve transmission could be affected by lead. Within the catecholaminergic nervous system, lead exposure has been demonstrated to cause alteration in the concentrations of noradrenaline and dopamine in addition to alterations in the enzymes tyrosine hydroxylase and phenylethanolamine-N-methyl transferase (6). Lead caused a decrease in the activity of the rate-limiting enzyme of catecholamine syntheses in median eminence, periventricular nuclei, and anterior hypothalamus, but not in other nuclei, a finding indicating that this effect may be regionally specific (7). In rats prenatally or postnatally exposed to lead, the norepinephrine and gamma aminobutyric acid levels were decreased while the glutamate and tyrosine levels were increased. Glutamate decarboxylase activity was decreased and monoamine oxidase activity was increased. No such effects were found in adult rats, and it thus seems that the brains of young rats are more sensitive to lead than those of adults (8). It has also been shown that chronic lead exposure affects dopamine receptor activity (9).

Lead has been shown to reduce monoamine oxidase and acetylcholinesterase activity in fish brain and also to decrease the gamma aminobutyric acid level and increase histamine and serotonin, as an indication of impairment of brain neurotransmitter function (10). Another study demonstrated an increased level of dopamine after exposure to lead (11).

Acetylcholine transmission, in particular the synthesis and release of acetylcholine, has been demonstrated to be impaired by lead exposure (12).

Lead also blocks the response mediated by the postsynaptic nicotinic receptor at a relatively low concentration (13).

Glia and myelin

Both astroglia and oligodendroglia cells seem to be sensitive to lead (14). Astroglia can serve as a protective function in the brain by acting as a lead depot. In addition glutamine synthetase activity in astroglial cells has been found to be affected in chronically exposed animals. In a study on fetal guinea pig the blood levels of aminolevulinic acid dehydratase were decreased and zinc protoporphyrin IX was increased, and these findings were regarded as biochemical evidence for the alteration of neuroglial function at low levels of lead (15) and may point to the nervous system of the fetus as an important target of lead.

Morphological effects on astroglial cells have also been demonstrated after exposure to low levels of lead (16).

Peripheral nerve demyelination has been demonstrated in several animal studies (17).

Central nervous system

Behavioral deficits after lead exposure have been related to limbic system dysfunction, the hippocampus,

and the amygdala (18). Dysfunction of the dorsal hippocampus, as measured by a deficit in acquisition and retention, was found in both maternally and permanently lead-exposed rats, an indication of the long-lasting effect of early lead exposure (19).

Long-term low-level exposure to lead has been shown to cause a decrease in spatial learning and short-time memory (20).

A study on extracellularly evoked responses in hippocampal neurons indicated that lead acts presynaptically on these cells (21).

Autonomic nervous system

In workers with blood lead levels of 16–60 (mean 34) $\text{mg} \cdot 100 \text{ ml}^{-1}$ [77–290 (mean 164) $\mu\text{mol} \cdot 100 \text{ ml}^{-1}$], the variations in the R-R interval were reduced (22).

Electrophysiology

Visual evoked potentials were affected in monkeys exposed pre- and postnatally to lead (23).

In peripheral nerves, dysfunction could be demonstrated by a slowing of nerve conduction velocity if the blood level of lead was above 70 $\text{mg} \cdot 100 \text{ ml}^{-1}$ (338 $\mu\text{mol} \cdot 100 \text{ ml}^{-1}$) (24).

Lead workers with blood lead levels below 65 $\text{mg} \cdot 100 \text{ ml}^{-1}$ (314 $\mu\text{mol} \cdot 100 \text{ ml}^{-1}$) showed prolonged latencies of visual and somatosensory evoked potentials and P-300 event-related potentials and also decreased motor and sensory conduction velocities in peripheral nerves; these findings were related to lead absorption (25). In addition auditory evoked potentials in the brainstem have increased interpeak latencies in workers with a mean blood lead level of 47.5 $\text{mg} \cdot 100 \text{ ml}^{-1}$ (229 $\mu\text{mol} \cdot 100 \text{ ml}^{-1}$) (26).

Behavior

In a study on humans, blood lead levels of 30–64 $\text{mg} \cdot 100 \text{ ml}^{-1}$ (145–309 $\mu\text{mol} \cdot 100 \text{ ml}^{-1}$) were shown to affect psychological performance, but the effects were reversible, as measured two years later (27).

It seems to be important to keep the blood lead level below 50 $\text{mg} \cdot 100 \text{ ml}^{-1}$ (241 $\mu\text{mol} \cdot 100 \text{ ml}^{-1}$), and after the blood lead level is reduced psychometric performance improves (28). In a study on children five years of age, higher postnatal blood lead levels were associated with poorer performance on all cognitive developmental subscales in the used test battery (29).

In monkeys, blood lead levels of 3–25 $\text{mg} \cdot 100 \text{ ml}^{-1}$ (14–121 $\mu\text{mol} \cdot 100 \text{ ml}^{-1}$) at birth and a steady level of 3–13 $\text{mg} \cdot 100 \text{ ml}^{-1}$ (14–63 $\mu\text{mol} \cdot 100 \text{ ml}^{-1}$) after the age of 200 d detrimentally affect the results of performance tests at the age of three years, a finding indicating that these levels are neurotoxic (30).

Genetic effects

The genetic effects of lead have been demonstrated in the rat, in which lead caused a dramatic increase in the pro-opiomelanocortin mRNA concentration, which was reversible and dependent on prolonged lead exposure (31). It was suggested that this finding could be evidence of early environmental influence and the expression of neuropeptide genes in the brain.

Children

In a study on children, the tooth lead concentration was examined, and a high-level group ($>18.7 \text{ mg} \cdot \text{g}^{-1}$; $>90 \mu\text{mol} \cdot \text{g}^{-1}$) was compared with a low-level group ($<5 \text{ mg} \cdot \text{g}^{-1}$; $<24 \mu\text{mol} \cdot \text{g}^{-1}$). Differences were found for some intelligence tests and psychometric tests, even after control for socioeconomic status (32). Similar results have been reported in another study, in which intelligence scores correlated with the lead level in teeth (33). In schoolchildren, lead absorption was related to impaired psychological test performance and difficulties at school (34).

An Australian study showed no effects on children whose umbilical cord blood levels were in the range of 0–29 $\text{mg} \cdot 100 \text{ ml}^{-1}$ (0–140 $\mu\text{mol} \cdot 100 \text{ ml}^{-1}$) (35). In another study (36) early postnatal blood lead levels at 10–25 $\text{mg} \cdot 100 \text{ ml}^{-1}$ (48–121 $\mu\text{mol} \cdot 100 \text{ ml}^{-1}$) were associated with low mental development among children in lower socioeconomic strata.

In a European multicenter study on children from eight countries, some behavioral tests showed a significant relation to the blood lead level [which was in the range of 5–60 $\text{mg} \cdot 100 \text{ ml}^{-1}$ (24–290 $\mu\text{mol} \cdot 100 \text{ ml}^{-1}$)]. The association with psychometric intelligence was poor and only borderline (37).

Conclusions

Lead affects the nervous system on many levels: cell metabolism, membranes, nerve transmission, myelin formation. In addition, it also causes a breakdown of the blood-brain barrier (38). In adults, the critical level of lead in blood seems to be about 30–40 $\text{mg} \cdot 100 \text{ ml}^{-1}$ (145–193 $\mu\text{mol} \cdot 100 \text{ ml}^{-1}$) for adverse effects on the peripheral and central nervous system in sensitive subjects (2). Children are more susceptible than adults, and their critical blood lead level seems to be 5–10 $\text{mg} \cdot 100 \text{ ml}^{-1}$ (24–48 $\mu\text{mol} \cdot 100 \text{ ml}^{-1}$).

Manganese

The neurotoxic effects of exposure to manganese can be acute and mainly psychiatric (known as manganese madness) or chronic with symptoms similar to Parkinson's disease with tremor, rigidity, and bradykinesia (slow movements).

Nerve transmission and nerve cells

Manganese increases dopamine autoxidation (39–41). This reaction, which seems to be irreversible (42), is probably one of the mechanisms behind the clinical picture of manganism with symptoms similar to those of Parkinson disease.

Manganese causes a reduction in striatal dopamine concentrations, and manganese toxicity has been found to be diminished by treatment with drugs that reduce the striatal dopamine turnover rate (43).

Apart from effects on dopamine, manganese has also been shown to decrease levels of gamma aminobutyric acid and substance P in striatal cells, and also impair energy metabolism by decreasing adenosine-5-triphosphate and increasing the lactate level. These findings indicate an impairment in oxidative metabolism (44).

Manganese inhibits, in an irreversible way, glutathione-S-transferase, a finding which suggests that manganese can cause an interneuronal accumulation of cytotoxic compounds (45).

Brain

Monkeys given manganese for 16 months developed signs of poisoning as unsteady gait and hyperactivity. Signs indicating degeneration of the dopamine nerve endings in the striatum have been shown in such animals, and by magnetic resonance imaging it has been shown that manganese accumulates in the globus pallidus, putamen, and caudate nucleus (46).

Neurophysiology

In subjects exposed to low levels of manganese, a slowing of alternating movements in the hands has been shown as an early indication of impairment in the function of the extrapyramidal nervous system (47).

Behavior

In workers exposed to manganese levels of less than $1 \text{ mg} \cdot \text{m}^{-3}$ ($18 \text{ } \mu\text{mol} \cdot \text{m}^{-3}$), an effect on performance was found in several psychometric tests (48). Such workers also showed an increase in neuropsychiatric symptoms (49).

Conclusions

Manganese acts by interaction with nerve transmission in dopaminergic nerve cells in the basal ganglia of the brain and thereby produces symptoms similar to parkinsonism. It also affects cell metabolism by impairing the oxidative metabolism in the same area.

Aluminum

From the human aspect, the most important effect of aluminum exposure is a possible relation to Alzheimer's disease or dementia similar to Alzheimer's disease, first discussed as a complication to dialysis

therapy in cases of chronic renal failure. However, so far, no epidemiologic studies have proved any relationship between aluminum exposure and Alzheimer's disease (50, 51).

Amyotrophic lateral sclerosis has also been suggested to be related to aluminum exposure. However, even for this disease nothing has been proved, and the reasons for connecting aluminum to amyotrophic lateral sclerosis are vague (52).

Membranes

Aluminum has been shown to impair transmembrane diffusion, and it changes selectively saturable transport systems without disrupting the integrity of the membranes or altering the hemodynamics of the central nervous system. Aluminum is also capable of membrane function at the blood-brain barrier and thereby acts as a membrane toxin (53).

Nerve cells

Aluminum causes neurofibrillary degeneration in different areas of the brain. A prominent neuropathological finding in Alzheimer's disease is called "neurofibrillary tangle." However the neurochemical profile of aluminum intoxication shows both similarities and discrepancies to that of Alzheimer's disease (54).

Cyclic adenosine-5-triphosphate synthesis has been found to be sensitive to aluminum, and this effect persists at least two weeks after the administration of aluminum. Modulation of the metabolism of cyclic nucleotides seems to play a role in the neurotoxicity of aluminum (55). Irreversible activation of adenylate cyclase has been suggested as a mechanism behind this phenomenon (56). Another demonstrated effect of aluminum is the inhibition of glutamate release, a finding suggesting an alteration of calcium channel function that indicates multiple targets for aluminum-induced alterations of neuronal function (57).

Nerve transmission

Aluminum is known to be transported by the iron transport protein transferrin. In chronic dialysis patients with renal failure it has been shown that the density of aluminum was high in forebrain areas with high transferrin receptor density, even in cases in which the brain gross level of aluminum was within the normal range [$<4 \text{ mg} \cdot \text{g dry weight}^{-1}$ ($19 \text{ } \mu\text{mol} \cdot \text{g dry weight}^{-1}$)]. In such cases, there seems to be a redistribution of iron, with the highest concentration in the globus pallidus, which is an area with low transferrin receptor capacity. This finding indicates that the distribution of neuropathological changes seen in dialysis encephalopathy, as well as in Alzheimer's disease, reflects the distribution of transferrin receptors (58).

Aluminum also seems to interfere with acetylcholine transmission. Thirty minutes after an intravenous

injection of aluminum chloride, a significant reduction in choline acetyltransferase was found in the basal forebrain and hippocampus, while acetylcholinesterase was increased in caudate nuclei (59).

Behavior

Aluminum given to rabbits produced behavior disturbances, and it was shown that the brain content of aluminum was highest in the frontal gray and hippocampal areas. It was also shown that the behavioral toxic effects were greater in adult and old animals than in younger ones (60).

An aluminum-induced reduction of choline acetyltransferase in the brain has been shown to be related to impaired learning ability (61).

In hemodialysis patients, an increasing aluminum level has been shown to be associated with decreasing performance on neurocognitive tests, but only for subjects with low premorbid intelligence. Subjects with higher intellectual capacity thus seem to compensate for neurocognitive dysfunctions (62).

Conclusions

Aluminum is a potent neurotoxic agent when in contact with nerve tissue. However it is not easily absorbed from the gastrointestinal tract, and therefore it can be used in high doses for the antacidic treatment of gastritis and gastric ulcers. The toxic effects are not sufficiently known, and the connections with diseases like dementia and motor neuron diseases are still not clear. Aluminum interferes with cell metabolism, cell membranes, and nerve transmission.

Mercury

The clinical findings following exposure to organic mercury are characterized by cerebellar ataxia, visual disturbance, and sensory disturbance (63). The most common symptom after exposure to inorganic mercury (inhalation of mercury vapors or dust) is tremor.

Nerve cells

Mercury causes an alteration of cell metabolism with a reduction in adenosine-5-triphosphate content in brain tissue and a decreased rate of total protein synthesis in brain cells (64).

Another sign of this effect is perturbation in the aminoacylation of tRNA (65).

Mercury has been shown to induce an increase in calcium ions, and also an increase in inositol phosphate levels in cerebellar neurons (66).

Exposure to mercury causes detectable levels in the nerves, but not in myelin membranes or in membrane packing (67).

Mercury has been demonstrated to accumulate in lower motor neurons in the spinal cord, probably due to retrograde axonal transport after uptake in motor nerve terminals (68).

Clinical findings

Workers exposed to mercury vapor giving a mean blood level of $2.4 \text{ mg} \cdot 100 \text{ ml}^{-1}$ ($12 \text{ } \mu\text{mol} \cdot 100 \text{ ml}^{-1}$) showed postural and intentional hand tremor (69).

Workers with long-term exposure to a mercury concentration of $0.033 \text{ mg} \cdot \text{m}^{-3}$ ($0.16 \text{ } \mu\text{mol} \cdot \text{m}^{-3}$) in air developed decreased performance on behavior tests for reaction time, finger tapping, mental arithmetic, and attention (70).

Conclusion

The mechanism behind brain dysfunction following mercury intoxication is probably an effect on nerve cell metabolism. The main target seems to be the cerebellum, but other sites, for example, anterior root cells, may be important.

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