Chapter 6
Cellular and Neurological Effects of Lead (Pb) Toxicity

Shubham Gudadhe, Sushma Kumari Singh, and Jawaid Ahsan

Abstract Lead (Pb^{2+}), a naturally occurring common heavy metal found in the earth's crust, replaces other cations in living creatures, disturbing many biological processes such as metal transport, energy metabolism, apoptosis, and cell signalling. Additionally, it has a significant influence on the central nervous system, specifically on the developing brain. It has severe neurotoxic effects on youngsters. Lead can act as a calcium ion replacement, crossing the blood–brain barrier and causing damage in brain areas, resulting in neurological problems. It possesses genotoxic characteristics and disrupts cellular activity. Neurotoxicity is a major problem, especially in the developing central nervous system, where it can cause long-term cognitive, motor, and behavioural deficits. Paediatric lead poisoning is more common, and early detection requires a high level of precision. The molecular processes and cellular effects of lead toxicity are discussed in this chapter. The pathophysiology, aetiology, and epidemiology of lead exposure are also reviewed in this chapter. It also investigates the neuropsychological issues linked with Intelligence Quotient (IQ), memory, executive functioning, attention, processing speed, language, visuospatial skills, motor skills, and effects on mood. The chapter also discusses lead-induced oxidative stress and its consequences. It will provide an in-depth understanding of the neuropsychological effects of lead toxicity at different levels, which will be helpful for its better management and finding remedies for the related toxic effects.

Keywords Lead · Cognition · Neurodevelopment · Oxidative stress · Signalling pathway · Toxicity

S. Gudadhe · S. K. Singh · J. Ahsan (✉)
Department of Biotechnology, Central University of South Bihar (CUSB), Panchanpur, Gaya, Bihar 824236, India
e-mail: jahsan@cub.ac.in

N. Kumar and A. K. Jha (eds.), *Lead Toxicity Mitigation: Sustainable Nexus Approaches*, Environmental Contamination Remediation and Management,
https://doi.org/10.1007/978-3-031-46146-0_6

6.1 Introduction

Lead (Pb) is considered to be a significant and naturally occurring toxic metal among the various heavy metals present in the Earth's crust. Lead, which has an atomic number of 82 and is derived from the Latin word Plumbum, is a prevalent toxic substance found throughout various locations (Patra et al. 2011). In ancient times, lead was used for several purposes (Maiti et al. 2017). The presence of lead can be identified in both living organisms and non-living surroundings. The increase in anthropogenic activities and vehicle emissions is primarily accountable for the increase in lead concentration within the human body through inhalation, ingestion, and dermal contact. In particular, the liver, spleen, and kidney have been recognised as significant target areas for lead poisoning. Lead in the form of a toxin generates a variety of biochemical, physiological, and behavioural dysfunctions (Bandyopadhyay et al. 2014). Lead is one of the most toxic heavy chemicals to people for humans and has been for thousands of years. Lead makes us sick when it gets into our bodies through food, air, and water because it reacts with biological molecules that contain sulphur, oxygen, or nitrogen (Maiti et al. 2017). Lead poisoning is usually found when the amount of lead in the blood rises. But short-term exposure to lead can cause problems like neurobehavioral and brain damage, memory problems, high blood pressure, and damage to the kidneys. The parts and systems of the body that are most likely to be affected by high levels of lead are the blood, kidney, reproductive, and central nervous systems (Assi et al. 2016). Jalali et al. state that when the amount of malondialdehyde (MDA) increases, the activities of erythrocyte superoxide dismutase (SOD) and glutathione peroxidase (GPx) increase along with the total number of erythrocytes (Jalali et al. 2017). Rats exposed to lead had a low number of cells, lymphocytes, and neutrophils, leading to microcytic anaemia. Chelation treatment is generally recommended for low levels of lead poisoning that have caused brain damage (encephalopathy). But researchers are still looking at treatments that use less medicine but last longer. An important part of treating chronic diseases is determining how much lead is in the body and what happens when people are exposed to low levels of lead in the surroundings (Singh et al. 2017). Heavy metal lead (Pb) is a common pollution in the environment, and it has been said to cause poisoning in many people (Karri et al. 2016). The detrimental impact of Pb-induced oxidative stress on the Central Nervous System (CNS) is widely acknowledged. Exposure of rodents to Pb has been found to be associated with persistent alterations in brain-derived neuronal factor (BDNF), β-amyloid (Aβ) aggregation, and oxidative damage. These findings pose significant environmental and public health challenges due to their close association with impaired intelligence and growth (Feng et al. 2015; Li et al. 2018).

A research study has shown that developmental exposure to Pb results in an over accumulation of Pb in the hippocampus, which is associated with a decline in cognitive abilities that is directly proportional to the dose of Pb (Wei et al. 2022). It is worth noting that exposure to environmental insults during developmental stages, specifically prepuberty and adolescence, has a substantial influence on neural plasticity

and subsequent behaviour in adulthood (Encinas et al. 2006; Sanders et al. 2015). Studies have shown that exposure to Pb during early stages of life in animals such as rodents and primates can lead to cognitive impairment and a subsequent increase in amyloid biomarkers that are relevant to Alzheimer's disease in later stages of life (Bihaqi et al. 2014a; Liu et al. 2014). The presence of increased apoptotic markers has been reported in conjunction with the aforementioned condition. The issue of childhood lead poisoning persists (Chandramouli et al. 2009).

6.2 Sources of Lead Exposure

Lead is a naturally occurring heavy metal that is very poisonous. Lead can be found everywhere in nature, but most of it comes from human actions such as mining, making things, and burning fossil fuels. There are three distinct forms of lead, namely metallic lead, inorganic lead, and lead compounds, also known as lead salts, as well as organic lead that contains carbon. Lead in the environment rarely occurs in its elemental state but rather in its + 2 oxidation state (Pb^{2+}) in various ores throughout the earth. Lead has been found in at least 1272 of the 1684 National Priority List (NPL) sites identified by the United States (U.S.) Environmental Protection Agency (EPA) (Gerberding and Falk 2005). Lead is one of the most durable heavy metals in nature. Groundwater, soil, dust from metal ores, brass plumbing fixtures, several industrial activities, folk remedies, burning petroleum, making lead battery, paint industries, and mining processes, contaminating food, and certain herbal products made with lead are all sources of lead in the environment (Fig. 6.1). People are always getting lead from things such as contaminated air, water, earth, house dust, and food, as well as by breathing it in. Lead paints and lead chips are the main and most common ways for children to get too much lead (Patra et al. 2011). Lead has various applications, such as in leaded petrol, paints, ceramics, ammunition, water pipes, solders, hair dye, cosmetics, farm equipment, aeroplanes, shielding for X-ray machines and in the production of corrosion and acid resistant materials utilised in the construction sector (Sanders et al. 2009). Various sources of lead poisoning include the production of ammunition, ceramic glazes, circuit boards, caulking, sheet lead, solder, certain brass and bronze plumbing, radiation shields, intravenous pumps, foetal monitors, as well as specific surgical and military equipment, such as jet turbine engines and military tracking systems, among others (Fig. 6.1). Employees are at an increased risk of being exposed to lead at different construction locations (Levin and Goldberg 2000; Mitra et al. 2017). When taking part in hobbies or activities that increase exposure, kids can be exposed to lead-based paint that is peeling or flaking or weathered powdered paint. Particularly at risk are kids with pica, which is the compulsive, habitual ingestion of non-food substances (Mitra et al. 2017). The severity of the toxic reaction depends on a number of things, such as the dose, the age of the person exposed, the stage of a woman's life (children, breastfeeding, menopause), the person's job, the length of time they were exposed, their health and lifestyle, and their nutritional status.

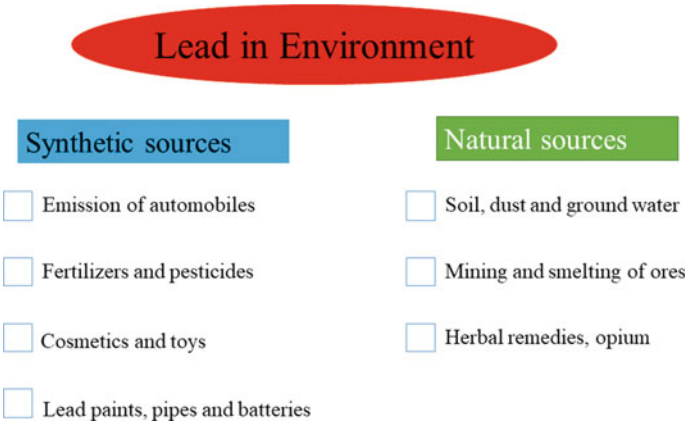

Fig. 6.1 Lead in the environment originates from both synthetic and natural sources

6.3 Lead Exposure in Humans

Exposure to lead (Pb) is still a major public health issue around the world. Pb is a toxic metal that can be found in the environment because of things like lead mining, battery recycling, and the use of lead petrol. Children and pregnant women are especially vulnerable to the effects of Pb exposure. The quantification of the exposure of Pb and its body burden in human studies is primarily accomplished by measuring the measurement of metal concentration in both blood and bone. There is a lack of consensus regarding the exposure levels required to elicit the initial symptoms of neurotoxicity in individuals who are occupationally exposed. However, the majority experts concur that overt neurotoxic effects can manifest at blood Pb levels of 60 μg/dL whole blood. Consequently, it is recommended that workers maintain a maximum concentration of approximately 40 μg/dL (CDC 2018).

But other studies found a link between exposure to lead and changes in thinking in workers whose blood lead levels were between 20 and 40 g/dL (Barth et al. 2002; Lucchini et al. 2012; Murata et al. 2009). The World Health Organisation says that adults who live in communities should keep the amount of lead in their blood below 10 g/dL. But there does not seem to be a safe amount of exposure to Pb, and levels of 1–3 g/dL have been linked to subtle neurotoxic effects (Kosnett et al. 2007). The concentration of Pb in bone is believed to be a measure of total exposure. It is measured mostly by K-shell X-ray fluorescence spectroscopy in the tibia and patella, which are cortical and trabecular bone, respectively. The half-life of Pb in bone is reported to be different depending on where it is in the body and on factors like age, previous exposure, and other situations that affect bone turnover (Farooqui et al. 2017).

According to a study done in China, children's mean BLL was 4.71 g/dL, with 41.4% of those having BLLs higher than 5 g/dL (Li et al. 2020).

6.4 Neuropsychological Effects of Lead Toxicity

Lead exposure has a wide range of adverse effects on cognitive functioning. Prenatal exposure, as assessed by lead levels in umbilical cord blood, has been linked to Cord blood, was associated with worse scores on the Bayley Scales of Infant Development in the sensorimotor and visuomotor subscales (Koller et al. 2004; McMichael et al. 1988). Numerous cross-sectional and longitudinal studies on children have demonstrated that lead exposure reduces children's overall cognitive functioning, but the majority of these studies examine global measures of intellectual functioning rather than domain-specific effects. Chronic exposure to lead is more detrimental to cognitive function in adults than acute exposure (Bellinger 2004; Koller et al. 2004; Lidsky and Schneider 2003; Needleman 2004). Studies on domain-specific cognitive affects are listed below.

6.4.1 Intelligence

Most of the time, when children are exposed to lead, their intelligence scores go down. Reviewing paediatric cross-sectional studies on brain problems caused by exposure to lead, it was found that IQ dropped by three points when blood lead levels went from 5 to 20 g/dL and dropped by 5.3 points when blood lead levels went from 5 to 50 g/dL (Winneke et al. 1996). When lead levels in the blood went from 10 to 20 g/dL, there was a pretty consistent link between a drop and a three-point drop (Pocock et al. 1994; Winneke et al. 1996). Based on these results, it seems that exposing someone to lead lowers their intelligence in a way that depends on how much lead they are exposed to. Even though it has not been seen as often in adults as it has in kids, some adults have shown signs of having less intelligence. The Task Group on the Effects of Inorganic Lead of the World Health Organisation's Programme for Chemical Safety (Joint FAO/WHO Expert Committee on Food Additives 2002). After conducting a comprehensive analysis of the existing literature, it was determined that human intellectual functioning may be negatively affected by blood levels below 25 μg/dL. Furthermore, it was found that for every 10 μg/dL increase in blood lead levels, there is a predicted decrease in IQ of 1–5 points. The findings suggest that there is a correlation between occupational lead exposure and decreased cognitive and intelligence scores in adults, with the effect being dependent on the dosage (Khalil et al. 2009). When researchers first looked at the effects of lead on the brain, they focused on how it affected the brain as a whole. However, more recent research shows that it is important to examine how lead affects the brain in different areas.

6.4.2 Memory

Several studies have indicated a decrease in learning and memory performance among adults who have been exposed to lead in their occupation. The findings indicate that lead exposure has a more pronounced negative impact on cognitive function in the elderly population, as evidenced by reduced scores in learning and memory tasks, among other cognitive impairments. Specifically, individuals 55 years and above appear to be more vulnerable to the deleterious effects of exposure to lead. Although older adults are particularly vulnerable, research has also observed reduced memory performance in individuals under 55 years of age who have been exposed to elevated levels of lead. Subjects exhibited a decline in their ability to recall verbal and visual information after exposure to lead (Khalil et al. 2009; Stewart and Schwartz 2007). There has been constant evidence of lower visuospatial memory scores, which suggests that lead exposure affects spatial skills and the ability to remember what you see. Lead exposure on the job is also linked to lower visual memory scores, especially a delay in remembering a complex figure (Schwartz et al. 2000). Lead exposure has also been associated with lower verbal memory scores, which affects instant recall, delayed recall, and identification. Chronic contact seems to not only affect both vocal and nonverbal memories, but also to cause them to get worse over time. In this group, the results on both verbal and nonverbal memory tests kept going down over time. This means that long-term contact may cause gradual loss of memory over many years (Mason et al. 2014).

6.4.3 Processing Speed

Lead poisoning has been shown to slow processing speed, and the results suggest that the link is dose-dependent. People exposed to high amounts of lead took longer to make decisions and respond. For example, significant slowing down of decision-making speed and wider gaps in a detection/reaction time task have been found to be caused by contact (Winneke et al. 1996). These results also revealed slight deficiencies in classification speed and precision during a category search task. Only individuals with blood lead concentrations of 40 g/dL or higher exhibited these deficits. The dose-dependence of neurobehavioral deficits was confirmed by a follow-up study with the same participants and testing battery. However, the primary finding of both studies was a delayed sensory-motor reaction time, which may have artificially hampered overall processing speed (Stollery et al. 1991).

6.4.4 Executive Functioning and Attention

Several investigations have demonstrated that occupational exposure to lead decreases executive functioning. Impaired executive functioning abilities in switching and inhibition tasks (Trails Making Test B and Stroop Task, respectively) were also observed in a group with a maximum lead exposure of 20 g/g (tibia bone lead measurement). Lower executive functioning scores were also discovered in earlier studies employing comparable assessments and scores (Schwartz et al. 2000, 2005).

6.5 Cellular Effects of Lead Neurotoxicity

In recent decades, new information about how lead affects cells and how it works has helped us to learn more about its neurotoxicity. Using cellular models of learning and memory, researchers have investigated how lead might cause brain problems. A new study shows that exposure to lead is bad for the Central Nervous System (CNS), that environmental factors make people more sensitive to lead, and that being exposed to lead as a child can cause neurodegeneration as an adult.

As the CNS is the main target of lead poisoning, the brain is the most studied when it comes to lead poisoning. Lead neurotoxicity occurs when the CNS is exposed to enough lead to change how it normally works and cause damage to the CNS. Lead's direct neurological effects include apoptosis (programmed cell death), excitotoxicity, which affects neurotransmitter storage and release and changes neurotransmitter receptors, mitochondria, second messengers, cerebrovascular endothelial cells, and both astroglia and oligodendroglia. Loss of memory, vision, cognitive and behavioural problems, and brain damage/mental retardation are some of the symptoms that can show up right away or later (Sanders et al. 2009). Although most of the early studies focused on the neurocognitive effects of lead, more recent research has shown that higher exposures are linked to morbidities such as antisocial behaviour, delinquency, and violence. To explain the mechanism of lead toxicity on the CNS, several theories have been put forth (Hwang 2007).

6.6 Effect of Lead on Signalling Pathways

The first publication pertaining to lead-mediated oxidative stress was released in 1965. The present study revealed that certain metals have the ability to increase the rate of oxidation of crucial fatty acids. The efficacy of lead as a material during that period was reportedly inadequate. Subsequent to a considerable period of time, it was noted that lead was responsible for the escalation in lipid peroxidation, as determined by the analysis of Malondialdehyde (MDA). The lead-induced lipid peroxidation in

rat brain was also documented by a number of researchers. A positive correlation was found between elevated lead concentration and increased lipid peroxidation, similar effect was observed in hepatic tissues as well (Shafiq-ur-Rehman 2003). Lead-induced oxidative stress is primarily attributed to cellular membrane and DNA, as well as inhibition of key enzymes such as catalase, GPx, SOD, and G6PD, and non-enzymatic antioxidant molecules such as thiols (GSH) in mammalian organisms (Flora et al. 2008; Valko et al. 2005).

Several studies have suggested that metal-induced toxicity involves a multifactorial mechanism, as illustrated in Fig. 6.3. Multifactorial mechanisms may be linked to various biological processes such as oxidative stress, enzyme inhibition, DNA damage, alterations in gene expression, and phenomena such as adventitious mimicry. The mechanism of metal-induced generation of free radicals, particularly Reactive Oxygen Species (ROS).

The precise mechanisms underlying lead-induced oxidative stress remain unclear, likely due to the limited capacity of lead to undergo rapid valence changes. Lead exhibits a propensity for covalent bonding with sulphydryl groups because of its electron-sharing affinities. The interaction between lead and GSH is crucial for the manifestation of its toxic effects (Hultberg et al. 2001).

In the context of a signaling pathway, lead acts as a calcium mimic and binds to the calmodulin protein (a Ca^{2+} 134 binding protein) that has been implicated in the induction of lead toxicity. The findings indicate that lead binding exhibits a higher relative affinity compared to calcium (Kirberger et al. 2013), as illustrated in Fig. 6.2. Various mechanisms for lead-mediated oxidative stress have been suggested.

6.7 Lead-Induced Neurotoxicity and Its Mechanisms of Action

One of the most vulnerable parts of the body to lead is the nervous system. In general, it damages the nervous system, but it affects children's brains a lot more. Neurotoxicity is also linked to the production of too many free radicals, which can change how the brain works. Lead quickly penetrates the Blood–Brain Barrier (BBB) and replaces calcium ions, disrupting intracellular calcium regulation in brain cells. Long-term lead poisoning in children can cause comas, seizures, and changes in their mental state. Several clinical studies have been conducted on the link between lead poisoning and the way the brain develops and works (Brochin et al. 2008). Blood lead levels are negatively correlated with neurological development and function. Lead-poisoned children exhibited abnormal behaviour such as melancholy, aggression, destruction, social withdrawal, and atypical body movements (Hou et al. 2013; Mărginean et al. 2016).

Neurological differences are mostly caused by the way ions work. When lead replaces calcium ions, it becomes able to cross the BBB at a good rate (Fig. 6.3). After crossing the BBB, lead builds up in astroglial cells with lead-binding proteins.

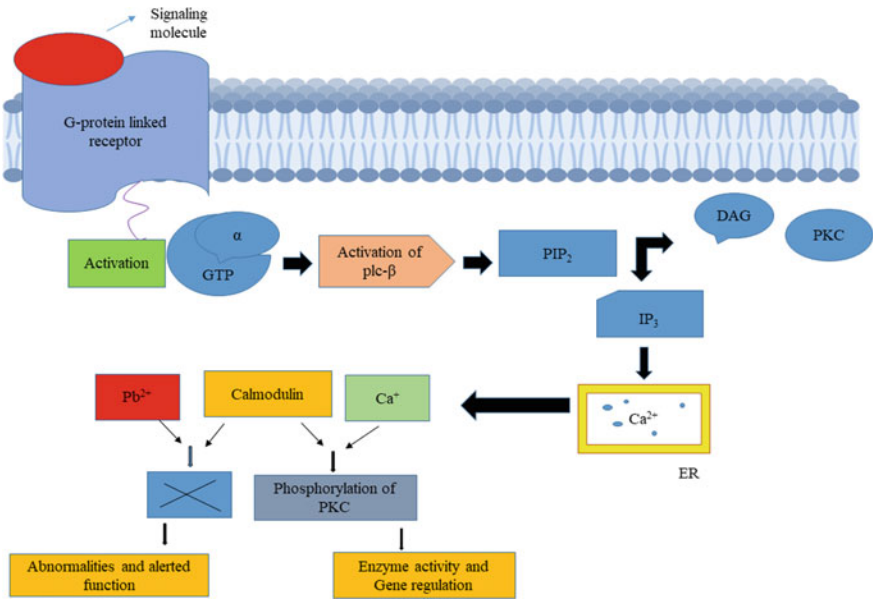

Fig. 6.2 Lead interference with calcium (Ca)-dependent inositol trisphosphate or inositol 1,4,5-trisphosphate pathway (ER = endoplasmic reticulum)

Lead is more dangerous for growing nervous systems because they do not have enough mature astroglial cells. Immature astroglial cells do not have any proteins that bind to lead. Lead can easily harm undeveloped astroglial cells and interfere with the development of myelin sheaths (Wang et al. 2011). Lead is also moved by Divalent Metal Transporter 1 (DMT1), a protein with 12 transmembrane domains that is found in capillary cells. DMT-1's job is to move essential metals, but it also moves toxic metals that look like important minerals (Moos et al. 2006). Protein Kinase C (PKC) is an enzyme that plays a crucial role in many physiological processes, including cell proliferation and brain development, and can be stimulated by subnanomolar concentrations of lead ions.

6.8 Lead Affects Movement of Calcium

Lead changes the brain and behaviour in complicated ways that are hard to understand. Still, work on cells and molecules has led to a better understanding of how lead affects how the brain works. The effects of lead on biological processes that rely on calcium are especially important. Calcium is an important ion for neural function, such as cell growth and development, the release of neurotransmitters, and biochemical reactions inside the cell.

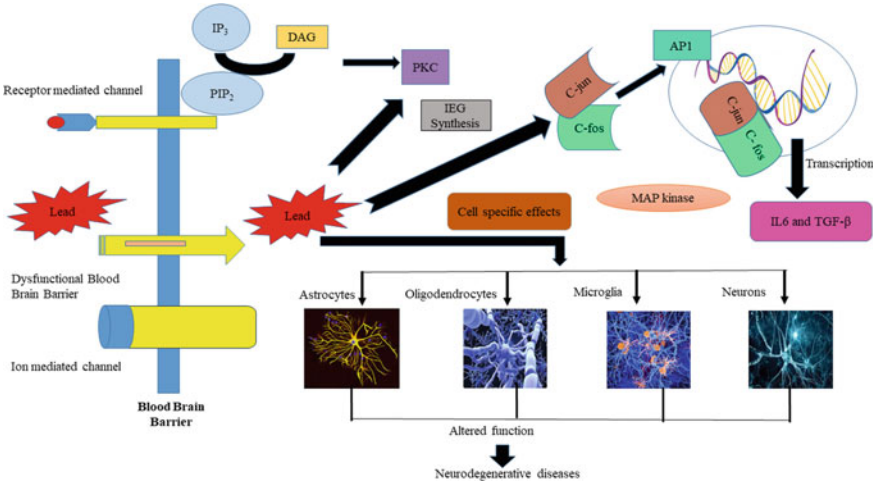

Fig. 6.3 Effect of lead on central nervous system (CNS) and on expression of interleukin-6 and TGF-β1. Lead exposure alters the expression of the genes encoding the cytokines IL-6 and TGF-1. Gene expression of cytokines IL-6 and TGF-1 is mediated by the entry of Pb into the cell and mobilisation of calcium ions, followed by the cleavage of phosphatidylinositol bisphosphate (PIP2) into inositol triphosphate (IP3) and diacylglycerol (DAG). DAG activates PKC, which increases the expression of IEG jun and fos genes. The mitogen-activated protein kinase (MAPK) pathway is essential for dimerization aphosphorylation of the c-jun and c-fos proteins, which resulted in the formation of the nuclear transcription factor AP-1 (activator protein 1) and increased expression of IL-6 and 214 TGF-1. Directly, lead increases the activation of PKC, c-fos, and c-jun protein expression. Lead's powerful effect on CNS cells results in neurodegeneration

Lead and calcium are divalent cations that share similarities in terms of their ionic charge and size. The capacity of lead to imitate or hinder calcium-mediated impacts is fundamental to its biological and behavioural consequences. A less regulated ligand in the human body in comparison to calcium.

A heavy metal that lacks regulation. Lead has the ability to bind to the same sites as calcium and can enter the cell via calcium channels. This results in the displacement, inhibition, substitution, and/or activation of calcium-dependent processes (Bridges and Zalups 2005; Habermann et al. 1983; Kerper and Hinkle 1997).

The widespread occurrence of calcium in cellular signalling and the crucial significance of the spatial and temporal arrangement of calcium signals in cellular operation imply that interference with calcium-dependent mechanisms can result in significant cellular outcomes. This notion is supported by various studies (Berridge et al. 2003; Bootman 2012; Bootman et al. 2001, 2002; Bridges and Zalups 2005). The impact of lead on the calcium dynamics of neurons provides insight into numerous extensive alterations in brain activity and conduct.

6.9 Effect of Lead on NMDA Receptor

Lead is an antagonist of the N-Methyl-D-aspartate receptor (NMDA-R) that operates in a non-competitive manner.

The N-methyl-D-aspartate receptors (NMDA-Rs) are a type of ionotropic receptor that is stimulated by the neurotransmitter glutamate. These receptors play a crucial role in various physiological processes, such as neural development, neuronal plasticity, learning and memory, and long-term potentiation, which is a physiological manifestation of learning (Cory-Slechta et al. 1997; Gilbert and Lasley 2007; Hubbs-Tait et al. 2005; Nihei and Guilarte 2001).

When glutamate binds to NMDA-Rs, calcium flows in through a ligand-gated ion channel. This can cause an excitatory post-synaptic potential and has a big effect on how neurons work by starting second messenger pathways that depend on calcium. The blocking of postsynaptic NMDA-Rs by lead results in the inhibition of activity-dependent calcium influx. This can subsequently interfere with NMDA receptor-dependent developmental processes, neural plasticity, learning and memory, as well as Long-Term Potentiation (LTP). The induction of LTP is hindered by chronic and developmental exposure to lead across a broad spectrum of concentrations, resulting in a higher threshold. This phenomenon is linked to compromised learning and memory (Lasley et al. 2001; Lasley and Gilbert 2000, 2002; Luo et al. 2011; Nihei and Guilarte 2001). Blocking NMDA receptors or other effects of lead on calcium-dependent processes may have something to do with how well LTP and learning work.

Apoptosis is another thing that happens when NMDA receptors are blocked. This is a type of cell death that is planned and caused by a well-known biological process (Anastasio et al. 2009; Hansen et al. 2004; Léveillé et al. 2010; Lyall et al. 2009; Yuede et al. 2010). During brain growth, apoptosis is usually used to get rid of unwanted links and 'sculpt' the brain. Pathological apoptosis, on the other hand, can happen in some situations. Low amounts of lead during development have also been shown to cause apoptosis and mess up brain development in both human and zebrafish models by blocking NMDA receptors (Dou and Zhang 2011; Dribben et al. 2011; Liu et al. 2010).

Due to the important role NMDA receptors play in many neuro and behavioural processes and the fact that lead can block NMDA receptors, knowing how lead affects the brain and behaviour depends on these receptors.

6.10 Effect of Lead on Calmodulin

Lead also targets calmodulin (CaM), or 'calcium-modulated protein', a significant intracellular calcium-activated protein (Heizmann and Hunzlker 1991). Calmodulin is involved in calcium signalling, neurotransmitter receptors, ion channels, and neural plasticity (McCue et al. 2010). Calmodulin possesses four distinct binding sites that

are naturally bound by calcium ions. Calmodulin exhibits functional activity upon complete binding of calcium to all four of its sites (Costa 1998).

According to several studies (Fullmer et al. 1985; Habermann et al. 1983; Sandhir and Gill 1994; Shirran and Barran 2009), at levels that are relevant to physiological processes, calmodulin exhibits a higher binding affinity towards lead compared to calcium, thereby leading to the activation of the protein. Upon the occurrence of this event, calmodulin undergoes activation in a manner that is not consistent with normal physiological processes. The signalling of calmodulin undergoes a state of tonic activation and becomes independent of external stimuli. The extensive involvement of calmodulin in calcium signalling implies that uncontrolled activation of calmodulin can result in various outcomes, including but not limited to the disruption of signal transduction that is dependent on calmodulin and interference with calmodulin-mediated learning and memory (Rocha and Trujillo 2019).

6.11 Effect of Lead on Protein Kinase C

Protein Kinase C (PKC) is an intracellular signalling enzyme that is dependent on calcium and phospholipids and is involved in diverse cellular functions (Markovac and Goldstein 1988). Protein Kinase C (PKC) catalyses the phosphorylation of proteins through the transfer of phosphate groups from Adenosine Triphosphate (ATP). The regulation of cellular growth and differentiation is reliant on the phosphorylation of transport proteins via PKC. The Protein Kinase C (PKC) has been found to be involved in cytoskeletal function and signal transduction (Pears 1995). Additionally, PKC has been observed to have a significant impact on learning and memory, as noted (Van der Zee et al. 1992; Xu et al. 2014).

Lead replaces calcium in the activation of PKC at a clinically meaningful picomolar dose, raising intracellular calcium, and obstructing neurotransmitter release (Goldstein 1993). According to Bouton et al. (2001), lead mimics calcium at the synaptotagmin site and competes for it with higher affinity than calcium. Extended exposure to lead results in elevated PKC activity, which in turn triggers a compensatory reduction in activity, potentially through downregulation or decreased effectiveness of calcium activity.

The significance of PKC in calcium-mediated long-term potentiation (LTP) has been established. Studies have shown that PKC inhibitors, such as polymyxin B, impede the initiation and preservation of calcium-induced LTP (Cheng et al. 1994). The negative impact of lead on cognitive abilities such as learning and memory is believed to be caused, at least partially, by interference with typical PKC operation. Furthermore, the influence of lead on PKC activity has consequences for various cellular processes such as cell division, neural communication, neural plasticity, and cytoskeletal organisation (Bressler et al. 1999) Additionally, it affects cellular proliferation and differentiation (Markovac and Goldstein 1988).

6.12 Lead as Neurotransmitter Releaser

Typically, the depolarization of neurons results in the activation of voltage-gated calcium channels, thereby facilitating the entry of calcium ions into the presynaptic terminal. Upon calcium influx, a series of enzymes are activated, thereby facilitating the fusion of the synaptic vesicle with the cellular membrane and subsequent liberation of neurotransmitters. Lead has been found to have a converging impact on neurotransmitter release by binding to voltage-gated calcium channels and subsequently decreasing the influx of calcium. Furthermore, it has been observed that lead engages in competition with calcium for the binding sites of various proteins that play a role in the release of neurotransmitters, such as calmodulin, CaM kinase II (CaMKII), and synaptotagmin (Bouton et al. 2001; Kern et al. 2000; Westerink et al. 2002).

Collectively, these measures lead to a decrease in the discharge of neurotransmitters at the presynaptic terminal. The inhibition of neuronal release of glutamate and GABA can be observed at nanomolar concentrations of lead. The perturbation of regular neurotransmitter release can result in diverse outcomes for the brain and conduct, contingent on the particular neurotransmitter and its placement within the brain (Braga et al. 1999).

6.13 Lead and Neurodegenerative Diseases

Recent studies offer compelling evidence that lead exposure has detrimental impacts on the CNS in both adult and paediatric populations. Lead-induced damage within the brain can result in various neurological disorders, including but not limited to brain damage, mental retardation, behavioural problems, nerve damage, and potential development of Alzheimer's disease, Parkinson's disease, and schizophrenia. The prefrontal cerebral cortex, hippocampus, and cerebellum are particularly vulnerable to such damage. These findings suggest the need for further investigation into the potential long-term effects of lead exposure on the brain (Sanders et al. 2009).

6.13.1 Alzheimer's Disease (AD)

Numerous research studies have examined the impact of lead exposure on cognitive abilities and IQ in children. However, investigations into developmental lead exposure in non-human primates and rodents have revealed associations with the onset of Alzheimer's disease during the later stages of life. Alzheimer's disease is widely recognised as the prevailing neurodegenerative disorder. The condition is distinguished by cognitive decline and dementia, accompanied by brain pathology consisting of proteinaceous plaques composed of Amyloid beta (Aβ). The globus

pallidus, dentate gyrus, temporal cortex, and temporal white matter of postmortem human brains affected by Alzheimer's disease have exhibited significantly elevated levels of lead in comparison to control healthy brains of the same age group, as per the findings of Haraguchi et al. (2001). The exposure to Pb has been found to raise the mRNA of Amyloid Precursor Protein (APP) and the aggregation of Aβ in rats, leading to amyloidogenesis and the deposition of senile plaques. Additionally, in nonhuman primates who were exposed to lead during infancy, there was an upregulation of APPs (Bihaqi et al. 2014a, b; Wu et al. 2008). Exposed mice to lead across the course of different life spans and discovered that there is a window of sensitivity to lead toxicity in the developing brain. Cognitive impairment only occurred in mice exposed to Pb as newborns, not as adults (Bihaqi et al. 2014a). According to Bihaqi et al. (2014a) and Masoud et al. (2016), the exposure of mice to lead during their early life stages results in increased expression of tau protein associated with Alzheimer's disease and changes in epigenetic markers linked to the development of the same disease (Bihaqi et al. 2014a; Masoud et al. 2016).

The relationship between lead exposure during infancy and AD is being explained by an emerging theory that suggests an epigenetic basis for the increased production of proteins relevant to AD and cognitive decline. Exposures experienced during the foetal or early developmental stages have the potential to induce epigenetic modifications in the brain, thereby resulting in gene reprogramming. According to Schneider et al. (2013), a study was conducted on rats that were exposed to Pb either in utero or in postnatally. The results indicated a reduction in the expression of DNA methyl transferase in the hippocampus of female rats that were exposed to Pb. This suggests that there may be a decrease in DNA methylation, which could lead to the expression of genes that are typically suppressed (Schneider et al. 2013).

The investigation conducted by Schneider involved the examination of gene expression pertaining to DNA methyl transferases, which was carried out at postnatal day (Schneider et al. 2013). On the other hand, a study was conducted by Dosunmu wherein infant mice exposed to Pb were subjected to genome-wide expression and methylation profiling until postnatal day 700. The results showed that a specific group of genes, which are typically expressed in aged mice, were repressed. The aforementioned genes were found to be implicated in the immune response, metal binding, and metabolism. Suppression of their expression resulting from developmental exposure to Pb has been observed to impede the brain's capacity to counteract stressors associated with ageing (Dosunmu et al. 2012).

6.13.2 Parkinson's Disease (PD)

According to research findings, lead has been observed to decrease the production of catecholamine as well as synaptic neurotransmission. The decrease in GABA (gamma-aminobutyric acid) could be a common factor in all human neurodegenerative disorders caused by unusual levels of calcium inside cells (Błaszczyk 2016). The

occurrence of oxidative stress resulting from chronic lead intoxication has been verified through the observation of elevated levels of lipid peroxide in the brain and liver of rats. Exposure to lead has been found to diminish dopaminergic neurotransmission through mechanisms such as mitochondrial dysfunction, oxidative stress, and heightened gliofilament expression in astrocytes (Patra et al. 2011).

Lead toxicity poses a greater risk to children through dietary exposure and can result in adverse effects on the nervous system and pica behaviour, as documented in literature (Zeng et al. 2016). The study conducted by Loikkanen et al. provides evidence that lead has an impact on cellular processes through the regulation of calcium and calcium-binding proteins. Additionally, the study suggests that lead affects the release and reuptake of various neurotransmitters. The aforementioned study indicates that it inhibits the acetylcholine and dopamine releases that are dependent on Ca^{2+} and activity (Loikkanen et al. 1998).

The hippocampus region of the brain is subject to tau hyperphosphorylation and α-synuclein accumulation, which are the primary factors that trigger apoptosis and autophagy. This phenomenon has been extensively studied and documented (Zhang et al. 2012). The study conducted by Rogers et al. revealed that the APP is a significant contributor to lead toxicity via iron regulatory pathways, as observed in human dopaminergic SH-SY5Y neuroblastoma cells.

The involvement of PKC in dopamine transport function and the induction of oxidative stress through PKC activation by lead, leading to neurotoxicity, has been reported (Rogers et al. 2016).

Lead is easily able to cross the BBB and binds to sulfhydryl groups, which changes anti-oxidant enzymes and raises the amount of lipid peroxidation. In the same way, lead poisoning can happen when –ALAD (Delta-aminolevulinic acid dehydratase) is stopped from working and too much of its substrate, –ALA, builds up. –ALA quickly oxidises to make free radicals and release ferrous ions, which start the process of lipid peroxidation (Ashafaq et al. 2016).

6.14 Conclusion

The neurotoxic effects of lead exposure and its considerable effects on human neuropsychology are discussed here. Pb toxicity can cause the central nervous system to suffer from a variety of negative consequences, altering cognitive functioning. Lead works by a mechanism that interferes with calcium dynamics, which are critical to many cellular activities. Lead obstructs calcium's ability to regulate itself, which impairs synaptic transmission and neuronal activity. In addition, mounting data point to a possible connection between lead exposure and the emergence of neurodegenerative disorders. An increased risk of neurodegenerative diseases including Alzheimer's and Parkinson's has been linked to chronic lead exposure. Complex processes, including oxidative stress, inflammation, protein aggregation, and mitochondrial dysfunction, underlie these correlations. It is crucial for public health to comprehend lead's neurotoxic effects and how they affect neuropsychology

in humans. Reduced lead exposure is essential for preventing neurodegenerative illnesses and long-term cognitive deficits in sensitive populations like children. To reduce the neurotoxic effects of lead on human neuropsychology, more study is required to understand the underlying mechanisms and create efficient preventive, early detection, and intervention measures.

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