Chapter

Epigenetics and Lead Neurotoxicity

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Abstract

Lead exposure continues to threaten human health in a worldwide perspective. Among the multiple target organs affected by lead, central nervous system (CNS) pervades in the adverse consequences by chronic lead exposure, leading to a variety of neurotoxic manifestations and neurological disorders. The epigenetic machinery plays a vital role in the control of key neural functions, particularly neuronal development. Faulty epigenetic gene regulation can have marked deleterious effect on the developing brain that can last for an entire lifespan. Mounting evidence suggests that lead exposure can pose detrimental effect on CNS through these epigenetic mechanisms. And this chapter reviews the current understandings of concrete epigenetic forms, exemplified by DNA methylation, histone modification, and ncRNAs, responding to lead exposure and moderating the consequent neurotoxicity. In addition, Alzheimer's disease (AD) is presented as a typical instance to explain how environmental lead exposure results in the occurrence of AD in an "early exposure, late onset" fashion. A future perspective, highlighting additional forms of epigenetic elements as well as interactive actions among different molecules, was also proposed. In summary, epigenetics was substantially implicated in regulating lead neurotoxicity.

Keywords: epigenetics, lead neurotoxicity, DNA methylation, histone modification, ncRNA, Alzheimer's disease

1. Introduction

Lead (Pb) is a ubiquitous and persistent neurotoxicant that continues to threaten human health in a global perspective [1]. Although lead has been removed from paints and gasoline, it remains a serious concern as it can still be found in a variety of daily products, including toys, batteries, food, and water [2]. Although Pb poisoning is a preventable disease, thousands of new cases in the United States were reported each year, and about 500,000 children under 5 years old have blood lead levels (BLLs) greater than a threshold level of 5 g/dl, according to Centers for Disease Control and Prevention (CDC) reports [3–7]. Elevated BLLs have become the first noninfection condition to be notifiable at the national level [7]. Lead can cause a series of adverse human consequences at a very low level exposure [8]. Therefore, CDC continually decreased the safe threshold of BLLs, and the current "safe" levels of exposure to lead are 5 mg/dl for children, but still there have been studies to identify cognitive impairments below that dosage, implying that "no level of lead exposure is safe" [6, 9].

Lead pervades many organs and systems in the human body, but the prime target of lead toxicity is CNS, both in adults and in children [10], resulting in the so-called "neurotoxicity." The developing brain is particularly susceptible to lead neurotoxicity, as demonstrated by several epidemiological and experimental studies [2, 3]. Due to the fact that lead can freely cross blood brain barrier, lead neurotoxicity can also be manifested in adults, with a larger exposure dosage. Particularly, it should be noteworthy that early life exposure to lead can produce persistent alterations in the brain structure of adults, causing lasting impairment of brain function and behavior [3, 11]. Adverse neurotoxic effects caused by lead include intellectual and behavioral deficits in children; deficits in fine motor function and coordination; and deficits in lower performance on intelligence tests [10]. Higher level of lead can cause a wide spectrum of neurological disorders, such as convulsions and coma, including multiple instances of neurodegenerative disorders, such as AD and Parkinson's disease [12–15]. Thus, there is a critical need to understand the mechanisms of lead neurotoxicity.

Among the cellular and molecular mechanisms suggested to underlie lead neurotoxicity, amounting evidence underscored roles of epigenetic molecules. This fast-moving filed of epigenetics has opened a novel avenue of research for understanding how environmentally toxic signals like lead exposure could be readily sensed by organisms and then relayed to reprogram the expression of key functional genes, consequently giving rise to neurotoxic manifestations [3, 16–19]. This chapter is aimed to discuss the advances of epigenetic alterations in response to lead-induced neural deficits, focusing on the concrete epigenetic species and their responsive details. We will also present a synoptic view of epigenetic implications in etiology of AD caused by long-term lead exposure and bring out the possible future perspectives of the related research topics.

2. Molecular mechanism of lead-induced neurotoxicity

Since lead was found to mediate severe neurological impairment toward both children and adults, myriad studies were appreciated to decipher the cellular and molecular alterations underlying this neurotoxic incident. Several routes of action have been most commonly proposed, such as oxidative stress, disruption of blood brain barrier, decreased cellular energy metabolism, deregulation of calcium signaling, and abnormal neural transmission [3, 20]. In terms of relevance to neuronal development and synaptic transmission, postsynaptic mechanisms represented by N-methyl-D-aspartate receptor (NMDAR), presynaptic mechanisms, and brain-derived neurotrophic factor (BDNF) signaling were shown to be involved in lead neurotoxicity [8, 21].

NMDR plays an essential role in hippocampus-mediated learning and memory, and its dysfunction is associated with spatial learning abnormalities, as well as dendritic atrophies [22]. Lead regularly disrupted NMDAR function by acting as a potent antagonist. Apart from it, lead exposure also disrupts normal NMDAR ontogeny, such as reducing NR2A content, altering expression of NR1 splice variants [23, 24].

Chronic lead exposure also results in impaired neurotransmission. A previous finding showed that chronic lead exposure reduced Ca^{2+}-dependent glutamate and γ-aminobutyric acid (GABA) release in the rat hippocampus [25, 26]. And in cultured hippocampal neurons, lead exposure was found to impair excitatory postsynaptic currents (EPSCs) and inhibitory postsynaptic currents (IPSCs) [27]. Our lab recently published a finding that chronic lead exposure can inhibit the release of neurotransmitters by interfering with its vesicle pool recycling, and the main protein impacted is synapsin 1, which expression and phosphorylation was prone to lead invasion [28].

An emerging theme involved in lead neurotoxicity is the disruption of brain-derived neurotrophic factor (BDNF) expression. BDNF is a trans-synaptic signaling molecule that is released from both dendrites and axons [29]. In response to lead exposure, BDNF levels in cell cultures were downregulated, and the exogenous addition of BDNF can rescue the deleterious effect of Pb [30]. As a regulator of Ca^{2+} signaling and homeostasis, BDNF perturbation in turn led to the disrupted Ca^{2+}-dependent pathways, which compromise severe neural representations caused by lead exposure [31]. As an alternative consequence, lead impaired the hippocampal dendritic spines, reduced their density, and changed their morphology [32].

These neuronal and molecular processes might reflect variable aspects of lead-induced neurotoxicity. Compared to it, roles of global regulators, such as the emerging epigenetic regulators, are not sufficiently understood. However, given the conformity with outstanding characteristics of lead neurotoxicity, like "early exposure, persisted effect," epigenetics was long hypothesized to be implicated in the etiology of lead-induced psychological disorders [3]. This was supported by further identification of lead exposure as a risk factor of Alzheimer's disease and schizophrenia. Our next section will focus on epigenetic determinants involved in lead-led neurological damages and diseases [33, 34].

3. Epigenetic mechanisms

Epigenetics is defined as the heritable changes in gene expression that are not related to alterations in the genetic code [3]. Epigenetic regulation is found to modify the conformational state of chromatin and the accessibility of specific gene promoters to the transcriptional machinery [14]. There are three main epigenetic mechanisms broadly studied: DNA methylation, posttranslational modifications of histones, and noncoding RNA (ncRNA) [35–37]. The basic modes of action of three epigenetic forms were shown in **Figure 1**. DNA methylation is the most-studied epigenetic mechanism, which involves primarily cytosine methylation of Cytosine Guanine dinucleotides (CpG) via DNA methyltransferases (DNMTs). CpG methylation is often linked with transcriptional inhibition as it interferes with the normal binding and activity of transcription binding proteins [38]. The exception to this is CpG islands, which are CpG-rich sequences that are densely populated with unmethylated CpGs [2]. CpG islands offer the possibility of being differentially regulated by the environmental signals, which are a prime site to study the influence of lead on epigenetic determinants of ensuing neurotoxic phenotypes [39].

Gene expression is also regulated by histone modifications [36]. Histones are alkaline proteins that wrapped around DNA in nucleosomes and moderated gene transcription by modulating chromatin compaction and accessibility [40]. The terminal tails of histone can undergo covalent posttranslational modifications (PTMs), which in turn alter their interaction with DNA. Diverse modification forms were discovered and studied, as well as their influence on transcription of objective genes, including acetylation, phosphorylation, methylation, and ubiquitination [2]. The complex forms of histone modifications could coexist in regulating a common gene or genome, establishing an intricate and complex regulatory network called "histone code" [41, 42]. The proposal of this definition opens an avenue to show the potential accuracy and delicacy of gene expression regulation, via the action of histone modifications, which are operated by corresponding enzymes, such as histone acetyltransferases, histone deacetylases, histone methylases, and histone demethylases. Among them, histone deacetylases have been widely studied and identified as key molecular targets for pharmaceutical interventions [43, 44].

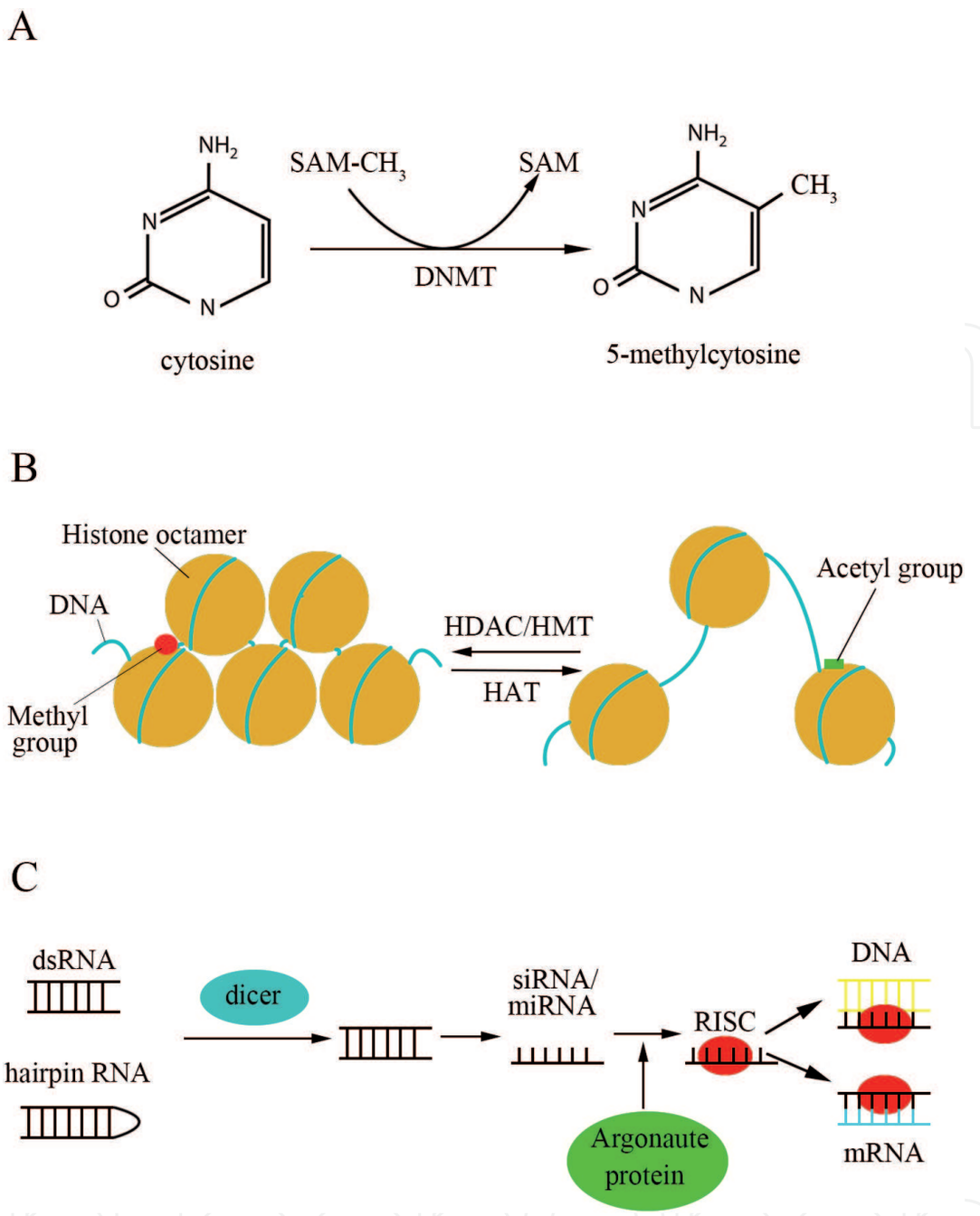

Figure 1.
Types of epigenetic modifications. (A) CpG methylation; (B) histone modifications represented by acetylation and methylation; (C) biogenesis and inhibitory action of microRNA (miRNA).

Another layer of epigenetic regulation involves noncoding RNAs (ncRNAs), defined as functional RNA molecules that are not translated into proteins [3]. The category of ncRNA with relevance with epigenetic regulation is composed of microRNA (miRNA), lncRNA, piRNA, and snoRNA, which regulate gene expression at both transcriptional and posttranscriptional levels [37]. miRNA received the most attention among them, and details of miRNA types involved in various epigenetic regulation and neuronal processes were studied comprehensively. For instance, a recent publication revealed that a series of miRNAs can respond to and mediate spinal muscular atrophy pathogenesis [45]; miR-137 participated in the modulation of neuronal maturation by targeting an ubiquitin ligase mind bomb-1 [46].

The different forms of epigenetic regulation are often functionally interlaced, showing an interactive relationship. DNA methylation was commonly accompanied by a specific form of histone methylation, establishing a so-called "hand-in-hand"

assembly [47]. Histone deacetylase can be recruited by DNA methylation or its functional partner, and these molecules can cooperate with each other to determine (most commonly inhibit) the expressional status of the objective gene [48]. DNA methylations and histone modifications are both involved in establishing patterns of gene expression, and they may play distinct roles in inducing persistent or intermittent gene expression changes [14].

Epigenetic mechanisms are implicated in neuronal development, maintenance of cell identity, and aging process [49, 50]. Meanwhile, epigenetic perturbations that lead to chromatin remodeling are in association with a number of neuropsychiatric and neurodegenerative disorders [14, 51], and they are particularly relevant in response to environmental toxicant exposure early in life [38]. The impact of epigenetic determinants can be long lasting, or even transgenerational, that is, the epigenetic traits and gene expression patterns can be sometimes inherited by next generations, which are not previously exposed to the causative agents [52].

4. Lead-induced epigenetic alterations in CNS

Considering that epigenetic factors are associated with CNS functioning and meanwhile susceptible to environmental exposure, we next discuss the epigenetic outcome brought by lead exposure and the roles of these changes in the etiology and development of lead neurotoxicity.

The relations of lead exposure with neural epigenetic alterations have long been established. Developmental lead exposure results in a variety of epigenetic changes, characterized by DNA methylation alterations, which can impact gene expression patterns and affect nervous system development [5]. Lead can promptly affect the dynamism of epigenetic determinants and promote the rapid turnover of DNA methylation [4]. Consistent with these findings and statements, lead is known to be an epigenetic modifier [53]. The following are advances of three main epigenetic systems associated with lead neurotoxicity:

4.1 DNA methylation

Lead exposure can result in the global changes of DNA methylation profiles in CNS, and the detailed orientation of methylome changes varied depending on the studied genetic microenvironment. Singh et al. stated that developmental lead exposure disrupted the hippocampal methylome, and the effect is dependent on the gender, timing, and level of exposure [5]. In particular, the global methylome alterations did not reflect the methylation status of the specific genes. That identified low-level lead exposure as a causative agent of gene-specific DNA methylation patterns in brain [54]. Senut et al. found that lead exposure disrupts global DNA methylation in human embryonic stem cells and alters their neuronal differentiation [4]. An epidemiological study investigated 105 children participants from birth to 78 months and tested peripheral blood DNA to quantify CpG methylation at Differentially Methylated Regions (DMRs) of 22 human imprinted genes. This study provided evidence that early childhood lead exposure resulted in gene-specific DNA methylation differences in the DMRs of PEG3, PLAGL1/HYMAI, and IGF2/H19 [51]. In 2009, Pilsner et al. published the first human study to reveal that maternal bone lead levels were associated with changes in DNA methylation levels in the umbilical cord blood leukocytes of the offspring [55]. In animal studies, DNA methylome-related genes, including DNA methyltransferases, methyl-cytosine-phosphate-guanine (Me-CpG) binding protein-2 (MeCP2), and methionine synthase, were recognized as the potential targets of lead exposure [56, 57]. Sanchez-Martin et al. reported

that lead exposure resulted in hypermethylation of three differentially methylated regions in the hippocampus of females, but not males [11]. Overall, lead is a strong environmental force to globally reshape DNA methylation landscape in brain, which is a susceptible organ for epigenetic regulations.

Apart from methylome, the gene-specific alterations of methylation may reflect the detailed influence of lead exposure in CNS. Zawia et al. examined the activity of DNA methyltransferase in the tissues of 23-year-old primates exposed to lead as infants. As a consequence, they found that activity of this methylation enzyme was selective for cytosine nucleotides in a CpG sequence and specific to ones that base-paired to methylated CpG sequence on the other DNA strand [25]. Some genes triggered during memory formation and synaptic plasticity, such as BDNF, showed marked changes in promoter methylation when DNMT activity is suppressed in mice hippocampus, indicating that BDNF can be potentially modulated by specified DNA methylation status [58]. Wu et al. investigated the association between prenatal maternal lead exposure and epigenome-wide DNA methylation. Among female infants, one CpG (cg24637308) showed a strong negative association with lead levels, and this CpG site was thought to be highly expressed in human brain [59]. Our previous study also measured CpG methylation levels in specific CpG-rich promoter regions of DAT1 and DRD4, two dopaminergic-related genes, in the children with higher blood lead levels. According to it, a specific CpG site located upstream of DRD4-coding region was found to be hypermethylated due to lead exposure, and this changes were negatively correlated with the expression levels of DRD4 [39]. The relevant literature pertaining to associations of lead neurotoxicity and DNA methylation was summarized and shown in **Table 1**.

A number of reports suggested that alteration in DNA methylation was largely gender- and tissue-dependent [73]. Early life lead exposure of 3 and 30 ppm led to gender-specific DNA hypermethylation at Rn45a and Sfi1 genes in the hippocampus of female mice only [11]. Another study also stated that maternal lead exposure caused gender-specific epigenetic outcomes for varying degree of vulnerability later in life [74]. These gender differences might be related to the action of sex hormone and the structural discrepancies of body structure resulting in the variance of lead metabolic routes.

CpG methylation was reprogrammed through the action of DNA methylases. Amounting evidence suggested that this pathway was utilized by lead to bring adverse neurological outcome. In a 23-year-old primate with early exposure of lead, protein levels of DNMTs and MeCP2 were significantly decreased. And this attenuation was consistent with hypomethylating effects at multiple genetic loci [14]. Another report found a decreased DNA methyltransferase activity in mouse cortical neuronal cells exposed to lead for 24 h and determined later in life [16]. In a mouse study with developmental lead exposure, DNMT3a in male mice displayed increased expression with 150 and 750 ppm of Pb, while female mice had decreased expression of DNMT3a in response to 150 and 375 ppm of Pb. Moreover, developmental lead exposure can also affect the expression of DNMT1 and MeCP2 in murine hippocampus, which gender and exposure periods were critical contributing factors [57]. Therefore, both expression levels and enzymatic activities of methylation-modifying enzymes can be modulated by lead exposure in CNS.

Except from a conventional methylation form, 5-hydroxymethylated cytosine (5hmC), a new modification and mostly implicated in promoting gene expression, was recently known to be altered by lead exposure in CNS. 5hmCs was extremely abundant in rodent brains, and they are closely associated with critical neurodevelopmental processes such as neuronal differentiation and synaptic function [75]. In light of it, Sen et al. reported that prenatal exposure to lead can alter the hydroxymethylation profile of 5hmC-riched clusters of imprinted genes, which resulted in an

Animal (Age)	Exposure duration	Epigenetic mechanisms	Pathophysiological outcomes (possible)	References
Human embryonic stem cell	A: day 1 B: day 5 C: days 0–19 D: days 11–19	DNA methylation status of genes crucial to brain development	Exposure to Pb subtly alters the neuronal differentiation of exposed hESCs	[4]
Newborns (prenatal)	Prenatal	DNA methylation at LINE-1 repetitive elements; UCB LINE-1 methylation	Epigenetic alterations have detrimental effects on the developing brain, neurological development, and disease	[38]
Newborns	From birth to 78 months	DMR methylation for PEG3 (A), IGF2/H19 (B), and HYMA/PLAGL1 (C)	Sex-dependent and gene-specific DNA methylation	[51]
Mice (10 months)	2 weeks prior mating and during gestation and lactation until PND21	Average brain methylation: IAP 110:80%	Neurodegeneration, narcolepsy	[60]
Mice (PND 20 and 700)	Gestational D13 until PND20	DNA hypermethylation	Gene repression in old age	[61]
Rats (PND55)	10 days prior breeding till weaning of 55D	↓DNMT1 with postnatal 150ppm Pb ↓DNMT1 with postnatal 375ppm Pb ↑DNMT1 with postnatal 750ppm Pb ↓DNMT1 will all perinatal Pb	Defects in neuronal maturation, synaptic plasticity, learning, memory, cognition, and behavior	[57]
Mice (PND20 and PND700)	Gestational D13 until PND20	501 downregulated genes and 647 upregulated genes	Affecting immune responses, metal binding, metabolism, transcription, and transduction	[56]
Mice (PND1 to PND20)	PND1 to PND21	↑Dlx1 methylation ↓Gene expression of Dlx1/2/5/6 ↑Gene expression of Tubb3	Hyperactivity, weight loss, abnormal behavior	[62]
Monkeys (23 years)	Birth until 400D	↓DNMT1 ↑APPmRNA ↑Aβ1-40mRNA ↑Aβ1-42mRNA	Alzheimer's disease	[16]
Mice (2 months)	2 months prior mating and during gestation and lactation until PND2	Hypermethylation in: Rn4.5s loci in chromosome2 Sfi1 loci in chromosome11 (Rn45s loci inchromosome17)	DNA methylation (sex and tissue specific)	[11]

Animal (Age)	Exposure duration	Epigenetic mechanisms	Pathophysiological outcomes (possible)	References
Mice (PND0 and PND6)	2 months prior breeding and throughout lactation	↓H3K9/14Ac:b/w PND0 & PND6 (HPC) ↓ H3K9Me3:b/w PND0 & PND6 ↓H3K9/14Ac ↓H3K9Me3 ↓H3K9/14Ac: 50% at PND0 with 100ppm Pb ↑H3K9/14Ac: 60% at PND0 with 100ppm Pb	Weight loss, abnormal brain development and cognitive function (sex, age, and brain region specific)	[63]
Rats	Perinatal to 60D	Acetylated H3 in hippocampus ↑p300 (HAT) mRNA ↑HDAC1 mRNA	Hyperactivity, behavioral disorder, neurological disorder, ADHD (dose specific)	[64]
Monkeys (3–6,12,23 years)	Birth until 400D	Altered gene expression (22) ↑APP mRNA and protein ↓Dnmt3a and Dnmt1 at 23years ↓MeCP2 at 23years ↑H3K9ac, H4K8ac, H4K12ac ↑H3K4me2	Neurodegeneration in old age, up and downregulation of genes	[14]
Mice (Weeks 20)	E1 to E10	Hypomethylated Chd7 gene ↑Chd7 gene expression (4.7 folds) Altered histone methylation	Autism-like behavior, multiple behavioral abnormalities	[65]
Mice (PND20, 180,270, 540, and 700)	PND1 to PND20	↓DNMT1 protein ↑DNMT3a mRNA at PND20 ↓MeCP2 at PND20 and 270 ↑MAT2A at PND270, 540 and 700 ↓H3K9Ac protein at PND700 ↓H3K4Me2 protein at PND20	Alzheimer disease	[15]
Transgenic mice (15) (PND20, 30, 40, and 60)	PND1 to PND20	Hyperphosphorylation (internal and external brain capsule) ↑ miR34c expression b/w PND20 and 50 ↑ tau mRNA at PND20 ↑CDK5 mRNA at PND40 ↑ Total tau protein at PND20 and 40 ↑CDK5 protein at PND40 and 60 ↑ Phosphorylated tau Ser396 protein at PND20 and 30	Alzheimer's disease, tauopathies	[66]

Animal (Age)	Exposure duration	Epigenetic mechanisms	Pathophysiological outcomes (possible)	References
Mice (PND20, 180 and 700)	PND1 to PND20	↑miR-106b at PND20 (1.5 fold) ↓ miR-34c at PND180 (1.6 fold) ↑miR-29b at PND20 (1.6 fold) ↑ miR-132 at PND20 (4.8 fold) ↓miR-124 at PND700 (2 fold)	Alzheimer's disease, tauopathies	[67]
Rats (20–22 days)	8 weeks	↑miR-211 with 300ppm Pb (1.75 old) ↓ miR-494 with 300ppm Pb (2.04 fold) ↑miR-449a with 300ppm Pb (2.89 fold) ↑miR-34c with 300ppm Pb (4.05 fold) ↑miR-34b with 300ppm Pb (4.48 fold) ↑miR-204 with 300ppm Pb (5.48 fold) ↑miR-448 with 300ppm Pb (30.51 fold) ↓mRNA with 300ppm Pb (Bcl2, Itpr1) ↓mRNA Map2k1 with 300ppm Pb	Neural injury, neurodegeneration, axon and synapse dysfunction, impaired neural development and regeneration, impaired performance, Alzheimer's disease, Parkinson's disease and depression	[68]
Rats (2-4 weeks and 12–14 weeks)	40D	Apoptotic cells with irregular nuclear membrane, chromatin clumping, and nuclear fragmentation	Apoptosis	[69]
Mice (10 months)	2 weeks prior to mating and continued throughout gestation to 3 weeks after birth	ARTN & C5aR1 methylation 32 ppm Pb exposure) Ankdd1b methylation 2.1 ppm Pb exposure)	Death of neurons, Alzheimer's disease, migraine, and major depressive disorder	[70]
Rat (PND55)	PERI: 10 days prior to breeding to PND 21 EPN: birth through weaning (PND 21) LPN: birth through postnatal day 55	Quantities of methylation changes at gene promotor region and varies according to genders	Schizophrenia, Alzheimer's disease, memory impairment, etc.	[5]
Mice (E18, PND0, PND6, and PND60)	2 months prior to breeding and throughout lactation	Changes of H3K9Ac, H3K4Me3, H3K9Me2, H3K27Me3 level	Cognition deficits, behavioral dysfunction, neurodevelopmental disorders	[71]

Animal (Age)	Exposure duration	Epigenetic mechanisms	Pathophysiological outcomes (possible)	References
Mice (PND0 and PND6)	Pb acetate for 2 months prior to breeding until sacrifice	Changes of H3K9/14Ac and H3K9Me3 level	Cognitive/behavioral problems during childhood	[63]
Mice (PND20 and PND50)	PND 1 to PND 20	↓MECP2 ↑Dnmt3a mRNA & miR-29b (PND50) ↓DNMT1 mRNA (PND50) ↑miR-148a(PND50) ↑SP1 mRNA(PND20) ↑miR-124(PND50) ↓APP mRNA(PND20) ↑miR-106b(PND50)	Tau-induced cell apoptosis in AD; neurodegeneration	[72]

Table 1.
Summary of some literature concerning epigenetic changes involved in lead neurotoxicity.

altered expression of objective genes in a gender-dependent manner. 5hmC may also serve as potential biomarkers for lead susceptibility to neurological diseases [76].

As a general rule, the changes of DNA methylation levels were often negatively correlated with the transcription levels of the objective genes. But this association was dependent on gender, the exposure periods, and their relative genetic locations. Interestingly, for females, genes regulated by DNA methylation were inclined to encode RNA- and protein-related processes; and for males, the enriched pathways included signaling pathways, stress, and neural responses to stimuli [5].

4.2 Histone modification

Compared to DNA methylation, fewer associations between histone modification and lead neurotoxicity were reported. Categorized by posttranslational forms, most studies focused on histone acetylation changes in response to lead exposure. A specific histone acetylation level results from the balanced counteraction of histone acetyltransferases (HATs) and histone deacetylases (HDACs). An acetylated form normally corresponds to a more relaxed chromatin status, leading to an enhanced expression of the target genes, and *vice versa* [77]. In 2014, our lab published a relatively novel article describing an increased acetylated form of histone H3 as exposed by 5 or 25 mg/l of lead. This alteration accompanies with the enhanced transcription of p300, a typical HAT [64]. Subsequently, the interesting point is that chronic lead exposure reduced the total level of H3K9ac, displaying an opposite tendency to total H3ac levels, which unveiled a specific alteration depending on the concrete acetylation sites, as well as the neural models and exposure conditions used [78].

Some innovative progresses were made in the primates with early life exposure. Bihaqi et al. observed that apart from DNMTs and MeCP2, lead also caused lifelong alterations of H3K9ac, H3K8ac, and H4K12ac, which levels were increased only in 23-year-old adults, not in 12-year-old primates [14]. In another instance, perinatal lead exposure downregulated H3K9ac levels in aging mice, a proof that key epigenetic regulators can be linked with development of Alzheimer's disease [15]. Murine hippocampus and frontal cortex were similar in lead-induced epigenetic changes, that is, H3K9/14ac was gradually reduced as exposure prolonged, factored by mixed actions of gender and prenatal stress [63]. The literature pertaining to histone modifications and lead neurotoxicity was shown in **Table 1**.

Different from histone acetylation, histone methylation gained a stricter site specificity and more stable to maintain gene expression patterns [79]. With the developmental exposure of lead, primates of 400-day olds were subjected to epigenetic examination in brains. H3K4me2 was found to be increased significantly, indicating an activated propensity of related gene expression [14]. In another animal study, H3K9me3 displayed a relatively stable tendency with treatment of lead in mice, and those cases varied depending on the studied brain regions and genders [63]. According to general knowledge gained in this field, H3K4me basically played roles in promoting gene expression, while H3K27me and H3K9me mostly displayed negative regulatory activity. Our previous finding underpinned the importance of H3K27me3 in modulating lead-induced spatial memory deficits [80]. We found that chronic lead exposure perinatally could reduce the global H3K27me3 levels in rat hippocampus, and this alteration led to a genome-wide reprogramming of this repressive epigenetic mark on the target genes. This result gave a picture of how an epigenetic change can give rise to a global genetic response and the ensuing adverse neurological outcomes.

In contrast with acetylation and methylation, very few studies were shown to investigate the interaction of lead neurotoxicity and other forms of histone modifications. In spite of deficiency of relevant literature, this study is supposed to be promising to totally decipher histone codes involved in lead neurotoxicity. H2A ubiquitination was recently found to be associated with DNA damage response, which suggested that site-specific histone ubiquitination organizes the spatiotemporal recruitment of DNA repair factors, and these recruitments facilitated DNA repair pathway choice between homologous recombination and nonhomologous end joining [81].

4.3 ncRNA

ncRNAs are epigenetic regulators susceptible to environmental signals. Among diverse forms of ncRNAs, microRNA (miRNA) was most extensively studied concerning their relations with lead neurotoxicity. In rats chronically exposed to lead, at least seven miRNAs were altered considering their expression levels. In details, miR-204, miR-211, miR-448, miR-449a, miR-34b, and miR34c were dramatically upregulated, while miR-494 was downregulated. These miRNAs were implicated in regulating genes involved in neurodegeneration, synaptogenesis, and neuronal injury [68]. Masoud et al. observed that early life lead exposure yielded a transient increase in the expression of AD-related miRNAs, such as miR-106b, miR-29b, and miR-132 [67]. Another rat exposure model with 100 ppm Pb also gave some evidence that some miRNAs, mainly targeting to a histone methyltransferase EZH2, were divergently regulated by lead in pup hippocampus. In response to lead, abundance of miR-137 and miR-101 was elevated, and miR-144d was decreased. The aberrant stimulation miR-137 may have important physiological relevance, as it formed a negative regulatory loop with EZH2, which drove the downregulation of H3K27me3 [80]. Some examples of miRNA changes during lead-induced neurotoxicity were shown in **Table 1**.

It is insufficient for other forms of ncRNAs remodeled by lead exposure in CNS. In 2018, Nan published an interesting article with relevance to this research field [82]. The authors identified a novel lincRNA (long noncoding RNA), namely lncRNAL20992, as a key responsor toward lead neurotoxicity. lncRNAL20992 was significantly upregulated in a lead-induced neuronal injury model. Four proteins were found to physically interact with lncRNAL20992 to mediate the lead-induced neuronal injury. To date, few associations of piRNAs or circRNAs were discovered with lead-induced neurotoxicity. Interestingly, a 98-nucleotide nuclear RNA with unknown function called Rn4.5s, as well as a RNA precursor Rn45s, showed changes in methylation in the hippocampus of females exposed to 3 ppm of lead [11].

5. Epigenetic mechanisms of lead-induced Alzheimer's disease

By modifying the global epigenetic landscape, early life lead exposure had not only immediate adverse consequences for brain development but also persistent effects till the later life. This toxic property may increase the susceptibility of organisms to diseases, especially CNS-related diseases [3]. It has been long established that chronic lead contact is an important risk factor for the pathogenesis of Alzheimer's disease [83]. This finding is significant because AD is the most common form of dementia, which affects aging individual. There were at least 25 million people worldwide affected by this disease in 2003, including at least 4.5 million people in the United States [84]. Similar to other neurodegenerative diseases, AD is a complex and heterogeneous disorder with both environmental and genetic etiology.

There are a variety of molecular mechanisms proposed to mediate the lead-induced pathogenesis of AD. In monkeys, Wu et al. discovered that with lead exposure in infants, the aging monkeys exhibited abnormal expression alterations of AD-related genes and a key transcriptional regulator specificity protein 1 (Sp1). This was manifested by increasing AβPP, b-site AβPP cleaving enzyme (BACE), and Aβ and by decreasing DNA methyltransferase activity [16]. In an epidemiological review toward the Mexican population, it was summarized that early-life lead exposure was a potential risk factor for AD in the Mexican population [85]. While these mechanisms partly explained the key cellular and molecular changes brought by lead exposure, it is still pivotal to figure out the "fetal programming" phenomenon involved in the studied pathogenesis.

Roles of epigenetics are much appreciated due to their similar modes of action with "fetal origin of adult disease," which characterizes the basic regularities underlying lead-induced pathogenesis of AD [3, 11]. One anticipated way to achieve long-lasting or permanent changes in gene expression is to alter the structural makeup of the DNA bases that led to hypermethylation or hypomethylation consequences. The changes of DNA methylation in promoters or other gene regulatory components are found to be extremely stable and can even transmitted to the next generation. This style of action is consistent with the neurotoxic course of Pb to induce AD and is anticipated to fetal program the key AD-related genes, enabling their long abnormal transcriptions. Compared to CpG methylation, histone modifications are normally unable to elicit permanent regulatory effect till aging period, as evidenced by previous findings that H3K9ac and H3K4me2 followed lifespan-dependent changing curves, whereas variable time points showed different altering orientations [15]. Therefore, CpG methylation might be a competent epigenetic mechanism of choice to be used to explain the long development of AD. In another aspect, susceptible response from specific histone modification may be used to early predict the risk of AD, on the basis of their potential genetic associations.

Given these observations, White et al. proposed the possible pathways by which epigenetic factors mediate Pb-led pathogenesis of AD (**Figure 2**) [25]. They regarded epigenetics, mainly represented by CpG methylation, as potential key mechanisms that manifested delay consequences of lead exposure and consequent Alzheimer's disease. According to this hypothesis, early-life lead exposure caused a cascade of molecular changes exemplified by reducing CpG methylations at promoters of key AD-related genes, such as APP and BACE. Assisted by the actions of MeCP2 or SP1, these methylation reductions promoted the gene expression toward the corresponding proteins. Subsequently, Aβ was synthesized and started to accumulate in the later life. When the accumulation reached to a threshold value,

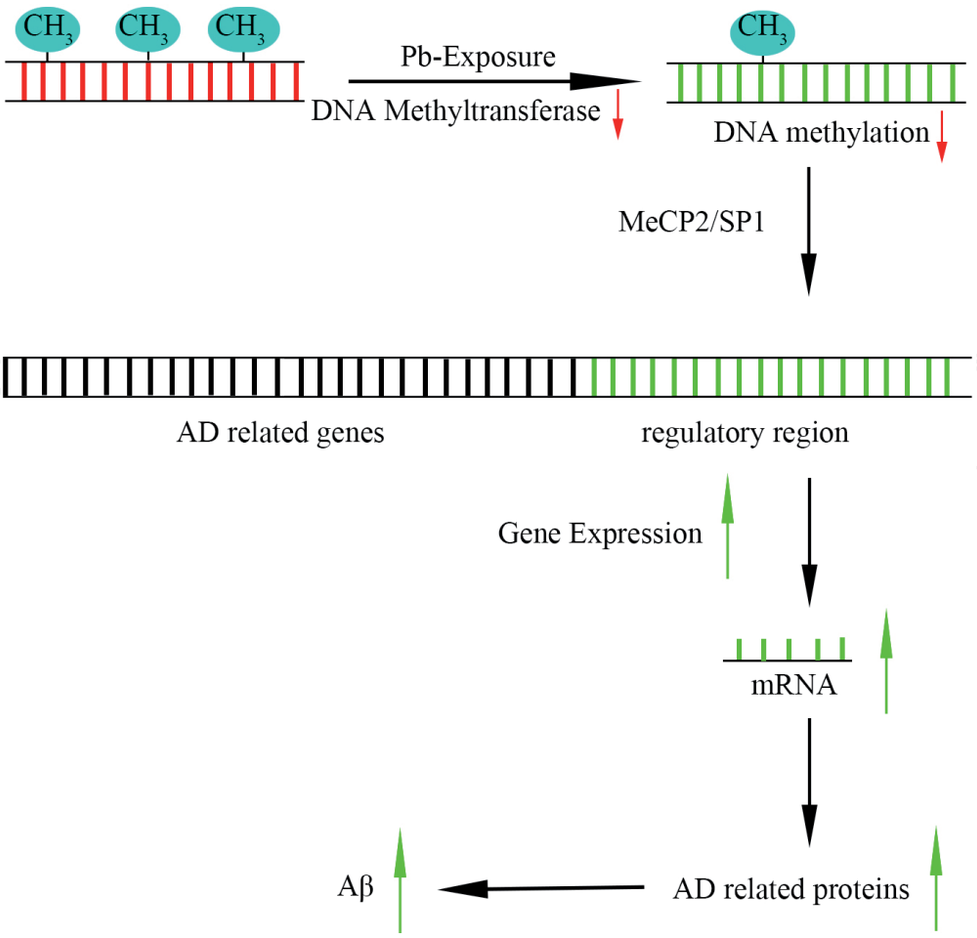

Figure 2.
Possible epigenetic mechanism of Alzheimer's disease induced by early life lead exposure.

AD symptoms started to emerge and progress. This hypothesis gives an intriguing example to implicate epigenetic factors with Alzheimer's disease induced by early-life lead exposure.

6. Conclusion and future directions

In conclusion, epigenetic factors played essential roles in mediating lead-induced neurotoxicity. Comprehensive investigations unveiled the importance of CpG methylations in multiple genetic loci in rodents and primates. CpG methylation on a specific gene promoter might give rise to a long-term suppression of gene expression, in which case formed a phenomenon of "fetal programming" of neurological disease. In addition, changes of histone modifications might reflect a relatively dynamic signal to moderate the ensuing molecular relay and neurotoxic manifestations. As a newly emerging research field, it is anticipated to have several future directions about relevant of epigenetic factors to lead neurotoxicity: (1) new epigenetic mechanisms, such as 5hmC, RNA methylation, and scarcely mentioned ncRNA forms, need to be thoroughly investigated regarding their associations with lead neurotoxicity; (2) most previous studies observed the huge impact of gender on the neurotoxic performances, but very few explanations were provided. Epigenetic differences and causing agents between the genders should be investigated with insight; (3) there are currently some medicine developed to target epigenetic sites, like HDAC inhibitors. However, the sole histone deacetylase is

unable to reflect the global epigenetic aspects and to use for intervention with full efficacy. Other specific reversing pharmaceuticals targeting epigenetic factors are warranted to be developed to interfere with development of neurological disease induced by lead exposure.

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Conflict of interest

The authors declare no conflict of interest.

Abbreviations

5hmC	5-hydroxymethylated cytosine
AD	Alzheimer's disease
BACE	b-site AβPP cleaving enzyme
BDNF	brain-derived neurotrophic factor
BLL	blood lead level
CDC	Centers for Disease Control and Prevention
CNS	central nervous system
CpG	Cytosine Guanine dinucleotides
DAT1	dopamine transporter 1
DMR	Differentially Methylated Region
DNMT	DNA methyltransferases
DRD4	dopamine receptor 4
EPSC	excitatory postsynaptic currents
GABA	γ-aminobutyric acid
H3K8ac	lysine acetylation at histone H3K8
H3K9ac	lysine acetylation at histone H3K9
H4K12ac	lysine acetylation at histone H4K12
H3K4me	lysine methylation at histone H3K4
H3K9me	lysine methylation at histone H3K9
H3K27me	lysine methylation at histone H3K27
HAT	histone acetyltransferases
HDAC	histone deacetylase
lncRNA	long noncoding RNA
IPSC	inhibitory postsynaptic currents
MeCP2	methyl-cytosine-phosphate-guanine (Me-CpG) binding protein-2
NMDAR	N-methyl-D-aspartate receptor
ncRNA	noncoding RNA
Pb	lead
piRNA	piwi-interacting RNA
PTM	posttranslational modifications
snoRNA	small nucleolar RNA
SP1	regulator specificity protein 1

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