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Lead Toxicity Induced Microglial Activation in the Brain

Kanhaiya Lal Kumawat[1, 2, #], Praveen Goswami[2, 3, #] and A.K. Sharma[2]

1. **National Brain Research Centre, Manesar, Gurgaon, India-122051**
2. **Dr. K.N. Modi University, Newai, Rajasthan, India-304021**
3. **Poddar International College, Jaipur, Rajasthan, India-302020**

Abstract - Lead (Pb) shows a considerable amount of heavy metal toxicity in the central nervous system. Neuronal death or neurodegeneration is related to the Pb induced inflammatory processes through microglial activation in brain. Pb induced activation of microglia leads to the expressions of different cytokines, chemokines and enzymes, such as TNF-α, IL-6, MCP-1, Cox-2, caspases, nitric oxide synthetase (NOS 2) etc. leading to trigger different signaling cascades, namely, Extracellular-signal-regulated kinases (ERK1/2), NF-κB Pathway, c-jun N-terminal kinases/stress-activated protein kinases (JNKs/SAPKs), p38 MAPK, Akt Pathway in neuroinflammation. Thus, the first line of defense mechanism homeostasis is disturbed by the Pb induced activation of microglia leading to neuronal death.

Keywords: ***Lead(Pb), Microglia, Brain, Neuroinflammation, Central Nervous System (CNS) and Neurotoxicity***

1. INTRODUCTION

Lead (Pb) is a toxic environmental agent that has debilitating effects on human health. It is considered as the 2nd most toxic substance according to ATSDR that is being used extensively due to its efficient properties of corrosion resistance and high malleability. Over the years it has been observed that several natural and anthropogenic activities have been the reason for lead contamination in the environment. Lead can come in the atmosphere by efflux from mining lead and other metals, and from industrial units that make or use lead, lead alloys, or lead compounds. Lead in the soil is mainly due to the weathering of lead based paints from the heavy structures like bridges and buildings that stick firmly to the soil particle and settles in the upper layer of the soil. Lead used in gasoline and unleaded petrol and released by the automobiles contributes to lead in air. These soil particles when enters the water bodies do contaminate them too. They may also contaminate the water by getting released from the leaded pipes when the water becomes acidic. Surface water lead contamination is also due to lead containing dust from the environment and industrial effluents of iron and steel industries along with urban run-off.

Global lead toxicity – resulting from human activities is responsible to the great increased circulation of lead in soil, water and air – remains significant. Despite a century of cumulative evidence about its threat to the health of children, lead remains to be added to paints, pigments, toys, traditional medications and other

consumer products, especially as manufacturing shifts to low-income countries that lack environmental and product content controls and policies.

Lead toxicity has been under the radar of the environmentalist since the 1960s. Biologists have been concerned about the negative impact on health due to lead poisoning. It has been recognized as the major pollutants of environment. Central nervous system (CNS) of late has been identified to be affected due to lead poisoning [1].As mentioned earlier lead toxicity in the nervous system by CNS impairment in children leads to cognitive deficits[2-4]. Chronic exposure of this heavy metal is debilitating to the functional behavior of an organism[2-4]. Studies have repeatedly shown that acute exposure to Pb can lead to glial activation and secretion of cyto-chemokines in both *in vitro*and *in vivo*models[5-8].

Acute lead poisoning affects various organs in our body including CNS[9-12], gastrointestinal (GI) tract[13], blood and kidneys[14-16]. Manifestation of lead poisoning in CNS has been marked through pain, muscle weakness, numbness and tingling, and, rarely, symptoms associated with inflammation of the brain[17]. Other acute symptoms are nausea, vomiting, diarrhea,abdominal pain and constipation[18]. People who survive acute poisoning often go on to develop symptoms of chronic poisoning[18].Inorganic lead has been speculated to damage the PNS (peripheral nervous system) by causing peripheral motor neuropathy with paralysis ("wrist drop" and "ankle drop")[19, 20].

Chronic cases of lead poisoning generally associated with multiple tissues or organs but an in depth research in the field tells us that there are these three main types oforgan systems that are affected most: gastrointestinal, neuromuscular, and CNS[17]. CNSand neuromuscular diseases due to lead toxicity usually result from intense exposure, showing gastrointestinal symptoms mainly[18]. Chronic exposure of lead in CNS showsshort-term memory andattention, depression, abdominal pain, nausea, loss of synchronization, and numbness and itchiness in the extremities[21]. In chronic lead poisoning these problems like fatigue, headaches, stupor, problems with sleep, garbled speech, and anemia can be found[17].Hyperkinesia or aggressive behavior disorders has been typically observed in children suffering from an enhanced lead concentration with the tissue[17]. Visual disorder may exists with progressivelydevelopingblurry vision because of central scotoma, initiated by toxic optic neuritis[22-27].

It also accounts for most of the cases of pediatric heavy metal poisoning as it is shown to interfere with the development of the nervous system resulting in permanent learningand behavioral disorders[28, 29].Lead poisoning affects the PNS (especially motor nerves) and the CNS[19, 20].PNS effects are observed more prominently in adults and CNS among children[30]. This difference may be attributed to the development of the Blood-Brain-Barrier (BBB) or the immune system of the body[31-33]. Lead causes the axons of nerve cells to degenerate and lose their myelin coats[34-39].Lead exposure in has been observed to cause learning disabilities[3, 40-44], and children with more than 10µg/dL concentration of lead in their blood has been reported to suffer from developmental disabilities[45-47].The increase in concentration of lead in blood has an inverse correlation with intelligence, nonverbal reasoning, memory, attention, reading and arithmetic ability, fine motor skills, emotional regulation, and social engagement[48].Unfortunately for lead toxicity no threshold has been determined to interpret the level of cognitive abilities in children. As for example it has been reported that children suffer from reduced academic performance with low blood lead levels even below and blood lead concentration of 5 µg/dL[48-50].Although adults were not reported to develop CNS problems due to lead poisoning some cases are there that tells about high blood lead levels in adults are also associated with the increase in lead concentration in blood. A decrease in cognitive performance and psychiatric symptoms such as depression and anxiety has been associated with increase in blood lead poisoning[51].In Korea,it was found in a large group of inorganic lead workers had lead levels in blood(20–50 µg/dL) were associated with cognitive defects[52].Increase in blood lead levels from about 50 - 100 µg/dL in adults have been diagnosed to be associated with persistent, and possibly permanent, impairment of CNS function[53, 54].In the PNS, the motor axons are the primary target of lead toxicity. Lead-induced pathological changes in these fibers consist of segmental demyelination and axonal degeneration.

Extensor muscle palsy with wrist and ankle drop has been identified since the time of Hippocrates as the conventional clinical sign of the peripheral neurological toxicity of lead; however, this basically occurs with chronic lead poisoning and is uncommon in acute exposure to lead. In the CNS, lead causes asymptomatic malfunction of neuro-behavioral function in children at doses not sufficient to produce clinical encephalopathy.

Pre-natal exposure to lead and direct interaction to lead in human milk from conception onward, lead that has been preserved in the mother's skeleton in years past is eluted into the circulation under the metabolic stress of pregnancy. Throughout pregnancy, lead readily passes from the maternal to the infant circulation, and the blood lead concentration of the infant appears virtually same to that of the mother[55]. Once in the infant, Pb can get into the immature BBB to enter the developing brain[56]. The maturing human brain is particularly vulnerable to lead, even at very low levels of exposure. The source of lead in an infant's blood may be a mixture of about 2/3rdof dietary and 1/3rdof skeletal lead, as shown by studies that exploited the dissimilarities in lead isotopes stored in the bones of women migrating from Europe to Australia[57]. Although lead is found in human milk, the concentration is near to that of plasma lead and much less than that found in whole blood, so little is transferred to the infant. Because infant formulas and other foods for infants also consists of lead (as may the water used to prepare these foods), women with generally encountered blood lead concentrations who breast-feed their infants expose them to lesser lead than if they do not breast-feed. In Mexico, providing women supplemental Ca during lactation resulted in a (less than 2 µg/dl) decrease in the mother's blood lead concentration, perhaps by decreasing skeletal resorption[58]. In theory, this could further decrease the transfer of lead through breast milk. Mechanisms of lead neurotoxicity is one of the mechanisms underlying the neurotoxicity of lead motivates in its ability to substitute for other polyvalent cations (mostly divalent cations, such as calcium (Ca^{2+}) and zinc (Zn^{2+})) in the molecular mechanism of living organisms[59]. In various instances, the characteristics of lead approve it to bind with greater affinity than Ca and Zn ions to protein binding sites. These interactions allow Pb to affect various biologically important processes that includes metal transport, energy reactions, apoptosis, ionic conductivity, cell attachment, intercellular and intracellular signaling, diverse enzymatic processes, protein development, and genetic control. Membrane ionic channels and signaling molecules predicted to be one of the most relevant molecular targets that leads to lead's neurotoxicity; the developing CNS is particularly susceptible[55]. Irreversibility of Pb neurotoxicity the neuro-behavioral changes associated with early exposure to lead appear to be continued and irreversible[60-64]. These alterations are not reversed or ameliorated by chelation therapy[65]. There is an inverse correlation between early childhood exposure to Pb and performance on cognition and behavior 10, 15 and 20 years after the blood lead burdens were measured[66]. Early exposures have also been related to increased rates of hyper-activity, inattentiveness, failure to pass from high school, bad behavior, juvenile de-linquency, drug abuse and incarceration[60-62, 67-70]. In addition to that it has been observed in the US that the murder rate decreased sharply after the removal of Pb from gasoline in a 20-year lag[71], a finding related with the idea that exposure to lead in early life is a strong determinant of behavior decades later in adult life. Animal studies provide experimental proofs that support the connection between lead and aggression [72]. Thus, it is now quite clear that there are adverse neuro-developmental effects at the lowest blood lead concentrations yet to be studied. On the basis of this proof it is possible today to confirm that low concentrations of Pb are harmful to brain development and cognitive function. A threshold for harmful effects of Pb at the population level, however, has not been recognized[49, 73, 74].

II. EFFECTS OF LEAD ON IMMUNE SYSTEM

The immune system are also highly affected by comparatively low levels of exposure to lead – which is, lower than 10 µg/dl[75-77]. Prenatal exposure to lead and susceptibility of lead in human milk from conception onward, lead that has been accumulated in the mother's skeleton in years past is released into the blood stream under the metabolic stress of pregnancy. Throughout pregnancy, lead readily across the placenta and the blood lead concentration of the infant becomes identical to that of the mother [55]. Once in infant,

lead can spearhead through the immature BBB to enter the developing brain [56]. The human brain in developing stage is susceptible to very low level of lead exposure.

In addition to this, lead exposure has also been shown to be related with neurodegenerative disorders which have been reported to be caused due to plethora of intracellular targets, thereby contributing in many pathogenic processes, which may be characteristic of such disorders such as mitochondrial dysfunction, oxidative stress, along with brain inflammation. It has been shown that exposure to lead in early phase of development of the brain can precondition for developing neurodegenerative conditions later in life and heavy metals can exert adverse effects through acute neurotoxicity or through slow accumulation during prolonged periods [78].

Brain is one of the major target organs of this heavy metal poisoning where severe neurological complications may arise after exposure. Lead has been reported to damage the nervous system microvasculature extensively [79]. In their study, Garcia-arenas et al. have theorized that lead exposure increases the production of inducible nitric oxide synthase (iNOS) in capillaries of the CNS [79]. However the findings of this study was in debated by the recent observations that suggested that inflammation may play a vital role in lead mediated toxicity [80]. Numerous studies on Pb neurotoxicity have indicated this metal to be a dangerous toxin, particularly during the developmental stages of higher organisms [81].

This phenomenon is accompanied by degeneration of neuronal cells and may be connected with inflammatory events owing to the production of a wide range of cytokines and chemokines [82]. Prolonged exposure to lead has also been examined in animal models including rats in a prenatal stage of their life cycle. In order to investigate its potential pro-inflammatory effects, morphology of microglia has been studied after exposure to high concentration of lead. Pb exposure leads to significant glial activation, and is marked by increased levels of glial fibrillary acidic protein (GFAP) and S-100 proteins in all parts of the brain [82]. These modifications are related to elevation of pro-inflammatory cytokines {interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)}in hippocampus and forebrain mostly. The results specify chronic glial activation is noticeable by inflammatory and neurodegenerative features as a new mechanism of Pb neurotoxicity in postnatal rat brains [7].

Before the acknowledgement of brain macrophages (microglia), the innate mechanisms driving the pathogen clearance were not well understood. It is now well accepted that activation of microglia is crucial for the clearance of pathogens within the CNS [83, 84]. However, an exaggerated and sustained response may prove to be detrimental for the health of neurons and therefore, acute as well as chronic activation of microglia is often associated with neuro-inflammatory and neurodegenerative conditions of the brain. Once activated, they may either release pro-inflammatory or anti-inflammatory cytokines, and a balance between the two decides whether it results in active inflammation. Pro-inflammatory mediators often result in a compromise of the integrity of the BBB allowing the peripheral leukocytes and macrophages to gain entry into the CNS. It has already been proven that lead can result in activation of microglia and production of proinflammatory cytokinesincluding IL-1β and TNF-αboth *in vivo* and *in vitro* [85]. These cytokines play an important role in neurodegeneration when microglia remains in a state of sustained activation.

III. NEUROINFLAMMATION AND IMMUNE RESPONSE

The central nervous system varies from the other body systems and its response to pathogenic encounters is a little changed. In compare to the remarkable view that the central nervous system (CNS) is an immune-privileged organ, deficient a lymphatic system and protected from the circulatory system by the blood-brain barrier current studies and evidences have led to noteworthy of this idea. The CNS has been found to have its own private system of fighting through inflammatory response and an adapted system of immune-surveillance with coordination with the systemic immune system is also evident [86, 87]. However,

the inflammatory reaction of the other tissues and the brain are different. This is most evident in leukocyte recruitment, which is rapid in many systemic organs, but modest and delayed in the brain. Although delayed response in recruiting leukocytes in brain against rapid activation of brain's own immune cells and release of inflammatory agents [88]. Inflammation in the brain is categorised by activation of glial cells (mostly micro-glia and astrocytes) and expression of key inflammatory mediators as well as neurotoxic free radicals. In CNS, microglia plays a key role in innate immune response as resident macrophages and astrocytes helps to maintain extra acellular ion balance and provide nutrients to the nervous system [89].The activation of those glial cells are giving key inflammatory response into the CNS.

IV. MICROGLIA: The immune cells of the central nervous system (CNS)

Microglia are the resident immune cells of the CNS and constantly patrol the cerebral microenvironment to respond to pathogens and damage. Microglial cells are ubiquitous throughout the CNS and are well placed to sense changes in the health of neurons and glia. They are believed to be of mesodermal origin, derived from bone marrow precursor cells that enter the CNS early in fetal development, and thus represent a cell population separate and distinct from peripheral macrophages [90-92]. They are positioned immediately adjacent to neuronal cell bodies and are interspersed among the oligodendrocytes and astrocytes of the white matter. In their resting or ramified state, they have long, highly branched processes that extend into the parenchyma of the CNS. Microglia possesses numerous cytokine and chemokine receptors, which endow them with the capacity to respond to cytokines released after insults to the CNS [93, 94]. The function of normal, resting microglia is not known, however it is thought that they serve as a surveillance and monitoring role in the CNS. Microglia are the primary glial cells implicated in CNS inflammation. They are of the monocyte/macrophage lineage, which are resident in the brain and are activated in response to infection, inflammation and injury [95]. Microglial cells are ubiquitous throughout the CNS and are well placed to sense changes in the health of neurons and glia. They are positioned immediately adjacent to neuronal cell bodies and are interspersed among the oligodendrocytes and astrocytes of the white matter. In their resting or ramified state, they have long, highly branched processes that extend into the parenchyma of the CNS. Microglia possesses numerous cytokine and chemokine receptors, which endow them with the capacity to respond to cytokines released after insults to the CNS [93, 94]. The function of normal, resting microglia is not known, however it is thought that they serve as a surveillance and monitoring role in the CNS.

V. ROLE OF MICROGLIA IN NEUROINFLAMMATION

Microglia are extremely sensitive to neuronal health and are often the first cell population in the CNS to respond to such changes. By acting as APCs and controlling the transition to the adaptive immune response, microglial cells are mediators of the innate response in the CNS [96-99]. Therefore, microglial activation is a hallmark of almost all brain pathologies, including although not limited to trauma, stroke and different viral and parasitic meningitis [100, 101]. Microglia are activated rapidly in response to such insults, and take on the morphology of activated macrophages. They are important phagocytic cells and release numerous inflammatory molecules, particularly cytokines [102, 103]. After stimulus microglial activation follows a stereotypic pattern of cellular response. Ramified, quiescent microglia, in response to an activation stimulus, proliferate and migrate to the site of injury or inflammation [104-107]. Once there they undergo additional immune-phenotypical and functional changes. They increase or express, de novo, a number of immune related proteins such as complement factors, cytokines (IL-1, IL-6, TNF-α, IL-18) [93, 100-102], chemokines (MCP-1, MIP-1α, MIP-1β, RANTES) [93, 108-110], major histocompatibility molecules (MHC) [111] vascular endothelial growth factor (VEGF) [112-114], lymph toxin, matrix metalloproteinases (MMPs) [115, 116]. VEGF, NO, and MMPs can weaken the BBB, thus enhancing the infiltration of leukocytes into the CNS. Functionally they release a repertoire of inflammatory mediators (like iNOS and Cox-2), prostaglandins

[115, 117] and reactive oxygen species (ROS) [118, 119].

Microglial activation may also be viewed as an adaptive response, whereby microglia release neuro-protective factors to facilitate the recovery of injured neurons and they phagocytose dying neurons, before they lyse and release toxic agents into surrounding areas. Experimental data concerning the role of inflammatory processes, including microglial activation, in CNS damage have shown that neuroinflammatory process can support neuronal survival through multiple mechanisms [120-123]. The temporal profile of neurotrophic factor induction that follows the endogenous production of pro-inflammatory cytokines after injury points to a potential role of the inflammatory response in mediating neurotrophic responses. TNF-α and IL-1 are two of the main cytokines that are detected within parenchymal microglia along the lesion site [124], and a role for IL-1β in the induction of nerve growth factor expression by astrocytes has been reported [125, 126]. Microglial-derived IL-1 is also required for the astrocytic production of ciliary neurotrophic factor (CNTF) [124] and insulin-like growth factor 1 (IGF1) [127], both of which promote repair of the injured CNS. Remyelination is impaired in mice that lack IL-1β, and there is also a profound delay in the differentiation of oligodendrocyte progenitors [127]. The activation of microglia and astrocytes, which is indicative of inflammation, occurs in the CNS of patients with Alzheimer's, Parkinson's and Huntington's diseases, multiple sclerosis and ALS [98, 128, 129]. The serum and cerebrospinal fluid of these patients show elevated levels of molecules of the innate immune system, such as IL-6, IL-1β and TNF-α[98, 128, 129]. IL-1β and TNF-α are secreted by activated parenchymal microglia and can be potent inducers of cell death in models of neurodegeneration, which can be alleviated by anti-inflammatory drugs and neutralizing antibodies [128, 130-133].

VI. MECHANISMS OF LEAD NEUROTOXICITY

One of the mechanisms influencing the neurotoxicity of lead lies in its ability to substitute for other polyvalent cations (particularly divalent cations, as for example calcium (Ca^{2+}) and zinc (Zn^{2+})) in the molecular machinery of living organisms [59]. Conventionally the characteristics of lead facilitates it to bind with greater affinity than calcium and zinc ions to protein binding domains affectingmetal transport, energy metabolism, apoptosis, ionic conduction, cell adhesion, different enzymatic processes, intercellular and intracellular signaling, protein maturation, and genetic modulation. Membrane ion channels and signaling molecules have been observed to be one of the most potent molecular targets that contribute to lead's neurotoxicity; the developing CNS is particularly vulnerable [55].
An overview of some of the key pro-inflammatory mediators relevant to our study and their effects on CNS are listed below.

6.1 Tumor Necrosis Factor (TNF)-*α*:

The 17kDaproinflammatory tumor necrosis factor-α binds to its receptor constitutively expressed in both neuron and glia [134]. TNF-α per se can be synthesized and released in the brain by astrocytes, microglial, and some neurons [130, 135-137]. Under various pathological conditions, such as trauma, ischemia, and inflammatory diseases (HAD, MS, AD), the expression and release of TNF-αare rapidly increased in the CSF and plasma [133, 138-140]. CNS damage can also increase TNF-αactive transport into the brain [141]. TNF-αis known to increase oxidative stress in the CNS through ROS generation[142]. TNF-α also induces caspase-3 activation that causes apoptotic neuronal cell death in hippocampal cultures [143]. Inflammatory factors found in brain trauma [144]such as TNF-αreleased by glia causingneuron degeneration *in vitro*[145, 146] and *in vivo*[147, 148].Previous results indicated that PKC-MEK-p42/44 MAPK is a common signaling pathway for lead induced TNF-αexpression in glial cells[148]. Maternal exposure to lead affects hippocampal long-term potentiation (LTP) leading to learning and memory deficits in mice offspring [85]. It also affects the expressions of multiple SNARE proteins (SNAP-25, VAMP-2, and Syntaxin 1A) in the hippocampus [149]. Pb can secrete cyto-chemokines, resulting in subsequent neuroblastoma death via BV-2 mouse microglial activation. Action of lead culminates into up-regulation of extracellular signal-regulated

kinase (ERK) and protein kinase B (Akt) pathways, along with activation of an important transcription factor, nuclear factor-κB (NF-κB) leading to increased level of TNF-α[5].

6.2 Interleukin-6 (IL-6):

IL-6 is a typical pleiotropic cytokine [150, 151], originally identified as a factor in the induction of immunoglobulin production in B lymphocytes. IL-6 is a glycoprotein cytokine that mediates signal transduction between immune cells, induces acute-phase protein synthesis, and controls growth and differentiation of cells of the immune and hematopoietic systems. In the nervous system, IL-6 likely is a trophic factor that, under some circumstances, supports neuronal and glial differentiation and survival [152]. In addition to these potentially beneficial effects of IL-6, there has been a growing appreciation of the destructive potential of elevated levels of IL-6 in the CNS [152]. IL-6 levels in the adult CNS are usually low or undetectable under baseline conditions, but increase dramatically in response to injury, inflammation, and CNS diseases like EAE. IL-6 produces its effects by binding to IL-6 receptors (IL-6Rs), which form complexes with gp130. Once formed, the IL-6/IL-6R/gp130 complex stimulates the 2 main signal transduction cascades (JAK/STAT and Ras/MEK/MAPK) that lead to activation of a number of transcription factors responsible for IL-6–mediated effects [153]. IL-6 is also involved in several neurological and neuropathological disorders. For example, IL-6 levels are elevated in the CNS during AD, multiple sclerosis, as well as during viral and bacterial meningitis [154, 155]. IL-6 is also known to enhance BBB permeability and inflammatory cell migration into the brain [156]. It has been also found that Pb exposure in C57BL/6J mice caused dose dependent reductions in interleukin 6 [157, 158].

6.3 MCP-1:

Chemokines are small, inducible, secreted, proinflammatory cytokines acting primarily as chemoattractants and activators of granulocytes, macrophages and other inflammatory cells [159, 160]. The accumulation of inflammatory cells, mediated by chemokines in the immediate microenvironment, is an early event in response to wounding and injury in peripheral organs [161-163] as well as the brain [164-166]. In vitro and in vivo data support the hypothesis that gradients of locally generated chemotactic factors are responsible for the recruitment of inflammatory cells into the CNS parenchyma leaking the BBB [167-169]. Each chemokine has cellular specificity and potency for the attraction of particular cells [160]. MCP-1 is one such chemokines, which is known to regulate BBB permeability [170] may be by altering the expression of tight junction associated proteins in brain microvascular endothelial cells [171]. MCP-1 was originally identified as a growth factor-inducible early-response gene in murine fibroblasts. More recent studies have shown that mature secreted MCP-1, a 76 amino-acid protein, has cytokine-like properties [172]. MCP-1 exerts its effects through its receptor, C-C chemokine receptor type 2 (CCR2), which can have both pro- and anti-inflammatory actions [173]. Pro-inflammatory cytokines, TNF-αand IL-1β also stimulate the production of MCP-1 from astrocytes and microglia. In addition, MCP-1 can also be stimulated by IL-6 and colony stimulating factor-1 (CSF-1). Several reports have shown that MCP-1 plays a role in the CNS diseases including human gliomas [174, 175], experimental autoimmune encephalomyelitis (EAE) [176] and may also play a crucial role in neuropathic pain as shown by studies in CCR2-knockout mice, which could be attributed to reduced macrophage infiltration in these mice [177]. The cellular source of MCP-1 in brain, however, remains controversial. Both macrophages and astrocytes have been suggested as a possible source of MCP-1 both in vivo and in vitro [176, 178-180]. Pb leads to secretion of cyto-chemokines, resulting in subsequent neuroblastoma death via BV-2 mouse microglial activation.Action of lead is also characterized by up-regulation of extracellular signal-regulated kinase (ERK) and protein kinase B (Akt) pathways, along with activation of an important transcription factor, nuclear factor-κB (NF-κB) leading to increased level monocyte chemoattractant protein-1 (MCP-1)[5].

6.4 Cox-2:

Also known as prostaglandin H synthase, Cox-2 catalyzes the rate-limiting step in the inducible production of prostaglandins like prostaglandin E(2) (PGE2) from arachidonic acid [181], which is then converted to active prostanoids by synthases [182]. Cox-2 is expressed in different brain cells, especially microglia and is responsible for the production of high levels of prostanoids during acute or chronic neuroinflammation [183]. A variety of stimuli, including growth factors, cytokines, bacterial endotoxins and phorbol esters can elicit Cox-2 expression [184]. PGE2 has the capability to down-regulate important glial functions including cytokine secretion by astrocytes and microglia. For example, in a study it was shown that PGE2 inhibited the up-regulation of IL-12p75 in microglia stimulated with inflammatory agents including LPS [185]. Pb induces secretion of cyto-chemokines, resulting in subsequent neuroblastoma death via BV-2 mouse microglial activation and up-regulation of Cox-2[5].Lead sets up a cascade to bring in COX-2 expression in glial cells.Study has confirmedthat for COX-2 induction in neurons and glia, lead toxicity played a key role [186].

VII. TRANSCRIPTIONAL REGULATION OF MICROGLIAL ACTIVATION

Secretion of cytokines is an active process and transcription factors play a crucial role in the activation of microglia. Owing to our knowledge of important regulators and key targets of inflammatory mechanisms in the CNS and immune responses to neurological diseases, it is clear that a complex nature of transcription biology operates at the heart of inflammation [187].Of the several pro-inflammatory transcription factors that are known to be involved in different aspects of inflammation [188], NF-κB is considered as one of the key transcription factors which culminates into inflammatory pathway activation via microglial activation [189].Any of the microglia mediated pro-inflammatory stimuli can activate NF-κB expression [190], which can further induce specific genes that regulate the expression of inflammation and acute phase genes leading to the continued elevation of inflammatory proteins.

7.1 NF-κB Pathway in neuro-inflammation:

NF-κB is a family of dimeric transcription factors involved in immune [191]and inflammatory responses [188, 192], cellular growth, differentiation, and apoptosis [193, 194]. They have also been implicated in cellular transformation and tumorigenesis [195]. Activation of NF-κB can occur through various stimuli, including cytokine stimulation, bacterial and viral infection, and oncogenic signals [194]. Although nuclear accumulation is an important step in NF-κB activation, post-translational modifications on p65 are proposed to be necessary for the transcriptional competence of nuclear NF-κB. For example, phosphorylation of p65 on serine 276 is required for stable interactions with the transcriptional co-activator CBP and to stimulate transcriptional activation of NF-κB target genes [196, 197].Other sites of phosphorylation have also been described that may contribute to the inherent transcriptional activity of NF-κB [198-200]. Evidence has also been presented that Akt, which functions downstream of PI3-kinase, can control the transcriptional activation function of the p65 NF-κB subunit through a mechanism dependent on IKK function but in a manner which does promote enhanced DNA binding potential [201, 202]. Pb enhances secretion of cyto-chemokines, culminating into subsequent neuroblastoma death via BV-2 mouse microglial activation. Up-regulation of extracellular signal-regulated kinase (ERK) and protein kinase B (Akt) pathways, along with activation of an important transcription factor NF-κB is also associated with action of lead upon CNS[5].

VIII. SIGNALING PATHWAYS INVOLVED IN MICROGLIAL ACTIVATION

Kinase and phosphate cascades induce microglial response to extracellular stimuli. p38 mitogen-activated protein kinases are a class of mitogen-activated protein kinases(MAPK) and are reported to respond to stress stimuli and have been demonstrated to play a significant role in activation of microglial cells which in turn leads to release of neurotoxic molecules and neuroinflammation [203, 204]. In vivo experiments also imply that p38 and p44/42 MAPKs play an important role in microglial activation in acute brain injury states such as stroke and in chronic neurodegenerative diseases such as Alzheimer's disease. A MAPK pathway generally consists of the following 4 sub-pathways:

8.1 Extracellular-signal-regulated kinases (ERK1/2):

Extracellular-signal-regulated kinases (ERK1/2 also known as p44/42 MAPK); Extracellular signal–regulated kinases(ERKs) or classical MAP kinases are widely expressed kinasemolecules that play vital roles in the regulation of meiosis, mitosis, and post mitoticfunctions in differentiated cells and many other signalling cascades. Many different stimuli including cytokines, virusinfection, growth, ligands for heterotrimeric G protein-coupled receptors, transforming agents and carcinogens result in the activation of ERK pathway therefore stimulating appropriate physiological response.Experimental evidence supports the fact that extracellular signal-regulated kinase 1/2 (ERK1/2) signaling plays a pivotal role in the embryonic development of the central nervous system (CNS) and in the maintenance of normal adult brain physiology [205].ERK1/2, one of the most well characterized members of the mitogen-activated protein kinase family which regulates plethora of processes ranging from metabolism, motility and inflammation, to cell death and survival [206-208]. In the nervous system, ERK1/2 regulates synaptic plasticity, [209, 210] brain development and repair [211-214] as well as memory formation [215, 216]. ERK1/2 is also reported to be a potent effector of neuronal death and neuroinflammation in many CNS diseases [206-208, 217-219]. Pb can secrete cyto-chemokines, resulting in subsequent neuroblastoma death via BV-2 mouse microglial activation and up-regulation of extracellular signal-regulated kinase (ERK) pathway[5].

8.2 c-jun N-terminal kinases/stress-activated protein kinases (JNKs/SAPKs):

C-Jun N-terminal kinases (JNKs), were originally identified as kinases that bind and phosphorylate c-Jun on Ser-63 and Ser-73 within its transcriptional activation domain.JNKs belong to themitogen-activated protein kinasefamily, and are responsive to stimuli, such ascytokines,UV irradiation, heat shock, andosmoticshock.T celldifferentiation [220, 221] and the cellularapoptosispathway are also reported to be modulated by JNK activity [222, 223]. Works support the fact that this signaling pathway contributes to inflammatory responses in mammals and insects [224, 225]. Inflammatory signals, perturbations in levels of reactive oxygen species, ultraviolet radiation, protein synthesis inhibitors, and a variety of stress stimuli may outcome in JNK stimulation.

One way this activation may occur is through disruption or alteration of the conformation of sensitive protein phosphataseenzymes which normally are reported to inhibit the activity of JNK itself and the activity of proteins linked to JNK activation [226].Following their activation, JNKs are reported to interact with scaffold proteins like JNK interacting proteins as well as their upstream kinases JNKK1 and JNKK2. JNK1 is elaborate in apoptosis [222], neurodegeneration [227], cell differentiation [220, 221] and proliferation [228, 229] inflammatory disorders and cytokine production [224, 225] mediated by AP-1 (activation protein 1) for example RANTES, IL-8 and GM-CSF [230].Recently reports have demonstrated JNK1 to modulate Jun protein turnover by phosphorylation followed by activation of the ubiquitin ligase Itch [231, 232].Studies showed that lead toxicity can be seen on adult neural stem cells and impair the normal processes in hippocampal neurogenesis which may be induced by activation of c-Jun NH2-terminal kinase (JNK) [233].

8.3 p38 MAPK:

P38 mitogen-activated protein kinasesare a class of mitogen-activated protein kinases (MAPKs) also known as Cytokinin Specific Binding Protein (CSBP) [234], respond to different stress stimuli such as cytokines, ultraviolet irradiation, LPS treatment, heat shock or osmotic shock. These proteins also take part in cell differentiation, apoptosis and autophagy [234].Lead toxicity leads to activation of p38 mitogen activated protein (MAP) kinase signaling pathway which may play a crucial role in neural degeneration [233].

8.4 Akt Pathway:

For survival and growth PI3K-Akt Pathway is a key signal transduction pathway which respond to extracellular signals. In this regard, proteins involved are phosphatidylinositol 3-kinase(PI3K)and Protein Kinase B (Akt).Functional Akt intermediates downstream responses, including cell proliferation, survival, cell migration, cellgrowth, and angiogenesis, by phosphorylating various intracellular proteins. Akt pathway is existing in all cells of developed eukaryotes and it is extremely well-preserved [235].The pathway consists of multiple mechanisms including cross talk with various signalling attributes. Akt phosphorylates several 100 diverse substrates, foremost to an extensive variety of effects on cells [236].Pb can secrete cyto-chemokines, resulting in subsequent neuroblastoma death via BV-2 mouse microglial activation and up-regulation of protein kinase B (Akt) [5].

IX. CONCLUSION

As relatively few studies are available particularly regarding the neurotoxicity by the activation of microglia due to exposure of lead, this topic is now of great concern as Pb toxicity is prevalent in natural resources. Though the process of inflammatory response due to lead toxicity in CNS is not fully demonstrated but it has some obvious key role in neurodegeneration. It is evident from studies related to expression of cytokines, chemokines and activities of enzymes consists of caspases, proteases, nitric oxide synthetase, cyclooxygenase-2 etc., which can immensely influence the cross-talk between the immune cells in the CNS (figure 1). Undoubtedly, the role of microglia in neurodegeneration due to heavy metal toxicity need further research to gain greater insights into the molecular and inflammatory processes as environmental pollution is now a relevant factor which is affecting the society on daily basis.

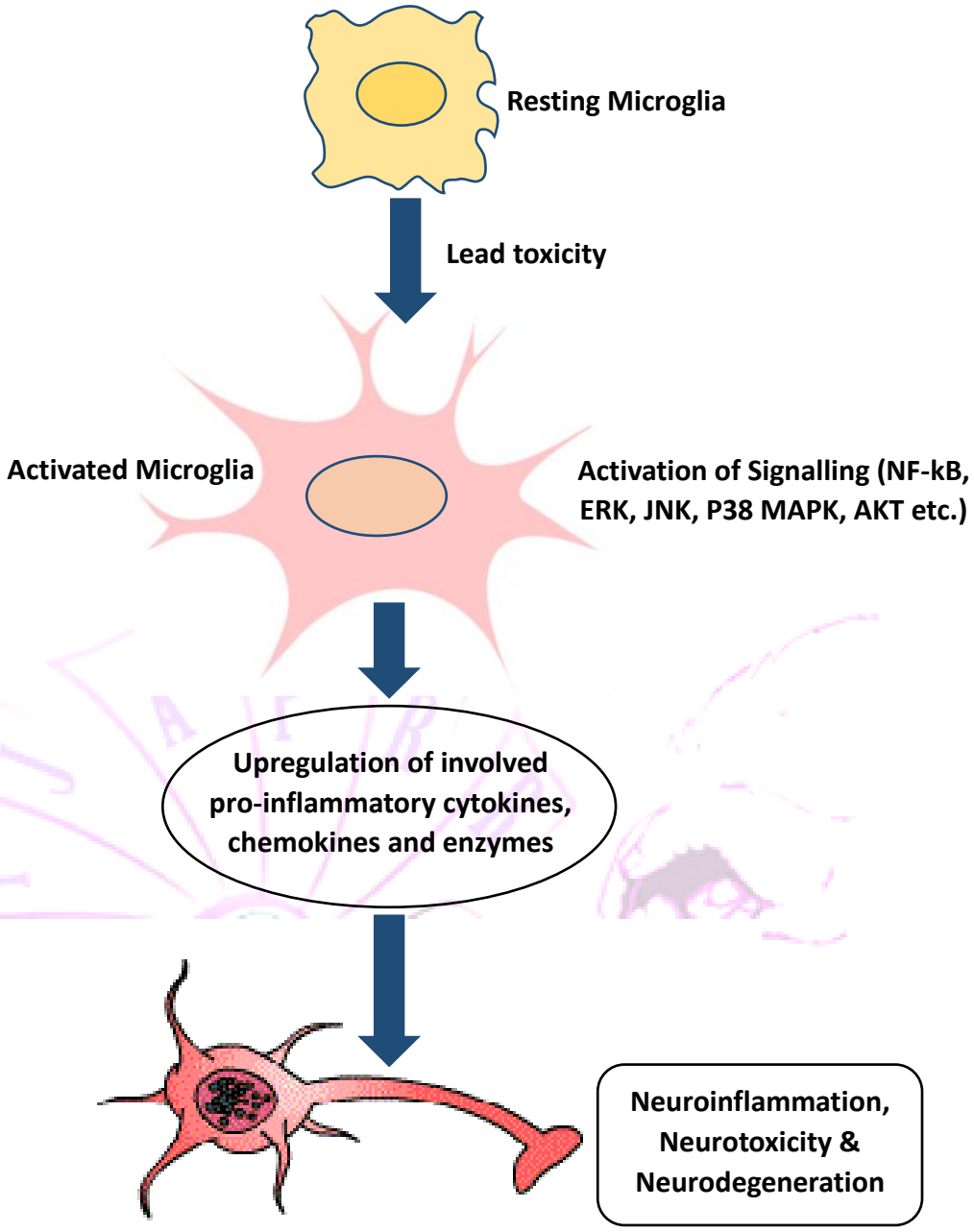

Figure: 1. Schematic diagram showing lead-induced microglial activation and neuronal

X. ACKNOWLEDGEMENT

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XI. CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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