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Metal coordination chemistry underlying environmentally driven neurological damage

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Abstract

Neurological damage associated with environmental metal exposure represents a convergence of coordination chemistry, redox biology, and neurophysiology. Metals such as lead, mercury, manganese, arsenic, iron, copper, nickel, aluminum, and cadmium possess distinct coordination behaviors that dictate their biological fate, cellular distribution, and neurotoxic potential. Unlike organic neurotoxicants, metals exert toxicity not through covalent modification but through coordination interactions with proteins, nucleic acids, membranes, and small-molecule ligands. These interactions alter enzyme activity, disrupt neurotransmission, destabilize metal homeostasis, and induce oxidative and nitrosative stress. In the nervous system, where redox balance, metal cofactors, and synaptic signaling are tightly regulated, even subtle perturbations in coordination chemistry can propagate into long-term neurodegeneration, cognitive impairment, and developmental deficits. This review synthesizes journal evidence linking environmental metal exposure to neurological damage through coordination-driven mechanisms, emphasizing metal speciation, ligand competition, redox cycling, protein misfolding, mitochondrial dysfunction, and neuroinflammation. Particular attention is given to how coordination geometry, oxidation state, and ligand environment govern blood–brain barrier transport, intracellular localization, and persistence of metals in neural tissue. The review concludes by identifying emerging analytical approaches and regulatory implications, arguing that neurological risk assessment must incorporate coordination chemistry rather than relying solely on total metal concentration.

Keywords: Coordination chemistry; Neurotoxicity; Metal speciation; Blood–brain barrier; Oxidative stress; Synaptic dysfunction; Protein misfolding; Mitochondrial damage; Neuroinflammation; Environmental exposure

1.0 Introduction: why coordination chemistry matters in neurotoxicity

The human nervous system is intrinsically a metal-dependent organ system. Essential metals such as iron, copper, zinc, and manganese serve as cofactors for enzymes involved in neurotransmitter synthesis, mitochondrial respiration, antioxidant defense, and synaptic plasticity [1, 2]. Their concentrations, oxidation states, and coordination environments are tightly regulated across neural compartments. Environmental

exposure to metals disrupts this balance not simply by increasing total metal burden, but by altering coordination equilibria, displacing essential metals, and introducing chemically incompatible species into finely tuned biochemical networks [3, 4]. Coordination chemistry governs how metals interact with biological ligands including amino acid side chains, cofactors, nucleic acids, phospholipids, and water molecules. These interactions determine whether a metal remains sequestered, participates in redox cycling, catalyzes reactive oxygen species formation, or binds aberrantly to proteins. In the nervous system, where long-lived cells and high metabolic demand prevail, mis-coordination events can accumulate over time, leading to irreversible damage [5, 6]. Traditional toxicological models often treat metals as uniform entities, assessed by bulk concentration or exposure dose [7-9]. However, neurotoxicity frequently arises at exposure levels that do not cause systemic toxicity, reflecting the nervous system's sensitivity to coordination perturbations rather than overt cell death [10]. Understanding environmentally driven neurological damage therefore requires reframing metal toxicity as a coordination chemistry problem, where ligand competition, redox state transitions, and geometric preferences determine biological outcomes.

2.0 Principles of metal coordination chemistry in biological systems

2.1 Coordination number, geometry, and ligand field effects

Metal ions interact with biological molecules through coordination bonds, whose strength and geometry depend on ionic radius, charge density, and electronic configuration. Coordination number and geometry tetrahedral, square planar, octahedral govern how metals fit into protein active sites or displace native cofactors [11, 12]. For example, zinc typically adopts tetrahedral coordination in enzymes and transcription factors, whereas iron commonly occupies octahedral environments [13]. Metals with incompatible geometries can distort protein structure when substituted into these sites. Ligand field effects also influence reactivity. Transition metals with partially filled d-orbitals can engage in ligand-to-metal or metal-to-ligand charge transfer, enabling redox activity. This is especially relevant in neurons, where metal-catalyzed electron transfer can intersect with mitochondrial respiration and neurotransmitter metabolism. Metals such as iron and copper, when improperly coordinated, can catalyze highly localized oxidative damage via Fenton-type reactions [14]. Importantly, coordination chemistry is context-dependent. A metal that is relatively inert in one ligand environment may become highly reactive in another. Environmental metals entering neural tissue encounter a complex ligand landscape, and their coordination behavior is often reshaped in ways that favor toxicity rather than physiological function.

2.2 Hard–soft acid–base theory and neural ligand preferences

The hard–soft acid–base framework provides insight into metal selectivity for biological ligands. Soft metals such as mercury and cadmium preferentially bind soft ligands like thiol groups in cysteine residues, while harder metals such as aluminum favor oxygen-donating ligands [15]. Neural proteins are rich in cysteine motifs, particularly in enzymes regulating redox signaling and synaptic function, making them prime targets for soft metal coordination [16]. When toxic metals bind preferentially to thiol groups, they can irreversibly inhibit enzymes, disrupt redox sensing, and alter protein folding [17]. This explains why mercury and cadmium exhibit pronounced neurotoxicity despite relatively low brain concentrations. Their coordination chemistry allows them to selectively target vulnerable molecular sites critical for neuronal survival.

3.0 Transport across the blood–brain barrier: coordination-driven selectivity

3.1 Mimicry of essential metals and transport hijacking

The blood–brain barrier (BBB) is a highly selective interface that regulates metal entry into the central nervous system [18-20]. Essential metals are transported via tightly regulated carriers, including transferrin receptors for iron and specific transporters for manganese and copper [21]. Toxic metals exploit coordination chemistry to mimic essential species, enabling them to hijack these transport systems. Lead, for example, can substitute for calcium due to similar ionic radius and coordination preferences, allowing it to enter neurons through voltage-gated calcium channels [22]. Manganese shares coordination and redox characteristics with iron, enabling uptake via iron transport pathways [23]. This mimicry explains that neurotoxicity often arises not from passive diffusion, but from coordination-driven deception at biological barriers. Once inside the brain, these metals are no longer efficiently cleared, particularly if they form stable complexes with intracellular ligands. The BBB thus serves as both a gatekeeper and a trap, with coordination chemistry determining which metals cross and how long they persist.

3.2 Speciation and ligand exchange at the BBB interface

` Metal speciation in blood plasma strongly influences BBB transport. Metals bound to low-molecular-weight ligands or loosely coordinated complexes are more likely to undergo ligand exchange at endothelial surfaces [24, 25]. In contrast, metals tightly sequestered by plasma proteins may be excluded. Environmental factors such as oxidative stress or inflammation can alter plasma ligand availability, indirectly modulating metal entry into the brain [26-28]. This dynamic highlights why neurological effects may intensify under conditions such as malnutrition, infection, or aging, where metal coordination equilibria are already perturbed.

4.0 Disruption of neurotransmission through coordination chemistry

4.1 Metal interference with neurotransmitter synthesis and metabolism

Neurotransmitter synthesis relies on metal-dependent enzymes, including tyrosine hydroxylase and monoamine oxidase. These enzymes require precise metal coordination for catalytic activity. Toxic metals can displace native cofactors or bind to regulatory sites, altering enzyme kinetics and reducing neurotransmitter availability [29]. Manganese neurotoxicity illustrates this principle. Excess manganese accumulates in basal ganglia regions and interferes with dopamine metabolism by disrupting iron-dependent enzymes and mitochondrial function [30, 31]. This coordination-based interference produces Parkinsonian symptoms without the classical dopaminergic neuron loss seen in idiopathic Parkinson's disease [32]. Similarly, mercury coordination to thiol-rich enzymes involved in glutamate metabolism can impair excitatory neurotransmission, contributing to excitotoxicity and cognitive dysfunction [33, 34].

5.0 Redox-active metals, coordination chemistry, and oxidative neural injury

5.1 Fenton chemistry and localized oxidative stress

Iron and copper are central to neural redox biology, serving as cofactors for enzymes such as cytochrome c oxidase and superoxide dismutase. However, when their coordination environment is disrupted, they catalyze Fenton and Fenton-like reactions, generating hydroxyl radicals that damage lipids, proteins, and nucleic acids. Neurons are particularly vulnerable to lipid peroxidation due to their high content of polyunsaturated fatty acids and limited regenerative capacity [35, 36]. Miscoordinated iron within mitochondria or lysosomes creates localized oxidative hotspots that impair energy production and trigger cell death pathways [37, 38]. Environmental exposure can increase labile metal pools by overwhelming storage proteins such as ferritin or by damaging membranes that normally sequester metals, while coordination chemistry thus links environmental exposure directly to intracellular redox catastrophe.

5.2 Mitochondrial metal dysregulation

Mitochondria are hubs of metal-dependent reactions and are highly sensitive to coordination disturbances [39, 40]. Metals that accumulate in mitochondria disrupt electron transport chain components, many of which contain iron-sulfur clusters or copper centers [41, 42]. Displacement or oxidation of these clusters impairs respiration and increases reactive oxygen species production. Manganese and iron accumulation in mitochondria has been linked to impaired ATP production and activation of apoptotic signaling in neurons [43-45]. Over time, this energy deficit contributes to neurodegenerative processes characterized by selective neuronal vulnerability.

6.0 Protein misfolding and aggregation driven by aberrant metal coordination

6.1 Metal binding and conformational instability

Protein folding depends on precise intramolecular interactions, including metal coordination where applicable. Toxic metals can bind nonspecifically to proteins, stabilizing misfolded conformations or promoting aggregation [46]. In the brain, this mechanism intersects with neurodegenerative disease pathology [47]. For example, copper and iron binding to amyloid-β peptides influence aggregation kinetics and redox activity, increasing oxidative stress in Alzheimer's disease [48-50]. While these metals are endogenous, environmental exposure that alters their coordination or redox state can increase aggregation tendencies. Similarly, manganese and nickel can promote misfolding of α-synuclein by altering its metal-binding regions, potentially accelerating parkinsonian pathology [51, 52]. These effects reflect coordination-driven conformational shifts rather than direct toxicity.

6.2 Proteostasis collapse and long-term accumulation

Neurons rely on efficient protein degradation systems to manage misfolded proteins [53]. Metal coordination to proteasomal components or chaperones impairs proteostasis, allowing aggregates to accumulate [54, 55]. Once formed, metal-stabilized aggregates are resistant to clearance and can propagate damage through prion-like mechanisms. This coordination-chemistry perspective explains why environmental metal exposure may not cause immediate neurotoxicity but instead increases susceptibility to age-related neurodegenerative diseases.

7.0 Neuroinflammation as a coordination-mediated process

Microglia and astrocytes play central roles in metal handling and inflammatory responses in the brain [56, 57]. Metals coordinated to microglial receptors or intracellular ligands activate inflammatory signaling pathways, including NF-κB and inflammasome complexes [58, 59]. Redox-active metals amplify this response by generating oxidative stress that sustains inflammatory loops. Chronic neuroinflammation alters metal homeostasis further by increasing permeability of the BBB and releasing metals from damaged cells, creating a self-reinforcing cycle [60]. Coordination chemistry thus links initial exposure to prolonged inflammatory damage even after environmental exposure has ceased.

7.1 Developmental vulnerability and long-term neurological outcomes

The developing nervous system is uniquely sensitive to coordination disturbances because metal-dependent processes guide neuronal migration, synapse formation, and myelination. Exposure to metals during gestation or early childhood can disrupt these processes at concentrations that have minimal effects in

adults [61, 62]. Lead, mercury, and manganese are particularly damaging during development, as their coordination chemistry allows them to interfere with calcium signaling, redox regulation, and gene expression. Epigenetic modifications induced by metal-driven oxidative stress can lock in altered neural trajectories, producing cognitive and behavioral deficits that persist across the lifespan [63-66].

Conclusion: coordination chemistry as the missing framework in neurotoxicity

Environmentally driven neurological damage cannot be fully understood without placing metal coordination chemistry at the center of analysis. Metals do not merely accumulate in neural tissue; they reconfigure molecular interactions, displace essential cofactors, catalyze redox reactions, and destabilize protein structure through specific coordination behaviors. These processes explain why neurological effects often occur at exposure levels below those causing systemic toxicity and why damage may persist or worsen long after exposure ends. Integrating coordination chemistry into neurotoxicology offers a unifying framework that links exposure, molecular mechanism, and disease outcome. It also has practical implications for risk assessment, biomonitoring, and intervention, emphasizing the need to measure metal speciation, ligand availability, and redox state rather than total concentration alone. As environmental metal exposure continues to intersect with aging populations and neurodegenerative disease burden, a coordination-centric perspective will be essential for protecting neurological health.

Declaration of Conflicting Interests

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