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Comparative Observations on Inorganic and Organic Lead Neurotoxicity

by M. Anthony Verity*

Environmental and occupational exposure to lead still generates concern, and recent studies have focused such concern on the role of body burden of lead during the fetal/neonatal period, especially in the genesis of disturbed central nervous system development. This discussion provides some comparative observations on the neurotoxicity of inorganic and organic lead species. The characteristic acute, predominantly cerebellar encephalopathy associated with neonatal high lead exposure contrasts to the subtle, axo-dendritic disorganization shown to be associated with low-level neonatal inorganic Pb^{2+} exposure. There is a preferential involvement of the hippocampus in both low-level inorganic Pb^{2+} and organolead exposure, and the clinical syndromes of irritability, hyperactivity, aggression, and seizures are common features of disturbed hippocampal function. Neurotransmitter system abnormalities have been described with inorganic Pb^{2+}, but recent attention has focused on the abnormalities in glutamate, dopamine, and/or γ-aminoboutyric acid (GABA) uptake, efflux, and metabolism. Abnormalities of GABA and glutamate metabolism are also found with the organolead species. While the pathogenesis is still unclear, the interactive role of Pb^{2+} on mitochondrial energy metabolism, Ca^{2+} uptake, intracellular Ca^{2+} homeostasis, and neurotransmitter influx/efflux is considered. Consideration is given to low-dose inorganic Pb^{2+} and organolead effects on mitochondrial and/or plasmalemmel membranes inducing either Cl^-/OH^- antiport-linked depolarization, inhibition of intracellular ATP biosynthesis and transduction, and/or abnormalities induced due to the preferential affinity of Pb^{2+} for intracellular Ca^{2+}-cytoplasmic proteins, e.g., calmodulin. Testable hypotheses are presented that may provide an understanding of the pathogenesis underlying dystrophic neuronal development under the influence of inorganic or organolead intoxication.

Prologue

"Recommendation 9-2: Emphasis and encouragement should be given to studies on mechanisms involved in the search for, and analysis of, appropriate chemically-induced single pathologic processes. . . in contrast to placing emphasis on research on experimental diseases in which multiple types of tissue damage are induced."

"Recommendation 14-52: . . . [chemical agents] special attention should be given to the evaluation of effects on the fetus, infant. . . uniquely vulnerable to environmental toxicants which damage the CNS."

(Report of Special Task Force for Research Planning in Environmental Health Science, submitted to Dr. David P. Rall, Director, National Institute of Environmental Health Sciences, December 21, 1976)

Introduction

Lead exposure from environmental and occupational sources still remains of great concern. Although low-level amounts of lead are present in man and all living organisms, indices of sublethal health effects and the nature of lead speciation are problems of recurrent concern. As indicated in this conference (*1*), lead toxicity in childhood was thought to be without residual effect in nonlethal cases; a misconception corrected by the studies of Randolph Byers who asserted in 1943 that lead not only killed cells but interfered with normal neuronal development. While the inorganic compounds of lead are recognized neurotoxicants in human and animal models, alkyl derivatives of lead are equipotent on a dosage basis and equally neurotoxic, comparable to observations on lead toxicity in bacteria and fungi (*2*).

This discussion provides some comparative observations between inorganic and organic lead neurotoxicity. Concerns referable to environmental source, routes of transport, absorption of the different lead species, partitioning, pharmacokinetic studies, and ancillary factors affecting the susceptibility of organ systems, in particular, the central nervous system, to lead toxicity will not be discussed. Attention will be focused on comparing the clinical and morphologic patterns of neurotoxic injury, comparing the effect of different lead species on neurotransmitter metabolism in defined neural systems, and proposing mechanisms of neuronal injury induced by the lead compounds of interest. The reader is referred to other reviews detailing the neurobehavioral consequences of inorganic lead exposure (*3,4*).

Clinical Patterns of Injury

Inorganic lead (Pb^{2+}) produces a clinically definable encephalopathy and neuropathy dependent upon age, route of administration, and dose. The neonatal developing brain

*Department of Pathology (Neuropathology), Brain Research Institute and Mental Retardation Research Center, Center for the Health Sciences, University of California at Los Angeles, Los Angeles, CA 90024.

is particularly sensitive to the effects of lead poisoning (*5–7*). Acute, high-dose lead administration in the neonate produces a classic clinicopathologic complex in human and experimental animals. Acute cerebral and cerebellar edema with hemorrhage are features of acute high-dose administration with the appropriate clinical manifestations of acute encephalopathy and seizures. The neuropathologic findings, while variable, are considered secondary to a proximate microvascular permeability change leading to red cell leakage, subacute endothelial proliferation, endothelial cell necrosis, microthrombosis, and perivascular periodic acid-Schiff (PAS)-positive exudation (*8–11*).

While all the steps in the pathogenesis of acute Pb^{2+} encephalopathy are still unclear, a likely hypothesis is based upon the encephalopathy being secondary to a Pb^{2+}-induced vasculopathy. A direct toxic effect of Pb^{2+} on neurons is still equivocal. The cause of the apparent preferential sensitivity of the neonatal brain compared to adult is still unanswered but may be a reflection of the primitive, noncoupled development between the neonatal endothelial cell and astrocyte composing the blood-brain barrier, known to be developmentally immature during early brain development. In this hypothesis, it is proposed that the mature astrocyte would provide a detoxification sink for removal of endothelial lead, thereby preventing excessive endothelial Pb^{2+} uptake, mitochondrial damage, and initiation of endothelial necrosis.

The neuroclinical and pathologic changes associated with low-level, chronic lead exposure are well documented. There is a high incidence of irritability, hyperactivity, retardation of normal development, seizures, and psychomotor disturbance. Lead exposure is associated with hyperactivity, in turn a known risk factor for antisocial and aggressive behavior. Unfortunately, clear-cut neuropathologic findings associated with low-level lead exposure in humans are ill-described, and animal models have revealed confusing results. The neuropathologic changes, if true, have been detailed through morphometric analysis and have revealed alterations in dendritic arborization and density of synaptic complexes in the cerebral cortex (*12,13*), a decrease in hippocampal pyramidal neuron spine density (*14*), reduction in dentate granule neuron dendritic field (*15*), decreased mossy fiber terminal proliferation in hippocampus (*16,17*), and abnormal dendritic branching of cerebellar Purkinje cells (*18*). In this latter study, the authors precluded the role of undernutrition in contributing to the dendritic abnormality and also demonstrated occurrence of these changes at blood levels insufficient to produce overt clinical toxicity. The described reduction in hippocampal development characterized by dysplasia in axonal and dendritic development of the hippocampal dentate granule cells would suggest a serious disturbance of normal hippocampal functioning. The reported behavioral changes in postnatally lead-exposed animals includes recurrent seizures (*19*), impairment in motor coordination (*20*), and increased aggressiveness (*21*).

The clinical syndrome caused by organolead, e.g., triethyl lead (TEL), the principal neurotoxic metabolite of tetraethyl lead, evolves through three phases: an initial phase of lethargy followed by tremors, hyperexcitability, hypermotility, and aggression leading finally to convulsions, ataxia, paralysis, and death (*22*). As with inorganic lead, acute and chronic syndromes may be identified. A single high dose (20 mg/kg TEL) produces a mixture of chromatolytic and necrotic neuronal changes, especially in the hippocampus and associated regions of the limbic system. Chronic, sublethal dosing also selectively produces a sporadic loss of neurons in the anterior pyriform cortex and hippocampus and effects on myelination in the developing brain (*23,24*). Of note is the relative sensitivity of the young adult animal to induction of this pathology compared to resistance of the suckling neonate. This age difference in dose response is in contrast to the inorganic lead model.

Organolead toxicity produces a restricted pattern of neural damage involving primarily the limbic forebrain and frontal cortex (*25,26*). Trialkyl leads produce a variety of neurobehavioral effects that resemble those induced by experimental damage to the limbic forebrain. The limbic system is thought to participate in the modulation of behavioral reactivity, motivation, learning, and memory (*27*). As previously mentioned, the neurotoxicity induced by the organoleads resembles the pattern of neurobehavioral deficits observed following limbic system damage. Notable is the similarity with perinatal exposure to inorganic Pb^{2+}. Table 1 summarizes some of the similarities between the neuropathologic and neurobehavioral effects of neonatal inorganic Pb^{2+} and adult organolead exposure. Table 2 identifies observations pertaining to changes in the limbic system induced by inorganic and organic lead species. Recent observations suggest that the organoleads might produce some of their behavioral effects by disrupting benzodiazepine processes in the limbic forebrain known to modulate reactivity to aversive environmental stimuli (*4*). Our *in vitro* synaptosomal studies (*28,29*) have revealed a relative preferential sensitivity of γ-aminobutyric acid (GABA) uptake to triethyl lead due to inhibition of GABA binding to the uptake site in synaptic membranes.

Table 1. Neuropathology of inorganic and organic lead.

Pathology	Pb^{2+}	Organic lead
Endothelial damage	Neonatal	No
Reversible astrocytosis	Yes	No
Hypomyelination	2° to axonal hypoplasia	Post-translational defect
Cerebellar necrosis	Neonatal	? In adults
Hippocampal necrosis	No	Adult
Decreased synaptogenesis in hippocampus	Yes	Yes

Table 2. Limbic system as target for lead neurotoxicity.

Observation	Reference
High endogenous lead	(*70,71*)
Decreased spine density in CA1	(*14*)
Decreased synaptogenesis	(*15,16*)
Decreased ACh turnover	(*72*)
Impaired spatial learning	(*73,74*)
Increased seizure	(*4,31*)

Comparative Studies of Brain Neurochemistry: Lead and Organolead

While the involvement of various neurotransmitter systems (e.g., cholinergic, noradrenergic, GABAergic, and dopaminergic) have been proposed (*30,31*), most attention has been devoted to examining the interaction of the inorganic or organolead species with glutamate and GABA. Early studies by Bondy et al. (*32*) compared the effect of organic and inorganic lead on high-affinity neurotransmitter transport in adult mouse brain homogenates. The uptake and release of dopamine was especially affected by organolead at 10^{-8} M; inorganic Pb^{2+} was several orders of magnitude less toxic. However, the ID_{50} for glutamate, dopamine, and GABA was found at approximately 10^{-6} M, suggesting a selective vulnerability of dopaminergic neurons to lead. Such selective vulnerability is also suggested by the nature of the neurological deficit characterized as fine tremor, hyperactivity, and irritability, stigmata of dopaminergic function. The uptake studies were performed following 5 min incubation, thereby avoiding the problem of depleted ATP caused by uncoupling of synaptosomal oxidative phosphorylation (*28,33*). It is likely, therefore, that the selective inhibition of uptake of dopamine > GABA > glutamate is a reflection of organolead interaction with specific uptake protein(s) within the membrane or with the immediate membrane environment as recently suggested for the GABA uptake site in the synaptic membrane (*29*). The lack of interaction with inorganic Pb^{2+} would appear to preclude a role for inorganic lead-induced deficits in neurotransmitter movement at low blood level concentrations in an understanding of the pathogenesis of lead toxicity.

Attempts have been made to link the neurobehavioral and physiological effects of low-dose, chronic Pb^{2+} exposure to dopaminergic activity (*34–36*). Particularly relevant in this respect is the observation by (*37*), who demonstrated that low-dose Pb^{2+} exposure of the developing rat central nervous system caused a permanent increase in lithium-induced polydipsia (LIP). Subsequent studies showed that the LIP response was dependent on an intact nigrostriatal dopamine system (*38*). It is possible that the nigrostriatal pathway, although an integral part of the neural circuit mediating LIP, may not be the proximate site of Pb^{2+} interaction. For instance, the angiotensin-2 receptors present in the third ventricle (and hypothalamus) may be the primary locus of Pb^{2+} interaction. The limbic system serves as an interface between the hypothalamus and neocortex, and an early onset developmental abnormality in dopaminergic neuron maturation may account for the apparent limbic system-mediated behavioral abnormalities.

The effects of lead on mitochondrial energy metabolism are potentially important in the pathogenesis of rat and human lead encephalopathy. Studies with inorganic Pb^{2+} have revealed effects on mitochondrial partial reactions significantly different from organolead. *In vivo* (*39*) and *in vitro* (*40*) effects of inorganic Pb^{2+} on immature rat brain mitochondrial respiration are comparable. With all substrates, low Pb^{2+} concentrations produced an increase in respiration. Higher concentrations produced an inhibition of respiration, inhibition of ADP-dependent (stage 3) respiration, decrease in respiratory control ratio (*41*), and apparent dependence on extramitochondrial $[PO_4^{3-}]$ and $[Mg^{2+}]$. Such effects, *in vitro*, were evident at approximately 1 to 5 μM lead concentrations. The Pb^{2+}-induced increase in respiration was shown to be associated with inward transport of Pb^{2+} by beef-heart mitochondria (*42*), an energy-dependent process with characteristics in common with mitochondrial Ca^{2+} accumulation (*43*). Mitochondrial Ca^{2+} uptake into mitochondria is competitively inhibited by Pb^{2+} at a lower concentration than the inhibition of respiration (*44*).

The possibility that disturbances of intracellular Ca^{2+} homeostasis may serve as a common pathway for neuronal injury allows for speculation on the possible mechanism underlying the acute cerebellar encephalopathy associated with Pb^{2+} exposure in immature rats and humans. The described effects on mitochondria will lead to a net decrease of mitochondrial Ca^{2+} uptake, increased mitochondrial Ca^{2+} efflux, increased mobilization of Ca^{2+} from endoplasmic reticulum, and interference with the ATP-driven Ca^{2+}-ATPase (*45*) located in the plasmalemma. It is possible, therefore, that the acute endothelial injury recognized as an early event in acute cerebellar Pb^{2+} encephalopathy is dependent on the abnormal mobilization of intracellular Ca^{2+} with a resultant increase of free cytosolic Ca^{2+}. This scenario does not preclude the idea that Pb^{2+} may also act as a calcium-mimetic agent, somewhat similar to Hg^{2+} (*46*). In either event, elevated intracellular Ca^{2+} appears to play an important role in the mechanism of cell death in certain pathologic conditions (*47–49*).

The organolead compounds are also well-documented toxins of energy metabolism in isolated mitochondria (*50–54*). While a potential relationship exists between the organolead-induced lesion in energy transduction and synaptic function, especially neurotransmitter reuptake and release, our studies (*28*) have not demonstrated such coupling for GABA uptake. Moreover, (*33*) confirmed the Cl^--dependent uncoupling of oxidative phosphorylation by triethyl lead (*28*) and increased cytosolic free Ca^{2+} in cerebro-cortical synaptosomes. Such Ca^{2+} was derived from the intraterminal mitochondria subsequent to the uncoupling of mitochondrial ATP synthesis from oxidation. In summary, the neurotoxicity of organolead suggests a more acute mechanism underlying the pathogenesis of cellular injury. In particular, the dependence on Cl^- and the changes in membrane depolarization coupled with the failure of bioenergetic potential and increased intracellular Ca^{2+} strongly suggest a mechanism of neuronal death analogous to the mechanisms of excitotoxic cell injury (*55*).

Recent findings indicate that inorganic Pb^{2+} can substitute for Ca^{2+} with certain intracellular Ca^{2+}-binding proteins (Table 3). Such observations suggest a variety of hypotheses for understanding the molecular basis of its toxic action, especially in reference to both the acute and low-level, chronic exposure models of neurotoxicity. Pb^{2+} interacts with calmodulin with an affinity at least equal to that for Ca^{2+} (*56*). Lead may substitute for Ca^{2+} in a variety of Ca^{2+}-dependent processes. Many of these processes are related to Ca^{2+} as a cytoplasmic second messenger, there-

Table 3. Inorganic Pb^{2+} may replace Ca^{2+} in select intracellular mechanisms (the Ca^{2+}-mimetic effect of Pb^{2+}).

Calmodulin-stimulated phosphodiesterase
Ca-dependent K^+ permeability (RBCs)
Stimulates brain protein kinase C
Mitochondrial uptake (respiration dependent)
Ca pump ATPase (RBCs)

by coupling Ca^{2+} to specific effector mechanisms. Other interactions are not calmodulin dependent, for instance Ca^{2+}-dependent exocytosis and Ca^{2+}-dependent K^+ permeability in the plasma membrane.

We have discussed the role of lead/calcium in mitochondrial bioenergetics, but of immediate interest to this discussion is the recent recognition that low concentrations of Pb^{2+} may stimulate brain protein kinase C (*57*). Protein kinase C is a Ca^{2+}-and phospholipid-dependent enzyme known to mediate cellular proliferation and differentiation via phosphorylation of regulatory proteins (*58*). Our interest in this reaction is twofold: first, the remarkable heavy metal specificity to Pb^{2+} and sensitivity at 10^{-10} M when contrasted to $CaCl_2$. Second, the effective intracellular concentration of 10^{-10} M would be reached following blood concentrations of between 5 and 10 μg/100 mL, representing approximately 10^{-6} M. Hence, the unique and marked sensitivity of protein kinase C to Pb^{2+} represents a potential interaction at low, nonsymptomatic, chronic Pb^{2+} concentrations, especially in the developing nervous system.

Continued bioelectric activity influences the survival of nerve cells during their early development (*59,60*). Prolongation of neuronal survival in culture is dependent on chronic depolarization usually maintained by high extracellular K^+ (*61–63*). How depolarization affects neuronal survival and differentiation is unclear but increased $[K^+]_e$ is known to activate voltage-sensitive Ca^{2+} channels (*64*), and Ca^{2+} entry has been implicated in the developmental effects of depolarization on neuronal survival and differentiation. Pb^{2+} uptake may occur via calcium channels (*65*). Simons and Pocock (*65*), using chromaffin cells, demonstrated an approximate 5-fold stimulation of Pb^{2+} uptake following K^+ depolarization, which was antagonized by external Ca^{2+} inhibited by Ca^{2+} channel blockers and stimulated by the Ca^{2+} agonist BAY K8644 (Table 4).

More specifically, Gallo et al. (*66*) studied the role of depolarization on the survival and differentiation of cerebellar granule cells in culture and found that neuronal survival was not influenced by the bioelectric activity but was critically dependent on the depolarization-induced transmembrane Ca^{2+} flux (Table 5). Moreover, inhibitors of calmodulin blocked the differentiating effect of K^+-induced depolarization. These observations link the survival and differentiation of neurons to a constant depolarization-coupled Ca^{2+} flux,

Table 4. Pb^{2+} uptake occurs via Ca^{2+} channels (*65*).

Stimulation by K^+ depolarization
Antagonized by Ca^{2+}
Inhibited by Ca^{2+} channel blocker, D-600 ($K_{0.5}$ = 0.4 μM)
Stimulated by Ca agonist BAY K8644

Table 5. Depolarization is coupled to survival and differentiation of neurons in culture (*66*).

High $[K^+]$ in medium
Need for depolarization-induced transmembrane flux of Ca^{2+} (voltage-dependent Ca^{2+} influx)
Ca^{2+} agonists could substitute for low $[K^+]$
Calmodulin inhibitors blocked neuronal survival and maturation

Table 6. Postulated mechanism of Pb^{2+}-induced encephalopathy.

Type	Mechanism
Acute	Uptake via Ca^{2+} channel
	Increased affinity for Ca^{2+}-modulated systems
	Block Ca^{2+} uptake into mitochondria and endoplasmic reticulum
	Increased cytoplasmic $[Ca^{2+}]$
	Ca^{2+}-mediated cell death
Chronic	Pb^{2+} uptake via Ca^{2+} channel (voltage dependent)
	Requirement for depolarization in neuronal differentiation
	Activation of protein kinase C
	Modification of calmodulin-dependent processes
	Cytoskeletal protein post-translation modifications
	Dysplastic neurite proliferation

itself transduced by a calmodulin-dependent event(s) to neuronal differentiation, especially neurite outgrowth, specification, and stabilization of synaptic contacts. A critical determinant of neurite organization is microtubule assembly regulated by the calmodulin-Ca^{2+} complex (*67–69*).

How then can we explain the apparent differences in brain injury resulting from acute contrasted to low-level, chronic inorganic Pb^{2+} intoxication? In the acute model we may propose that Pb^{2+} uptake via Ca^{2+} channels (voltage sensitive and insensitive) into immature capillary endothelial cells will trigger intracellular processes leading to defective mitochondrial bioenergetics and mobilization of intracellular Ca^{2+}, leading to cellular (endothelial) necrosis. In contrast, low-level, chronic Pb^{2+} exposure is manifested by subtle defects in axodendritic architecture and neurite organization secondary to defective cytoskeletal organization. The need for continued depolarization in neuronal development is linked to stimulation of Pb^{2+} uptake and the resultant high-affinity binding to Ca^{2+} binding proteins, especially calmodulin. The abnormal and possibly prolonged activation of calmodulin-dependent processes, especially the activation of protein kinase C, will lead to distorted transmembrane signalling and defective neuronal differentiation (Table 6).

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