Lead neurotoxicity: exploring the potential impact of lead substitution in zinc-finger proteins on mental health

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Lead poisoning is a costly and largely preventable public health problem that lowers IQs, decreases attention spans, and leads to the development of other childhood intellectual disabilities. Furthermore, recent evidence links developmental lead poisoning with the etiology of disorders that appear much later in life, such as Alzheimer’s disease, Parkinson’s disease, and schizophrenia. Little is known about how lead influences the onset of these disorders. This paper reviews the evidence that lead substitution for zinc in zinc-finger proteins contributes to the development of Alzheimer’s disease, Parkinson’s disease, and schizophrenia. The zinc-finger proteins potentially impacted by lead include DNA methyltransferase 1 (DNMT1) and Presenilin 1 and 2 (PSEN1/2) in Alzheimer’s disease, the dopamine receptor in Parkinson’s disease, and the NMDA receptor, zinc-finger protein 804A (ZNF804A), and disrupted-in-schizophrenia 1 (DISC1)-binding zinc-finger (DBZ) in schizophrenia.

I. Introduction

Lead poisoning is a costly and largely preventable public health problem that persists primarily due to the pervasive use of lead in paint throughout much of the 20th century and its continuing presence in housing stock, especially in low-income and minority neighborhoods. The CDC estimates that approximately 2.6% of U.S. children ages 1 to 5 have blood lead levels of 5 μg dl\(^{-1}\) or higher. Lead poisoning is four times more likely in children living below the poverty line than those above it, and two times more African-American children than Anglo-American children have elevated blood lead levels. The impacts of lead poisoning are felt throughout society. In the United States, the cost of lead-poisoning is estimated to be between $192–$270 billion per cohort of lead-poisoned children. These costs include medical costs, lost earnings, special education costs and incarceration expenses. This estimate may rise as the effects of lead poisoning on mental health are further elucidated.

Lead poisoning during childhood lowers IQ, decreases attention span, and leads to intellectual disabilities. Recent work links lead poisoning during development with the later onset Alzheimer’s disease, Parkinson’s disease, and schizophrenia. The complexity of these diseases makes it likely that lead exposure is merely one factor among others, including hereditary and environmental factors, that contribute to their onset. This critical review focuses on one possible link between the cellular biology of lead and its neurotoxic effects: the link between Pb\(^{2+}\) substitution for Zn\(^{2+}\) in zinc-finger proteins and mental illness in adulthood.

Lead toxicity is caused by the substitution of Pb\(^{2+}\) for other divalent cations in a wide range of important biomolecules, including Ca\(^{2+}\), Fe\(^{2+}\), and Zn\(^{2+}\). Some important biological targets of lead include: voltage-gated calcium ion channels, which are important for the function of neurotransmitters in the central nervous system, and dopamine receptors. There is evidence that divalent metal transporter 1 (DMT1), the major protein for iron transport from the intestines into the bloodstream, can also transport ingested lead, and that iron deficiency increases the uptake of lead by intestinal cells. Under low-iron conditions, DMT1 activity is up-regulated to increase iron uptake, likely leading to an uptake of lead as well. Lead substitution for zinc has been shown in many zinc-finger proteins including specificity protein 1 (Sp1), early growth factor 1 (Egr-1), and transcription factor IIIA (TFIIIA), as well as in proteins involved in heme biosynthesis.

The zinc-finger domain is a DNA binding motif that is important for DNA replication, transcription, and translation. There is strong evidence that lead competes for the zinc binding site in the zinc-finger proteins Sp1, Egr-1, and TFIIIA,
and that this substitution changes the timing and affinity of binding to DNA.\textsuperscript{29,32,33}

Dozens of other zinc-finger proteins are linked to neurological disorders. These include DNA methyltransferase 1 (DNMT1),\textsuperscript{4} and Presenilin 1 and 2 (PSEN1/2)\textsuperscript{6} in Alzheimer’s disease, the dopamine receptor\textsuperscript{7} in Parkinson’s disease, and the NMDA receptor,\textsuperscript{8} zinc-finger protein 804A (ZNF804A),\textsuperscript{9} and disrupted-in-schizophrenia 1 (DISC1)-binding zinc-finger (DBZ)\textsuperscript{10} in schizophrenia. Although none of these are known to be directly impacted by lead, there is evidence that lead poisoning is linked to each disorder and strong evidence that lead can bind to zinc-finger proteins. Lead substitution for zinc in zinc-finger proteins could, hence, be a contributing factor for lead-exposed individuals in the onset of each disorder. This critical review summarizes what is known about the potential role of lead substitution in zinc-finger proteins on the etiology of Alzheimer’s disease, Parkinson’s disease, and schizophrenia.

II. The zinc-finger proteins: evidence for lead substitution

A. Specificity protein 1

Specificity protein 1 (Sp1) is a ubiquitously expressed zinc-finger transcription factor that binds to GC-rich promoters (Fig. 1).\textsuperscript{35} It is part of the Sp-family of transcription factors (Sp1, Sp2, Sp3, and Sp4) that all regulate the same genes with different results.\textsuperscript{36} Each contains three Cys₂–His₂ zinc-finger motifs\textsuperscript{37} that bind to the DNA consensus sequence 5’-GGGGCGGGGC-3’.\textsuperscript{38} Sp1 is the best characterized of the Sp transcription factors; however, because the zinc-finger domains are conserved,\textsuperscript{36} what is known about lead interactions with Sp1 can be extrapolated to the other three. The concentration of Sp1 is 100 times higher in differentiating cells than in mature tissues, reflecting its importance in development.\textsuperscript{39} Its transcriptional activity is critical to cell differentiation\textsuperscript{40} and growth,\textsuperscript{41} cell cycle control,\textsuperscript{42} hormonal regulation,\textsuperscript{42} immune response,\textsuperscript{43} DNA damage control,\textsuperscript{44} angiogenesis,\textsuperscript{42} apoptosis\textsuperscript{41} and chromatin remodeling.\textsuperscript{45}

Lead disrupts these processes, as has long been known, and has an effect on the expression of important developmental genes.\textsuperscript{36} More recently it has been suggested that this could be due to the disruption of transcription regulators such as Sp1.\textsuperscript{29}

Studies utilizing NMR and UV-Vis spectroscopy provide strong evidence that lead binds to the zinc binding site of Sp1.\textsuperscript{30} NMR studies in a synthetic Sp1 peptide show characteristic shifts in histidine proton resonances when coordinated to metal ions.\textsuperscript{30} Razmiasfahari et al. showed that similar peaks appear in the presence of lead indicating that lead binds at the same site.\textsuperscript{30} UV absorption studies show characteristic absorption peaks for thiol coordination to tetrahedral sites when zinc is bound to the Sp1 zinc-finger region;\textsuperscript{31} these peaks remain when lead is bound.\textsuperscript{31} Interestingly, there are slight difference in the spectrum for the lead-bound form, suggesting small structural changes when lead binds.\textsuperscript{31} It has been suggested that lead coordinates in a trigonal pyramidal formation as opposed to zinc’s tetrahedral coordination.\textsuperscript{47} If true, this would alter the structure of the protein, contributing to its differing activity. In an \textit{in vitro} competition study, spectral changes show that lead can replace zinc and indicate that lead binds more tightly than zinc and that the two may directly compete for Sp1 binding \textit{in vivo}.\textsuperscript{31}

\textit{In vitro} and \textit{in vivo} studies examining Sp1 binding to DNA suggest that lead binding in the zinc-finger site could disrupt the timing of gene expression during development, leading to the phenotypic differences observed in lead-poisoned individuals. \textit{An in vitro} gel shift assay showed that Sp1 containing lead binds to DNA at lower concentrations of protein than Sp1 containing zinc,\textsuperscript{31} suggesting that lead binding changes the conformation of Sp1 in such a way that its DNA affinity increases. \textit{In vivo} studies of Sp1 activity in mice postnatally exposed to lead compliment the \textit{in vitro} results. These mice displayed a peak in the binding of Sp1 to DNA about 10 days earlier than control mice in both the hippocampus\textsuperscript{30} and the cerebellum.\textsuperscript{48} The timing and coordination of gene expression are critical to normal development. Sp1 regulates a number of genes associated with schizophrenia.\textsuperscript{49}

B. Early growth response transcription factor 1

Early growth response transcription factor 1 (Egr-1) is part of a family of transcription factors that regulate genes important for plasticity, learning, and memory.\textsuperscript{50} Egr-1 regulates genes that are involved in cell growth and differentiation\textsuperscript{52} and is important for the development of long-term memory.\textsuperscript{51} Like Sp1, Egr-1 contains three Cys₂–His₂-type zinc-finger motifs that bind to GC-rich promoter sequences (Fig. 2).\textsuperscript{32}

In DNA binding assays lead affects Egr-1 binding to DNA in a manner similar to that seen with Sp1. Radiolabeled Egr-1 binds earlier in development to DNA in brain extracts from lead-exposed mice.\textsuperscript{32} When mice were supplemented with zinc, Egr-1 binding to DNA was less altered,\textsuperscript{32} providing good evidence for competition between lead and zinc for the zinc-finger site in Egr-1.

C. Transcription factor IIIA

Transcription factor IIIA (TFIIIA) is a zinc-finger enzyme that positively controls the transcription of the 5S ribosomal subunit
by binding to the internal control region of the gene.\textsuperscript{33} TFIIIA contains 9 Cys–His\textsubscript{2} type zinc-finger regions (Fig. 3).\textsuperscript{33} The binding of TFIIIA to DNA has been shown to be significantly impaired at low concentrations of lead and completely inhibited at slightly higher concentrations.\textsuperscript{52} But when TFIIIA was bound to 5S RNA, which blocks the zinc-finger site, lead had no effect.\textsuperscript{52,53} The inhibitory activity of lead was not easy to reverse when supplemented with excess zinc.\textsuperscript{52}

The structure and function of TFIIIA is quite different than Sp1 and Egr-1; it contains nine zinc-finger regions and promotes rRNA transcription. The fact that there is similar evidence of lead substitution for zinc despite the differences suggests that such effects in zinc-finger proteins may be universal, or at least widespread.

III. The mental disorders: implications of zinc-finger disruption

Studies involving Sp1, Egr-1, and TFIIIA support the hypothesis that lead competes with zinc for zinc binding sites, and that this alters the conditions under which these transcription factors bind to DNA.

Sp1 and Egr-1 are involved in brain development and have been associated with Alzheimer’s disease, Parkinson’s disease and schizophrenia. Dozens of other zinc-finger proteins have important roles in the brain, and their disruption by lead could cause a variety of detrimental effects in development and later life, contributing to mental illness.

A. Alzheimer’s disease

Alzheimer’s disease is a progressive, irreversible, and fatal brain disease whose symptoms include loss of memory, thinking skills, and ability to perform everyday tasks.\textsuperscript{54} The disease affects 1 in 9 people over age 65 and is the most common cause of dementia in the elderly.\textsuperscript{54,55} Alzheimer’s disease is characterized by neuronal death, neurotransmitter loss, inflammation of neurons, tangling of neurofibers, and formation of $\beta$-amyloid plaques.\textsuperscript{56–58} Studies have shown that Alzheimer’s monozygotic concordance rate—the percentage of identical twins who both develop the disease—is 60–80%; it is clear, then, that Alzheimer’s disease has a strong genetic component.\textsuperscript{56,59} However, environmental or psychosocial factors likely also impact the etiology of the disease. Indeed, association studies have positively associated depression,\textsuperscript{60} diabetes,\textsuperscript{61} and head trauma\textsuperscript{62} with Alzheimer’s disease. Elevated lead levels could, similarly, act as a stressor in people who are genetically predisposed to Alzheimer’s disease.

Decreased cognitive function, increased hippocampal gliosis, and build-up of amyloid-$\beta$ plaques—all key Alzheimer’s disease symptoms—have also been linked to lead poisoning. Decreased cognitive functioning, including recall of words, identification of objects, and pattern memory, has been associated with both blood and bone lead levels.\textsuperscript{63–66} Magnetic resonance imaging (MRI) studies show that elevated lead levels are associated with an increase in hippocampal gliosis, a major symptom of Alzheimer’s disease.\textsuperscript{67} Most importantly, elevated lead levels during development have been linked to overexpression of amyloid-$\beta$ precursor protein (APP) which forms (eventually fatal) plaques during the onset of Alzheimer’s disease.\textsuperscript{68} This overexpression may be due to epigenetic modification caused by lead exposure during development.\textsuperscript{15}

The dysregulation of several zinc-finger proteins include DNA methyltransferase I (DNMT1), Sp1 and Egr-1, has been implicated in the onset of Alzheimer’s disease.

(1) Amyloid-$\beta$ precursor protein. Amyloid beta (A$\beta$) is overexpressed in Alzheimer’s disease and builds up in plaques.\textsuperscript{13} The formation of plaques is thought to be one of the major causes of symptoms in AZ. A$\beta$ is a filamentous protein and forms spherical plaques that are 6–10 nm wide.\textsuperscript{69} It contains a zinc-finger type binding site where zinc is coordinated by four histidine residues (Fig. 4).\textsuperscript{5} The plaques are sticky and can block cell-to-cell signalling, which is critical to normal brain function.\textsuperscript{12} A$\beta$ is cleaved from amyloid-$\beta$ precursor protein (APP), which is normally present in all tissues.\textsuperscript{69} APP can be cut in several places by an unidentified cleavage factor known as $\gamma$-secretase; A$\beta$ is just one of the possible products.\textsuperscript{59} APP transcription is positively regulated by Sp1.\textsuperscript{70–72} Lead substitution in Sp1 could lead to the upregulation of APP transcription, causing the build-up of A$\beta$ in the brain and leading to Alzheimer’s disease. Indeed, APP production is known to increase in the presence of lead.\textsuperscript{73}

(2) DNA methyltransferase 1. One of the major causes of Alzheimer’s disease, it has been suggested, could be epigenetic
modification during development that can lead to Alzheimer’s later in life. One of these modifications is the improper methylation of genetic elements including the APP promoter region. DNA methyltransferase 1 (DNMT1) is the protein responsible for this methylation. DNMT1 dysregulation has been implicated in the etiology of Alzheimer’s disease. Lead is known to reduce the activity of DNMT1. A study performed in monkeys showed that lead exposure during development leads to Alzheimer’s-like symptoms later in life and that DNMT1 expression was decreased.

Structural studies of DNMT1 show that the protein contains four zinc ions in Cys2–His2 zinc-finger structures (Fig. 5). Lead could directly interact with the DNMT1 zinc binding sites, replacing zinc and causing modifications in protein structure. This could contribute to decreasing the activity of DNMT1 by changing its DNA binding properties, as seen in Sp1, Egr-1, and TFIIB.

In addition, DNMT1 transcription is negatively regulated by Sp1. Since Sp1 binds to DNA more strongly when bound to lead than to zinc, lead exposure could cause Sp1 to bind the DNMT1 promoter prematurely, shutting down transcription and epigenetically modifying the APP transcript, leading to the build-up of plaques much later in life.

(3) Presenilin 1 and 2. Presenilin 1 (PSEN1) and 2 (PSEN2) are homologous subunits of z-secretase, the enzyme that cuts APP to form Aβ, leading to plaque buildup. The two enzymes are 67% identical, and both subtypes can cut APP to form Aβ. However, in a mouse model PSEN1 produced 169 times more Aβ than PSEN2. PSEN1 and 2 are not zinc-finger proteins, but they are regulated by several zinc-finger proteins. They are known to be important in Alzheimer’s disease.

PSEN transcription is regulated by Egr1 and ZNF237, which are both zinc-finger transcription factors. Egr1 upregulates the transcription of PSEN2, while ZNF237 down regulates transcription of PSEN1. Additionally, PSEN1 has at least one binding site for Sp1, suggesting that Sp1 may also play a role in its transcription regulation. The importance of zinc-finger transcription factors for the proper regulation of PSEN1 and 2 suggests that, should lead substitute for zinc and cause dysregulation, PSEN1 and 2 expression could be affected, leading to increased Aβ plaque formation and Alzheimer’s disease symptoms.

B. Parkinson’s disease

Parkinson’s disease (PD) is the second most common neurodegenerative disorder after Alzheimer’s disease, affecting 1% of the population over age 60. Parkinson’s disease is caused by the death of neurons that produce dopamine. This leads to dysfunction in neurotransmission in the basal ganglia motor circuit, causing tremors, rigidity, and loss of motor control. In addition to these motor deficits, patients with Parkinson’s disease experience deficits in memory and thinking skills, mood changes, obsessive-compulsive behavior, and vision problems.

Studies have shown an association between lead poisoning and the development of Parkinson’s disease in later life. Coon et al. used bone lead level to estimate lifetime lead exposure and compared this between patients with Parkinson’s disease and a healthy control group. They concluded that the risk of Parkinson’s disease was doubled for people in the highest quartile for lead exposure.

Dopamine receptors. Dopamine is a major neurotransmitter in the mammalian brain. It controls motor activity, cognition, emotion, response to positive reinforcement, and endocrine system regulation. There are five distinct classes of dopamine receptor proteins, D1, 2, 3, 4, and 5, all of which contain seven transmembrane domains. The classes differ in the length and chemical properties of these domains. The D1 and D2 receptor subtypes are known to contain zinc binding sites, and zinc is known to regulate the binding of D1 and D2 agonists.

Lead has been shown to impact the dopaminergic system, but the molecular mechanisms by which it operates are hard to disentangle. There are several zinc-finger proteins connected to expression of dopamine receptors. Sp1 is a transcription factor for the dopamine receptor and its disregulation due to lead binding could cause an upregulation of dopamine receptor transcription, which could lead to diminished levels of synaptic dopamine. The dopamine receptor regulator factor, DRRF, which is also a zinc-finger protein, has been shown to silence the D2 gene in some neurons. An increase in DRRF mRNA levels has been correlated with chemically-induced parkinsonian-like symptoms.
Sp1 activates transcription from the DRRF promoter, suggesting that Sp1 and DRRF levels could be connected in complex ways.\textsuperscript{58}

The dopamine transporter (DAT), which is involved in the reuptake of dopamine, has been shown to be regulated by a zinc-finger protein.\textsuperscript{89}

C. Schizophrenia

Schizophrenia is a severe psychiatric disorder characterized by hallucinations, delusions, disorganized thinking, flat affect, lack of energy, lack of emotions, and slowed speech.\textsuperscript{60} Symptoms of schizophrenia usually appear in the late teens or in early adulthood and lead to lifelong disability.\textsuperscript{20} The worldwide prevalence of schizophrenia is 1%.\textsuperscript{90} The monozygotic concordance rate is 30–40%, meaning that environmental or psychosocial factors are important in its etiology.\textsuperscript{91}

Evidence suggests that the development of schizophrenia later in life could be influenced by lead poisoning during development.\textsuperscript{83} When researchers compared symptoms of mice whose genomes contained a mutant disrupted-in-schizophrenia 1 (DISC1) gene to regular mice when exposed to chronic levels of environmental lead, they found that mice containing the DISC1 gene were significantly more likely to display schizophrenia-like symptoms than normal mice when both were exposed to lead,\textsuperscript{92} suggesting that lead could be an environmental factor that increases the odds of developing schizophrenia among those who are genetically predisposed.

A study of serum samples from pregnant women\textsuperscript{93} showed that the risk of developing schizophrenia doubled if the mother had blood lead levels higher than 15 $\mu$g dl\textsuperscript{-1} during pregnancy.\textsuperscript{19} The serum samples were tested for $\delta$-aminolevulinic acid (ALA), a biomarker of lead exposure, and showed a correlation of ALA levels and schizophrenia with an $r^2$ value of 0.64.\textsuperscript{19} Later the same researchers used a different cohort of subjects and found that there was a twofold chance of developing schizophrenia when maternal blood lead levels were higher than 15 $\mu$g dl\textsuperscript{-1}, according to the ALA measurement.\textsuperscript{94}

It is possible that lead substitution in zinc-finger proteins, including NMDAR, ZNF804A, and DISC1 binding zinc-finger protein (DBZ), has a role in antagonizing schizophrenia symptoms in those who are genetically predisposed.

(1) NMDAR receptor. The $N$-methyl-$d$-aspartate receptor (NMDAR) is a voltage-dependent glutamate receptor that transports calcium ions in the mammalian brain.\textsuperscript{95} Its patterns of functioning are critical to development, learning, and memory.\textsuperscript{96} The NMDAR is composed of the NR1 subunit along with NR2 and/or NR3.\textsuperscript{97} NMDAR dysfunction has been shown to be affected by elevated lead levels and has been shown to be a factor in the etiology of schizophrenia.\textsuperscript{98}

Lead is a noncompetitive inhibitor of NMDAR.\textsuperscript{99} There are two main theories for how lead acts as an inhibitor. Zinc is an allosteric inhibitor of NMDAR function (Fig. 6). It is possible that lead substitutes in the zinc-binding site of the NMDAR protein, causing a conformational change of the receptor and inducing a change in function. A study by Guilarte et al. showed that the presence of lead decreases the inhibitory effect of zinc, suggesting that the two metals compete for binding in the zinc binding site.\textsuperscript{8}

Fig. 6 The structure of the NR2B subunit of the rat NMDA receptor as determined by Karakas et al. by X-ray crystallography.\textsuperscript{101} This image was prepared using CN3D.

Lead may also prevent expression of the NMDAR gene by substituting for zinc in Sp1, which upregulates its transcription.\textsuperscript{100} It is known that lead competes for binding in the zinc-finger region of Sp1; the induced conformational change may reduce the expression of NMDAR. Indeed, experiments have shown that as Sp1-to-DNA binding decreases with chronic lead supplementation, the expression of NMDAR also decreases.\textsuperscript{29} The lead-induced decrease in NMDAR activity may be due to a decrease in transcriptional activity by Sp1.

Low NMDAR activity is associated with schizophrenia.\textsuperscript{102} Additionally, NMDAR agonists, such as the psychotic drug sernyl, have been shown to trigger short-term, schizophrenia-like symptoms in healthy patients and cause an increase in symptoms in stable schizophrenia patients—further evidence that schizophrenia symptoms are associated with the NMDAR receptor.\textsuperscript{104}

(2) ZNF804A. ZNF804A is a zinc-finger transcription factor which is widely expressed in brain cells.\textsuperscript{105} It is a transcription regulator for schizophrenia risk genes SMARCA2, PRSS16, COMT, PDE4B, and DRD2 among others.\textsuperscript{106,107} Additionally, ZNF804A is very strongly associated with the schizophrenia phenotype as shown in studies performed in multiple populations.\textsuperscript{108,109} Rs1344706, a small nuclear protein exon of ZNF804A, is highly associated with schizophrenia.\textsuperscript{9} All that is known about the structure of ZNF804A is that it contains a Cys$_2$–His$_2$ type zinc-finger.\textsuperscript{110} Since ZNF804A contains the same type of zinc-finger motif as Sp1, it seems highly likely that lead substitutes for the zinc residue in a similar fashion causing structural and functional differences.

(3) DISC1 binding zinc-finger protein. Disrupted-in-schizophrenia-1 (DISC1) is a protein-coding gene that is highly expressed in brain regions including the hippocampus.\textsuperscript{111} The disruption of this gene, caused by translocation or frameshift mutation, is associated with both schizophrenia and a related disorder, schizoaffective disorder.\textsuperscript{112,113} DISC1 itself is not a zinc-finger protein, but it is transported by DISC1-binding zinc-finger protein (DBZ).

DBZ, also known as ZNF365 and Su48, is a Cys$_2$–His$_2$ type zinc-finger protein that is specifically expressed in the central
nervous system and has been shown to regulate the growth of axons and dendrites when bound to DISC1. Since axonal abnormalities are known to be associated with schizophrenia symptoms, this function of the Disc1–DBZ complex is likely to be involved. So disruptions in DBZ due to lead poisoning could have effects similar to mutations in DISC1, leading to the schizophrenia phenotype. Should lead substitute in the zinc-finger region of DBZ, as it can in Sp1, Egr-1, and TFIIA, these effects seem likely.

IV. Conclusions

Lead substitution in zinc-finger proteins has the potential to disrupt optimal neurological functioning during development and much later in life. Evidence indicates that lead binds to zinc-finger sites in zinc-finger proteins associated with neurological diseases, causing changes in the timing and affinity of DNA binding. Children under six are most at risk for lead poisoning due to childhood brain development, so it is easy to understand how lead substitution in zinc-finger proteins could have an effect on childhood brain development, intelligence, and attention span. Less easy to explain is the temporal delay seen between lead poisoning and the associated adult-onset mental disorders: Alzheimer's disease, Parkinson's disease, and schizophrenia.

The delay may be due to epigenetic modification and the irreversible build-up of lead in the brain. The hypothesis that epigenetic modifications are responsible for the effect of lead on the onset of neurological diseases in later life is supported by the timing of and genetic predisposition to each of these disorders. Alzheimer's disease and Parkinson's disease tend to develop when people are sixty or older while schizophrenia tends to develop in the late teens to mid-twenties. The age of onset suggests that the effects of lead poisoning lie dormant until gene expression changes with age, at which point the effect becomes irreversible. Lead substitution in DNA-modifying zinc-finger proteins, such as DNMT1, causes DNA modification, changing protein structure and leading to symptoms when the gene is expressed in later life. A person with a genetic predisposition to a disorder may get the disorder if their DNA is epigenetically modified, consistent with the diathesis stress model.

The accumulation of lead in the brain is irreversible. If it enters the brain during childhood, it can continue to impact the phenotype in later life. Lead has been shown to bind to zinc-fingers with greater strength than zinc, suggesting that even a small amount of lead could cause detrimental effects. When genes are differentially expressed during different stages of development and aging, lead can affect different zinc-finger proteins being transcribed, leading to the onset of disease in adulthood.

Zinc-finger proteins are involved in other illnesses, including bipolar disorder, a chronic, lifelong mood disorder characterized by swings between depression and mania. A multitude of zinc-finger proteins, including protein kinase C (PKC), ZNF804A, and NMDAR, are implicated in the etiology of bipolar disorder. Hence, lead substitution in zinc-fingers could affect the etiology of bipolar disorder as well; further research should investigate the role of lead substitution in zinc-fingers in other neuropsychological diseases and other aspects of mental health.

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Notes and references


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