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Review

Chelator combination as therapeutic strategy in mercury and lead poisonings

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ABSTRACT

The chelating thiols dimercaptosuccinate (DMSA) and dimercaptopropane sulfonate (DMPS) are effective in enhancing urinary excretion of mercury and lead. However, strategies for mobilization of toxic metals from aged brain deposits may require combined use of a water soluble agent, removing circulating metal into urine, as well as lipophilic chelator, being used to facilitate the brain-to-blood mobilization. Pb(II) and Hg(II) ions are coordinated with DMSA through one —COOH and one SH group. However Pb(II) can bind with racemic DMSA through two SH groups in non-aqueous solvents (when —COOH groups are esterified). Generally, such Pb(II) and Hg(II) complexes have a composition of 1:1 and 1:2. However, binuclear and polynuclear species with DMSA like 2:1, 2:2, 2:3, 3:3 have been identified for Hg(II) ions. Both Pb(II) and Hg(II) ions are formed with BAL 1:1 and 1:2 complexes with coordination through two mercapto groups. Early experiments showed promising results with the SH–dextran–Britis h anti-lewisite (BAL) combination. Later insight indicates that the DMPS–BAL could be preferred in cases of long-term Hg exposure. In cases of lead poisoning DMSA has been the recommended antidote due to its low toxicity. However, DMSA is distributed extracellularly, and its efficacy might be improved when combined with a brain-to-blood shuttling agent. Thus it has been found that the ionophore Monensin can improve its effect by increasing the egress of intracellularly deposited Pb. Previously, BAL was combined with ethylenediaminetetraacetic acid (EDTA) in severe cases. Today, it is reasonable that low-dosed BAL can facilitate mobilization of Pb from brain to blood during DMSA-treatment.

Contents

Abbreviations: BAL, British anti-Lewisite; BBB, blood–brain barrier; DMPS, 2,3-dimercapto-1-propansulfonate; DMSA, Meso-dimercaptosuccinic acid; DPA, D,L-pencillamine; EDTA, ethylenediaminetetraacetic acid; GABA, γ-aminobutyric acid; MCT, o-mercapto-4-methyl-5-thiazole acetic acid; Mi-ADMSA, mono isoamyl ester DMSA; Mi-HDMS, mono-n-hexyl dimercaptosuccinate; MMSA, monomercaptosuccinic acid; NAPA, N-acetyl-D,L-penicillamine; NMDAR, N-methyl-D-aspartate receptor.

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1. Introduction

In nature, toxic metals like lead (Pb), cadmium (Cd), mercury (Hg) and aluminum (Al) exist in geochemical complexes with other compounds [1]. However, due to intensive development of heavy industry, metals are extracted from naturally occurring minerals [2]. As a result humans may be exposed to high concentrations of toxic elements, e.g., of mercury and lead. These elements tend to deposit in vital structures including liver, brain, bones, and kidneys [3].

Lead is known as a neurotoxic metal for more than 100 years [4]. Multiple studies have demonstrated the association between lead exposure and various neuropsychiatric and neurodevelopmental disorders including impaired memory, language, intelligence, motor and visuospatial skills [5], as well as schizophrenia, Alzheimer's and Parkinson's disease [6]. Recent studies have demonstrated that even low-dose lead exposure is associated with IQ loss [7–9]. Moreover, Pb-induced IQ loss is associated with significant economic damage in low-, middle-, and high-income countries [10]. These effects are mediated through various mechanisms of lead neurotoxicity. It seems that the major effects of lead in the neural system may be mediated through its universal mechanisms of toxicity including the ability to mimic essential metals like Ca^{2+} and Zn^{2+} [11] and prooxidant activity [12]. Impairment of N-methyl-D-aspartate receptor (NMDAR) signaling through Pb^{2+} binding to Zn^{2+} allosteric site [13] is believed to be the one of the key mechanisms of Pb^{2+} neurotoxicity [11]. Furthermore, lead-induced impairment of NMDAR may be also associated with downstream inhibition of brain-derived neurotrophic factor, transsynaptic neurotrophin, ultimately leading to altered synaptophysin and synaptobrevin production [14]. Moreover, lead interferes with NO signaling in the central nervous system [15], that is also known to be NMDAR-dependent [16]. Other targets may also include acid-sensing ion channel 1a (ASIC1a), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and kainate [17]. In general, these mechanisms result in altered synaptic formation, plasticity, and function [18]. Lead is capable of substitution for zinc in zinc-finger proteins, with various proteins being affected in different disorders [19]. Pb exposure is also associated with altered production and balance of neurotransmitters like glutamate (Glu), glycine (Gly), and γ-aminobutyric acid (GABA) [20]. In parallel, lead exposure also results in increased proapoptotic signaling and extracellular amyloid-beta accumulation [17].

Lead is heterogeneously distributed in brain with the highest levels in hippocampus and amygdala, lower deposition in medulla oblongata and cerebellum, and the lowest concentrations in corpus callosum and optic tract [21]. It has been demonstrated that half-life of lead in blood accounts for 35 days, whereas that in soft tissues is slightly longer (40 days). The maximal half-life of lead is observed in bones (20–30 years) [22].

Mercury exposure is associated with multiple disorders of neural system including Minamata disease, presumably also autism spectrum disorders, Alzheimer's disease [23], Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis [24]. Even low dose Hg exposure is associated with significant structural and functional alterations including mental retardation [25]. Earlier studies have demonstrated that the increase in hair Hg by 1 ppm is associated with a loss of 0.18–0.465 IQ points [26]. Moreover, lost productivity due to Hg-induced IQ loss has been estimated to $8.7 billion annually [27]. Certain mercury species including MeHg and mercury vapor readily cross the blood–brain barrier (BBB) and enter the brain [28]. A speciation study demonstrated that in the case of MeHg exposure, mercury is deposited in brain cortex as HgSe, $Hg(SR)_2$, and MeHgCys [29]. It is also notable that the half-life of mercury in the human brain is extremely long, accounting for years and decades [30], therefore, the neurotoxic effects of Hg exposure may persist for a long time.

One of the key mechanisms underlying neurotoxic effects of mercury is induction of oxidative stress. Mercury possesses high affinity to SH and SeH groups thus inactivating multiple enzymes including antioxidant selenoproteins like glutathione peroxidase and thioredoxin reductase [31]. Antioxidant enzyme depression is also associated with increased oxidation of macromolecules (RNA, DNA, proteins) and impairment of their synthesis [32]. The latter, hypothetically, occur due to Hg binding to SH groups and secondary conformational changes in nucleic acids and ribosomal proteins [33]. Mercury, like lead, is also capable of affecting voltage-gated calcium channels, thus resulting in altered intracellular calcium handling and neurotransmitter release [34]. Moreover, both lead- and mercury-induced neuronal death is associated with reorganization of cytoskeleton [35]. In particular, Hg binding to sulfhydryl groups of microtubules is associated with their depolymerization and dysfunction, ultimately resulting in impaired axonal and dendritic transport, as well as impaired cell growth and differentiation [33]. Toxic effects of Hg exposure may also be mediated through overactivation of NMDAR, resulting in cytoskeleton instability [36]. In parallel with NMDAR activation, Hg overexposure results in alteration of glutamate removal by astrocytes with subsequent excitotoxicity [37]. All these pathways may be associated with Hg-induced neuronal death [38].

As far as therapy of lead and mercury poisoning is concerned, the basis of treatment regimens is provided by the development of chelating agents. Chelation, from the Greek word "chelos" meaning claw, involves the incorporation of a metal ion or cation into a complex ring structure by an organic molecule, the chelating agent. Electron-donor atoms in a chelating agent include sulfur, nitrogen, and/or oxygen [39]. The use of chelating agents in medicine started about a century ago to alleviate the toxicity of arsenic (As) compounds, which at that time was used for treatment of syphilis [40]. Examples of traditional chelating agents are BAL [41,42] and CaEDTA (calcium ethylenediamine tetraacetate) [43]; penicillamine [44] and acetyl-penicillamine [45]. An important consideration in chelation therapy is the solubility of the chelator and the chelate, in water or in lipids (Table 1) [46]. Aqueous solubility facil-

Table 1
Examples of extracellularly distributed agents and chelating agents that can penetrate cellular membranes.

Group	Extracellularly distributed (polar) chelating agents	Chelators that can penetrate cellular membranes and act as shuttling vehicles
Chelators	Mercaptodextran (SH-10) CaEDTA DMSA DMPS	BAL (dimercaprol) Acetylpenicillamine Mono-isoamyl-DMSA (MiADMSA) Monensin (an ionophore)