Lead and Excitotoxicity

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Abstract

Lead (Pb^{2+}) is a known neurotoxicant that impairs learning and memory. However, the mechanism through which it impairs learning and memory is not clearly understood, despite being thoroughly investigated. Of many pathways that are targeted by Pb^{2+}, the most mechanistically relevant is the excitotoxicity caused by modulation of the N-methyl-D-aspartate-type glutamate receptors (NMDAR) in glutamatergic synapses. Pb^{2+} affects not only the expression of different subunits of the NMDARs but also the ontogenic developmental switch of these NMDAR subunits, which is essential for learning and memory. Overactivation of serine/threonine protein phosphatases (PPs) appears to be involved in these synaptic changes. PPs may affect the functions of NMDAR directly, by modulating the phosphorylation state of its subunits, and indirectly by modulating the phosphorylation state of its downstream effectors like the cyclic AMP response element-binding protein (CREB) and other proteins involved in this process. Overexpression of the neuron-specific metallothionein-3 and the subsequent dysregulation of zinc (Zn^{2+}) homeostasis in the synapse is another proposed mechanism of Pb^{2+}-induced excitotoxicity. Upregulation of the kynurenine pathway of tryptophan metabolism and overproduction of quinolinic acid in the brain by Pb2+ may also result in excitotoxicity. The excitotoxic effects of Pb^{2+} thus appear to be multifaceted, and Pb^{2+} is likely to act in coordination with other modulator of excitotoxicity like glutamate, metallothionein-3, quinolinic acid, protein phosphatases, and Zn^{2+}. There is a great need to put these isolated pieces of information together and workout the pathway(s) that are disturbed in Pb^{2+}-induced impairment of learning and memory.

Keywords

Lead · Excitotoxicity · NMDA receptor · Protein phosphatases · Metallothionein-3 · Quinolinic acid

Abbreviations

BDNF	Brain-derived neurotrophic factor
CaBP	Calcium-binding protein
CaM	Calmodulin
CaMKII	Calcium/calmodulin kinase II
CaMKIV	Calcium-/calmodulin-dependent protein kinase IV
CREB	Cyclic AMP response element-binding protein
DG	Dentate gyrus
EPSP	Excitatory postsynaptic potential
ERK	Extracellular signal-regulated kinases
GABA	γ-aminobutyric acid
GPCRs	G-protein-coupled receptors
IDO-1	Indoleamine-2,3-dioxygenase-I

IEG	Immediate early genes
KP	Kynurenine pathway
LTD	Long-term depression
LTM	Long-term memory
LTP	Long-term potentiation
mGluR	Metabotropic glutamate receptors
MT-3	Metallothionein-3
NCS-1	Neuronal calcium sensor-1
NMDARs	N-methyl-D-aspartate-type glutamate receptors
Pb^{2+}	Lead
PK	Protein kinases
PKC	Protein kinase C
PND	Postnatal day
PP	Protein phosphatases
QA	Quinolinic acid
STM	Short-term memory
VSCC	Voltage-sensitive calcium channels

1 Introduction

Lead (Pb^{2+}) is a toxic heavy metal with no known physiological functions in the body. Because of its excessive use in industry, humans have been, and are constantly being, exposed to Pb^{2+} (ATSDR 2017; Caito and Aschner 2017; Ettinger et al. 2020). In the body, Pb^{2+} is distributed in blood, soft tissues (liver, kidney, brain, etc.), and bones. With time, and continuous exposure, it accumulates in bones and becomes a source of internal exposure during bone remodeling (Al-Saleh et al. 2008; El-Sawi and El-Saied 2013). Although Pb^{2+} poisoning in both its acute and chronic forms has gradually declined over the last four decades through several public health regulations and activities controlling the use and emission of Pb^{2+} in the environment (Dignam et al. 2019), it still remains a problem of public health importance (O'Connor et al. 2018). Pb^{2+} gets into the body through food and water, environmental pollution, agricultural technology, and food processing. Absorption and retention in the body depend on age, chemical environment of the gastrointestinal tract, and nutritional status of the individual. Generally, conditions that favor calcium absorption also favor Pb^{2+} absorption and retention. The total body amount does not affect absorption, as there is no feedback mechanism for its absorption (ATSDR 2017).

Due to increased awareness of the toxic effects of Pb^{2+} in children, particularly the neurological toxicities, the acceptable blood Pb^{2+} level (safety limit) has been progressively decreased from 60 μg/dL in 1960s to 10 μg/dL in 1991 (Dignam et al. 2019). Based on the reports of adverse health outcomes at levels below this safety limit, particularly in children, in 2012 the CDC established a new cutoff of 5 μg/dL at which intervention needs to be initiated and stated that no level of Pb^{2+} exposure in children is safe (CDC 2016). In adults, the cutoff of <5 μg/dL, as safety limit, was established in 2015 by the National Institute for Occupational Safety and Health

(NIOSH 2015). In children, lowering the reference level to <3.5 μg/dL is currently being considered (Paulson and Brown 2019).

Pb^{2+} is considered as a multisystem toxicant associated with neurological, nephrological, cardiac, gastrointestinal, and hematological manifestations (WHO 2010). The severity of these toxic effects depends on the duration of exposure, dose, and the developmental stage of the subjects. Children are particularly at increased risk of toxicity because of their frequent exposure and increased absorption and retention capacity. The hemopoietic, renal, and reproductive systems are affected at relatively high doses, whereas the central nervous system (CNS) is affected by low doses (ATSDR 2017).

2 Neurotoxicity of Lead

Pb^{2+} neurotoxicity is known since the late nineteenth century (reviewed by Toscano and Guilarte 2005). While high blood Pb^{2+} levels (>70 μg/dL) are known to cause overt encephalopathy (Chisolm 2001), low levels (<10 μg/dL) in children are associated with neurobehavioral and endocrine alterations such as an increase in hyperactivity and distractibility, delayed puberty, and cognitive deficits in the form of IQ changes (Mason et al. 2014; Vorvolakos et al. 2016; Santa Maria et al. 2019). Studies have demonstrated a cognitive deficit of 5.0–7.4 points on the IQ scale in children who had blood lead levels in the range of 5–<10 μg/dl (reviewed by Santa Maria et al. 2019). The economic impact of this reduced IQ has been estimated to be around US$ 977 billion, which is equivalent to about 1.2% of global GDP (Attina and Trasande 2013).

In experimental animal models, Pb^{2+} exposure causes deficits in spatial learning and long-term potentiation (LTP) (Altmann et al. 1991; Kuhlmann et al. 1997; Gilbert and Mack 1998; Nihei et al. 2000). It has been suggested that there is a “developmental window” that spans from gestation through lactation, in which exposure to low levels of Pb^{2+} is able to cause long-lasting cognitive deficits (Kuhlmann et al. 1997). This concept of developmental window has been demonstrated by the reports that children that were previously, but not currently, exposed to Pb^{2+} exhibited lasting neurobehavioral and cognitive deficits (reviewed by Sanders et al. 2009; Caito and Aschner 2017).

The hippocampus plays a pivotal role in learning and memory processes, and it has been suggested that this structure is particularly affected by Pb^{2+} (Bielarczyk et al. 1996; Sharifi et al. 2002). The most troubling aspect of Pb^{2+} toxicity in children is that neurotoxicity caused by Pb^{2+} exposure is irreversible. Chelation therapy, which is the primary means of treating children with blood Pb^{2+} levels of >45 μg/dL, can reduce the body burden of Pb^{2+} but does not reverse the cognitive or behavioral deficits associated with Pb^{2+} exposure (Rogan et al. 2001; Dietrich et al. 2004). This highlights the possibility that Pb^{2+} exposure induces long-lasting (or permanent) changes in the brain during a critical period of development in childhood (Neal and Guilarte 2010).

The underlying biochemical mechanism of the neurotoxic effects of Pb^{2+} is not well understood at present despite the large body of research done on this topic (Toscano and Guilarte 2005; White et al. 2007; Neal and Guilarte 2010). Many biochemical changes have been reported in the brain that may explain the mechanism of Pb^{2+} neurotoxicity. Some of the reported biochemical alterations caused by Pb^{2+} exposure in the brain include altered adenylyl cyclase activity, reduction in the heme-containing enzymes, and lower energy metabolism in the developing brain (Clarkson 1987); interference with cell adhesion molecules (Silbergeld 1992); reduced activity of alkaline phosphatase (Antonio and Lert 2000); decreased expression (Nihei et al. 2001) and activity (Xu et al. 2005) of protein kinase C; decreased production of transthyretin and low availability of thyroid hormone to the developing CNS (Zhang et al. 1996); decreased levels of nitric oxide in the hippocampus (Sun et al. 2005); altered neurotransmitter activity in the hippocampus (Reddy et al. 2007; Wang et al. 2007); and altered protein phosphorylation and impairment of the glutamatergic synapse transmission (Neal and Guilarte 2010). More recently, dopaminergic dysfunction by Pb^{2+} toxicity has been reported in *C. elegans* (Akinyemi et al. 2019). None of these biochemical changes alone explains the learning and memory deficits caused by the low-dose Pb^{2+} exposure. There is a need to put these pieces together and work out the pathway(s) involved in learning and memory that are affected by Pb^{2+} exposure. The understanding of such pathway(s) is essential to devising any therapeutic/intervention strategies to combat Pb^{2+}-induced neurotoxicity. Of the many biochemical changes studied, the most relevant and best studied area is the excitatory effect of Pb^{2+} at the glutamatergic synapses. This chapter is aimed to focus on the excitotoxic effects of Pb^{2+} and to summarize recent advances in this field of research.

3 Hippocampal Plasticity, NMDA Receptor, and Learning

Hippocampus is the main brain region involved in the acquisition and consolidation of higher brain function, particularly spatial learning and memory. The disruption of hippocampal function by a variety of methods produces deficits in such brain functions (Izquierdo 1993; McNamara and Skelton 1993). The major cellular mechanism within the hippocampus believed to be responsible for acquisition of new memories is the long-term potentiation (LTP), which is a long-lasting increase in synaptic efficacy following brief periods of stimulation of specific synapses (Malenka and Nicoll 1999; Hashemzadeh-Gargari and Guilarte 1999; Nihei et al. 2000, 2001; Shimizu et al. 2000).

Some forms of LTP in the hippocampus, specifically those induced in the Schaffer collateral-CA1 and perforant path-dentate gyrus synapses, are dependent upon N-methyl-D-aspartate-type glutamate receptor (NMDAR) activation (Madison et al. 1991; Malenka and Nicoll 1993, 1999; Teyler and DiScenna 1987; Zalutsky and Nicoll 1990). LTP requires presynaptic glutamate release and subsequent activation of the postsynaptic NMDAR (Collingridge and Bliss 1987; Massicotte and Baudry 1991; McNaughton 1993). Disruption of NMDAR function pharmacologically or by

deletion of specific NMDAR subunits, using gene knockout techniques, is associated with disruption of hippocampal LTP and learning and memory (Gilbert and Mack 1990; Robinson and Reed 1992; Morris et al. 1986; Neal and Guilarte 2010).

4 Overview of Glutamate Receptors

Glutamate receptors are classified into metabotropic and ionotropic subtypes according to whether they exist as G-protein-coupled receptor or as an ion channel. Both these receptor types mediate the actions of glutamate. Metabotropic glutamate receptors (mGluRs) have been extensively studied in hippocampal physiology (reviewed by Niswender and Conn 2010). mGluRs are composed of eight isoforms (mGluR1–8), which are classified into three groups (I–III). Of these, mGluR5 which belongs to group I is primarily postsynaptic and is coupled preferentially to Gq/11 and its downstream effectors. Recent studies have demonstrated that mGluR5 is involved in learning and memory. mGluR5 has been shown to be critically important for both hippocampal synaptic plasticity and hippocampus-based learning and memory (reviewed by Xu et al. 2009a, b). Inhibition of mGluR5 with specific antagonist MPEF impaired the acquisition and consolidation of hippocampus-dependent memory, whereas its activation by specific agonist showed the opposite results (Gasparini et al. 1999).

Ionotropic receptors are further classified based on their selective agonists as NMDA, AMPA, and kainate receptors (Hassel and Dingledine 2006). These receptors bind with glutamate with different affinities. Of these, NMDARs are the most tightly regulated and the most extensively studied. Activation of the NMDAR plays a central role in brain development, learning, and memory as well as in neurodegenerative diseases (Collingridge and Lester 1989; Ozawa et al. 1998; Scheetz and Constantine-Paton 1994). These receptors are located primarily not only in the hippocampus but also in the cerebral cortex (Monaghan et al. 1983; Monyer et al. 1994; Moriyoshi et al. 1991) and play an essential role in hippocampus-mediated learning and memory (Morris et al. 1982, 1986).

NMDAR is a tetrameric complex assembled from two obligatory NR1 subunits in combination with two NR2 or NR3 subunits (reviewed by Vyklicky et al. 2014). NR1 subunit is a constitutional component of NMDA receptors and is widely expressed throughout the CNS at all ages, whereas NR2A and NR2B are functional components whose expression varies with the developmental stage and region of the brain (Xu and Rajanna 2006). A single gene encodes NR1, but at least eight splice variants of NR1 subunits (NR1A to NR1H) have been found (Laurie and Seeburg 1994; Zukin and Bennett 1995). These splice variants of NR1 impart different pharmacological characteristics to the NMDAR (Durand et al. 1992). Alternatively, spliced exon 5 at the N terminus (N-cassette) encodes for a 21 amino acid sequence. Splicing of exon 5 results in transcripts designated as lacking (NR1-a) or containing (NR1-b) the N-cassette (Zukin and Bennett 1995). Exons 21 and 22 encode for two C-terminus cassettes, C1 and C2, which code for 37 and 38 amino acid sequences, respectively. The individual splicing of the C1 or C2 cassette results in transcripts designated as NR1–2 and NR1–3. The presence or absence of both C-terminus cassettes results in NR1–1 and NR1–4 variants. Deletion of the C2 cassette alters the

reading frame and results in the creation of an additional coding region of 22 amino acids, the C2` cassette (Toscano and Guilarte 2005).

Compared to NR1, NR2 and NR3 are more complex and mostly determine the function of NMDAR channel. NR2 subunits are encoded by four distinct genes (NR2A–NR2D), while NR3 subunits are encoded by two distinct genes (NR3A and NR3B). NR2 subunits play positive roles in gating the NMDAR channel, while NR3 subunits play negative roles by forming an unconventional channel (Perez-Otano and Ehlers 2004). The molecular biology of these subunits, their deferential developmental and regional expression, and their distinct intracellular protein associations and functions are thoroughly reviewed by Neal and Guilarte (2010). Together, the associations between NR1 splice variants with other subunits exhibit an exquisite degree of heterogeneity and specialization and play essential roles in synaptic activity (Neal et al. 2011).

NMDAR subunits play critical roles in hippocampal synaptic plasticity. Blockades of NMDAR containing either NR2A or NR2B subunits lead to a selective defect in either LTP or long-term depression (LTD), respectively (Liu et al. 2004). The differential expression of various NMDAR subunits across the developmental time span of peak LTP and hippocampus-mediated learning, together with the impairment of learning due to targeted knockout of NMDAR subunits, strongly supports the essential role of NMDAR in synaptic plasticity and learning and memory (Neal and Guilarte 2010).

5 Activity-Dependent Expression of NMDA Receptor Subunit

The expression of synaptic NMDAR subunit is controlled not only by a genetically programmed development of excitatory circuitry but also by the level of activity present at the synapse. Both in vivo and in vitro studies from neuronal cultures have provided evidence for the activity-dependent modifications in NMDAR subunit expression (Toscano and Guilarte 2005). The expression of NR2A subunit, but not NR2B, has been shown to be dependent upon calcium influx mediated by NMDAR and L-type calcium channels since pharmacological blockade of NMDAR and L-type calcium channels decreased NR2A subunit expression but had no effect on NR2B expression. This resulted in the expression of NMDAR complexes with higher proportion of NR2B subunits with the corresponding functional implications (Hoffmann et al. 2000). A reduction in presynaptic exocytosis produced similar results (Lindlbauer et al. 1998). In addition, activity-dependent changes of NMDAR subunits also occur at the postsynaptic density (PSD). Pharmacologically blocking of the sodium channels resulted in decreased PSD levels of NR2A but increased levels of NR1 and NR2B subunits, whereas activating these channels had the opposite effects (Ehlers 2003).

6 Lead and Synaptic Transmission

It has been suggested that a number of neurotoxic effects of Pb^{2+} may be due to its interference with neurotransmitter systems, particularly those which involve cellular calcium homeostasis and calcium-dependent enzymes (Guilarte 1997; Finkelstein

et al. 1998; Savolainen et al. 1998a, b; Bressler et al. 1999; Goyer and Clarkson 2001; Nihei and Guilarte 2001; Gilbert and Lasley 2002). Establishment of neuronal circuitries in the developing central nervous system depends on the pattern of electrical activity going through the synapses. At early stages of brain development, most neurons fire spontaneously, and this spontaneous electrical activity is believed to be required for axonal outgrowth, pruning of synaptic connections, and maturation of neuronal signalling properties (Moody 1998). Therefore, it can be inferred that Pb^{2+}-induced impairment of learning and memory in children is a result of altered synaptic activity in the brain, particularly in hippocampus which is involved in cognitive processing (Swanson et al. 1997).

The mechanism by which Pb^{2+} alters synaptic activity remains unknown. It has been proposed that Pb^{2+} affect synaptic activity by mimicking the activity of calcium (Ca^{2+}). The ability of Pb^{2+} to substitute for Ca^{2+} is one of the primary mechanisms proposed for Pb^{2+} toxicity in the brain. This Ca^{2+}-mimetic ability of Pb^{2+} has been reported to not only enhance spontaneous neurotransmitter release but also inhibit evoked neurotransmitter release due to impeding Ca^{2+} influx through voltage-sensitive Ca^{2+} channels (Minnema et al. 1988; Kober and Cooper 1976; Atchison and Narahashi 1984; Braga et al. 1999a; Peng et al. 2002; Xiao et al. 2006). Pb^{2+} is also known to bind with intracellular Ca^{2+}-binding proteins and may prevent the detection of Ca^{2+} signalling essential to neurotransmission (Bouton et al. 2001; Marchetti 2003). Some of the neuronal Ca^{2+}-binding protein (CaBP) that are targets for Pb^{2+} are calmodulin (CaM), synaptotagmin, neuronal calcium sensor-1 (NCS-1), NMDAR, and family C of G-protein-coupled receptors (cGPCRs) (reviewed by Gorkhali et al. 2016). The effect of Pb^{2+} could be stimulatory or inhibitory of the function of these proteins depending on the concentration and the binding kinetics of Pb^{2+} to these proteins. Three potential modes of Pb^{2+} activity have been described. These include (1) binding of Pb^{2+} at the Ca^{2+}-binding sites with the subsequent inhibition of its function due to structural modulation, (2) binding of Pb^{2+} at the Ca^{2+}-binding sites with the subsequent activation by mimicking the function of Ca^{2+}, and (3) allosteric modulation of the function of the CaBP due to binding of Pb^{2+} outside the Ca^{2+}-binding sites (Gorkhali et al. 2016).

Pb^{2+} is also known to affect the neurotransmission of glutamate, which is the most abundant excitatory neurotransmitter in the brain. Glutamate and its receptors have an important role in LTP and synaptic plasticity, which are fundamental processes involved in learning and memory (Malenka and Nicoll 1999). Chronic developmental Pb^{2+} exposure of rats as well as in vitro acute Pb^{2+} exposure of hippocampal cultures and slices has been reported to decrease the release of glutamate and γ-aminobutyric acid (GABA) (Lasley and Gilbert 2002; Braga et al. 1999b; Xiao et al. 2006).

7 Lead and LTP

The effects of Pb^{2+} on hippocampal LTP have been demonstrated since the early 1990s. Developmental Pb^{2+} exposure increases the threshold for hippocampal LTP induction, reduces the magnitude of potentiation, and accelerates its decay (reviewed

by Toscano and Guilarte 2005; Altmann et al. 1994; Gilbert and Mack 1998; Gilbert et al. 1999a, b). Animals exposed to Pb^{2+} from early life showed deficient excitatory postsynaptic potential (EPSP) as well as cellular (population spike) components of this field response, and these effects persisted to adulthood despite termination of Pb^{2+} exposure at weaning (Gilbert et al. 1996, a). Similar effects of Pb^{2+} exposure on LTP were also reported in hippocampal slices from exposed animals (Altmann et al. 1993; Sui et al. 2000). These data indicate that Pb^{2+} exposure reduced LTP magnitude and thus impaired the efficacy of the cellular mechanisms that support learning in the hippocampus (White et al. 2007). These Pb^{2+}-induced deficits in hippocampal LTP have been suggested to be associated with a reduction in Ca^{2+}-dependent glutamate release (Lasley and Gilbert 1996; Lasley et al. 2001). However, the induction of LTP in mossy fiber-CA3, which is dependent upon an increase in glutamate release, is not affected by Pb^{2+} exposure (Kawamura et al. 2004), while the induction of LTP at excitatory synapses that are not dependent on increased glutamate release but are NMDAR dependent (i.e., Schaffer collateral-CA1 LTP or perforant path-dentate gyrus LTP) is impaired in the Pb^{2+}-exposed brain. These results clearly indicate that Pb^{2+}-induced deficits in LTP are NMDAR-specific (Toscano and Guilarte 2005).

8 Lead, Calcium, and Glutamate Release

Pb^{2+} mimics Ca^{2+} and disrupts cellular calcium homeostasis as well as the role of Ca^{2+} as an important intracellular second messenger (Gorkhali et al. 2016). Voltage-sensitive calcium channels (VSCCs), which regulate Ca^{2+} influx, are essential for many neuronal processes such as neurotransmitter release (Kobayashi and Mori 1998). Pb^{2+} may affect neuronal functions in two ways, first by inhibiting the entry of Ca^{2+} into the cell, as Pb^{2+} is a very potent inhibitor of VSCCs (Audesirk 1993; Busselberg et al. 1993; Evans et al. 1991; Minnema et al. 1988). Second, Pb^{2+} itself may enter cells through Ca^{2+} channels and by mimicking Ca^{2+} may affect its functions (Reviewed by Loikkanen et al. 2003).

A dose-dependent reduction in glutamate release in animals developmentally exposed to Pb^{2+} has been reported (Gilbert and Lasley 2007). Chronic Pb^{2+} exposure beginning in utero or in the early post-weaning period and continuing throughout life alters presynaptic release of glutamate in the rat hippocampus. However, this Pb^{2+}-induced glutamate release appears to be dose-dependent. At lower Pb^{2+} levels, synaptic release of glutamate was diminished, and this effect was reversed at higher level of Pb^{2+} exposure (Lasley and Gilbert 2002). This biphasic dose response indicates the presence of more than one mechanism of Pb^{2+} action. Similar findings were reported from acute exposure of cultured hippocampal neurons to Pb^{2+} (Braga et al. 1999a, b). The diminished glutamate release at lower Pb^{2+} levels appears to be due to the blocking of VSCC by Pb^{2+}. The increased glutamate release at higher level of Pb^{2+} exposure suggests the diminution of the K^{+}-stimulated transmitter response (White et al. 2007), or through increased production of quinolinic acid (QA) (Rahman et al. 2018b). The loss of proteins involved in vesicular release,

namely, synaptophysin and synaptobrevin, is also involved in Pb^{2+}-induced modulation of transmitter release (Neal et al. 2010).

In addition, nicotinic modulation of synaptic transmission has also been implicated in Pb^{2+}-induced transmitter release (Nihei et al. 2000). Hippocampal neurons exposed to various concentrations of Pb^{2+} inhibited somatodendritic α4β2 nAChRs and α7 nAChRs and caused substantial inhibition of transmitter release. This effect was found to be due the direct interaction of Pb^{2+} with these receptors (Ishihara et al. 1995; Mike et al. 2000). It has also been hypothesized that Pb^{2+}-induced inhibition of nicotinic cholinergic modulation of action potential-dependent transmitter release is mediated by a PKC-dependent mechanism (Braga et al. 2004). It has been suggested that Pb^{2+} activates PKC which in turn phosphorylates nAChRs, proteins associated with the receptors, and/or proteins linking the receptors to the action potential-dependent transmitter release process. Direct phosphorylation of nAChRs by PKC has been shown to reduce receptor activity in sympathetic neurons (Downing and Role 1987). However, this hypothesis has been disputed by other investigators (Seguela et al. 1993; Moss et al. 1996; Fenster et al. 1999).

9 Lead and NMDA Receptor

NMDARs are one of the most important targets of Pb^{2+} (reviewed by Xu and Rajanna 2006). The observation that Pb^{2+} exposure during development affects NMDAR-dependent LTP (LTP dependent on increased glutamate release) but not NMDAR-independent LTP in hippocampus provided the first experimental evidence that Pb^{2+} targets NMDARs (Gutowski et al. 1998; Kawamura et al. 2004). Since then, several studies demonstrated that Pb^{2+} is a selective and potent non-competitive inhibitor of the NMDAR (Toscano and Guilarte 2005; White et al. 2007; Neal and Guilarte 2010; Neal et al. 2011). Pb^{2+} in micromolar concentration causes a reversible inhibition of the current activated by glutamate through the NMDAR channel in cultured and acutely dissociated neurons and reduces access to the NMDA receptor channel in brain tissue homogenates (Marchetti 2003; Lasley and Gilbert 1999). Decreased NMDA-specific glutamate receptor binding has also been reported in the brain of Pb^{2+}-exposed rats (Rajanna et al. 1997). A possible mechanism for this Pb^{2+}-induced inhibition of the NMDAR is the binding of Pb^{2+} at the zinc (Zn^{2+}) regulatory (inhibitory) site of the NMDAR in a voltage-independent manner (Lasley and Gilbert 1999).

The effect of Pb^{2+} on NMDA-activated current is dependent on developmental stages and NR subunit types (Ishihara et al. 1995; Omelchenko et al. 1997; Ujihara and Albuquerque 1992). In addition to acting as an NMDAR antagonist, Pb^{2+} exposure also disrupts normal NMDAR ontogeny. Pb^{2+}-induced changes in NMDAR subunits during development may form the basis for the effects of Pb^{2+}on synaptic plasticity and cognitive function (Reviewed by Lau et al. 2002). Developmental Pb^{2+} exposure has been shown to cause alterations in NR1 splice variant expression, NR2 subunit ontogeny, and NMDAR-dependent signalling (Neal et al. 2011). Adult rats exposed to Pb^{2+} during development and post-weaning into

adolescence suffered marked reductions in gene expression of the NR1 subunit of the NMDAR in the hippocampus (Monyer, et al. 1992). Chronic developmental Pb^{2+} exposure in animals is known to alter expression of NR1 splice variants (Guilarte and McGlothan 2003; Xy et al. 2002; Guilarte et al. 2000). The mechanism of these Pb^{2+}-induced deficits in NR1 is proposed to be the altered targeting and cell surface expression of NMDAR subunits to the synapse due to changes in NR1 splice variant expression. The lower levels of NR1 subunit mRNA expressed in the Pb^{2+}-exposed hippocampus are principally due to decreased levels of the NR1-4 and NR1-2 splice variants. A unique characteristic of these splice variants is that they lack the C1 cassette and impart the highest cell surface expression, PKC potentiation, and calcium kinetics to NMDAR complexes (Neal et al. 2011).

NR2A and NR2B are abundantly expressed in the hippocampus and may be involved in mediating Pb^{2+} toxicity (Guilarte and McGlothan 2003; Lau et al. 2002; Marchetti 2003; Nihei and Guilarte 1999, 2001; Nihei et al. 2000; Perez-Otano and Ehlers 2004; Toscano et al. 2002; Waters and Machaalani 2004). Chronic Pb^{2+} exposure alters the composition of the NR2 subunits of the NMDR in the rat brain (Nihei and Guilarte 1999). Specifically, developmental Pb^{2+} exposure in animals decreased expression of the NR2A subunit with no change or a small increase in NR2B subunit expression (Nihei et al. 2000; Nihei and Guilarte 1999; Zhang et al. 2002; Guilarte and McGlothan 1998; Toscano et al. 2002; Neal et al. 2011). Chronic Pb^{2+} exposure not only reduces NMDAR level but also prevents or delays the developmental switch of NR1/NR2B complex to NR1/NR2A complex with reduction of activity-dependent synaptic plasticity in the mature brain. During early development, NR2B-containing NMDARs predominate until a developmental switch occurs, resulting in the incorporation of the NR2A subunit (Monyer et al. 1994). It is suggested that this developmental switch from predominately NR2B-containing NMDARs to NR2A-containing NMDARs is delayed or impaired during Pb^{2+} exposure (Toscano et al. 2002; Toscano and Guilarte 2005).

These NR2 subunit specific effects of Pb^{2+} could be explained by the differential sensitivities of different subunits to Pb^{2+}. Gavazzo et al. (2008) have shown that Pb^{2+} interacts at the Zn^{2+} regulatory site of NMDAR complexes containing the NR2A but not the NR2B subunit. The NR2 subunits have different Zn^{2+} binding sites. NR2A-NMDAR binds Zn^{2+} at a high affinity (in nM range), while the NR2B-NMDAR binds Zn^{2+} with lower affinity (in μM range) (Paoletti et al. 2000; Rachline et al. 2005). These findings have been corroborated by the observations that recombinant NR1/NR2A complexes are more sensitive to Pb^{2+} inhibition than NR1/NR2B complexes (Omelchenko et al. 1996). Since Pb^{2+} and Zn^{2+} have similar potencies in inhibiting the NMDAR (Guilarte et al. 1995, 1994), it is likely that changes observed with NR2A-NMDARs but not NR2B-NMDARs may be a result of preferential inhibition of Pb^{2+} for NR2A-NMDARs (Guilarte et al. 1995; Gavazzo et al. 2008).

Furthermore, different concentrations of Pb^{2+} have differential influence on NMDAR subunits, and different subunits of NMDAR display different sensitivities to Pb^{2+}. A dose-dependent reduction by Pb^{2+} in NMDAR-NR1, NR2A, and NR2B protein levels has been reported (Lau et al. 2002). The rank order of sensitivity of

different subunits to Pb^{2+} inhibition has been reported as NR1A-NR2B > NR1A-NR2A > NR1A-NR2C (Gavazzo et al. 2001) and NR1B-NR2A > NR1B-NR2C > NR1B-NR2D > NR1B-NR2AC (Omelchenko et al. 1997).

Region-specific effects of Pb^{2+} on the expression of NR1 and NR2B subunits have also been reported. In cortical neurons, expression of NR1 was unchanged, but that of NR2B was significantly increased by Pb^{2+}. In contrast, expression of both NR1 and NR2B was significantly decreased in hippocampal neurons. Thus, it is likely that the toxic effects of Pb^{2+} may cause differential damage to different types of memory that are mediated by cortical and hippocampal neurons, respectively (Lau et al. 2002). Furthermore, both regional and developmental differences in the hippocampal neurons have been reported in Pb^{2+}-exposed rats. For example, the expression of NR1-2a mRNA in Pb^{2+}-exposed rats was significantly increased in areas CA1, CA4, and dentate gyrus (DG) at postnatal day (PND) 14–15 but in areas CA4 and DG at PND20–21 (Zhang et al. 2002; Guilarte and McGlothan 1998; Guilarte et al. 2000). On the other hand, Pb^{2+}-induced decreased expression of NR2A was observed in areas CA1, CA2, CA3, and DG at PND15 and areas CA1, CA3, and DG at PND20. Similarly, NR3A mRNA levels were also significantly decreased in CA1, CA4, and DG subfields at PND15 and CA1 and DG subfields at PND20 in Pb^{2+}-exposed rats (Zhang et al. 2002). These regional and developmental regulations of NMDAR mRNA splicing may lead to abnormality of natural NMDAR stoichiometry, control sensitivities to phosphorylation, and therefore kinetic properties of the NMDA channels and their involvement in LTP and synaptic plasticity (Zhang et al. 2002). Thus, this disruption of the ontogenetically defined pattern of NMDAR subunit expression and NMDAR-mediated calcium signalling in glutamatergic synapses appears to be the mechanism of Pb^{2+}-induced neurotoxicity and deficits in learning and memory. These changes are associated with deficits in LTP in the hippocampus and impairment of spatial learning (Nihei and Guilarte 2001; Toscano and Guilarte 2005; Zhang et al. 2002; Gilbert et al. 1996; Neal and Guilarte 2010).

10 Lead and NMDA Signalling

It has been reported that synaptic NMDARs mediate cAMP response element-binding protein (CREB) and extracellular signal-regulated kinases (ERK) activation, synaptic plasticity, and survival pathways. On the other hand, extra-synaptic receptors are associated with a CREB shut-off pathway, ERK inactivation, and induction of cellular death pathways (Hardingham et al. 2002; Vanhoutte and Bading 2003; Ivanov et al. 2006). Changes in NMDAR subunit composition can result in altered NMDAR-dependent signalling. Many signalling pathways are dependent on NMDAR subunit composition and/or localization. Pb^{2+}-induced alterations in NMDAR subunit composition could interfere with the downstream signalling pathways including MAPK signalling (Cordova et al. 2004), calcium/calmodulin kinase II (CaMKII) activity (Toscano et al. 2005), protein kinase C (PKC) activity (Bressler et al. 1999), and CREB phosphorylation status and binding affinity (Toscano et al.

2002, 2003). CREB is a transcription factor for many NMDAR activity-dependent immediate early genes (IEGs), which play an essential role in memory consolidation (Athos et al. 2002; Bourtchuladze et al. 1994). Thus, CREB plays an important role in signal propagation from synapses to the nucleus by linking NMDAR activation and calcium-dependent signalling to the expression of genes necessary for synaptic plasticity (Bredt et al. 1992). Altered IEG expression in animals exposed to Pb^{2+} has been observed (Kim et al. 2002), indicating that altered CREB activity due to Pb^{2+}-mediated disruption of NMDAR signalling may result in impaired learning and memory processes.

CREB phosphorylation is an important element of LTP. Induction of LTP (and learning) increases CREB phosphorylation (Mizuno et al. 2002; Schultz et al. 1999; Viola et al. 2000), whereas pharmacological inhibition of NMDAR-mediated signalling decreases CREB phosphorylation (Athos et al. 2002). CREB phosphorylation at serine-133 facilitates the recruitment of CREB-binding proteins and the assembly of transcriptionally active complex at the start site of CRE-containing genes (Chirivia et al. 1993). Pb^{2+} exposure decreases CREB phosphorylation without affecting the total CREB levels and alters the ability of CREB family proteins to bind with CRE (Toscano et al. 2003), suggesting that the phosphorylation of CREB at serine-133 and the binding ability of CREB family proteins may be altered by Pb^{2+} exposure. This may affect the transcription of genes associated with learning, memory, and synaptic plasticity.

11 Lead and BDNF Signalling

Another potential signalling pathway that may be involved in Pb^{2+}-induced neurotoxicity is impaired NMDAR-dependent retrograde signalling of neurotrophic factors, particularly of brain-derived neurotrophic factor (BDNF). Pb^{2+}-exposed hippocampal neurons exhibit reduced proBDNF expression and BDNF release. Furthermore, complete recovery of Pb^{2+}-induced changes in presynaptic protein levels and vesicular neurotransmitter release has been reported in hippocampal neurons incubated with exogenous BDNF (Neal et al. 2010). Retrograde BDNF signal from the postsynaptic side has been implicated in axon morphology, synaptic connectivity, and synaptic ultrastructure (Neal and Guilarte 2010; Neal et al. 2010). NMDAR activation results in the generation and release of BDNF (Hartmann et al. 2001; Jiang et al. 2005; Walz et al. 2006), which may be essential to the generation or un-masking of presynaptic neurotransmitter release sites (Walz et al. 2006). BDNF signalling is known to modulate the expression of several pre- and postsynaptic proteins (Pozzo-Miller et al. 1999; Tartaglia et al. 2001). Of particular interest is the enhancement of NR2A expression but not the expression of NR2B in hippocampal slices exposed to exogenous BDNF (Small et al. 1998; Caldeira et al. 2007). These results are further supported by the reduced expression of NR2A but not the NR2B subunit and reduced vesicular release in BDNF knockout mice (Margottil and Domenici 2003). These observations suggest that NR2A-NMDARs may be preferentially linked to BDNF signalling. The altered expression NR2A subunit by both

Pb^{2+} exposure and impaired BDNF signalling strongly supports the hypothesis that the disruption of NMDAR activity-dependent BDNF signalling is involved in Pb^{2+}-induced toxicity in synapses (Neal et al. 2010).

12 Lead and Other Brain Cells

Most of the work on Pb^{2+}-induced neurotoxicity has focused on neuronal cells. Other support cells, which are several folds greater in number than neurons and regulate/modulate the function of neurons, may also be affected by Pb^{2+} and thus may be involved in Pb-induced neurotoxicity. Of the support cells, astroglia are capable of uptaking 14-fold more Pb^{2+} than neurons. The uptake of Pb^{2+} by astroglia is suggested to be through voltage-dependent Ca^{2+} channels (Simons and Pocock 1987). This Ca^{2+}-dependent uptake of Pb^{2+} by astroglia may be induced by their interaction with neurons (Tiffany-Castiglioni 1993; Lindhal et al. 1999) and may involve glutamate-dependent increase in intracellular Ca^{2+} (Cornell-Bell et al. 1990). The accumulation and storage of Pb^{2+} in astroglia may be a mechanism of protection for neurons which are more sensitive than astroglia to the toxic effects of Pb^{2+} (Holtzman et al. 1987; Tiffany-Castiglioni et al. 1986; Tiffany-Castiglioni 1993). On the other hand, such storage of Pb^{2+} in astroglia may provide a reservoir for its continuous release and thereby may contribute to the toxicity of adjacent neurons or astroglia themselves (Struzynska 2009).

13 Lead and Metabotropic Glutamate Receptors

Of the metabotropic glutamate receptor, mGluR5 has also been linked to Pb^{2+}-induced deficits in learning and memory. The impact of developmental Pb^{2+} exposure on hippocampal mGluR5 expression and its potential role in Pb^{2+}-induced neurotoxicity has been investigated both in vitro and in vivo (Xu et al. 2009a, b). Decreased expression of mGluR5 mRNA and protein by Pb^{2+} dose-dependently suggests that mGluR5 might be involved in Pb^{2+}-induced neurotoxicity. Impairment of mGluR5-dependent LTD (Huang and Hsu 2006) and decreasing NMDAR-dependent or protein synthesis-dependent long-term potentiation have been hypothesized as potential mechanisms of Pb^{2+}-induced neurotoxicity (Toscano and Guilarte 2005; Topolnik et al. 2006; Manahan-Vaughan et al. 2003; Manahan-Vaughan and Braunewell 2005; Naie and Manahan-Vaughan 2004; Neyman and Manahan-Vaughan 2008).

14 Protein Phosphatases and Lead-Induced NMDAR-Dependent Neurotoxicity

The major serine/threonine (Ser/Thr) protein phosphatases (PPs) in mammalian brain are PP1, PP2A, and PP2B (Liu et al. 2005). Overactivation/overexpression of these Ser/Thr PPs has been implicated in impairment of learning and memory.

PPs are strong molecular constraints on learning and memory (Lee and Silva 2009). PPs are also involved in cognitive decline in aging (Mansuy and Shenolikar 2006; Knobloch et al. 2007) and in favoring forgetting (Genoux et al. 2002). Overactivation of PP1 is associated with learning and memory impairment (Genoux et al. 2002; Koshibu et al. 2009; Graff et al. 2010; Haege et al. 2010; Genoux et al. 2011; Koshibu et al. 2011). PP2A and PP2B also adversely affect learning and memory (Bennett et al. 2003; Havekes et al. 2006; Yamashita et al. 2006; Mauna et al. 2010; Oberbeck et al. 2010). Overactivation of PP2A induces LTD in vivo (Thiels et al. 1998), and inhibition of PP2A abrogates LTD induction (Mauna et al. 2010).

Whether the overactivation/overexpression of these PPs is involved in Pb^{2+}-induced impairment of learning and memory has not been thoroughly investigated, but the few studies available on this topic suggests a role of PPs in Pb-induced neurotoxicity. In the cultured human fetal neurons exposed to physiologically relevant concentration of Pb^{2+}, a significant increase in total PPs and PP2A activities was observed. Pb^{2+} exposure significantly increased the expression of PP1 and PP2B but significantly decreased the expression of PP2A and PP5 in cultured human fetal neurons (Rahman et al. 2011). In rats exposed to Pb^{2+} during early development, learning, short-term memory (STM), and long-term memory (LTM) were significantly impaired at PND 21, and this impairment of learning and LTM was associated with decreased synaptogenesis and increased expression and activities of PP1 and PP2A in the hippocampus. On the other hand, at PND 30, learning and short-term memory (STM), but not the LTM, were impaired by Pb^{2+}. At this developmental stage, expression and activity of hippocampal PP1 were increased, but that of PP2A was decreased. These results suggest that increased PP1 activity in hippocampus is involved in the impairment of learning and LTM, whereas increased PP2A activity is involved in the impairment of STM (Rahman et al. 2012a, b).

LTM involves protein synthesis, growth, and formation of new synapses (Martin et al. 1997; Ma et al. 1999; Toni et al. 1999; Bozdagi et al. 2000; De Roo et al. 2008). By contrast, STM involves covalent modification of proteins in the presynaptic or postsynaptic structures (Kandel 2001; Malinow and Malenka 2002). The major covalent modification underlying these long-lasting changes in synaptic communication is protein phosphorylation, which is regulated by a balance between protein kinases (PKs) and PPs. Increased activity of PKs results in increased protein phosphorylation which has been implicated in LTP. On the other hand, increased activity of PPs results in decreased protein phosphorylation, which has been implicated in LTD (Roberson et al. 1996; Winder and Sweatt 2001; Blitzer et al. 2005). Reversible protein phosphorylation regulates presynaptic and postsynaptic events in excitatory and inhibitory neurons. The major substrates for PPs at these synaptic sites include ligand-gated ion channels and G-protein-coupled receptors, whose functional properties, trafficking, and synaptic organization are controlled by reversible phosphorylation (Swope et al. 1999).

Several mechanisms have been proposed to explain the role of PPs in learning and memory. These include dephosphorylation and the subsequent deacetylation of histone proteins and chromatin remodeling and altered expression of CREB and

NF-κB (Kandel 2001; Fischer et al. 2007; Miller et al. 2008; Koshibu et al. 2009, 2011; Oberbeck et al. 2010). Both PP1 and PP2A dephosphorylate CREB (Mauna et al. 2010) and thereby reduce CREB-mediated gene expression (Wadzinski et al. 1993; Alberts et al. 1994; Genoux et al. 2002; Oberbeck et al. 2010). Other mechanisms include dephosphorylation by PP1 and PP2A of NMDAR and MAPK (Chan and Sucher 2001; Oberbeck et al. 2010), calcium-/calmodulin-dependent protein kinase IV (CaMKIV) (Westphal et al. 1998; Anderson et al. 2004), ERK (Davis et al. 2000; Norman et al. 2000; Silverstein et al. 2002; Ho et al. 2007), and the AMPA receptor (Thiels et al. 2002).

Of particular significance in the Pb^{2+}-induced excitotoxicity is the dephosphorylation and subsequent inhibition of the NMDAR-associated signalling pathways. Protein phosphorylation has been established as an important mechanism for the regulation of NMDAR function. LTP is accompanied by increased glutamate receptor phosphorylation through various protein kinases and a concomitant decrease in protein phosphatase activity (Bliss and Collingridge 1993; Mulkey et al. 1993; Soderling and Derkach 2000). In contrast, LTD has been shown to be dependent on glutamate receptor dephosphorylation mediated by an increase in the activity of protein phosphatases, possibly PP1 and PP2A (Lee et al. 1998, 2000; Thiels et al. 1998). Thus, coordination of kinase and phosphatase activities is crucial for the modulation of synaptic plasticity. Both kinases (PKA) and phosphatases (PP1 and PP2A) are located in physical proximity to NMDAR (Chan and Sucher 2001). Synaptic NMDARs are phosphorylated or dephosphorylated depending on synaptic stimulation. Phosphorylated NMDARs have enhanced channel openings and a consequent increase in Ca^{2+} influx, and this influx is necessary for inducing long-term neuronal changes (Levitan 1999; Prybylowski and Wenthold 2004; Raymond et al. 1994; Roche et al. 1994). Following excitatory neurotransmission and Ca^{2+} influx, NMDARs are phosphorylated by PKA and then rapidly dephosphorylated by PP1, PP2A, or PP2B. This reversible phosphorylation controls synaptic strength, memory formation, and storage by the induction of LTP or LTD (Blitzer et al. 2005). Several PKs, including CaMKII, PKC, PKA, and ERKs, have been implicated in LTP induction and maintenance, whereas PPs are implicated in the induction of LTD. Previous studies have shown that LTD is dependent on the change of the phosphorylation state of glutamate receptors in general (Lee et al. 1998, 2000) and the activity of PPs, particularly PP1 and PP2A (Mulkey et al. 1993, 1994; Thiels et al. 1998). Stimulation of NMDAR activates PP1, PP2A, and PP2B whose substrate specificity is primarily determined through interaction with regulatory and targeting proteins (Mansuy and Shenolikar 2006).

NMDAR activity is attenuated by PP1, PP2A (Wang et al. 1994), and PP2B (Mulkey et al. 1994; Wang and Kelly 1997). PP1 diminishes NMDAR-mediated synaptic currents in an activity-dependent manner in the hippocampus (Wang et al. 1994; Westphal et al. 1999). PP1 and PP2A appear to decrease the single channel open time in cultured rat hippocampal neurons and thus reduce NMDAR activity (Wang et al. 1994), with PP1 having a more prominent role than PP2A in dephosphorylating the NMDAR.

Both positive and negative effects of PP2B on glutamate receptor functions have been reported. PP2B reduces NMDAR-mediated currents by dephosphorylating the NR2A subunit of the NMDAR and reduction of the open time of individual channels (Lieberman and Mody 1994) and desensitization of the receptor (Krupp et al. 2002; Tong et al. 1995). On the other hand, PP2B has been reported to potentiate NMDAR-induced metabotropic mGluR5 receptor activity by dephosphorylating PKC-dependent sites on the mGluR5 C terminus and attenuating mGluR5 desensitization (Alagarsamy et al. 2005). PP2B-mediated dephosphorylation also contributes to the developmental switch of NMDAR subunits and thus modulates NMDAR subunit composition. In the developing cerebellum, it counteracts the TrkB- and ERK1/2-dependent upregulation of the NR2C subunit, which then exchanges with NR2B to promote synaptic transmission from mature mossy fibers onto granule cells (Suzuki et al. 2005).

The role of PP2A in NMDAR regulation and functioning has been well studied and best understood. There are intriguing functional similarities between PP2A and NMDAR. Both contribute to the regulation of neural functions such as synaptic transmission and plasticity. Immunoprecipitation studies indicated that the carboxyl domain of NR3A subunit of NMDAR forms a stable complex with the catalytic subunit of PP2A in the rat brain in vivo (Chan and Sucher 2001). Further studies demonstrated that NR3A constitutively associates with the PP2A holoenzyme, but not the core enzyme in rat brain synaptic plasma membranes. A sequence of six amino acids between leucine 958 and histidine 974 of the NR3A is critical for binding to PP2A, as deletion or mutation of this sequence disrupted the NR3A-PP2A interaction (Ma and Sucher 2004). Association of PP2A with NMDAR leads to an increase in the activity of PP2A and the dephosphorylation of serine 897 of the NMDAR subunit NR1. Stimulation of NMDAR leads to the dissociation of PP2A from the complex and the reduction of PP2A activity (Chan and Sucher 2001).

The NR1 subunit is phosphorylated by both PKA and PKC (Tingley et al. 1997). PKA is associated with NMDAR through the scaffold protein yotiao (Westphal et al. 1999), and this NMDAR-associated PKA has been shown to phosphorylate the Ser-897 of NR1 (Chan and Sucher 2001). PP2A associated with NR3A dephosphorylates this serine residue of NR1. PP1 has also been shown to be associated with NMDAR through the same scaffold protein. These PP2A- (and possibly, PP1-) induced changes in phosphorylation of NR1 decrease NMDA currents through the attenuated opening of the NMDAR-gated channels (Wang et al. 1994). PP2A may also indirectly modulate the phosphorylation of NR1 subunits by modulating the function of PKC. It has been reported that PP2A dephosphorylates and inactivates PKC in vitro and inhibition of PP2A by okadaic acid prevents dephosphorylation of PKC and enhances the function of PKC (Hansra et al. 1996; Millward et al. 1999; Ricciarelli and Azzi 1998).

In addition to NR1, PP2A is also known to dephosphorylate NR2B subunit. It is known that CaMKII binds to the C-terminal region of the NR2B subunit of NMDAR and phosphorylates it at Ser-1303 (Mayadevi et al. 2002). PP2A may regulate the phosphorylation of this site of NR2B subunits by modulating the function of CaMKII. CaMKII autophosphorylated at Thr-286 is active, whereas the activity is

decreased by dephosphorylation of this site (Colbran 2004; Otmakhov et al. 2004). CaMKII autophosphorylated at Thr-286 was first reported to be exclusively dephosphorylated by PP1 in isolated synaptosomes (Shields et al. 1985).

15 Metallothionein and Lead-Induced Excitotoxicity

Metalloproteinsplay critical roles in the normal physiology of the cell. Toxic heavy metals, including Pb^{2+}, can displace essential metals from the metal-binding sites of various critical metalloproteins and enzymes in the cell (Pérez-Zúñiga et al. 2018; Basha et al. 2003) and may result in either the loss or gain of function of essential metal-binding protein/enzyme (Gorkhali et al. 2016; Mattiasson et al. 1978; Goering 1993; Sharma et al. 2008). One of the protective mechanisms adopted by living organisms against these toxic metals is to sequester heavy metals through thiol-rich proteins or peptides such as metallothionein (MT) (Sharma et al. 2008; Stillman 1995; Hirata et al. 2005). Mammalian MTs are cysteine-rich peptides (approximately 60 amino acids with one-third of amino acids as cysteine). The sulfhydryl (thiol) groups in the cysteine side chain sequester metal ions (Asano et al. 2010). MT gene expression is upregulated in response to a variety of physical (cold exposure, strenuous exercise) and chemical (heavy metals, certain hormones, free radicals, and irradiation) insults (Aschner 1996; Miles et al. 2000). Four isoforms of MT have been identified (MT-1 to MT-4). Of these, MT-3 is CNS specific, MT-1 and MT-2 have a wider tissue expression pattern, and MT-4 is mainly expressed in the skin epithelial cells (Pérez-Zúñiga et al. 2018; Erickson et al. 1997). In the CNS, MT-1 and MT-2 are mainly expressed by astrocytes and spinal glia and are almost absent from neurons (Hidalgo et al. 2001; Tokuda et al. 2007). MT-3, on the other hand, is abundantly expressed in neurons and astrocytes (Hozumi et al. 2008) and plays a significant role in Zn homeostasis (Frazzini et al. 2006).

In addition to the sequestration of toxic heavy metal, mammalian MTs have several physiological functions. These include homeostasis of essential metal ions like copper (Cu^{2+}) and Zn^{2+} (Erickson et al. 1997; Vasak and Meloni 2017) and the modulation of glutamate and GABA signalling in neurons and astrocytes (Aschner 1996). MT-3 also has growth inhibitory effects and is reported to inhibit neurite outgrowth (Palmiter 1994; Palmiter et al. 1992; Palmiter and Erickson 1996; Uchida et al. 1991). As such it has been implicated in the neuropathology of neurodegenerative diseases.

High levels of MT-3 can affect brain function in three ways. First, MT-3 can affect neuronal function through modulating Zn^{2+} homeostasis. Zn^{2+} plays a crucial role in modulating glutamatergic and GABAergic signalling in neurons (Cuajungco and Lees 1997). MT-3 is abundantly expressed by the Zn^{2+}-containing neurons in the hippocampus, the piriform cortex, and the amygdala. The mossy fiber projections of the dentate granule cells contain the highest concentration of Zn^{2+} in the brain. MT-3, in Zn^{2+}-containing neurons or neurons exposed to high concentrations of Zn^{2+}, is proposed to play an essential role in the distribution, recycling, or buffering of Zn^{2+} in these neurons (Palmiter et al. 1992; Masters et al. 1994; Ashner 1996;

Palmiter and Erickson 1996). Some of the MT-3 expressing neurons are glutamatergic (pyramidal cells of the hippocampus and the granule cells of the dentate gyrus), whereas others are GABAergic (Purkinje cells of the cerebellar cortex). It is believed that the concomitant release of Zn^{2+} along with glutamate or GABA at neuronal synapses modulates the activity of these neurotransmitters (Fredrickson and Moncrief 1994). MT-3 may also function to sequester Zn^{2+} from the synapse, maintaining homeostatic control over neurotransmitter levels within the synaptic cleft. Second, overexpression of MT-3 may result in decreased number of neurites and subsequently reduced number of synapses, as MT-3 has been shown to inhibit neurite outgrowth (Palmiter 1994, 1995; Palmiter et al. 1992; Palmiter and Erickson 1996; Uchida et al. 1991). Third, by sequestering essential metal ions (Cu^{2+}, Mn^{2+}, and Zn^{2+}), high levels of MT-3 can result in lower activities of several metal-dependent enzymes in the brain.

Zn^{2+} is released at glutamatergic synapses in response to depolarization and acts through the ionotropic glutamate receptors (Palmiter 1994). Neuronal response to Zn^{2+} depends on its concentration and the receptor subtype. At lower concentration, it potentiates the activities of AMPA and KA receptors, whereas at higher concentrations (>100 μM), it inhibits the activities of both receptors (Fredrickson and Moncrief 1994). On the other hand, Zn^{2+} inhibits the activities of NMDA and GABA receptors (Fredrickson and Moncrief 1994). It has been suggested that MT-3 serves as a neuromodulator through regulating Zn^{2+} homeostasis in neurons (Palmiter et al. 1992; Fredrickson and Moncrief 1994).

The effect of Pb^{2+} exposure on the expression of MTs (MT-1/MT-2) in other tissues, particularly the liver and kidney, has been well documented (Ikebuchi et al. 1986; Tokuda et al. 2007; Wang et al. 2009; Nakao et al. 2010; Gillis et al. 2012; Peterson et al. 2011; Dai et al. 2013; Nascimento et al. 2016). A more than threefold increase in the expression of MT genes was observed in cultured human peripheral blood mononuclear cells in response to Pb^{2+} exposure (Gillis et al. 2012). Intracerebral administration of Pb^{2+} resulted in significantly increased expression of MTs (Nakao et al. 2010). However, the effect of Pb^{2+} expossure on the expression of MT-3 in the brain is not well studied. A recent study reported the overexpression of MT-3 in the hippocampus, thalamus, and cerebral cortex of Wistar rats exposed to Pb^{2+} during the pre-weaning period (Rahman et al. 2018a). Whether MT-3 overexpression has any direct role in Pb^{2+}-induced impairment of learning and memory remains to be investigated. The reduced number of synapses in a similar model of Pb^{2+}-exposed rats supports a role of MT-3 overexpression in Pb^{2+}-induced neurotoxicity (Rahman et al. 2012b). In the brain, Pb^{2+} binds with MT-3 with higher affinity than Zn^{2+} (Pérez-Zúñiga et al. 2018; Carpenter et al. 2016; Wong et al. 2017). During Pb^{2+} toxicity, Pb^{2+} may replace Zn^{2+} from MT-3 and as such may affect brain function by interfering with normal glutamate and GABA signalling. The displacement of Zn^{2+} by Pb^{2+} has been recently confirmed (Pérez-Zúñiga et al. 2018). Pb^{2+} is also known to displace Zn^{2+} in several Zn^{2+}-finger proteins. These include DNA methyltransferase 1, presenilin 1 and 2, dopamine receptor, NMDA receptor, zinc finger protein 804A, and disrupted-in-schizophrenia 1-binding zinc finger. Such modulation of these zinc finger proteins by Pb^{2+} has been implicated in

Alzheimer's disease, Parkinson's disease, and schizophrenia (Ordemann and Austin 2016). Therefore, overexpression of MT-3 in the brain may be one of the potential mechanisms of Pb^{2+}-induced neurotoxicity and impairment of learning and memory.

16 Quinolinic Acid in Lead-Induced Excitotoxicity

Under physiological conditions, brain's tryptophan is metabolized by the serotonin/melatonin pathway and to a lesser extent by the kynurenine pathway (KP) converting it into nicotinamide adenine dinucleotide (NAD^+) (Lovelace et al. 2017). However, during neuroinflammation, approximately 95% of the brain's tryptophan is catabolized through the KP to produce several other metabolites with neuroactive properties (Guillemin 2012). Of these, quinolinic acid (QA) is an NMDAR agonist and a known neuro- and gliotoxin (Guillemin 2012). Increased levels of QA are implicated in several neurodegenerative diseases such as Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, AIDS dementia, depression, and schizophrenia (Guillemin 2012; Guillemin et al. 2005a, b; Lim et al. 2017a, b; Chen et al. 2010; Steiner et al. 2011; Rahman et al. 2009; Colín-González et al. 2015).

QA is toxic to astrocytes (Lee et al. 2010), oligodendrocytes (Sundaram et al. 2014), and neurons (Kerr et al. 1998; Chen et al. 2011), particularly in the hippocampus, striatum, and neocortex (Guillemin 2012). QA-induced apoptosis has also been reported in these cells (Cammer 2002; Guillemin et al. 2005a, b; Kelly and Burke 1996). The mechanisms of QA-induced neurotoxicity include direct activation of the NMDAR and the subsequent excitotoxicity, increasing the levels of extracellular glutamate and its related excitotoxicity, increased oxidative stress and lipid peroxidation, stimulation of protease activity and apoptosis, destabilization of the cytoskeleton, and energy depletion (Guillemin 2012; Colín-González et al. 2015; Rahman et al. 2009; Muller et al. 2007; Santamaría et al. 2001; Pierozan et al. 2010). QA can increase glutamate release by neurons, inhibit its uptake by astrocytes, and inhibit astroglial glutamine synthetase, leading to excessive microenvironment glutamate concentrations and neurotoxicity. It was also recently demonstrated that QA is transported by the excitatory amino acid transporter 3 (EAAT3) and then accumulates in neurons (Braidy et al. 2020). The major and rate-limiting enzyme of the KP, indoleamine-2,3-dioxygenase-I (IDO-I), is expressed in astrocytes, microglia, and neurons. The expression of IDO-I is increased by inflammatory mediators and cytokines such as amyloid peptides, lipopolysaccharides (LPS), interlukin-1β (IL-1β), interlukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interferon gamma (IFN-γ) (Lovelace et al. 2017; Guillemin et al. 2003a, b). The other major enzyme of the KP that converts kynurenine (the first stable metabolite of KP) into QA is kynurenine 3-monooxygenase, which is also abundantly expressed in microglia, macrophages, and monocytes. The expression of this enzyme is also upregulated by pro-inflammatory mediators (Jones et al. 2015). Thus, a pro-inflammatory environment highly favors the generation of QA in the brain. In addition to the local activation of the KP and synthesis of QA in the CNS,

kynurenine produced systemically can cross the blood-brain barrier and can be converted into QA within the CNS (Vécsei et al. 2013).

Both Pb^{2+} and QA share several features of neurotoxicity. For example, both Pb^{2+} and QA impair learning and memory (Rahman et al. 2012b; Misztal et al. 1996a, b; Furtado and Mazurek 1996), destabilize the cytoskeleton (Rahman et al. 2009, 2012a), trigger oxidative stress (Lovelace et al. 2017; Jones et al. 2015; Pierozan et al. 2012), and increase synaptic glutamate levels (Guillemin 2012; Braga et al. 1999b). Pb^{2+}, a pro-oxidant metal, may increase QA levels by microglial and astroglial activation and may increase the expression of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, and IFN-γ) (Liu et al. 2012, 2015; Sobin et al. 2013; Kumawat et al. 2014). These cytokines are known to activate the KP and increase production of QA (Lovelace et al. 2017; Jones et al. 2015; Guillemin et al. 2003a, b). Pb^{2+} is thus expected to increase the brain levels of QA, which subsequently may cause excitotoxicity. This hypothesis was recently tested in a rat model in which exposure of rat pups to Pb^{2+} during early postnatal period increased the levels of QA in the blood (by ~58%) and increased the number of QA-immunoreactive cells in the cortex and CA1, CA3, and dentate gyrus regions of the hippocampus (Rahman et al. 2018b). In further studies, it was shown that infusion of QA into the brain produced behavioral and biochemical abnormalities similar to Pb^{2+} exposure. These results support the hypothesis that increased QA production in response to Pb^{2+} exposure is involved in learning and memory impairment. These studies were further supported by the observations that the toxic effects of both Pb^{2+} and QA in cultured hippocampal neurons could be mitigated by treatment with memantine, an NMDAR antagonist (Rahman et al. 2019). Neuroprotection with memantine from both Pb^{2+} and QA suggests a common mechanism of excitotoxicity through NMDAR activation. Alternatively, it is possible that Pb^{2+} exerts its neurotoxic effects through QA. The reported finding that Pb^{2+} exposure increases the levels of QA in rats supports the notion that Pb^{2+} exerts its neurotoxic effects, at least in part, through increased QA production. This hypothesis appears to contradict the earlier reported findings in which Pb^{2+} exposure was shown to lower the NMDAR function and LTP (Neal and Guilarte 2010; Neal et al. 2011). This apparent contradiction, however, can be explained by the differential effects of Pb^{2+} at different concentrations and different NMDAR subtypes. It has been reported that the effect of Pb^{2+} on NMDAR is dose- and NMDAR-type dependent. At lower concentrations ($<1\ \mu M$), Pb^{2+} acts as an agonist of NR1-2AB and NR1-2AC receptors, whereas at higher concentrations, it inhibits NR1-2AB and NR1-2AC receptors, but with less potency compared to NR1-2A or NR1-2B (Omelchenko et al. 1996, 1997).

Increased production of QA by Pb^{2+}, mechanistically, seems logical. Pb^{2+}, a pro-oxidant metal, may increase QA production by microglial activation. Microglial activation in the brain, particularly in the hippocampus, has been reported in Pb-exposed rats and mice. This microglial activation was associated with increased expression of pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α (Liu et al. 2015; 2012; Sobin et al. 2013; Kasten-Jolly et al. 2011; Struzynska et al. 2007; Baranowska-Bosiacka et al. 2012; Sansar et al. 2011). Similarly, in vitro exposure to Pb^{2+} of BV-2 mouse microglia resulted in increased expression of pro-inflammatory cytokines and chemokines (TNF-α, IL-6, MCP-1) and the pro-inflammatory enzyme COX-2 (Kumawat et al.

2014). Activation of TLR4-MyD88-NFkB signalling cascades has been suggested as the mechanism of increased expression of pro-inflammatory cytokines (Kumawat et al. 2014; Pomilio et al. 2016). Furthermore, QA, a pro-oxidant, may further increase microglial activation and increased QA production through a positive feedback loop. Furthermore, Pb^{2+} is reported to increase the spontaneous release of glutamate from the presynaptic terminals of rat hippocampal neurons in a concentration-dependent manner (Braga et al. 1999b). This increased glutamate release is likely to be caused by increased QA production/synthesis induced by Pb^{2+} exposure. A non-receptor-mediated mechanism of QA-induced cytotoxicity has also been suggested in which QA is reported to form a complex with Fe^{2+}, and this QA-Fe^{2+} complex enhances hydroxyl radical production (Pláteník et al. 2001). A similar QA-Pb^{2+} complex may be more cytotoxic than either of these alone by enhancing free radical generation by the QA-Pb^{2+} complex. The synergistic toxic effects of both QA and Pb^{2+} in cultured hippocampal neurons (Rahman et al. 2019) support this hypothesis.

17 Conclusion

The literature reviewed above clearly indicates that our knowledge about the mechanism of Pb^{2+}-induced neurotoxicity is still patchy and there is a need to put these isolated pieces of information together to understand how the pathway(s) involved in learning and memory are affected by Pb^{2+}. The excitotoxic effects of Pb^{2+} appear to be multifaceted, and Pb^{2+} is likely to act in coordination with other modulator of excitotoxicity like glutamate, MT-3, QA, protein phosphatases, and Zn^{2+}. The in vitro protective effect of memantine against Pb^{2+} toxicity in cultured neurons is an interesting observation which needs to be tested in animal models.

18 Cross-References

▶ Ionotropic Receptors in the Central Nervous System and Neurodegenerative Disease
▶ Manganese Neurotoxicity
▶ Pathogenesis of Alzheimer's Disease
▶ Quinolinic Acid and Related Excitotoxins: Mechanisms of Neurotoxicity and Disease Relevance
▶ The NMDA Receptor System and Developmental Neurotoxicity

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