A Review of the Pb-induced Impairment of Learning and Memory in Developing Rats

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**Introduction**

Lead (Pb+2) is a neurotoxicant which adversely alters neurodevelopmental processes in developing brains (White, Diamond, Proctor, Morey & Hu, 1993). Developing brains are remarkedly vulnerable to even low levels of lead because it is found that subsequent Pb+2 toxicity produces cognitive impairments (White et al., 1993). Nonetheless, young children continue to experience high rates of lead-poisoning (Meilke, 1999). The Hippocampal CA1 region is a key brain site for learning and memory. One cellular mechanism for learning and memory is Long-Term Potentiation (LTP) in hippocampal CA1 pyramidal neurons. Particularly, the activation of N-methyl D-Aspartate Receptors (NMDA) and the subsequent calcium influx are required for the induction of LTP within this hippocampal region (Zhao et al., 2018). NMDA receptors are an ionotropic subtype of the glutamate receptor and calcium, the main signaling ion for the body, is the principal ion for the NMDA receptors. However, lead poisoning is particularly detrimental because the hippocampal CA1 brain region of a developing brain is particularly vulnerable to low levels of Pb+2 exposure. Research has proposed that Pb+2 binds to the zinc (Zn+2) regulator site on NMDA receptors (Alkondon, Costa, Radhakrishnan, Aronstam, & Albuquerque, 1990). While there is debate as to which type of interaction occurs between Pb+2 and the NMDA receptor, it is shown that Pb+2 selectively inhibits the conductance of the calcium current through the NMDA receptor (Neal & Guilarte, 2010). As a result, electrophysiological studies show that Pb+2 impairs the NMDA receptor-dependent induction of LTP (Wang et al., 2016). This literature review primarily supports the correlation between decreased hippocampal pyramidal neurons and reduced cognitive function in rats with low-level lead exposure. However, I will also explore how both the Pb-induced inhibition of LTP in hippocampal pyramidal neurons and the inactivation of NMDA receptor can partially contribute to the cognitive deficits and morphological changes observed in exposed humans and animals.

Research on Pb+2 toxicity began in the 1990s, and studies show that infants and young children are at risk of exposure to harmful levels of Pb+2 in their daily environments (Brody et al., 1994). As a result, the time of lead exposure is a factor in whether the produced cognitive and behavioral effects can be reversed in these young children. The 3 main time periods of exposure are perinatal (in uterine), early developmental (gestation to lactation), and late developmental (juvenile to adult) (Wang et al., 2016). It is unethical to experimentally study the neurodevelopmental effects of lead exposure in humans because the Institutional Review Board (IRB) has mandated regulations and restricts clinical research from exposing human subjects to toxic substances. Nonetheless, animal laboratory paradigms produce results that closely translate to humans when relevant doses and experimental conditions are applied. The ethical study of low-level lead-exposure in animal subjects also allows researchers to experimentally manipulate the Pb+2 level, the type of cognitive process targeted, and the time of exposure. This subject is important because Pb+2 is an environmental toxicant that produces detrimental alterations in developing brains and potentially permanent cognitive deficits. In addition, child exposure to Pb+2 and neurotoxicity occurs disproportionally in low-income communities. As a result, research on this subject may help to attenuate the lifelong educational and social burdens produced by developmental Pb+2 exposure (Brody et al., 1994).

My aim with this literature review is to investigate the impairment of learning and memory associated with Pb+2 toxicity in developmental stages. My approach is to complete a comprehensive summary of the current state of research out there on the cognitive effects observed in animal subjects exposed to low levels of lead. Due to the broad impact of Pb+2 on neurodevelopment, this paper focuses on two of the neurodevelopmental effects mainly observed with Pb+2 toxicity: morphology via structural changes in brain regions and functional plasticity via decreased synaptic transmissions (Zhao et al., 2018). I will present literature in detail on these two developmental effects. My literature review analyzes the morphological change in brains, the proposed type of learning affected, and additional plasticity mechanisms observed in developing rats with lead neurotoxicity. Ultimately, the data collected from these neurodevelopmental studies will help to restore normal functioning in already affected children and protect future children and families.

**1. Markers of Pb-induced Cognitive Deficits**

If a young child is exposed to lead during development, they have an increased chance to develop Pb+2 toxicity and, thus, to be subjected to a more difficult life. The life projection for a child with early development Pb+2 toxicity is saddening because the produced cognitive deficits are presumed to be irreversible (Brody et al., 1994). Nonetheless, this grim reality prompted researchers worldwide to investigate the effects of low-level developmental Pb-exposure and Pb+2 toxicity. The neurotoxicant, Pb+2, itself was initially speculated to be the cause of the cognitive deficits linked to Pb+2 toxicity. Therefore, the first aim of researchers was to confirm that Pb+2, rather than other environmental conditions, diminishes cognitive ability. The subsequent findings created the groundwork for future research investigation of Pb+2 toxicity. Rats experimentally treated with Pb-infused water were found to have significantly higher concentrations of Pb+2 in the hippocampal CA1, CA2, and CA3 regions as compared to rats in the untreated control groups (Baranowska-Bosiacka et al., 2013). Because these brain regions are considered to be the site of spatial learning and hippocampal-dependent memory, it makes sense that these areas are vulnerable to toxins during their developmental stages. As a result, the previous experimental results confirmed that Pb+2 does indeed specifically target brain regions responsible for cognitive processes.

The opinion that Pb-exposed individuals demonstrate reduced cognitive abilities persisted, but the nature of the relationship lacked scientific evidence. So, researchers began to examine whether Pb+2 exposure causes impairment of cognitive function. Research investigating Pb+2 toxicity commonly assess cognitive function ability of rats through 2 tests: The Morris Water Maze test and The Radial Arm Maze test. The first common methodology, The Morris Water Maze, evaluates the spatial learning and memory ability of a rat. This test reveals how fast and how well an animal can learn a specific task. Experiments found that rats treated with low-level Pb+2 developmental exposure require a significantly greater number of trials to learn the task in the Morris Water Maze test (Kuhlmann, McGlothan, & Guilarte, 1997). In addition, rats experimentally treated with low-level Pb+2 developmental exposure exhibited a significantly larger average escape latency (or mean latency) in the Morris Water Maze task as compared to the control group (Kuhlmann et al.,1997). This means that the Pb-exposed rat spent less time in the [correct] quadrant that previously contained the hidden platform. The second common methodology, The Radial Arm Maze, assesses the reference and working memory of a rat. The Kuhlmann et al. study also found that rats experimentally treated with developmental Pb+2 exposure committed a greater number of errors in the Radial Arm Maze as compared to the control group. In conclusion, rats with developmental low-level Pb+2 exposure did significantly worse in both of the spatial tasks (The Morris Water Maze test and The Radial Arm Maze test) compared to untreated rats (Kuhlmann et al., 1997). These results provided sufficient evidence for researchers to assert the notion that Pb+2 toxicity produces adverse cognitive deficits.

**2. Current Hypotheses for Pb-induced Hippocampal Alterations**

There are consistent findings for Pb-induced learning and memory deficits which can attest to the necessity of an intact neural network for proper cognitive function. Next, this literature review dissects research studies that propose and investigate potential hypotheses for the cognitive deficits observed in rats with low-level developmental Pb+2 exposure. The following findings are the most commonly cited and accepted explanations in current literature for the production of Pb-induced cognitive deficits in rat subjects.

**2.1 Reduced Number of Hippocampal Pyramidal Neurons**

It can be argued that the cognitive impairments produced by Pb+2 toxicity consequently reduces one’s educational potential and societal success over a lifetime. Research today indicates a strong correlation between fewer hippocampal pyramidal neurons and reduced cognitive function. It is widely accepted that low-level Pb+2 exposure causes a significant decrease in the size of the hippocampal CA1 region and a significant decrease in the number of pyramidal neurons in this area (Baranowska-Bosiacka et al., 2013). As a result, additional studies have been done to investigate the potential explanations for how Pb+2 toxicity reduces hippocampal neuron quantity. Neurogenesis and differentiation are key developmental processes that contribute to the number of neurons that the adult rat will later have. Studies have found that low-level Pb-exposure during early developmental stages can inhibit neurogenesis and the differentiation of neural stem cells (Xiao et al., 2014). For this reason, researchers began to investigate additional ways that Pb+2 toxicity aids in the reduced number of pyramidal neurons in the hippocampus and, ultimately, further impair cognitive processes.

BDNF or brain-derived neurotrophic factor is a key protein for the maintenance of the number of differentiated neurons in the hippocampus (Gassowska et al., 2016). Studies support that a decrease in BDNF of a developing rat causes a reduction in the number of hippocampal neurons in the adult rat. These findings helped guide to the conclusion that Pb+2 toxicity causes a significantly reduced presence of hippocampal BDNF which aids in the significant reduction of hippocampal pyramidal neurons (Baranowska-Bosiacka et al., 2013). Findings from the Xiao et al. study in 2014 support the hypothesis that rat groups with significantly fewer hippocampal pyramidal neurons due to low-level developmental Pb exposure did portray cognitive deficits. The Pb-exposed rats exhibited impaired spatial learning and memory through their significantly larger mean latency escape time in the Morris Water Maze as compared to control groups (Xiao et al., 2014). The current state of literature suggests that investigating the molecular mechanisms of Pb+2 toxicity will pave the way for more specialized treatments of the produced cognitive deficits.

**2.2 Structural Changes of Hippocampal Pyramidal Synapses**

After researchers came to the agreement that Pb+2 does indeed alter hippocampal neuron levels, there was a demand for an investigation of the additional ways that Pb+2 affects brain regions of hippocampal-dependent learning and memory. Synapses are the main site of neural communication because they allow neurons to communicate and relay information between each other. Thus, an intact structural composition of a synapse is necessary for accurate and efficient neurotransmission. As a result, research progressed on to identify the specific ways in which Pb+2 may compromise synaptic regions in the hippocampal CA1 region and, consequently, reduce cognitive functions. It was found that developmental low-level Pb-exposure induces the following synaptic structural alterations: size of the synaptic cleft, the thickness of the postsynaptic density, synaptic curvature, and more in rats (Xiao et al., 2014).

Morphological changes within these hippocampal regions are correlated with reduced neurotransmission and cognitive impairment, similar to the effects observed in those with developmental low-level Pb-exposure. Thus, studies found that Pb+2 toxicity causes a significant decrease in spinal density of hippocampal CA1 pyramidal neurons (Zhao et al., 2018). This reduction of spine density indicates a decrease in synapse formation which means there will be less neural communication and fewer responses to external stimuli. In addition, the reduction of spine density also indicates decreased synaptic transmission efficiency which means the remaining neural communications will be less accurate and less sustainable. Due to the fact that these changes occurred within hippocampal-dependent learning and memory regions, it can be concluded that Pb-exposure significantly diminishes hippocampal-dependent learning and memory processes. As a result, a possible hypothesis for Pb+2 toxicity is that low-level Pb+2 developmental exposure produces significant structural alterations which then decreases synaptic transmission efficiency and impairs learning and memory processes (Zhao et al., 2018).

**2.3 Decreased Efficacy of Hippocampal Pyramidal Synapses**

In addition to the necessary preservation of a synapse’s structure, proper neurotransmission also requires a synapse to have sufficient efficacy. “The efficacy of synaptic transmission is thus governed by the probability of neurotransmitter release, the amount of transmitter released from the presynaptic terminal, the type and number of postsynaptic neurotransmitter receptors, and their response to the released transmitter” (Duguid & Smart, 2009). Rats with long-term lead exposure display cognitive impairments, so it is proposed that Pb+2 toxicity both decreases neurotransmitter release and the efficacy of excitatory synaptic transmission within the hippocampal CA1 region. Thus, researchers looked for Pb-induced presynaptic modifications like any changes in the formation of the SNARE complex or the subsequent vesicle fusion, because both of these processes are required for quantal release of neurotransmitters (NT) into the synaptic cleft. Vesicle fusion is the process through which a vesicle containing NT merges with the presynaptic membrane prior to release. The SNARE Complex, formed by the merge of presynaptic proteins, is the actual machinery of vesicle fusion.

One study found that rats with developmental Pb-exposure had significantly reduced levels of the presynaptic proteins Syntaxin-1 and SNAP-25 within the hippocampus (Gassowska et al., 2016). Syntaxin-1 and SNAP-25 are 2 presynaptic proteins required for the formation of the SNARE Complex. It is also proposed that the release of neurotransmitters depends on the ability of calcium (Ca+2) to induce the binding of Syntaxin and Synaptotagmin I, another presynaptic protein (Bouton, Frelin, Forde, Godwin, & Pevsner, 2001). Consequently, one study showed that low-levels of Pb+2 can compete with Ca+2 and block this needed induction process. Accordingly, this study proved that if hippocampal pyramidal synapses receive long-term exposure to Pb+2, calcium fails to induce the required binding of 2 presynaptic proteins (Bouton et al., 2001). While Pb+2 toxicity alters overall presynaptic proteins to reduce excitatory synaptic transmission, Pb+2 also alters presynaptic vesicles. One study found that chronic Pb+2 exposure can significantly alter vesicular release and vesicular distribution in asymmetric synapse terminals of hippocampal CA1 and CA3 regions (Guariglia, Stansfield, McGlothan, & Guilarte, 2016). As a result, it is suggested that Pb+2 toxicity selectively targets presynaptic processes required for synaptic transmission so to reduce the efficacy of synaptic transmission within hippocampal-dependent learning and memory regions.

**2.4 Inhibition of Hippocampal NMDA Receptors**

NMDA-dependent LTP induction in the hippocampus is a cellular mechanism for learning and memory. Thus, identifying the routes of Pb+2 could unravel potential mechanisms for pharmacological interventions and prevention of the Pb-induced cognitive deficits. Findings show that Pb+2 toxicity inhibits hippocampal NMDA receptors and reduces synaptic transmission (Neal, Worley, & Guilarte, 2011). Activity-dependent NMDA receptors in presynaptic areas of the hippocampus are heavily regulated because their function is crucial for certain types of learning and memory processes. NMDA receptors have multiple regulation binding sites, but the Zinc (Zn+2) site is also an inhibitory binding site. Within this understanding, research began to study the potential mechanisms for the Pb-induced inhibition of NMDA-R current in hippocampal regions. It is widely accepted that Pb+2 can interact with the aforementioned site which then inactivates activity-dependent NMDA receptors within the hippocampus (Alkondon et al., 1990). NMDA receptors are heavily regulated due to their conductance of calcium and their important role in mediating synaptic transmission. Thus, the neurotoxicant Pb+2 inhibits the subsequent calcium influx through the NMDA receptors which also blocks downstream signaling pathways.

A notable downstream effect of NMDA receptors is the synaptic modification LTP. Learning and memory are affected by LTP because it produces permanent changes that strengthen synaptic connections and makes synaptic transmission more efficient. Therefore, the Pb-induced inhibition of NMDA receptor-dependent LTP-induction in hippocampal regions is at least in part responsible for the consequential reduced cognitive function observed in Pb-exposed rats (Alkondon et al., 1990). However, it is also possible that there are alternative synaptic plasticity mechanisms (in addition to hippocampal-dependent LTP) utilized for different types of behaviors. One study provides evidence that rats with developmental Pb-exposure may lack the ability to abandon a conditioned fear (McGlothan, Karcz-Kubicha, Guilarte, 2008). As a result, this study suggests that the mediation and plasticity by activated NMDA receptors are also required for the extinction of a learned fear response (McGlothan et al., 2008).

**3. Period of Pb-Exposure and Corresponding Cognitive Deficits**

As stated earlier, additional compensatory mechanisms for new learning and memory formation may arise as a result of Pb-induced inhibition of NMDA receptor-dependent LTP-induction. However, research suggests that these proposed cellular mechanisms may be specific to the time of low-level Pb+2 exposure. Research findings indicate that the cognitive deficits produced by Pb+2 toxicity may be reversible depending on the time of developmental exposure. Therefore, identifying which stages of development produce cognitive impairments that are reversible is crucial because this can result in tailored pharmaceutical interventions and treatment for young children with lead poisoning. One study suggests that the cognitive and molecular deficits produced in rats with gestational Pb-exposure, or early developmental exposure, can be reversed (Guilarte, Toscano, McGlothan, & Weaver, 2002). Evidence from this paper shows that rearing a Pb-exposed rat in an enriched environment can reverse previous spatial learning impairments back to control levels (Guilarte et al., 2002). While the possibility that Pb+2 toxicity will no longer produce lifelong deficits is encouraging, it is important to note that these findings are specific to rats with low levels of Pb-exposure during gestational development.

Perinatal or maternal lead exposure is when the parents were exposed to Pb+2 continually for some time before mating, up until 9 weeks after pups were weaned from the mother (Xiao et al., 2014). One study found that rats with low-level lead exposure during the perinatal developmental stage had a significantly reduced number of hippocampal neurons and synapses as compared to the control group and the group with early developmental exposure (Xiao et al., 2014). However, because these alterations were uncompensated, the paper proposes that perinatal lead exposure may produce cognitive deficits that are difficult to restore (Xiao et al., 2014). In addition, another study investigated rats with permanent or continuous exposure where in which rats are continually exposed to Pb+2 from the time of conception and through their adulthood (Kuhlmann et al., 1997). In this paper, rats with permanent Pb+2 exposure showed cognitive impairment but experienced deficits to a lesser extent than rats with only maternal Pb-exposure (Kuhlmann et al., 1997). These results support the earlier proposal that compensatory neural mechanisms may arise in the continuous presence of low-level Pb+2 (Kuhlmann et al., 1997). Nonetheless, research continues to propose molecular differences as a possible explanation for the variation of cognitive impairments produced from the time of Pb-exposure.

**General Discussion**

In conclusion, it is important to note that a young child has no decision in many of the factors that will ultimately shape their life course. These influencing factors include, but are not limited to, physical environment, social environment, and parental behaviors. Nonetheless, these factors will either increase or decrease a child’s risk of Pb-exposure during their development. As stated earlier, young children are most often exposed to Pb+2 via soil, lead-based paint, and dust particles. While it is a positive feat that the frequency developmental low-level Pb exposure has decreased over the years within the U.S., it is also important to recognize that Pb+2 toxicity is still prevalent in the U.S. In addition, a higher proportion of these incidents occur within low-income and urban communities.

The purpose of this paper is to provide a comprehensive literature review for the research on Pb+2. The goal is to convey a story of the processes that occur after developmental Pb-exposure and subsequent lead-poisoning. This paper is a collection and comparative analysis of the scientific literature on Pb+2 which in turn will be able to guide future research towards new discoveries. The pieces of literature included in this paper have identified the characteristics, target regions in the brain, observed cognitive effects, and compositional nature of Pb+2 toxicity. In addition, various studies investigated the particular mechanisms of Pb+2 within hippocampal-dependent learning and memory regions when exposure occurs in the developmental stages.

Research continues to progress towards the discovery of novel ways to convert Pb-induced cognitive deficits from irreversible to reversible. Identifying these routes is important because, as a result, young children will be freed from the lifelong deficits of developmental Pb-exposure. Thus far, it has been found that the timing of the Pb-exposure and rearing in an enriched environment are the two most promising factors that can restore cognitive abilities (Guilarte et al., 2002; Kuhlmann et al., 1997). With this data, future prevention measures and treatments for Pb+2 toxicity will have a better chance of reviving a young child’s health. Timely detection of Pb+2 toxicity may diminish the consequences of developmental lead-exposure. Therefore, attention must be given to at-risk mothers prior to conception and continuously through pregnancy.

Continuing research of this subject is vital because as we investigate the cellular level of Pb+2 toxicity, we also further our understanding of developmental low-level Pb-exposure. The long-term goal of this research is to provide legislators and community leaders with the scientific backing required to enact legislation that will further reduce Pb-exposures within vulnerable communities. Children and adults with low-level exposure to Pb+2 during development are later found to have reduced graduation rates, hindered social mobility, and fewer economic opportunities as compared to the national average. As a result, it can be suggested that proper education can potentially eliminate the occurrences of developmental Pb-exposure in young children. It is very important that current research is communicated to the community and not only within academia. Disseminating the findings from this research subject also has the ability to increase overall health and favorable life outcomes. Nonetheless, there must also be a push to pass this life-saving education to low-income families because the young children of these families experience disproportionately higher rates of Pb+2 toxicity. In conclusion, this literature review intends to convey that low levels of Pb-exposure during development is detrimental due to the Pb-induced disruption of various neural pathways and the consequential cognitive impairments.

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