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Lead and developmental neurotoxicity of the central nervous system

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Abstract

The desirable characteristics of lead - a malleable heavy metal resistant to corrosion - have resulted in its extensive use, especially in building construction, for the past several millennia. There is no known physiological relevant role for lead in the body; however, its harmful effects are numerous. Lead interferes with a variety of body processes and it is toxic to many organs and tissues. Like mercury, another heavy metal, lead is a potent neurotoxin that damages the nervous system and causes brain disorders. Although current lead usage has been minimized, lead exposure is still a risk because environmental lead is stable and no safe threshold for lead exposure has been established. Here, we review the current understanding of the effects of lead on the developing nervous system at the physiological, cellular, and molecular level. The effects of lead are particularly damaging to the developing nervous system, causing potentially irreversible learning and behavior deficits in children. Increased understanding of the deleterious effects of lead on the developing nervous system is vital to inform the safety guidelines associated with lead exposure.

Keywords: lead neurotoxicology, neurodevelopmental disorders, lead poisoning

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Introduction

Lead (Pb, relative atomic mass 207.2) is a nonphysiological metal that has been used by humans for many years, from a wine sweetener in ancient Greece to more recently as an additive in paint or gasoline [1-4]. Even though current lead usage has been drastically minimized due to the recognition of the damaging effects of lead poisoning, human lead exposure remains a clear and present danger because lead does not degrade in the environment and persists in the soil [4]. Common sources of lead exposure include paint chips from old construction and contaminated dust, soil and drinking water [3-4]. Routes of exposure for this heavy metal include ingestion, inhalation and dermal contact [5]. In humans, lead was shown to have widespread effects, targeting the nervous system, cardiovascular system, reproductive system, red blood cells and kidneys [1, 6]. Lead remains in the human body for a long time, with a half-life of approximately 36 days in blood [1]. Lead is also known to be sequestered in bone tissue with an estimated half-life of 27 years [1]. Among the organ systems affected by lead, the central nervous system (CNS) has received much attention; in particular, the impact of lead exposure on neurodevelopment in children [2].

Acute high dose lead poisoning causes encephalopathy, with symptoms including coma and ataxia, often leading to death [6-7]. However, as lead usage has been placed under strict regulation in recent years, the likelihood of acute high dose exposure is significantly decreased [7-8]. On the other hand, chronic low dose exposure to lead and the possibility of asymptomatic lead toxicity has become the focus of current research efforts [7-8]. Children appear more vulnerable to lead exposure due in part to higher likelihood of ingesting lead-containing materials and higher rates of lead absorption after ingestion [9]. Furthermore, the developing CNS appears to be more prone to lead insult [9]. In this review, recent studies aimed at increasing our understanding of the developmental neurotoxicity of lead are summarized (**Table 1**).

Pathophysiology

The pathophysiology of lead in the CNS includes impairments of cognitive function, behavioral deficits and physical tissue damage. Many epidemiological studies in the past few decades have examined the impact of low dose lead exposure on children's cognitive function [10]. These studies suggested a dose-response relationship between lead exposure and learning disabilities and hyperactivity [7, 10]. Such studies prompted the Centers of Disease Control and Prevention (CDC) to lower the blood lead level (BPb) safety guideline in the 1960s from 60

μg/dl to 25 μg/dl and eventually to the current BPb of 10 μg/dl [8, 10]. However, research efforts indicate that there remain risks of lead effects at blood concentrations even as low as 10 μg/dl. For example, in 1994, Schwartz published a meta-analysis study using data from many published epidemiological studies in an attempt to identify a lower threshold of lead exposure and its negative effects associated with intelligence quotient (IQ) [11]. The author concluded that a threshold for lead effects at 10 μg/dl was not plausible and that there was no sign of an absolute safe lead level down to 1 μg/dl [11]. Other studies echoed Schwartz's finding of lead's negative effect on cognitive function below a BPb level of 10 μg/dl. Lanphear and colleagues found an inverse relationship between BPb level at less than 5 μg/dl and arithmetic, reading, nonverbal reasoning skills and short term memory in subjects between 6 and 16 years old [12]. Surkan et al. found reduced IQ, attention and working memory associated with higher BPb in 6-10 year old children [13]. Similarly, Chiodo et al. observed a correlation between increased BPb and a reduction in IQ and attention in 7-year-old children with an average BPb at 5 μg/dl [14]. The authors also noted that the magnitude of IQ reduction was small yet significant [14]. In a recent study, Kim et al. found an association between BPb and reduced IQ in school children with average BPb of 1.73 μg/dl [15]. In short, many studies have established a clear association of lead exposure and cognitive function impairment in children at BPb levels below the current CDC recommended safety margin of 10 μg/dl.

Table 1. Summary of recent studies on lead neurotoxicity

Subjects	Exposure/dose	Average BPb (μg/dl)	Main findings	Reference
Rats (male Wistar, 2-4 weeks or 12-14 weeks)	500ppm lead acetate in drinking water for 40 days	9.8, 9.1	Increased Bax protein expression but no change in Bcl-2 in hippocampus	[55]
Mice (CBA/CaJ)	0.01 or 0.1mM lead acetate in drinking water, gestation until postnatal day 21	8.0, 42.3	Decreased VDAC expression in auditory neurons in the brainstem	[57]
Rats (male Wistar, adult 250-270g)	125, 250, or 500 ppm lead acetate in drinking water for 14 days	16.2, 18.1, 21.2	Decreased nNOS and eNOS expression in hippocampus in the 500 ppm group	[59]
Rats (male SD, 30 days old)	2, 20, or 200 mg/kg/day lead acetate intragastrically for 6 weeks	6.83, 12.82, 19.37	Reduced XIAP mRNA levels in the 200 mg/kg/day group, and increased apoptosis in hippocampus	[37]
Human adults average age 22.9	Environmental exposure	12.9 (childhood)	White matter diffusion alterations associated with childhood BPb	[31]
Rats (SD, 21 days old)	0.05%, 0.2%, or 0.5% lead acetate in drinking water, until postnatal day 21	18.48, 56.81, 185.91	Significant mGluR5 expression decrease in 0.2% and 0.5% treatments	[60]
Human children average age 9.7	Environmental exposure	1.73	Lead and manganese levels associate with reduced IQ and the effects from the two metals may be additive	[15]
Mice (Swiss albino)	0.2% lead acetate in drinking water, until postnatal day 21	Not available	Reduced antioxidant enzyme activities in the brain. Increased lipid peroxidation. Zinc showed protection against oxidative stress	[33]
Rat (male SD, 8-9 weeks old)	50 mg/kg lead acetate intraperitoneal injection	40 (data from previous study)	Aβ accumulation and reduction in LRP1 levels in choroid plexus	[61]

Researchers have also attempted to use both linear and nonlinear models to explain the relationship between IQ and lead exposure. Canfield et al. found a 4.6 point IQ drop per 10 μg/dl increase in BPb using a linear model,

while a non-linear fit showed a 7.4 IQ decrease for BPb level increase from 1 to 10 μg/dl [16]. In addition, Schnaas et al. showed a non-linear dose-dependent relationship between lead exposure and its association with IQ [17]. Jusko et al. agreed that the non-linear model is the better fit in their publication, where children whose BPb never exceeded 10 μg/dl were examined and increments at lower BPb correlate to bigger declines in IQ [18]. Together, these studies support a non-linear relationship between lead exposure and IQ decline, whereby lower levels of lead are still likely to impact children intelligence in a significant and negative manner.

Whether lead exposure-associated cognitive function decline occurs on a reversible basis remains inconclusive. Winker et al. found no cognitive deficits in adults with past lead exposure [19]. On the other hand, Needleman et al. showed in a 11-year follow-up study that previously measured lead levels from toddler teeth were still associated with deficits in neurobehavior such as reading skills, hand-eye coordination, verbal and grammatical reasoning, reaction times and attention [20]. Stewart and Schwartz hypothesized that there are progressive effects of lead toxicity in addition to the initial insult, even after years of elimination of heavy metal from the brain [21]. However, the studies done by Winker et al. and Stewart and Schwartz were mainly of subjects with lead exposure during adulthood [19, 21]. Age and duration of exposure, dosage and time from last exposure are all potential factors that could affect reversibility. Thus, there is still uncertainty regarding the reversibility of lead neurotoxicity.

In addition to impairments of cognitive function, lead exposure is associated with aggression, hyperactivity and inattentiveness. Using BPb 15 μg/dl as a cutoff for high and low exposure groups, Sciarillo et al. observed that children in the high exposure group were more likely to exhibit aggressiveness and hyperactivity [22]. Mendelsohn et al. examined children between 1-3 years of age with BPb between 10 and 25 μg/dl and found an association between increased lead exposure and adverse behavioral effects such as hyperactivity, distractibility and frustration [23]. Evidence also exists to support a correlation between behavior deficits and BPb levels below 10 μg/dl. Braun et al. found a strong association between increased BPb and attention deficit hyperactivity disorder (ADHD) in children with BPb as low as 5 μg/dl [24]. Chiodo et al. similarly reported deficits in attention, executive function, visual-motor integration, social behavior and motor skills with BPb levels as low as 3 ug/dL in developing children [25]. In an exploratory study, Stretesky found an association between airborne lead levels and crime rates in property and violence, though the author stated that further efforts are required to elucidate the relationship [26].

Therefore, similar to the cases of cognitive function and lead exposure, many studies have associated negative behavior effects with BPb under 10 μg/dl.

Physical insults on the CNS were also associated with lead exposure. Struzynska et al. treated adult rats with lead acetate and observed blood brain barrier (BBB) damage as well as the presence of lead in synaptosomes and capillaries [27]. Similarly, Wang et al. uncovered BBB damage in developing rats exposed to lead [28]. Cecil et al. used magnetic resonance imaging (MRI) and observed decreased brain volume in adults with childhood lead exposure [29]. In addition, Stewart et al. found white matter lesions in workers with previous high exposure to lead [30]. In a more recent study, Brubaker et al. used diffusion tensor imaging to observe the white matter microstructure of adults with childhood lead exposure in vivo [31]. The authors identified damage in myelin and axonal fibers associated with increased lead levels [31]. Physical damage to the BBB can compromise brain function and thereby increase the potential for future CNS-related complications.

Cellular toxicity

To determine the mechanism of lead toxicity, the effects of lead at a cellular level have been explored (**Figure 1A**). Lead was shown to cause oxidative stress, promote apoptosis and affect synaptic transmission. Glial cells in the CNS also appear to be a target of lead toxicity. For instance, in mice exposed to lead, Wang et al. reported reduced activity of antioxidative enzymes such as superoxide dismutase (SOD), glutathione peroxidase and glutathione reductase [32]. Prasanthi et al. similarly found reduced antioxidative enzyme activities of SOD, xanthine oxidase and catalase in multiple mice brain regions including hippocampus, cortex, cerebellum and medulla [33]. On the other hand, lipid peroxidation was increased [33]. Using a rat model, Bolin et al. compared accumulated 8-hydroxy-2'-deoxyguanosine (oxo^{8}dG, a product of DNA oxidation) levels in neonates and adults [34]. They concluded that early exposure of lead caused stronger oxidative DNA damage in cerebral cortical tissue [34]. Penugonda et al. showed decreased glutathione (GSH) and phospholipase A2 (PLA2), indicating oxidative damage, while malondialdehyde (MDA), a product of oxidative stress, was increased in PC12 cells treated with both lead and glutamate [35]. Increased oxidative stress in brain cells could cause damage and eventually cell death.

Both in vitro and in vivo models of lead neurotoxicity indicate that developmental exposure to lead increases apoptosis. Using a dissociated rat hippocampal neuron model, Li et al. showed that neuronal cell death was de-

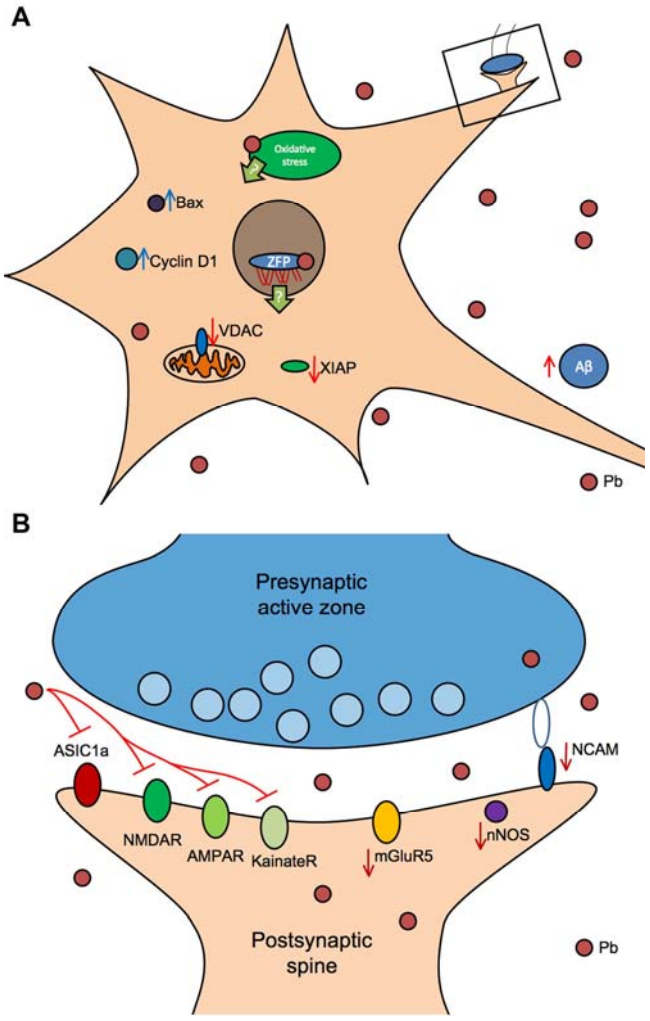

Figure 1. *Schematic representation of the cellular and molecular effects of lead in neurons.*
(A) The expression level of numerous molecules changes after lead treatment. X-linked inhibitor of apoptosis protein (XIAP) and voltage dependent anion channels (VDAC) expression are reduced while Cyclin D1 and Bax are overexpressed [36-37, 55, 57]. Extracellular amyloid beta (Aβ) accumulation is elevated in the presence of lead [61]. Possible mechanisms include oxidative stress and Zinc finger protein (ZNF) induced gene expression changes (indicated by arrows with question marks).
(B) At synapses, certain Calcium permeable ion channels at the postsynaptic spine are blocked by lead, including acid-sensing ion channel 1a (ASIC1a) and the glutamate receptor subtypes N-methyl-D-aspartate (NMDAR), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPAR) and Kainate [50, 52-53]. In addition, lead reduces expression of membrane-associated proteins such as metabotropic glutamate receptor 5 (mGluR5), neuronal nitric oxide synthase (nNOS) and neuronal cell adhesion molecule (NCAM) [58-60]

pendent on lead dosage and exposure time [36]. The authors also found increased expression of cyclin D1, which activates CDK4 and could subsequently induce apoptosis [36]. Injecting lead acetate into rats led to a dose-dependent reduction of the X-linked inhibitor of apoptosis protein (XIAP) expression in the hippocampus, which promotes apoptosis [37]. Wang et al. showed lead exposure in rat cortex resulted in apoptosis through the MAPK signaling pathway, via phosphorylation of ERK and JNK protein kinases [38]. Lead induced apoptosis could potentially contribute to tissue damage in the CNS reported in studies discussed above.

Lead effects on synaptic transmission have been shown in long term potentiation (LTP) and long term depression (LTD), in both excitatory and inhibitory neurons. LTP and LTD are thought to be cellular mechanisms of memory formation and learning whereby synapses are strengthened (LTP) or weakened (LTD) subsequent to synaptic activity. Zaiser et al. exposed rats pre- and postnatally to lead, and examined hippocampal CA3-CA1 LTP [39]. Rats treated with 1000 parts per million (ppm) lead in their drinking water did not exhibit LTP while those treated with 500 ppm were able to exhibit LTP but were unable to maintain the potentiated effects [39]. Altmann et al. chronically exposed rats to lead and examined active avoidance learning (AAL) as well as LTP in the CA1 region of the hippocampus [40]. The authors found impaired AAL and LTP amplitudes in rats exposed prenatally or postnatally, but those exposed after development were not affected [40]. Chen et al. permanently exposed rats to lead until 60-80 days of age and examined synapse plasticity in the dentate gyrus (DG) of hippocampus [41]. Input/output functions, paired pulse reactions, and LTP were all impaired in treated rats [41]. Tang et al. showed reduced LTP and field excitatory postsynaptic current (fEPSC) recordings in the CA1 region of hippocampal slices obtained from lead-treated rats compared to controls [42]. Sui et al. found reduced LTD magnitude in hippocampal CA1 and DG regions [43]. Interestingly, the difference in magnitude of LTD between controls and lead-treated groups in the CA1 region seemed to diminish in older pups, while in DG, the difference in magnitude became more severe [43]. Furthermore, using nimodipine (L-type calcium channel blocker) and AP-5 [blocker of N-methyl-D-aspartate (NMDA)-type receptors] to separate voltage-gated calcium channel-dependent LTD (VGCC-LTD) and NMDA receptor-dependent LTD (NMDA-LTD), Sui et al. were able to observe reduced LTD magnitude for both components in treated neurons [44]. The alterations in both LTD and LTP could affect brain functions such as memory formation, and could explain lead's associated effects on cognitive functions.

The effects of lead on signal transduction are not restricted to LTD and LTP of excitatory synapses. Xiao et al. observed a dose dependent inhibition of spontaneous inhibitory postsynaptic currents (IPSCs) as well as reduced amplitude of evoked IPSCs [45]. However, there was no observable effect on frequency or amplitude of miniature IPSCs, suggesting an effect of lead toxicity on GABAergic presynaptic neurons [45]. In addition, overall neuronal excitability is altered by lead. Yan et al. showed acute low level lead exposure on rat hippocampal slices increased evoked action potential (AP) firing rate of CA1 neurons, and showed that the presence of calcium and T-type voltage-dependent calcium channels (VDCC) are necessary for lead to affect the AP firing rate [46]. The alterations in signal transduction caused by lead could explain the association with cognitive and behavioral deficits observed in epidemiological studies.

In addition to affecting neurons, lead also appears to target glial cells in the CNS. Tiffany-Castiglioni et al. analyzed four different cell types: oligodendroglia, astroglia, meningeal fibroblasts and a human neuroblastoma cell line SY5Y, in an in vitro study of lead's targets [47]. Only oligodendroglia was shown to be sensitive to lead-induced cell death, however, astroglia and meningeal fibroblasts took in lead and concentrated the metal intracellularly, supporting the previous hypothesis that glial cells act as cellular sinks for lead [47]. Zhang et al. showed lead can disturb astrocyte cell cycle in dissociated rat hippocampal cells [48]. In addition, cyclin D1 protein level was drastically reduced and glucose regulated protein of 78 kDa (GRP78), a chaperone protein of the endoplasmic reticulum (ER), was overexpressed in astrocytes, indicating a possible increase in the unfolded protein response (UPR), which is an ER stress response [48]. Because glial cells are important components of the CNS, providing critical support for neuronal function, abnormalities in glial cells could lead to various complications or diseases. For example, oligodendroglia cells are important for myelin sheath generation, and lack of myelin insulation leads to diseases such as multiple sclerosis.

Molecular targets

Molecular effects of lead include alterations of channel properties and changes in protein expression (**Figure 1B**). Lead is a divalent cation and is able to bind to both calcium and zinc sites with greater affinity in proteins, and this higher affinity has been hypothesized to be the mechanism of lead toxicity [3, 49]. Marchetti and Gavazzo showed that lead can block NMDA receptors composed of NR1 and NR2 subunits in a voltage independent manner, with an IC_{50} of around 2.4 μM [50]. The authors suggest the possibility of lead binding at the zinc ion binding site in the amino terminal domain of NMDA receptor [50]. Yan et al. found that cultured rat hippocampal neurons treated with lead showed altered voltage gated sodium channel properties such as increased activation threshold and delayed inactivation/deactivation kinetics [51]. Sui et al. used cobalt uptake experiments to examine calcium permeable channels in rat hippocampal slices [52]. They found that cobalt uptake is blocked in neurons treated with lead in the presence of AP-5 and/or CNQX [inhibitor of kainate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type receptors], suggesting that calcium permeable AMPA/Kainate receptors may be affected [52]. Wang et al. examined the effects of lead on acid-sensing ion channel 1a (ASIC1a), a subunit of the ASIC protein channel thought to play a role in synaptic function, in rat spinal dorsal horn and hippocampal CA1 neurons [53]. The authors observed a dose-dependent competitive inhibition of ASIC channels, shown by a reduction of pH sensitivity for channel opening [53]. Lead's effects on channels and receptors could serve as an explanation for the changes observed in synaptic transmission and signal transduction in neurons.

The presence of lead also affects expression levels of numerous proteins that are involved in inflammation or apoptosis. Glial fibrillary acidic protein (GFAP) expression in developing rat brain was examined by Struzynska et al. [54]. Lead was found to increase GFAP levels as well as inflammatory protein levels such as cytokines (interleukine-1β and 6) and tumor necrosis factor-alpha (TNF-α) [54]. The authors suggested that chronic activations of glial cells generate an inflammatory response that could explain neuronal damage, such as the decreased level of synapsin I and synaptophysin observed in their experiments [54]. Sharifi et al. showed an increase in Bax (a pro-apoptotic protein) expression in the hippocampus of rats chronically treated with lead [55]. The authors also investigated Bcl-2, an anti-apoptotic protein, but did not find a significant difference between lead-treated and control groups [55]. The change in expression levels of molecules relevant to apoptosis such as Bcl-2 could provide an explanation of lead's role in causing cellular apoptosis in the CNS.

In addition to inflammation and apoptosis, certain signal transduction molecules such as protein channels and receptors show altered expression levels in the presence of lead. Prins et al. found decreased expression of voltage dependent anion channels (VDAC) in PC12 and SH-SY5Y cells, both in vitro models for neurons [56]. VDAC is located on mitochondria and regulates energy levels through ATP synthesis in neurons. Reduced expression of VDAC has been associated with decreased ATP synthesis [56]. In a separate study, Prins et al. were

able to show reduced VDAC expression in auditory neurons in the brainstem of mice after lead intake [57]. Hu et al. showed decreased expression of neuronal cell adhesion molecule (NCAM) and its glycosylated form in hippocampus of rat pups after low level maternal lead exposure [58]. Neuronal nitric oxide synthase (nNOS) and endothelial NOS (eNOS) were shown to have reduced expression levels in rat hippocampi with subacute doses of lead exposure (500 ppm) for 2 weeks [59]. Both nNOS and eNOS enzyme activities are calcium dependent, and the authors suggested that lead could potentially imitate calcium ions to affect the enzymes [59]. In addition, NO was shown to play a role in LTP, and lead induced reduction in these NOS levels could be a mechanism of toxicity [59]. Xu et al. examined cultured rat hippocampal neurons in rat pups after maternal lead exposure and found a dose-dependent reduction of metabotropic glutamate receptor 5 (mGluR5) mRNA and protein presence [60]. The activation and inhibition of mGluR5 was shown to be important in learning and memory [60]. Lead was suggested to be a risk factor for Alzheimer's disease (AD), and workers with past lead exposure showed brain degeneration similar to that of AD patients [61]. Behl et al. showed increased β-amyloid (Aβ), a peptide associated with onset of AD, in rat choroid plexus after lead treatment [61]. In addition, the authors observed reduced expression of lipoprotein receptor protein-1 (LRP1), thought to be involved in transport of Aβ across the BBB into blood [61]. Accumulation of Aβ in the brain extracellular space is often associated with pathogenesis of AD [61]. Thus, lead's effects on protein expression could lead to abnormal cellular functions and maybe even diseases such as AD.

Outlook and Conclusions

In summary, lead is a nonphysiological metal that is present in the environment today, even though current usage is minimal in many countries. Lead toxicity affects several organs, including the CNS. In addition, it is difficult to eliminate from the human body. Low level exposure of the metal has been associated with several asymptomatic effects on humans, especially children whose nervous systems are still immature. It is interesting to note that even under the CDC recommended 'safe' BPb level of 10 μg/dl, lead has been linked to reduced cognitive functions, decreased attention, increased aggression and hyperactivity. Damage to human brain tissue and the BBB were also associated with 'safe' BPb levels. Current research efforts have begun to elucidate the cellular and molecular mechanisms of lead toxicity. In the CNS, lead was shown to promote oxidative stress and apoptosis, as well as alter synaptic transmission properties of neurons. Glial cells also appear to be a target of lead toxicity, with the possibility of astroglia serving as temporary sinks for the metal. Being a divalent cation, lead possibly interacts with calcium and zinc sites in proteins. At the molecular level, this heavy metal was shown to alter channel properties as well as affect the expression level of numerous proteins. To this day, the exact mechanisms and scope of lead toxicity remains unclear. Solving the lead puzzle will not only inform public policy for necessary preventive measures, but may also help to identify strategies for therapeutic intervention as well as elucidate toxicity mechanisms of other heavy metals such as mercury.

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