HHS Public Access

Author manuscript

Toxicology. Author manuscript; available in PMC 2017 January 02.

Published in final edited form as:

Toxicology. 2016 January 2; 339: 58–72. doi:10.1016/j.tox.2015.11.001.

Mechanisms of Divalent Metal Toxicity in Affective Disorders

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Abstract

Metals are required for proper brain development and play an important role in a number of neurobiological functions. The Divalent Metal Transporter 1 (DMT1) is a major metal transporter involved in the absorption and metabolism of several essential metals like iron and manganese. However, non-essential divalent metals are also transported through this transporter. Therefore, altered expression of DMT1 can modify the absorption of toxic metals and metal-induced toxicity. An accumulating body of evidence has suggested that increased metal stores in the brain are associated with elevated oxidative stress mediated by the ability of metals to catalyze redox reactions, resulting in abnormal neurobehavioral function and the progression of neurodegenerative diseases. Metal overload has also been implicated in impaired emotional behavior, although the underlying mechanisms are not well understood with limited information. The current review focuses on psychiatric dysfunction associated with imbalanced metabolism of metals that are transported by DMT1. The investigations with respect to the toxic effects of metal overload on behavior and their underlying mechanisms of toxicity could provide several new therapeutic targets to treat metal-associated affective disorders.

Keywords

Cadmium; Divalent Metal Transporter 1; Emotion; Iron; Lead; Manganese

INTRODUCTION

Transition metals are essential for maintaining proper body functions through a number of biological processes. In particular, the brain requires several important transition metals including iron (Fe), cobalt (Co), manganese (Mn), copper (Cu) and zinc (Zn) for optimal physiological function, and their transport to the brain is regulated by unique transport systems. In the central nervous system (CNS), these metals function as catalysts for biochemical reactions, regulators of gene expression, second messengers in signaling pathways and cofactors for many vital enzymes. For example, several enzymes involved in antioxidant functions use metals as cofactors; superoxide dismutase requires Mn in the

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The authors have no conflicting financial interests.

mitochondria and Zn/Cu in the cytosol [1,2]. Also, both Zn and Fe are cofactors for serine/threonine phosphatases and kinases like human calcineurin [3]. Imbalanced metal homeostasis either by deficiency or by overload of metals is associated with organ dysfunction that leads to various disorders. For example, anemia due to nutritional iron deficiency or gene mutations results in impaired production of iron-requiring proteins (e.g. hemoglobin), inhibition of cell growth and ultimately cell death. In contrast, iron overload causes tissue damage due to elevated oxidative stress. Because of the consequences of metal imbalance, the homeostasis of metals in healthy organisms is tightly regulated at the levels of uptake, metabolism and excretion of metals.

Non-essential metals can exert toxic effects even at low levels. Inorganic salts of several metals, such as aluminum, lead and alkyl derivatives of lead, mercury and tin have toxic effects on behavior and brain function. The toxicity of metals occurs by the disruption of metal homeostasis and is manifested by DNA damage, alterations of gene expression and damage by oxidative stress [4–7]. The role of metal toxicity in neurological disorders by redox mechanisms has been well-documented [8]. Metal overload is also associated with altered expression of nuclear factors like NF-κB, activator protein-1 (AP-1), nuclear factor of activated T-cells (NFAT) and the tumor suppressor protein p53 [9–11]. Alteration of these nuclear factors result in dysregulation of cell proliferation, apoptosis and cell cycle progression, which ultimately leads to cancer, likely by distinct mechanisms occurring in metal deficiency [12].

The absorption of metals from dietary sources occurs by a number of metal transporters to provide specific needs for individual nutrient metals. In particular, the Divalent Metal Transporter 1 (DMT1) is a major iron transporter essential for iron absorption from diet [13–15]. DMT1 also plays an important role in the uptake of several other divalent metals, including cadmium (Cd) and lead (Pb) which are significant toxicants in our environment. Since the expression levels of DMT1 are regulated by several factors, such as body iron status, gene polymorphism and inflammation [16,17], changes in these factors could also alter the transport and neurotoxicity of metals. For example, iron deficiency up-regulates intestinal DMT1 levels [18] and increases the absorption of Mn and Cd [19,20]. Environmental and physiological factors alter the expression of DMT1, which in turn alters systemic and brain metal status [21,22]. While the role of metal overload in cognitive function in the context of neurodegenerative diseases has been extensively reviewed [23–25], the current review discusses the behavior dysfunctions, with a focus on affective disorders, caused by overload of four metals that are transported by DMT1 [26–28], as well as potential mechanisms of toxicities induced by these metals. The metals selected in this review are two essential nutrient metals (Fe and Mn) as well as two non-essential metals (Pb and Cd) that are prominently found in the environment. The investigations with respect to the toxic effects of metal overload on behavior and their underlying mechanisms of toxicity could provide several new therapeutic targets to treat metal-associated affective disorders.

DIVALENT METAL TRANSPORTER 1 (DMT1): DISTRIBUTION AND FUNCTION

Intestine and erythroid cells

DMT1, coded by the Slc11a2 gene, is a transmembrane protein widely expressed almost throughout the body, although the magnitude of its expression levels varies in different tissues. In the duodenum, DMT1 is primarily involved in the dietary absorption of iron as well as other essential divalent cations, including Mn^{2+} and Zn^{2+} [14,15]. The transport of copper through DMT1 has been called into question; DMT1 may transport Cu^{+} [29], whereas Illing et al. [30] claimed that DMT1 does not transport copper. DMT1 also plays an important role in the uptake of iron into erythroid cells and promotes heme synthesis. Studies have demonstrated that ferrous iron uptake into reticulocytes (immature red blood cells) is DMT1 dependent [31,32]. Briefly, transferrin-bound iron in the circulation is endocytosed by interaction with membrane-associated transferrin receptor 1 (TfR1). In the acidic pH of the endosome, the complex is dissociated and releases iron, while DMT1 expressed in endosomes and lysosomes [33,34] exports iron to the cytosol. The essential role of DMT1 in iron transport was confirmed by two rodent models that carry mutations in DMT1: the *mk/mk* mice and Belgrade (*b*) rats. Both *mk* mice and *b* rats have a missense mutation (G185R) of DMT1 in transmembrane-4, which causes the expression of non-functional DMT1 [35,36]. As a result, these animals display hypochromic, microcytic anemia [35,37]. DMT1 is also expressed in the outer membrane of the mitochondria [38], suggesting its involvement in mitochondrial iron acquisition, potentially coupled with mitoferrin which is localized to the inner membrane [39]. The exact mechanisms about how these two proteins collaborate for the transport of iron into the mitochondria remains to be elucidated.

Liver and kidney

Other tissues also express DMT1. Mixed results exist with respect to DMT1 expression in the liver. Trinder et al. [40] determined that DMT1 is evenly distributed in the liver and its expression is up-regulated in iron loading and downregulated in iron deficiency states after 8 weeks of diet. However, Nam et al. [41] demonstrated that liver DMT1 levels are increased in iron deficiency and decreased during iron loading after 3 weeks of diet. It is possible that prolonged exposure to iron could have caused a compensatory up-regulation of DMT1 to import and store excess iron in the liver. Further studies to determine the relationship between the activity of liver DMT1 and duration of iron overload/deficiency will help to address this question. In the kidney, DMT1 is believed to participate in the reuptake of divalent cations. Although kidney DMT1 levels are reduced in both *mk* mice and *b* rats [42,43], Ferguson et al. [43] found that DMT1 mutation does not alter urinary excretion of iron and suggested that lack of DMT1 is compensated by an unidentified alternate mechanism. A study by Veuthey et al. [44] demonstrated that *b* rats exhibit higher expression of lipocalin-2 (LCN-2), a protein that sequester iron. It can be postulated that this up-regulation may aid in regulating iron excretion in DMT1 mutations. Further investigation is required to accurately determine and identify these mechanisms.

Respiratory tracts

Human lungs are a site of abundant DMT1 expression [45,46]. In rat lungs, DMT1 protein is predominantly found in normal airway and alveolar epithelium, especially in type II cells [45]. Several investigations have identified that both external stimuli and internal changes can regulate DMT1 activity in the lung. For example, proinflammatory cytokines, such as TNF-α and interferon-γ, as well as inorganic fiber like asbestos, promote DMT1 up-regulation in bronchial epithelial cells [47,48]. Interestingly, DMT1 deficiency is associated with elevated pulmonary inflammation [49]. Increasing evidence has suggested that pulmonary DMT1 functions to provide a protective barrier from toxic effects resulting from inhaled metals [49–51]. DMT1 is also found in the olfactory epithelium [52], where the transporter could mediate the nasal uptake of inhaled divalent metals. In support, up-regulation of DMT1 in response to iron deficiency is associated with increased uptake of intranasal Mn into the brain [52,53]. These results suggest that altered expression of DMT1 in the airborne routes could modify the neurotoxicity of environmental metals.

Brain

In the brain, DMT1 expression is highest in the neurons of the striatum, cerebellum and the vascular and ependymal cells lining the third ventricle [54]. The transport of metals through the blood-brain barrier (BBB) is the first step in regulating the entries of these metals into the CNS, as well as in maintaining their levels at proper concentrations [55]. Transferrin receptor-mediated endocytosis is the primary mechanism by which iron is transported across the BBB based on the accumulating body of evidence from functional and genetic studies [56,57]. Although DMT1 is expressed in brain vascular endothelial cells, its role in iron transport through the BBB is unclear [58]. After uptake through the BBB, iron is transported into various neuronal and non-neuronal cells by DMT1-dependent pathways. Neuronal cells exhibit high expression of DMT1 [59], presumably transporting iron into neurons. DMT1 is also expressed in astrocyte cells located near the BBB [60], likely buffering the neurons from iron overload. Siddappa et al. [61] found that iron deficiency during gestation results in regional up-regulation of DMT1 in the brain. Belgrade rats carrying DMT1 mutation exhibit decreased brain iron levels in various regions, suggesting direct involvement of DMT1 in brain iron transport [62]. The role of DMT1 in brain metal transport is discussed in detail in the following sections for individual metals.

Regulation of DMT1 expression and metal transport

The homeostasis of essential metals is disrupted by changes in DMT1 activity. Conversely, altered status of metals can modify DMT1 expression. DMT1 is up-regulated by Mn exposure, iron deficiency or hypoxic conditions [63–66] and down-regulated in dietary iron overload conditions [67]. These changes can increase the uptake of other metals that are transported by DMT1. For example, it has been recognized that Pb absorption is enhanced in iron deficiency anemia [68,69]. Similarly, Mn uptake is up-regulated in iron deficiency [52]. Taken together, these observations indicate that altered expression of DMT1 could modulate the systemic and brain toxicity of several divalent metals. In this following section, we discuss the neurobehavioral effects of four metals that are transported by DMT1 and potential mechanisms of neurotoxicity as well as the impact of DMT1 on metal toxicity.

IRON

Iron and iron deficiency

Iron is the most abundant transition metal in the body. The metal is essential for various body functions, including ATP production, DNA synthesis and oxygen transport. In the brain, iron is the second most abundant metal, after zinc. Brain iron is required for myelination [70] and serves as a cofactor for indispensable enzymes like tyrosine hydroxylase and tryptophan hydroxylase, which are involved in neurotransmitter synthesis and metabolism [71,72]. Dietary iron deficiency is widespread worldwide in both developing and developed countries. In the United States, an estimated 9–16% adolescent and adult females and 7% of toddlers suffer from iron deficiency [73]. The development of iron-deficiency anemia is of importance, especially in the prenatal and early postnatal life because of increased iron utilization during these periods [74,75]. While more comprehensive information about the role of brain iron in emotional and cognitive behavior is available in recent reviews [76–78], here we have captured several important points for iron overload in the context of mood-associated behaviors along with recent updates.

Iron overload and behavioral dysfunction

Iron overload is best represented by hereditary hemochromatosis (HH), an iron overload disorder most prominently found in North American populations. HH is characterized by significantly higher body iron stores, resulting in liver cirrhosis, cardiomyopathy, diabetes, arthritis, hyperlipidemia and premature death [79–81]. HH is primarily caused by mutations in the HFE (High Fe) gene, which is responsible for regulating body iron status. H63D and C282Y are the two most common mutations associated with HH [82]. While most individuals with HH do not display increased iron levels in the brain, several case studies have demonstrated iron accumulation in the brain in HH patients [83], likely due to pathological events secondary to HH. In addition, other types of brain iron overload have been identified; these include Friedrich ataxia, Kufor-Rakeb disease, Pantothenate kinase 2-associated neurodegeneration, collectively known as ‘neurodegeneration with brain iron accumulation’ (NBIA) [84]. Fewer studies have been conducted with a focus on iron overload than deficiency in the context of neurobehavioral function. Rats exposed to iron overload diet demonstrated decreased activity, startle reflexes, habituation and conditioned avoidance responses [85]. In addition, these iron-loaded rats displayed enhanced prepulse modulation of startle, indicating impaired sensorimotor functioning [85]. Studies have also determined that traumatic brain injury (TBI) results in brain iron overload [86]. Excess brain iron found in TBI is associated with increased free radicals and decreased antioxidant enzymes. The behavioral effects of TBI have been extensively studied and reviewed [87–89]. Oxidative stress in TBI is associated with neuronal dysfunction and reduced learning capacity [90], which is improved by the iron chelator deferoxamine [91,92].

Mouse models of brain iron loading provide a useful tool to study emotional response and the behavioral consequences of iron-associated neurotoxicity. Mice that carry H67D mutation in the mouse Hfe gene, homologous to the H63D HFE mutation in humans, display elevated brain iron levels [93]. These mice have shown increased repetitive behavior, a symptom associated with psychiatric disorders [94], indicating that either HFE mutation or

iron loading causes behavioral dysfunction. Mouse models of HFE deficiency (Hfe-knockout mice) show systemic iron overload and recapitulate HH in humans [95–97], but Hfe-deficient mice do not show brain iron loading and do not exhibit abnormal behavioral phenotypes [98,99]. These data indicate that behavior disorders caused by iron overload are more dependent on brain iron rather than systemic iron status. Since most HH patients do not display brain iron loading, hemochromatosis may not directly predispose to behavioral disorders. Alternatively, these studies suggest that brain iron loading could be caused by gain of mutant function rather than loss of HFE function (Hfe-knockout). Likewise, it would be of interest if brain iron loading during development is necessary for abnormal behavior and also if therapeutic intervention (i.e. iron chelation) can reverse impaired behavior. The consequence of the C282Y mutation, another prevalent HFE mutation, should also be tested in the future.

The behavioral influences of iron overload appear to be dose-dependent; Maaroufi et al. [100] demonstrated that 3.0 mg/kg administration of iron sulfate, but not 1.5 mg/kg, produced significant changes in the performance of adult Wistar rats during the elevated plus maze test. Furthermore, there have been incidences of schizophrenic spectrum disorders in patients with thalassemia [101], a secondary (transfusion) iron overload disorder resulting from abnormal hemoglobin production [102]. Bock et al. [103] found an increase in iron-related proteins transferrin and ceruloplasmin, an enzyme that catalyzes the oxidation of ferrous iron, in the blood of psychiatric patients. A study conducted by Blasco et al. [104] demonstrated that brain iron levels correlate with cognitive dysfunction in obese women. This study suggests that brain iron may be potentially used as a biomarker for cognitive dysfunction associated with obesity. These animal and clinical studies have demonstrated the involvement of iron overload in impairment of neurobehavioral functioning. Freret et al. [105] discovered that chronic treatment with the iron chelator, deferoxamine, improves impaired behavior after ischemia. Deferoxamine has also improved symptoms of Alzheimer’s disease in both human patients and animal models. McLachlan et al. [106] demonstrated that chronic deferoxamine administration significantly reduces the progression of dementia in Alzheimer’s disease. Fine et al. [107] demonstrated that intranasal deferoxamine treatment results in ameliorating the loss of spatial memory in mouse models of Alzheimer’s disease and restored inflammatory and protein oxidation markers to normal. These chelator studies further strengthen the possible involvement of metal overload in inducing neurobehavioral disorders. Thus, normalizing brain iron levels should be explored as a probable therapy for restoring dysfunctional behavior. Further investigation is required to determine if deferoxamine and other chelators may be successfully implemented as therapies for brain iron loading disorders.

Potential mechanisms of behavioral dysfunction in iron overload

Since excess iron can generate reactive oxygen species (ROS) and increase oxidative stress, most of iron overload studies have been focused on the negative effects on behavioral organization. The effect of iron-induced oxidative stress has been extensively studied in the area of neurodegenerative diseases. Xian-Hui et al. [108] found that brain iron overload associated with DMT1 mutations, in conjunction with aging, may be responsible for the neurodegeneration associated with Alzheimer’s disease. Honda et al. [109] have reviewed

the alteration of iron metabolism in Alzheimer's disease with an emphasis on oxidative stress. Hydroxyl radicals resulting from elevated free iron levels are known to cause lysosomal rupture and leakage of cytosolic contents which promote cell damage [110].

In addition to inducing oxidative stress, iron also influences behavior by altering neurotransmitter turnover. The emotional dysfunction caused by iron overload is in part attributed to impaired dopamine metabolism. Chang et al. [94] found that iron overload caused by Hfe mutation results in decreased dopamine transporters and increased dopamine D2 receptors. In addition, animals fed iron-loading diet decrease brain serotonin and dopamine concentrations [111]. The behavioral deficits by iron overload may be caused by a combination of increased oxidative stress and alterations of the dopaminergic signaling pathway. Less is known about the metabolism of other neurotransmitters like GABA and glutamate under iron overload. Impaired GABA/glutamate homeostasis is implicated in schizophrenia and other psychotic disorders [112–115]. Notably, glutamic acid decarboxylase 67 (GAD67) is decreased in schizophrenic subjects, whereas both GAD65 and GAD67 are reduced in the prefrontal cortex of schizoaffective disorder [114], in which cognitive function is often preserved.

Several lines of evidence suggest that GABAergic pathways are directly affected by iron and also by iron-catalyzed ROS [116–119]. Injections of iron into the brain impairs the release GABA and decreases GABA levels [120,121]. Likewise, increased lipid peroxidation alters GABA uptake [122,123]. These changes can contribute to the neurochemical pathogenesis of mental disorders. Quantitative characterizations of the behavioral and neurochemical phenotypes using animal models of dietary iron overload and/or genetic mutations should provide important information about the role of iron in the development of psychiatric disorders.

Hippocampal DMT1 knockout mice have been generated to study the effect of iron deficiency in the brain without systemic anemia. Carlson et al. [124] postulated the involvement of DMT1 in the hippocampus with spatial memory training. Pisansky et al. [125] found that hippocampus DMT1 knockout mice display alterations in sensorimotor gating, as evidenced by impaired prepulse inhibition and long term potentiation. These studies indicate that altered DMT1 expression in the brain could influence the development of affective disorders. Further investigation is required to determine if DMT1 expression in the brain could be used as a marker for behavioral disorders.

MANGANESE

Manganese physiology and deficiency

Like iron, manganese (Mn) is also an essential trace metal for various biochemical functions. It is required for bone formation and metabolism of carbohydrates and lipids. Studies from animal experiments have demonstrated that dietary Mn deficiency results in various physiological alterations including skeletal abnormalities and alterations in lipid metabolism [126,127]. Since Mn is a cofactor for Mn-dependent (mitochondrial) superoxide dismutase (MnSOD), an essential antioxidant enzyme, Mn deficiency results in decreased activity of MnSOD, thereby increasing mitochondrial lipid peroxidation [128]. Mn is also

required for neuronal and glial cell functions. For example, Mn serves as a cofactor for enzymes in neurotransmitter pathways, including glutamine [129,130].

Mn deficiency is not common in humans because a sufficient amount of the metal is provided from the diet. However, Mn deficiency is found in several neurological problems, including bipolar disorder and Hungtington's disease, as well as epilepsy [131–134]. For example, patients with bipolar affective disorder display a significant decrease in plasma Mn by 18–38% compared with healthy control subjects [131]. Also, Mn levels in the brain cortex are significantly reduced in subjects with Huntington's disease [135]. Epileptic patients exhibit a decrease in blood Mn [133]. Likewise, deficiencies in MnSOD or Mn-requiring arginase result in a number of neurodegenerative and psychiatric disorders [131,136–139]. These findings suggest that brain Mn transport should be tightly regulated for proper function. Since the role of several metal transporters (e.g. DMT1, ferroportin and SLC30A10) in the uptake and clearance of Mn has been discussed elsewhere [140–144], the current review will focus on the influence of Mn overload on behavioral problems and potential neurotoxic mechanisms.

Manganese exposure and behavioral dysfunction

Manganese absorption occurs through ingestion, dermal absorption and inhalation. A significant association exists between Mn exposure and neurobehavioral and cognitive deficits. Mn neurotoxicity resulting in a Parkinson-like disorder, such as apathy, anorexia, pain in muscles and joints, bradykinesia and rigidity, has been well-documented in people drinking contaminated water, workers employed in mining and Mn ore processing and agricultural workers exposed to Mn-containing pesticides [145–155]. Mn intoxication has also been observed in children during long-term parenteral nutrition and in patients with chronic liver diseases. While psychiatric and overt behavioral problems are observed in children with high Mn exposure, epidemiological studies have also suggested that neurological dysfunction results from chronic, low-level Mn exposure [156–159]. While intestinal bioavailability of Mn is limited due to hepatic first-pass elimination [160], inhaled Mn absorption is much greater than intestinal absorption, indicating that inhalation is the most toxic route of exposure for Mn neurotoxicity [161].

In children, elevated Mn levels have been found in developmental disorders. Increased Mn levels in the hair have been extensively reported in hyperactive children with learning disabilities [162]. Also, in a study by Benko et al. [163] children with ADHD show significantly higher serum Mn concentrations. Hong et al. [164] demonstrated a correlation between blood Mn levels and behavioral problems like anxiety, social behavior and aggression in ADHD. A cross sectional study by Khan et al. [165] demonstrated a dose-response relationship between blood Mn levels and externalizing behavior problems like disruptive behavior and conduct problems. Neurobehavioral toxicities associated with Mn overload include behavioral disinhibition, impulsive errors and attention problems [166]. In addition, impaired psychomotor skills and altered catecholamine metabolism in children has also been linked to prenatal Mn exposure [157]. The behavioral toxicity of Mn could be a consequence of mixed effects on these brain components by dose- and time-dependent manners. Follow up studies must be conducted to determine the effect of Mn exposure on

alterations of gene functions involved in neurological processes. The identification of these targets has therapeutic implications to treat Mn-induced neurological disorders.

Mechanisms of Mn-associated neurotoxicity

Mn exposure has been linked to alterations in neurotransmitter pathways like dopamine [167–169] and consequently the development of psychiatric disorders. Kern et al. [170] have demonstrated that prenatal Mn exposure induces behavioral disinhibition and disrupts learning by altering the levels of dopamine receptors and transporters. Tran et al. [171] showed a relationship between striatal dopamine and Mn exposure along with behavioral deficits in rats. Impaired metabolism of GABA and glutamine is also associated with affective disorders caused by Mn exposure. Erikson et al. [172] found a negative correlation between Mn levels in the caudate putamen and GABA concentrations. Other studies, however, have reported increased GABA concentrations and elevated GABA-to-glutamate ratio following Mn overload diet [173]. The effects of Mn exposure on cholinergic systems have received increasing attention and have been reviewed [174]. It has been postulated that Mn toxicity in astrocytes occurs due to the alteration of glutamate transporters. For example, Mn exposure down-regulates the expression and function of glutamate transporters, thereby reducing glutamate uptake [175]. Impaired expression of glutamate/glutamine transporters results in increased extracellular glutamate levels, which promotes excitatory neurotoxicity. The exact mechanism by which Mn-induced neurotransmitter dysfunction causes affective disorders must be characterized by studying the downstream effects of altered neurotransmitter signaling.

An increasing body of evidence suggests that Mn neurotoxicity also results from impaired homeostasis of non-neuronal cells in the brain. Non-neuronal cell injury by Mn exposure results from activation of microglia and astrocytes [176,177]. Mn concentration in astrocytes is much higher than that in neurons, and within the astrocytes, its concentration is highest in the mitochondria [178,179], resulting in mitochondrial dysfunction [180]. Mn exposure causes oxidative stress by inducing nitric oxide synthases (NOS) in neuronal cells [181], which lead to an increased release of inflammatory mediators, such as prostaglandins, cytokines and nitric oxide [182,183]. Moreno et al. [184] found that subchronic Mn exposure causes increased activation of microglia and astrocytes in various regions of the brain. They also found that juveniles were more prone to microglial activation, whereas astrogliosis was more prominent in adults. These results suggest that Mn induced behavioral neurotoxicity occurs by multiple mechanisms that depend on the age and duration of exposure. To accurately characterize the mechanisms responsible for Mn-induced neurotoxicity, prenatal and postnatal exposure studies with different doses and duration should be conducted. It has been postulated that Mn neurotoxicity indirectly results from the production of glial-derived inflammatory products. Dodd et al. [185] demonstrated that Mn exposure alone has a minimal effect on the induction of inducible heme oxygenase (HO-1), an enzyme involved in regulation of oxidative stress, but Mn potentiates the lipopolysaccharide (LPS)-induced expression of HO-1. Loss of HFE function has been associated with protective effects against Mn-induced neurotoxicity [186]. The exact relationship between Mn-induced behavior and neurotransmitter dysfunction and the underlying molecular mechanisms remains to be elucidated. These studies will provide

novel molecular targets to treat neurobehavioral dysfunctions induced by heavy metal exposure.

Potential role of DMT1 in Mn neurobehavioral toxicity

The transport of Mn and iron is intimately related; some iron transporters mediate Mn uptake and clearance, including DMT1, transferrin receptor 1 (TfR1) and ferroportin. The importance of DMT1 in Mn transport has been noted in Mn deficiency in Belgrade rats [187]. Erikson et al. [188] demonstrated that Mn uptake into astrocytes occurred *via* DMT1 and was dependent on iron status. Although the affinity of intestinal DMT1 for Mn is relatively high, the transport of Mn through DMT1 to the brain has been called into question. Crossgrove et al. [189] determined that Mn transport to the brain occurred by mechanisms independent of DMT1. Aschner et al. [190] found that Mn transport across the BBB occurs through transferrin-TfR1 interaction. Mn exposure influences iron concentrations in various brain regions, as well as expression of iron-related proteins, such as ferritin and transferrin [191]. Although DMT1 mediates the absorption of Mn, its exact role in brain Mn transport is still unclear. Further investigation is required to accurately determine the involvement of DMT1 in transporting Mn to the brain. These studies will help elucidate the role of DMT1 in Mn-induced neurotoxicity.

LEAD

Lead exposure and toxicity

Lead (Pb) is an environmental toxicant with no known biological function. Pb is often used in industrial settings worldwide and can be found in many aspects of daily lives such as drinking water, food packaging products, dietary supplements, and even ceramics [192–194]. There are reports of increased blood levels of Pb that can be traced back to Pb glazes used for ceramics produced in Southern Europe [193]. Pb has also been used in various commercial products, such as gasoline and paint, in order to enhance the economic and functional benefits of such products throughout the world. Leaded gasoline and paint were banned due to increased observations of Pb toxicity. However, old houses that are still painted with leaded paint, and Pb that has been emitted to the environment as a result of use of leaded gasoline still remain potential sources of Pb toxicity [192–194]. Past mining areas, as exemplified by the Tar Creek in Ottawa County, Oklahoma, USA, also serve as significant sources of Pb and other toxic metals [195]. Various biological damages including hypertension and sterility in adults and delayed puberty in children have been caused by Pb toxicity [192,193]. Pb exposure in females poses a more serious problem due to the fact that Pb can be stored in bones for decades and leaks out to the fetus *via* placental transport during pregnancy [194].

Effect of lead on behavioral function

Behavioral effects of Pb have been extensively studied in both animal models and humans [196]. For example, monkeys receiving dietary Pb acetate demonstrated impaired learning and social function [197]. A recent link has been found between Pb toxicity and development of Alzheimer's disease (AD) with an association between Pb-induced apoptosis and its accumulation in amyloid plaques that are known to promote AD [198,199].

Another proposed link is that Pb exposure decreases DNA methyltransferase and amyloid precursor protein (APP) promoter methylation which in turn increases APP mRNA and amyloid β protein levels [200–202]. Although Pb has been implicated in neurodegenerative diseases, less is known regarding the relationship between time and duration of Pb exposure and the initiation and accumulation of amyloid plaques. Thus, Pb-induced dementia is a field that warrants further investigation, especially in the context of epigenetic regulation of Pb neurotoxicity.

A number of studies have been conducted to evaluate the effects of Pb in humans and many are targeting children due to the fact that Pb toxicity influences affective behavior that is mainly observed in children from an early age. Also, children are more susceptible to heavy metal toxicity due to 1) incompletely developed BBB and CNS, 2) increased absorption of Pb from the gut of children and 3) increased exposure caused by hand-to-mouth activities [203]. Children with increased blood Pb levels were shown to exhibit increased anxiety, social problems and inattention [204]. Analysis of the behavior of 301 school children with elevated bone Pb levels indicates aggression and restlessness in these children [205]. The behavioral effects of Pb are also manifested as hyperactivity and irritability, and these symptoms are not well characterized until children attend school [206]. Mendelsohn and colleagues [207] found that children with Pb levels of 25 μg/dl had significantly lower scores in the Behavior Rating Scale of the Bayley's Scales of Infant Development. Moreover, Sciarillo et al. [206] found that children who were exposed to Pb had significantly worse results in the Total Behavioral Problem Score in the Child Behavior Checklist. This study found that the Pb exposed children displayed behavioral problems (e.g. aggression and destructive behavior) and reported somatic and sleep problems [206]. In mice, Kasten-Jolly et al. [208] explored the effect of gestational and lactation Pb exposure and found that early Pb exposure resulted in significant alterations in exploratory behavior and spatial memory and was associated with emergence of aggressive behavior. Nation et al. [209] demonstrated that Pb-associated behavior problems lead to other secondary problems. For example, Pb exposure increases consumption of free choice and force choice alcohol, possibly due to a tranquilizing effect of alcohol on Pb-induced irritability.

Mechanisms of Pb-induced neurotoxicity

The mechanism of Pb absorption to the brain, and therefore its neurotoxic mechanisms, is not completely understood. Neurobehavioral toxicity by Pb exposure results by multiple mechanisms that are dependent on age and onset and duration of exposure, as well as brain structure.

Neurological damage induced by Pb exposure can be attributed to the alteration of the overall structure of the brain. For example, acute Pb poisoning leads to brain damage by causing swelling, ventricular compression, herniation and interference in collagen synthesis and vascular permeability [210]. Occupational exposure to high concentrations of Pb was associated with enhanced pinocytic activity and increased openings of interendothelial cells, which caused leakage of microvessels [211]. Pb exposure results in the distortion of the BBB structure [212] and the disruption of myelin morphology [213] in rodents. Moreover, Hu et al. [214] found that Pb administration during lactation alters synaptogenesis. There are

damages caused at more microscopic levels as well. Pb is a divalent metal cation which binds to the sulfhydryl groups on proteins with strong affinity and results in the structural distortion of enzymes and other functional proteins [215]. Also, Pb exposure alters gene expression, such as an upregulation of proinflammatory genes in the brain, which can lead to problems in the pathways required for the formation of various brain regions [208]. Pb exerts neurotoxic effects by altering the status of various redox parameters. Mateo et al. [216] demonstrated Pb exposure increases lipid peroxidation and glutathione levels and decreases the activity of anti-oxidant enzymes like glutathione peroxidase. These Pb-induced morphological and functional damages in the brain are subsequently manifested as behavioral alterations.

Other proposed mechanisms of toxicity involve the alteration of various neurochemical pathways. Bielarczyk et al. [217] found that developmental Pb exposure results in a decrease in cholineacetyltransferase. Also, administration of Pb to rodents alters dopaminergic and glutamatergic systems and thereby impairs learning [218]. Finkelstein et al. [219] observed an increase in tyrosine hydroxylase in the hippocampus, which resembles the surgical disruption of septohippocampal pathways. These results suggest that the cognitive and memory dysfunctions following Pb exposure may be due to denervation of the cholinergic hippocampal pathway. Further investigation of the mechanisms involved in Pb induced neurological damage can provide new therapies to prevent neurobehavioral problems, especially in Pb poisoning.

Role of metal transport in lead toxicity

Pb is well-absorbed through ingestion, inhalation and skin penetration and can be transported to the CNS *via* similar pathway as essential metals. Transporters, such as DMT1, allow the entry of essential metals into the CNS and are responsible for the systemic absorption of non-essential heavy metals, such as Pb and mercury (Hg) [26,220,221]. Pb, along with other divalent metals, can be transported by DMT1 [222,223]. Iron deficiency in both animals and humans results in increased blood Pb levels [224,225]. Moreover, Wang et al. [212,226] demonstrated that iron supplementation reduces both blood and brain Pb levels in the rats exposed to Pb and therefore provides a protective role against Pb-induced brain toxicity. However, the involvement of brain DMT1 in the absorption and neurotoxicity of Pb remains unclear, and Pb has been postulated to gain entry into the CNS by other mechanisms. Mounting evidence has indicated that the transport of Pb into the brain is mediated by the same mechanisms as Ca. Pb uptake by brain capillary endothelial cells has been associated with Ca-ATPase, whereas Pb entry into astroglia and neurons is mediated by voltage-sensitive Ca channels [227–229]. Once inside the cells, Pb is accumulated in the mitochondria, the same compartment involving the storage of Ca^{2+}, and thereby disrupts intracellular Ca^{2+} transport and metabolism and alters Ca signaling pathways like Protein Kinase C [230]. Thus, Ca status appears to play a role in the severity of Pb transport and thereby its toxicity. In addition, Cheong et al. [231] demonstrated that there exists an unidentified mechanism in the brain which has higher affinity for Pb transport as compared with DMT1. These studies also found that, at the neutral pH in the brain, Pb transport is not influenced by iron status and that upregulation of DMT1 does not increase cellular Pb content [231]. From these results, it may be postulated that though DMT1 in the brain could

be involved in cellular transport of essential metals to neuronal and non-neuronal cells and exerts neurotoxicity. Since Pb shares similar pathways with other essential metals for transport and interferes with their physiological function, supplementation of essential metals including zinc and iron are often used for the treatment for Pb toxicity [232]. However, such essential metals can also lead to related toxicity when overdosed. Thus, caution must be exercised in using metal supplements as therapies for protecting against Pb toxicity.

CADMIUM

Cadmium exposure

Cadmium (Cd) is a non-essential transition metal. Exposure to Cd is mainly occupational and occurs in metal industries, production of batteries, electroplating processes. Tobacco consumption is a significant source of Cd exposure since Cd levels are high in cigarettes. Occupational Cd exposure has been associated with cancers in various organs (e.g. lungs, prostate, kidney) and therefore Cd was classified as a human carcinogen [233,234]. The most commonly affected organ is kidney; Cd exposure leads to chronic renal failure [235]. Cd also affects hormones that regulate the human reproductive system, thereby causing infertility and premature birth [236]. Cd toxicity has also been linked to hypertension in rats [237], signifying a possible relationship between Cd exposure and cardiovascular diseases.

Behavioral disorders by cadmium

Cd exposure has also been linked to behavioral deficits. Lehotzky et al. [238] demonstrated that prenatal exposure to different doses of Cd alters of motor coordination, avoidance tasks and sociability. Cd exposure in children has been linked to developmental disorders, especially autism spectrum disorder (ASD). Studies have found elevated levels of Cd in the hair and blood of patients with ASD [239–241]. Cd exposure has also been linked to mental retardation and impaired learning and cognitive functions in children. There exists an inverse correlation between levels of Cd in children’s hair with Intelligence Quotient (IQ), learning difficulties and dyslexia [242–244]. In addition to these behavioral deficits, Cd exposure has also been implicated in drug seeking behavior and has been shown to exacerbate drug-induced symptoms and has been linked to an increase in the intake of ethanol and cocaine [245–247]. Thus, increased Cd burden may enhance the vulnerability to the negative effects of psychoactive drugs. Animal studies involving Cd exposure also exhibit behavioral alterations. Rats exposed to Cd had decreased memory, as well as altered anxiety and fear responses [248]. These behavioral deficits correlated with levels of oxidative stress markers in the hippocampus of these rats [248].

Mechanisms of Cd neurotoxicity

Oxidative stress is one of the proposed mechanisms of Cd toxicity. Lopez et al. [249] showed that Cd exposure resulted in ROS formation in cortical neurons. Tobwala et al. [250] also demonstrated that exposure to Pb and Cd in brain microvascular endothelial cells altered cell viability, glutathione levels and catalase enzyme activity by the production of ROS. In addition to oxidative stress, Cd also results in neurological damage as demonstrated by Wong et al. [251] who found that Cd exposure in newborn rats resulted in brain damage,

manifested as lesions and cystic cavities in brain regions, and behavioral dysfunctions, which were not observed in adult rats. Thus the age appears to play a significant role in the extent of Cd toxicity. Also, similar to Pb, Cd has increased the affinity for sulfhydryl groups thereby causing structural distortion of enzymes and other functional proteins [252]. At a cellular level, Cd exerts neurotoxic effects by inducing cell apoptosis, altering gene expression and cell signaling [253–255]. Gonçalves et al. [248] demonstrated that N-acetyl cysteine (NAC) reverses cognitive decline induced by Cd. This suggests antioxidant therapies may be utilized to reverse Cd-induced behavioral dysfunctions.

Some neurochemical alterations have also been observed as a result of Cd exposure. Gupta et al. [256] demonstrated a difference in catecholamine metabolism following Cd administration between growing and adult rats; while growing rats showed a decrease in 5-hydroxytryptamine and 5-hydroxyindole acetic acid in most brain regions, adult rats displayed an increase in these catecholamine metabolites. Another study that measured norepinephrine, 5-hydroxytryptamine, and dopamine demonstrated that mean concentrations of these monoamines increased as a result of acute 24-hr exposure to Cd in anterior, mediobasal, and posterior hypothalamus of rats [257]. These observations suggest that the neurobehavioral problems could result from the neurochemical alterations induced by Cd exposure. Studies on temporal and spatial changes in neurotransmitters and regulation of their transporters and receptors are required to provide insights into the mechanisms by which Cd exposure causes behavior dysfunction.

Effect of cadmium transport on neurotoxicity

The absorption of Cd is similar to other divalent metals and occurs from the intestine primarily by DMT1 and is influenced by the status of other metals in the body [258,259]. Park et al. [20] demonstrated that intestinal absorption of Cd through DMT1 increases during iron deficiency. The metabolism of Cd in impaired DMT1 is relatively unknown. In addition to DMT1, some other transporters have been examined in the context of Cd absorption. In adults, intestinal Cd absorption can be mediated by ferroportin, a transmembrane protein involved in cellular iron transport [260]. Neonatal Cd absorption has been linked to multidrug resistance associated protein 1 (MRP1), a transporter involved in the efflux of a number of chemicals and drugs from enterocytes [261]. Absorbed Cd does not generally reach the adult brain due to the presence of the BBB, but this structure is under-developed in children, who may be more susceptible to the neurotoxic effects of Cd. The exact mechanisms that govern Cd transport must be studied in order to determine the susceptibility of underdeveloped BBB to Cd neurotoxicity. Nasal mucosa and olfactory pathways involving olfactory neurons provide an alternate pathway that can bypass the BBB for the absorption of Cd to the brain [262–264]. Accurately characterizing the pathways by which Cd gains entry into the CNS will provide further insights into the mechanisms involved in Cd-induced neurotoxicity.

POLY-METAL EXPOSURE

The expression and activity of the components of metal metabolism is influenced by systemic metal status. This, in turn, affects the absorption and elimination of other metals in the body. Thompson et al. [52] found that the expression of DMT1 is increased in iron-

deficient anemia, which enhances olfactory absorption of manganese. Gu et al. [265] found that co-administration of Pb and Cd increases DMT1 expression, thereby altering the transport of toxic metals into the CNS. Combined iron deficiency and Pb exposure potentiates cognitive dysfunctions and neuronal development, as compared with iron deficiency or Pb exposure alone [266]. Concurrent exposure to Pb and Mn leads to increased accumulation of Pb in the brain and alters various behavioral patterns like anxiety and hyperactivity [267,268]. An epidemiological study conducted by Wright et al. [158] demonstrated that Mn and arsenic alters memory function in children and that a significant interaction effect exists between the two metals. Time and duration of exposure are important contributors to poly-metal toxicity. Chandra et al. [267] showed that poly-metal exposure during prenatal and early postnatal life alters brain function, as compared with the exposure during lactation alone. Since poly-metal exposure represents real-life metal exposure and often exhibits synergistic toxicity, more quantitative understanding is necessary to provide therapeutic benefits for the development of metal-induced behavioral disorders and resultant psychiatric alterations following concurrent exposure to multiple metals.

FACTORS INFLUENCING METAL-INDUCED BEHAVIORAL TOXICITIES

Figure 1 depicts the potential mechanisms of brain metal overload in the development of mental disorders and neurodegenerative diseases, and here we discuss several factors that can influence emotional and affective behavior due to metal overload.

Metal and nutritional status

Since transition metals possess redox potential, they are selectively involved in a variety of physiological processes, such as gene expression, signaling pathways and electron transport. Thus, it is not surprising that the body has developed complex physiological processes to limit the absorption, distribution and excretion of these metals. The regulation of body metal status is achieved by altering the expression of DMT1 and other metal transporters. For example, iron absorption from the intestine is increased in iron deficiency and decreased upon iron overload [269,270]. Body iron status also influences the pharmacokinetics of other metals in the body; evidence suggests the competitive absorption of Mn and iron from the intestine [271]. Following intravenous injection of ^{54}Mn, rats fed iron overload diet cleared blood Mn more rapidly compared with normal rats [272]. Since both uptake and clearance of metals are affected by the concentrations of other metals in the body, altered body metal status could influence the susceptibility to metal toxicity and potentially to mental disorders.

Gene polymorphism and lifestyle

Other factors, such as gene polymorphisms and different lifestyle, also influence the expression of metal transporters, which in turn alter metal uptake kinetics and toxicity in the body. For example, intestinal Mn absorption is increased in a mouse model of hemochromatosis [273] and this is correlated with elevated activity of iron transporters (ferroportin and DMT1) in hereditary hemochromatosis [274,275]. However, the steady-state concentrations of blood Mn in hemochromatosis are decreased [276], suggesting that

Mn clearance is greater than absorption in elevated body iron stores. In addition to these factors, body metal status is also influenced by lifestyle. Smoking is a significant source of cadmium and nickel, while alcohol consumption has been associated with altered iron metabolism [277,278]. These alterations are associated with neurobehavioral dysfunctions. Sassine et al. [279] found that concurrent exposure to Mn, followed by disorders associated with alcohol consumption, were risk factors for psychological distress. Alcohol consumption influences body iron status by regulating the components involved in iron metabolism. Ethanol alters the expression of transcription factors by inducing hypoxia and the expression of hepcidin, a hormone that down-regulates iron transporters, like DMT1 and ferroportin [280–282]. Better understanding of altered metabolism of metals due to gene polymorphism and different lifestyle will help to determine if metal disorders are important risk factors for psychiatric and neurodegenerative diseases.

Sex

Sex differences exist in metal disorders like anemia, with females being more susceptible to these alterations due to a higher prevalence of anemia [283]. Sex differences also exist in behavior and susceptibility to behavior disorders. It is interesting to note that women have been shown to be more predisposed to depression and associated behaviors like apathy and fatigue [284]. Ikeda et al. [285] demonstrated that decreased estrogen levels in ovariectomized mice are associated with decreased levels of hepcidin, the master regulator of iron transport, which ultimately elevates body iron status. The regulation of hepcidin by estrogen is mediated by G-protein coupled receptor 30 (GPR30) signaling and down-regulation of bone-morphologic protein-6 (BMP-6), establishing a molecular relationship between estrogen and hepcidin. On the contrary, Yang et al. [286] showed that estrogen inhibits induction of hepcidin *via* an estrogen-response element. Notably, testosterone supplementation suppresses the production of hepcidin [287,288]. These studies suggest that body iron status is regulated by additional factors like gender and gonadal hormones. Sex differences also exist between behavior disorders induced by other metals. Menezes-Filho et al. [289] demonstrated that females are more susceptible to attention problems caused by Mn exposure. Anderson et al. [290] also demonstrated sex differences in spatial memory after Pb administration. Studying the correlation between metal metabolism and sex differences in the context of behavioral disorders may help in determining if these molecular mechanisms influence the susceptibility to behavior disorders. The influence of gonadal hormones on metal metabolism provides an important avenue to novel therapeutics to explore molecular targets for behavior disorders that have been linked to hormonal imbalances, e.g. depression.

FUTURE DIRECTIONS

Metals are worthy of evaluation for their effects on the nervous system and subsequent behavioral changes. Many metals in excess have been implicated in the development of neurodegenerative diseases (e.g. Alzheimer’s disease) by catalyzing redox reactions that promote oxidative stress [6]. Since body metal status is dependent on the components of its metabolism, the dysfunctions caused by alteration of components involved in metal metabolism must be studied. He et al. [291] have proposed a possible link between single

nucleotide polymorphisms in DMT1 and the occurrence of Parkinson's disease. This indicates altered metal transport could be closely related to the development of neurodegenerative disorders. The progression of these neurodegenerative diseases is linked to age, and it has been demonstrated that there is an age-dependent increase in brain metal concentrations [292,293]. The effects of time and duration of metal exposure will help to determine the long term effects, including neurodegeneration and behavior disorders, induced by metal overload. Conversely, further studies that integrate the mechanisms associated with developmental metal overload and behavior dysfunctions, including therapeutic interventions through the mom, will provide possible new therapies to prevent/treat metal-induced behavior disorders in children. Another important factor to be considered is the route of exposure to these metals. These factors are of critical importance, especially in the context of occupational and lifestyle exposure. Studies must be conducted to determine the effects of particulate and soluble metal exposure. Examining these toxicities at the cellular and molecular level will provide insight into the mechanisms by which overload is associated with emotional dysfunction.

Drugs that alter the molecular mechanisms associated with metal overload can provide new therapeutic targets in the treatment of metal induced behavior disorders. Chelator treatments for metal-induced neurological disorders are a promising therapeutic strategy. Many chelators (e.g. deferoxamine) have been shown to improve cognitive function in rat pups after hemorrhage or traumatic brain injury [91,92,294]. Most chelators, unfortunately, have been shown to interfere with the homeostasis of essential nutrient metals. For example, meso-2,3-dimercaptosuccininic acid (DMSA) administration has been associated with minor changes in copper metabolism [295]. Therefore, it is important to analyze the chemical interactions between different classes of chelators and their metal targets to develop chelators that are highly specific and have minimum effects on other metals in the body. Recent advances in chelator research have provided several drugs that specifically chelate fewer metals. These include the iron chelators deferasirox and Bp44mT that have been developed with higher affinity for iron as compared to zinc or copper [296,297]. The chelation therapy with improved binding specificity and capacity holds great promise for ameliorating psychiatric and neurological disorders, as well as metal-induced neurotoxicity. Another potential therapy for correcting metal-induced oxidative stress is antioxidant supplementation. Indeed, antioxidant therapies have already been shown to alleviate oxidative stress occurring in neurodegenerative disorders and improve behavior symptoms in psychiatric and impulsive disorders [298–300]. Studies have found that antioxidants and chelators, both individually and in combination, reduce the deleterious neurological damage caused by metal overload [301,302]. More mechanistic and quantitative investigations on the association of metal overload with emotional behavior may help in developing new therapeutic targets for psychiatric disorders. The use of drugs that can modulate the levels of neurotoxic metals and resultant oxidative stress (e.g. chelators and antioxidants) provides molecular and pharmacological basis for therapeutic and nutritional intervention for behavior dysfunctions.

ACKNOWLEDGEMENTS

This work was supported by the NIH R00 ES017781 (J.K.).

Abbreviations

BBB	blood-brain barrier
Cd	cadmium
CNS	central nervous system
Cu	copper
DMT1	divalent metal transporter 1
Fe	iron
Mn	manganese
NBIA	neurodegeneration with brain iron accumulation
Pb	lead
Se	selenium
ROS	reactive oxidative species
SOD	superoxide dismutase
Zn	zinc

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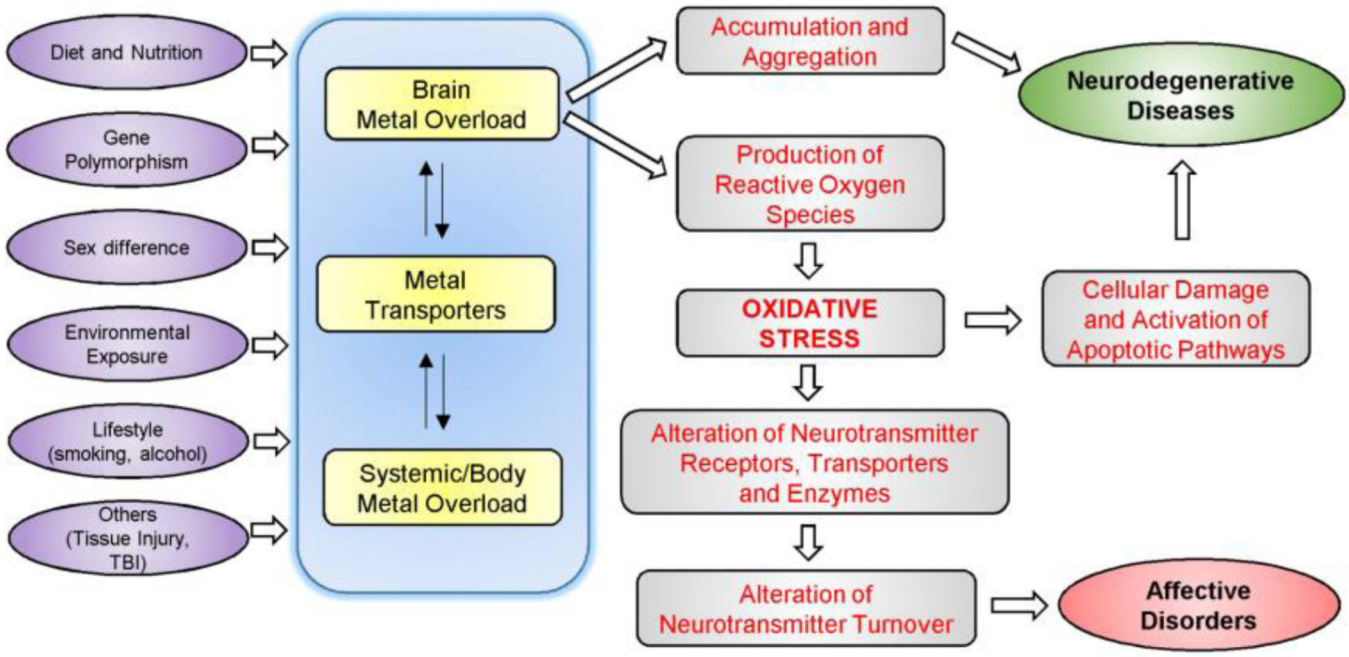

Figure 1. Potential mechanisms of brain metal overload in the development of affective disorders and neurodegenerative diseases

Various factors alter components of metal metabolism, thereby influencing metal status in the body and brain. Brain metal overload causes neurodegeneration and neurotransmitter dysfunction by inducing oxidative stress. Reactive oxygen species (ROS) impair various components of neurotransmitter pathways, which ultimately manifests as psychiatric/ affective disorders.