Mechanistic Effect of Heavy Metals in Neurological Disorder and Brain Cancer

Sandeep Kumar Agnihotri and Kavindra Kumar Kesari

Abstract Industrialization era is considered as a part of important human development. Industrialization increases the extensive use of different metals from earth crust because of their materials demand. Extensive use of these materials in daily life and their improper disposal are the reasons for environmental pollution. Toxic metals are highly causative in an open environment and because of this human gets exposures frequently. These toxic metal like cadmium (Cd), lead (Pb), Arsenic (As), Mercury (Hg), Thallium (Th) cross the blood brain barrier to enter into the brain and leads to development of neurodegenerative diseases. Heavy metals play an important role by inducing the reactive oxygen species, mitochondrial dysfunction, calcium ion efflux, an activation of immunogenic response, and suppression of anti-oxidants like catalase, superoxide dismutase (SOD), glutathione. Moreover, the brain-derived neurotrophic factor (BDNF) causes the depletion in cognitive dysfunctions and impairs the memory functions with several other neurological diseases like Alzheimer's and Parkinson's diseases. Here we have tried to illustrate the metals evoked mechanism, which impaires the function of neurons and generate the neurotoxicity and neurodegenerative diseases.

Keywords Cancer · Heavy metals · Neurotoxicty · Neuronal diseases

1 Introduction

The environment has started polluting after the industrialization and this led to contamination of water, air and whole atmosphere with unnatural gases. Pollution disturbs the ecosystem with all forms of industrial waste in the modern age of human civilization and development, pollution level is at its peak and responsible for severe human illness and diseases. Toxic environment affects more than 200 million people

S. K. Agnihotri (✉)
School of Life Science and Technology, Harbin Institute of Technology, Harbin, China
e-mail: sandeepagnihotri33@yahoo.com

K. K. Kesari
Department of Applied Physics, Aalto University, Espoo, Finland

K. K. Kesari (ed.), *Networking of Mutagens in Environmental Toxicology*, Environmental Science,
https://doi.org/10.1007/978-3-319-96511-6_2

worldwide and its worst effects are on newborn babies. Babies' health and development are impaired the most because pollution impact when immunity is weak and a recent UNICEF report shows that pollution causes the defect in development of the brain of babies along with causing cardiovascular and respiratory diseases.

Metals are very important for the living system and their homeostasis. However, if homeostasis collapsed, metal binds to the different site of protein (Nelson 1999) may impaired and lead to cause different kind of diseases (Halliwell and Gutteridge 2007). Metals also affect the gene regulation (Arini et al. 2015) and signaling pathways, which may be responsible for the cell growth and differentiation (Christie et al. 2013). However, deregulation of cell growth and differentiation leads to the cancer and apoptosis growth (Tykwinska et al. 2013).

Heavy metal is used in many occupations like, welding, smelting, pipe industries, painting, household utensils industries and many innumerable industries. Heavy metal has become a big problem with intractable outcome. This is affecting every individual in a direct or indirect way and leads to the varied diseases related to cardiovascular, respiratory, reproduction and cancers (Carpenter and Jiang 2013). Heavy metals are associated with neurodegenerative diseases such as multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease, Wilson disease and Alzheimer's disease (Giacoppo et al. 2014; Dusek et al. 2015).

Natural environment is a habitat for all biological living organisms. Most of the biological organisms have been evolving with the ages and show enormous development in respect to their previous generations. Humans belong to this category and the enormous level of development in all the areas makes life stress-free. Progress of human society increased rapidily with an industrialization in the 18th century. In the expansion of industrialization, we have builded roads for transportation, motor vehicles to transport materials, and for this, we have extracted the materials from the Earth crust and instigated the environmental damage. As the industrialization progresses, the spreading of wastes materials started polluting the atmosphere. These waste materials comprises an enormous amount of heavy metals, which gradually enters into our body system, accumulate and impaires the body homeostasis. Homeostasis is necessary to maintain the inner physiological activity and body organ functions. However, any kind of disruption due to heavy metals may start damaging the function of organs. Heavy metals commenced to disrupt the functions of all the organs including the brain (Agnihotri et al. 2015). Brain is an organ of our central nervous system, which is a most complex and it comprises of networks of billions of neurons, responsible for homeostatic activity of body, behavior, mood, muscular activity, memory etc. Brain functions affected by heavy metals may induce toxicity to interrupt the regular functions of central nervous system (Zhang et al. 2016). Heavy metals role has been understood in major neurobiological diseases such as Parkinson's disease, Alzheimer's disease, autism, multiple sclerosis (MS), amyotrophic lateral sclerosis/motor neuron disease (ALS/MND), dementia and cognitive disorder (Notarachille et al. 2014; Kumudini et al. 2014; Carocci et al. 2014; Caffo et al. 2014) (Fig. 1).

Heavy metal toxicants exists in dissimilar form in the environment and introduced in a human body by water, air and food. It is difficult to degrade the heavy metal by

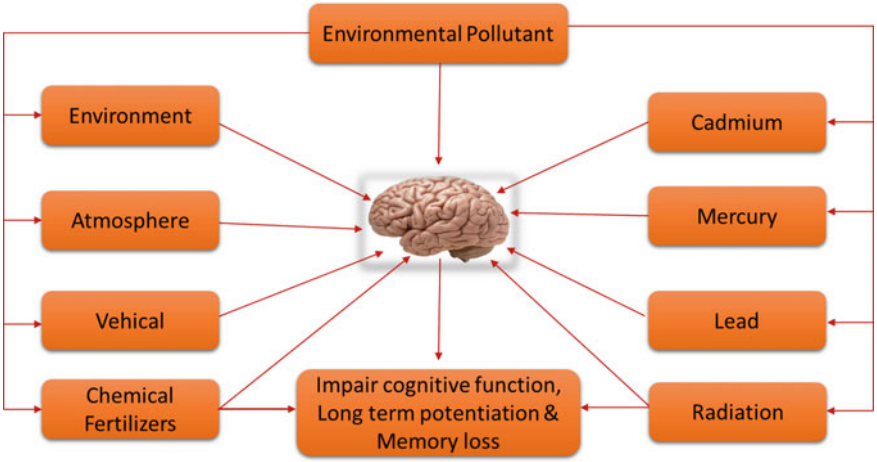

Fig. 1 Brain is very important part of our body, and is extremely sensitive too. Environmental pollutant and other heavy metals impact on brain and impairs the cognitive functions, causing long term potentiation and memory loss, and also impairing an important part of decision making

existing proteins and enzymes in the body. Therefore, proteins (metallothionein) bind with heavy metal and excrete from the body and reduce the toxicity of heavy metal (Liu et al. 2014). However, heavy metal dissolves in blood and circulate through different organs of body that persuades signaling mechanism to generate toxicity. Brain has specific respect to other organs of the body because; it has blood brain-barriers (BBB), which separates the circulating blood from brain and extracellular fluid of the central nervous system (CNS). Blood brain barrier allows the passage of glucose and amino acid by some selective transport mechanism, however, water, gases and lipid soluble molecules may transported with passive diffusion. Blood brain barrier is a vital part of brain to prevent neurodegeneration from external toxicants (Zheng et al. 2003) and is used as a defense mechanism for the brain (Nathanson and Mischel 2011). Heavy metal impairs the blood brain barrier and induces the oxidative stress, which instigates the cell death and initiates the neurodegeneration through different signaling pathway (Caserta et al. 2013).

Toxicity of heavy metal pollutant is enormously hazardous for developing central nervous system. In offspring's, small amount of intoxication affect their ability to learn and memorize their cognitive ability. At the developmental stage, low level of heavy metal impedes the development of the brain and generates neurodegenerative diseases likes' autism but the mechanism is completely obscure (Mohamed Fel et al. 2015; Yassa 2014). Here, we have discussed about the impact of heavy metals on neurodegenerative diseases and related mechanism.

2 Heavy Metal and Blood Brain Barrier

Etiology of neurobiological disorder is not completely attributed to acquired behaviors, proposing that heavy metals and other environmental factors possibly contribute too. Blood brain barrier (BBB) has been involved in metal transport and neural defense mechanism. BBB transport energy (glucose and amino acid) and important ions to maintain the homeostasis of neurons and glial cells and excrete the waste materials from the brain. Metal ion is exchanged extremely slowly between plasma and brain compared to other tissues (Serlin et al. 2015). Metals deposits with an accumulation of proteins have instigated the inflammatory process near the endothelial wall of BBB (Joana et al. 2016; McCarthy et al. 2018) within brain parenchyma, which leads to neuronal damage and loss (Cherry et al. 2014; Greter and Merad 2013). This progression of the brain degeneration for an extended period leads to disability and demise of neural cells. Alzheimer disease and Parkinson diseases are old age diseases that reflect the inflammation caused by the metals and accumulated proteins (Zeineh et al. 2015; Heppner et al. 2015). These metals are found in many forms around us since birth and accumulate in brain slowly as aluminum (Al), copper (Cu), iron (Fe), manganese (Mn) lead (Pb), mercury (Hg) and zinc (Zn) as an essential and non-essential manner. It has been noticed that impede mechanism of homeostasis triggered by metals indicate the sporadic form of Alzheimer disease (Li et al. 2015; Grubman et al. 2014). Al, Cu, Fe and Zn are the metals identified for sporadic form of Alzheimer disease (Grubman et al. 2014). Fe and Cu deficit have been analyzed in the substantia nigra of Parkinson's diseases (Loef and Walach 2015). Epidemiological studies suggests that Al, Cu, Fe, Pb, Mn, Hg and Zn are risk factors for Parkinson's disease (Salvador et al. 2010; Zucca et al. 2017; Greenough et al. 2013; Meyer et al. 2015; Doorn and Kruer 2013). Amyotrophic Lateral Sclerosis (ALS) is a motor neuron disease in which death of neurons controlling the voluntary muscle in around 20% of cases is caused by mutation of Cu, Zn-superoxide dismutase (SOD1) (Desai and Kaler 2008; Roos et al. 2006). ALS patient have minimum amount of Ca and Mg and elevated amount of Al, Cu, Pb, Mn and Hg (Fondell et al. 2013; Robison et al. 2015).

Heavy metals may enters in our body system through polluted air, contaminated water and food products and absorbed by intestine, lungs, and also through skin. Further, they mixed in blood and circulated to central nervous system (CNS) by crossing the BBB or choroid plexus (CP) to cerebrospinal fluid (CSF) or by diffusion to CNS (Yokel 2006). Although few other metals can be absorbed by a sensory nerve in the nasal cavity and enters into the brain (Oliver and Fazakerley 1998; Dorman et al. 2002). Mn and Ni also enters through nasal cavity (Rao et al. 2003). Moreover, glucose is the primary energy substrate of the brain, and its metabolism accounts for nearly all of the oxygen consumption in the brain (Mergenthaler et al. 2013). Brain glucose demands greatly and exceeds the rate of glucose diffusion across the BBB, where, Glut-1 mediates the brain glucose uptake to meet the brain's needs (Bélanger et al. 2011; Camandola and Mattson 2017). Glucose metabolized by the brain is of two or three times higher (Hyder et al. 2006) than any other organs of the body. If

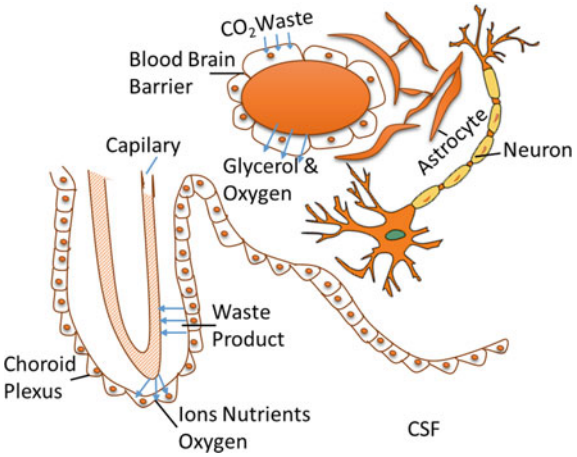

Fig. 2 Tight junction between epithelial cells make the blood brain barrier between capillary and cerebrospinal fluid, which passes the ions, nutrients, oxygen from blood capillary to cerebrospinal fluid (CSF) and remove the waste from CSF to capillary, in ventricle of the choroid plexus. BBB exchange materials and gas by diffusion or by specific transporter from blood to brain. Astrocytes remove the toxicants through BBB and take glucose and oxygen from blood and supply to neurons

BBB is damaged and compromised with energy delivery in the brain, that it may leads to seizures, mental retardation, compromised brain development and low CSF glucose concentrations in children (Yang et al. 2013) (Fig. 2).

Metals also transported by some transporter proteins as divalent metal transporter (DMT1, DCT1, Nramp2), which transports only divalent metals (Ca, Fe, Mn, Cd, Cu, Ni, and Pb) (Harris 1983). However transporter proteins as transferrin (transferrin mediated endocytosis) binds to metal and transported to CSF passing through BBB (Yokel 2006), diffusion, fluid phase endocytosis, receptor mediated endocytosis.

Aluminium (Al) reaches into the brain after crossing the BBB through transferrin-mediated endocytosis (TfR-ME) within 4 hours, when it passes into the body as aluminium citrate (Davson et al. 1987). Copper is transported by ATP receptors (ATP7A, ATP7B and CTR1) at BBB. Fe is also transported by (1) transferrin-receptor mediated endocytosis, (2) non-transferrin dependent mechanism, (3) DMT1 at BBB to the brain. Transportation of lead (Pb) through BBB in the brain is done by passive diffusion as $PbOH^+$ and cation channel (ATP dependent Ca pump). Mercury is transported only as methyl mercury (MeHg), not in any other form (Aschner 2007), but some study suggests that it makes complex with L-cysteine and transported through L-system (Aschner and Clarkson 1989). Mn is passed through BBB by diffusion, and transferrin mediated endocytosis to reach the brain where, Zn transported by Zip1 and Zip 6 at the BBB. Cd enters via the olfactory bulb and goes through central neurons, and damages the BBB permeability (Chowanadisai et al. 2005). BBB crossed metals reached to CSF and effluxes by astrocytes (protect the brain by taking out the

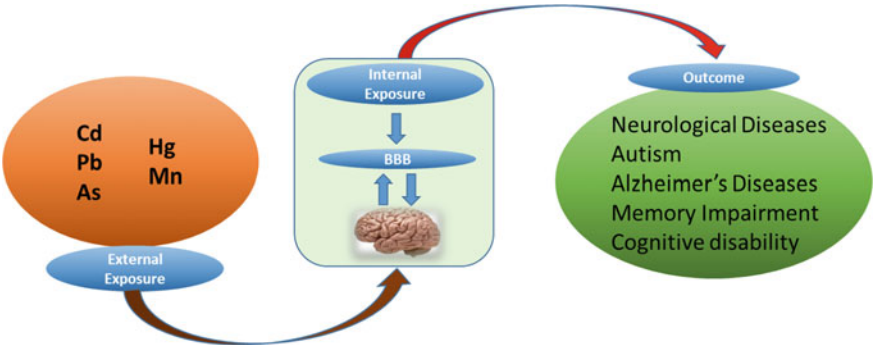

Fig. 3 Representation of different metals, present in the environment crossed the blood brain barrier (Ankley et al. 2010) and evoked neurodegenerative diseases with memory impairment and cognitive deficit

leftover and surplus material) to prevent any oxidative damage or reaction, which instigates numerous signaling processes to develop neurological diseases (Fig. 3).

3 Heavy Metal and Neurological Disease

Metals are divided in two categories, essential and non-essential metals, according to need of the living organism. Essential metals comprise the property to modulate the enzymatic and cellular activity, which controls the physiological actions such as protein reformation, signaling pathways, electron transport, redox reactions, metabolism of protein (carbohydrate and Fat), transportation of molecules, immune reactions and neurotransmitter synthesis and transportation (Wu et al. 2018; Lopez et al. 2002; Giralt et al. 2000; Murakami and Hirano 2008). These metals are essential for cellular lifespan, however, deficiencies of these metals linked to several neurodegenerative diseases. Moreover, the elevated levels may also induces the intracellular process, and causes the apoptosis, autophagy, mitophagy, signal transduction, protein misfolding, oxidative stress, mitochondrial dysfunction (Wegst et al. 2015; Szabo et al. 2016; Peres et al. 2016). This might be vulnerable to the normal brain functioning and cause many neurodegenerative diseases. Metals also affects the memory dysfunction, cognitive ability, muscular dysfunction, neurons apathy, amyotrophic lateral sclerosis, huntington's disease, menkes disease, Wilson's Disease, Friedreich's ataxia, gulf war syndrome, manganese multiple sclerosis, autism, insomnia, anorexia, anxiety, depression, Alzheimer's disease and Parkinson's disease (Sparks and Schreurs 2003; Mohandas and Colvin 2004; Koppenal et al. 2004; Andrade et al. 2017; Caito and Aschner 2015).

Aluminium (Al) reached into body or different organs through drinking water and food. Epidemiological survey identified that higher concentration of Al in drinking water may develops dementia, like Alzheimer's disease (Yokel and Florence 2006;

White et al. 1992; Killin et al. 2016). Exposure to miner concentration (inhale fine Al & Al_2O_3) may cause cognitive impairment, slow psychomotor response, and memory loss (Hosovski et al. 1990). Moreover, several other diseases such as, fatigue, working memory and learning behaviors were found in shipyard Al welders (Riihimaki et al. 2000). However, the role of Al is controversial for AD, because several other studies reveals that AD patients had the same amount of Al as control group in the urine and plasma (Graves et al. 1998). Study also suggests that changes occurs in AD brain were the same as found in AD (Perl 2001), where, Al increases the plaque deposition, Aβ protein aggregation and polymerization, and Aβ production in the brain (Clauberg and Joshi 1993; Mantyh et al. 1993; Kawahara et al. 1994). Aluminium hydroxide impede the neurological functions and persuade autism, increase anxiety, depression, long-term memory loss and neuronal death in spinal and motor cortex (Shaw and Tomljenovic 2013). Brain impairment depends on the exposure of Al concentrations and period causes physiological changes, which appear later in life. Manganese (Mn) mostly used in fuel additive, to reduce the combustion of the engine and released in air as manganese sulphate and phosphate (Lynam et al. 1999). Therefore the environment polluted air (manganese sulphate and phosphate) ingested by humans lead to the brain exposures. Mn may interrupt the brain functions and causes parkinsonism-like syndrome, which is initially apparent through apathy, anorexia, insomnia, extreme fatigability, somnolence, and a labile mood (Rudgalvyte et al.2016; Martinez et al. 2013; Farina et al. 2013; Gorojod et al. 2015). Mn exposure increases the progression of Parkinson's like symptoms tremors, abnormal movements, hypokinesia, speech disturbance, increased muscle tone, increased sweating and salivation (Tuschl et al. 2012; Quadri et al. 2012). However, brain was found pathologically different from PD in substancia nigra and basal ganglia (Shen and Dryhurst 1998). Epidemiological surveys on miners, workers on dry cell batteries and children's from buried dry cell batteries site have exhibited the neuropsychological behaviors, cognitive dysfunctions, emotional and motor defectiveness concomitant with an alteration (speedy) movement.

Arsenic is a major toxicant, found mostly in contaminated ground water which, makes an alloy with other metals (Prakash et al. 2016). Inorganic and methylated forms of arsenic accumulated near the different part of the brain and impair the normal functional mechanism of brain (Waly et al. 2016). Though, arsenic acts as teratogen, which may cross the placenta, and impairs the brain development through the formation of neural tube (Martinez et al. 2008). At the biochemical and molecular level, arsenic obstructs the cellular and molecular mechanism, where, an imbalance of Ca^{++}, mitochondrial dysfunction, and oxidative stress, disruption of ATP, altered membrane potential, cellular morphology, neuronal death and reduction on glial cells were reported (Yin et al. 1994). These biological changes in the brain leads to physiological impairment on vocabulary, mental acuity, language precision, total IQ and comprehending abilities such as difficulty in assembling the pictures with sequencing. Arsenic induces the beta amyloid formation which has been known for the main cause of AD (Giasson et al. 2002). It impairs the quality of life and metal health with a high level of depression, anxiety with psychiatric disorder and insomnia (Ashok et al. 2017). Arsenic play a major role as carcinogen if present in a

small amount of drinking water and causes severe intestinal pain, vomiting, diarrhea, muscle cramps, cardiac arrhythmias (Jarup 2003).

Cadmium has been used in many industrial factories of batteries, electroplating, solder, nuclear reactor shield, cigarette smokers and dental amalgams. Most of the cadmium enters in the body by inhalation via the olfactory bulb, which interrupts the function of BBB (Evans and Hastings 1992). Cd exposure induce the function of the nervous system and generates neurological disorder (Wang and Du 2013). Cd is well known factor of AD and PD (Jiang et al. 2007; Okuda et al. 1997). Cd also accelerates the accumulation of the *Tau* proteins, which is responsible for AD (Jiang et al. 2007). It mostly impact the brain in comparison to other organs (Agnihotri et al. 2015) and develops the neurological dysfunctions like decrease in learning ability, headache, and olfactory dysfunction (Mason et al. 2014). Cd has been known for morphological changes in axons and dendrites of the brain, decrease in size and inhibits the neurite growth (Baker et al. 1983). Cd produces free radicals in the brain, which radically damages the neurons and oligodendrocytes (Parkinson et al. 1986). Oligodendrocyte used to form the myelin sheath around neurons, which conduct the nerve signal in the form of electrical impulses, obstructs the signal by Cd induced free radical damage. Cd directly abolishes choroid plexus structure, by which a barrier of CSF and spifflicate the filtration process of unsolicited materials (Pal et al. 1993) that defects the motor disabilities, learning inability, behavior defects, brain lesions and neurochemical changes. Effects of Cd toxicity, maximum in, cerebral cortical neurons of brain have been identified (Bishak et al. 2015), where oxidative stress induced by mitochondrial dysfunction disrupts the Ca^{++} ion signaling process and leads to apoptosis in primary murine neurons (Orrenius and Nicotera 1994a). Neurogenesis is also affected by Cd, which leads to less number of neuronal and glial cells (Gottofrey and Tjalve 1991; Chow et al. 2008). Apoptosis is a major concern at the time of development, proliferation and differentiation, where in some cases, proliferation reduced to 50%. Epigenetic effects of Cd is also known because of weak association with DNA, and methylation, which disrupts the whole gene functions (Zevin and Benowitz 1999). DNA methylation is the best study of the epigenetic process that regulates the gene silencing (Fig. 4).

Lead (Pb) is used in many industries of coloring material such as painting industry, hair coloring, batteries, cables, solder, electroplating and in petroleum industries. Lead (Pb) is absorbed by children in much more amount than adults due to underdeveloped BBB. It has been reported that even a very low level (250 ppm) of Pb can injure the hippocampus (Jett et al. 1997). Lead (Pb) can get accumulated in different regions of brain and mainly in the hippocampus (Jett et al. 1997). Lead (Pb) contact outcomes in discrepancy in language, memory, executing the task, verbal concept formation, poor reasoning, and poor command following (Hussien et al. 2018). Lead (Pb) is reported to increase the Tau protein phosphorylation in the cortex and cerebellum, which is a primary cause of AD and PD (Rai et al. 2010). Blockade of receptor on the membrane or disruption in the structure of membrane receptor by Pb influences the mechanism of neural plasticity, affects the long-term potentiation and memory loss (Rai et al. 2010; Baranowska-Bosiacka et al. 2012). Schizophrenia, autism, Attention-Deficit Hyperactivity Disorder (ADHD) has chance to exposure

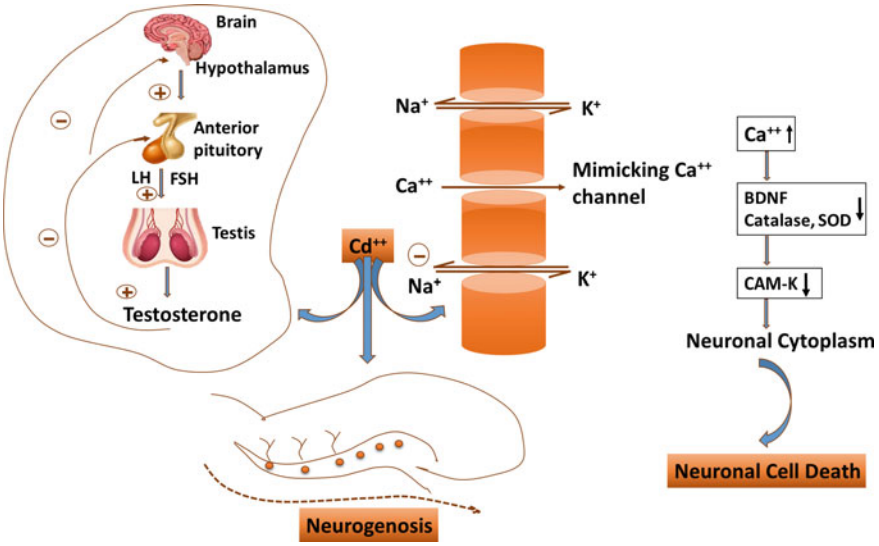

Fig. 4 Cadmium impaired the function of Na^+/K^+ ATPase enzyme and mimicking the function of Ca^{++} channel in neurons, which inhibited the expression of brain-derived neurotrophic factors (BDNF), catalase, superoxide dismutase (SOD) and increase the intracellular Ca^{++}, increased the free radicles which causes cell death. Cadmium has been detected as a reason to inhibit proliferation and differentiation in the hippocampus. Cadmium mimics the estrogen effects, in the reproductive system and disturbs the hypothalamic-pituitary-gonadal (HPG) axis

from environmental pollution from Pb (Modabbernia et al. 2016). With an increase of environmental pollutants, Pb toxicity has increased in humans, especially in children. However, if Pb toxicant reaches to the body in early childhood, may be disastrous for life, and produces abnormal behavior. This may results to brain toxicity and influence the learning and cognitive ability, memory impairment, and retrieval of memory, by affecting the normal life. Exposures to Pb may cause severe neurological diseases in children during childhood. Moreover, this may perturb the BBB, disrupts the NMDA receptor, phosphorylation of Tau/AB protein for AD and PD. This may also imbalance the Ca^{++} ion concentration, by increasing the PKC activity, and diminishing the BDNF level due to oxidative stress and which develops Autism, AD, PD, depression, anxiety, ALS (Zheng et al. 2003) (Fig. 5).

Mercury (Hg) as heavy metal, is widespread used in several industrial process. Mercury is mostly used in chemical research industry, laboratory purposes, medicine, electric industry, cosmetics, firearms and mercury lamp industry. Prevalent uses of mercury in industrial purposes, may affect the worker's life and its contamination in water and air persuades many biological irregularities. Inorganic Hg is incapable to cross the BBB but its alloy, methyalmercury (MeHg) cross the BBB and impairs the brain (Sheehan et al. 2014). Hg of aquatic arena mostly methylated and modified to MeHg due to presence of sulphate reducing bacteria (Parks et al. 2013). MeHg easily binds with aquatic and sea animals, therefore the consumption of these food chain

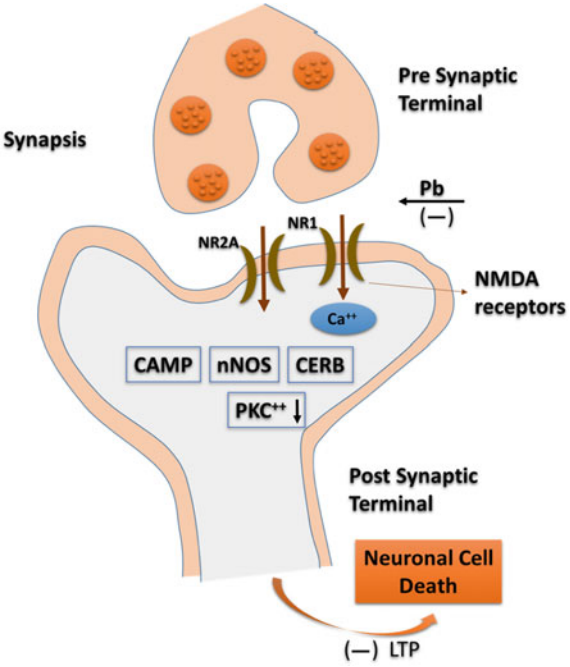

Fig. 5 High affinity of Pb^{++} towards NMDA receptor make complex, which inhibited to take glutamate, released from presynaptic neuron and NR2A (subunit of NMDA receptor) released the Ca^{++} in low amount, in postsynaptic neuron disrupts the cognitive dysfunction and memory impairment

organisms by human remains fundamental form of exposure to Hg. High affinity of MeHg towards sulphur increases the binding to thiol group of protein and may cross the BBB (Suzuki et al. 1976). MeHg crosses the BBB as amino acid transporters and can bind to cysteine amino acid and mimic methionine (Takeda et al. 2000). It crosses the BBB and gets distributed in the different parts of brain like occipital lobe, basal ganglia and cerebellum (Davis et al. 1994), to impede the neuronal activities. This also includes dopamine secretion, neural stem cell differentiation, aberrant mitophagy, mitochondrial dysfunction, due to oxidative stress (Chang et al. 2018; Yuntao et al. 2016). Some population-based study has reveled mercury in the blood of children suffering from autism (Pamphlett and Kum Jew 2016), that risks children of 2–5 years of age.

Thallium (TI) is heavy metals found in the earth crust. Thallium has been used in several industries such as electronics, mercury lamps, jewelry, pigmentation, scintillation counters, and semiconductors for different purposes. Thallium is also used in cement and rodenticide industry, and from there, thallium contaminate the soil and gets exposed to human body (Galván-Arzate and Santamaría 1998; Cvjetko et al. 2010). Thallium enters into the body with skin contact or by inhalation of thallium contaminated air and consumption of food from contaminated soil or water. Thallium is reasoned behind numerous neurological diseases and non-neurological diseases. Non-neurological symptoms of thallium are anorexia, vomiting, gastrointestinal bleeding, abdominal pain, paresthesia, alopecia, cardio-toxicity with arrhythmias,

and coma like life threating diseases occurs due to expoures. Thallium is also reasoned to cause seizure, fatigue, emotional changes, delirium, hallucination, ataxia, and loss of sensation, cranial-nerve deficit, and polyneuropathy like neurological symptoms in a dose dependent manner (Saha 2005; Zhao et al. 2008; Pelclová et al. 2009). Cortex, cerebellum and brain stem are the main regions of brain which are affected by thallium (Ríos et al. 1989). Moreover, toxicity was activated through lipid peroxidation and lysosomal enzyme beta-galectosydase in brain regions into dose dependent manner (Osorio-Rico et al. 2017). High concentration of thallium accumulated in hypothalamus and the potassium ion concentration may leads to many neurodegenerative diseases (Diaz and Monreal 1994).

Several metal in mixture of different concentration changes the homeostasis of biological environments of the body but have not been studied very extensively and minutely. Pb, As, Cd, Hg metals are studied in animal models as a mixture to examine the toxicity level and their multiple implications on various mechanisms, which may lead to neurological disorder.

4 Neurotoxicity Mechanism Induced by Heavy Metals

Heavy metals are used in our daily life, where, minute quantity may cause major impact in homeostasis, tiny quantity affects the enzyme activity in the brain and an excess quantity may generate neurotoxicity, which leads to neurodegenerative disorder. Most of the neurological diseases are developed during late old age and the reasons are unknown. However, it can be assume that these heavy metals may changes the behavior of enzymatic activity, oxidation of cellular molecules, mitochondrial dysfunctions, and molecular or cellular activities in the minute level at the initial stage in the brain. Metal absorption is different in the brain from other organs, where, most of the metals absorbs in gastrointestinal tract, skin, lungs, olfactory organs, and mixed in the circulatory system. Metals reached inside the brain to cross the BBB from blood to CSF and CSF to the inner side of the brain (Lemercier et al. 2003). Metal diffused from blood, through BBB, to CSF. In some cases, metal disrupts the BBB, and make permeable to other pathogens, compounds to generate autoimmune and neurological diseases like meningitis, epilepsy, multiple sclerosis, de novo diseases, cerebral edema, brain trauma, an damyotrophic lateral sclerosis.

Metals have an affinity towards divalent metal ion-transporter-1 (DMT-1) and transferrin (Tf) receptors; interact with BBB and brain tissue (Yokel et al. 2006). Passing through the BBB, glial fibrillary acidic protein (GFAP) expression reduced. Metals effect and disrupts the BBB, and make permeable to pathogens to generate autoimmune neurodegenerative diseases like multiple sclerosis, epilepsy, amyotrophic lateral sclerosis, meningitis, cerebral edema, and systematic inflammation. Divalent cation transporter (DMT-1) and transferrin transporter also binds with heavy metals at BBB and takes to CSF, where they accumulate in different parts of the brain. Metals involves in the mechanisms to bind with NMDA receptors, which are important for the cognitive behaviors and memory. Generally, NMDA recep-

tors responsible for glutamate balance in postsynaptic regions and bind to glutamate induced the efflux of Ca^{++} to neuronal cytoplasm of postsynaptic region (Farina et al. 2013). Mostly Pb causes irreversible inhibition of NMDA receptors by binding, and disrupts the Ca^{++} signaling in neuronal synapsis (Kim et al. 2005). This may also generates pathological neurobiological symptoms which has been accountable for memory function (Neal et al. 2011). Pb transformed the NMDA receptor subunits NR2A and NR2B ratio which perturb the Ca^{++} signaling in hippocampus and altered the BDNF, n-NOS, CERB, liable for memory and long-term potentiation inhibition (Guilarte et al. 2000). Calcium ion is an indispensable for neuron homeostasis, which maintains the intracellular signaling of presynaptic terminal, cell body, and dendritic arbor by balancing the Ca^{++} efflux (Rai et al. 2010). Pb causes the disruption of Ca^{++} concentration and activates the phosphor kinase C (PKC) and phosphor lipase C (PLC). This may unregulates the phosphor kinase A (PKA) and calmodulin dependent protein kinases (CMKII), followed to decreased the BDNF, CERB, antioxidant enzyme with increased ROS and MAPK signaling might leads the demise of neuronal cell (Reinholz et al. 1999). Pb affects the pre-syneptic (VAMP1/2, synaptophysin, synaptotagmin-1, SNAP25, syntaxin-1) and postsynaptic proteins (PSD-95), which may induce the pathological changes in the cerebellum, forebrain cortex and hippocampus. Moreover, synaptic region had swollen, elongated and shrunken mitochondria in Pb treated animals (Gassowska et al. 2016). These symptoms implies the synaptic dysfunction and disruption of neurotransmission mechanism due to Pb, and leads to neurodegenerative disorder and neurobiological diseases (Ashok et al. 2015).

Excessive accumulation of metals, found in different parts of the brain, may particiapte in the mechanism of oxidative damage to the brain cells by deformation of protein, accumulation of amyloid protein, disrupting the Na^{+}/K^{+} ATPase pump, upset acetylcholine esterase (AchE), and imbalance of ubiquitous Ca^{++} ions (Kinoshita et al. 2014). The Cd induced oxidative stress and mitochondrial dysfunction were recognized by Kumar et al. (2013). Cd exposure increased the Ca^{++} concentration in the cytoplasm and nucleus of neurons and such changes may abandone the cellular functions (Orrenius and Nicotera 1994a, b). Ca^{++} signaling affects the mitochondrial dysfunction and generate excess amount of ROS in neurons. Therefore, it consequently reduce the defense mechanism by changing the levels of the anti-oxidant like, glutathione, catalase, and superoxide dismutase activity. Increased ROS level induce the apoptosis mechanism in neuronal cells by affecting caspase-3 and caspase-9 activity, resulting in neuronal cell death in various parts of the brain (Jung et al. 2008), which may lead to cause ALS, a neurodegenerative diseases (Hart and Gitler 2012). Cd reduce the mitochondrial membrane potential of mitochondria (Hossain et al. 2009), (a major source of energy for neurons). It also reduces the capacity of mitochondria to produce ATP by oxidative phosphorylation and interrupt the transportation of mitochondria in distal part of neurons (Han et al. 2017). Disruption in mitochondrial transportation implicated in several neurodegenerative diseases as Alzheimer, Huntington and Parkinson's diseases (Jiang et al. 2007). Abnormal Ca^{++} homeostasis and mitochondrial dysfunction also evokes ROS and active free radicals. These free radicals move to the nucleus for mutation in DNA of pre and post synaptic

proteins. Increased level of ROS also reduces the BDNF level, which has vital role for memory and cognitive function in brain hippocampus (Baranowska-Bosiacka et al. 2012).

Hg proceeded as an organic form in humans, and its minute quantity has a major impact in the brain (Lohren et al. 2015). Hg found in mother milk also, which influences the brain development in new born (Johansson et al. 2007), resulting in cognitive dysfunction and disruption in learning behavior over the years. Hg interacts in cellular level and disrupts the function of neurotransmitter, microtubule and Ca^{++} homeostasis (Lafon Cazal et al. 1993). MeHg increased oxidative stress in cerebral cortex (Chang et al. 2013; Yuntao et al. 2016), causes the neuronal injury which induces amyotrophic lateral sclerosis/motor neuron diseases (ALS/MNS) (Chang et al. 2013; Yuntao et al. 2016). Thiol (-SH) group has high tendency to react with MeHg (Suzuki et al. 1976; Straka et al. 2016), present in cysteine and methionine amino acid of protein. MeHg impedes the thiol metabolism, which is a prime cause of autism (neurological disease of children at the age of 6), blamable for biochemical changes on transketolase, oxidative stress, abnormal thiamine homeostasis. Impeded thiol metabolism and oxidative stress decreased the glutathione (GSH), an anti-oxidant, present into high amount in the brain, and inhibited the activity of Na^{+}/K^{+} ATPase, NADH dehydrogenase, glutathione reductase and oxidative stress, makes neural vulnerable for neurodegenerative diseases (Gibon et al. 2010). MeHg, is responsible for glutamate (Glu) toxicity in brain (Moretto et al. 2005), block uptake of glutamate in astrocytes, and further, glutamate amount increased in the extracellular fluid, causes toxicity in the spinal cord. Toxicity in spinal cord and high concentration of glutamate by MeHg affects the synaptic activity of neurons, leading to devastating neurodegenerative diseases (Moretto et al. 2005). Hg inhibits the activity of superoxide dismutase (SOD), glutathione peroxidases and elevates the ROS level, which may increase the oxidative stress in cerebral cortex. Moreover, NF-E2-related factor 2 (Nrf-2) pathway get activated (Yang et al. 2017) and Ca^{++} ATPase activity inhibited, by increased intracellular loading of Ca^{++} and unbalanced Ca^{++} signaling in neurons. This may inhibit the process of electro-chemical activity of neuron, which is essential for the information transfer between neurons in every part of the brain. Hg causes the disruption in mitochondrial membrane potential by abandoned Ca^{++} in mitochondria (LeBel et al. 1990) and inhibits the mitochondrial electron transport chain (ETC) in cultured neural cells. Mercury enhance nitric oxide production and the activates the glial cells in brain, which reduces the glutathione level in brain (Simmons-Willis et al. 2002). All these mechanisms induced by MeHg make the brain vulnerable for neurodegenerative diseases.

Exposure to heavy metals results into neurodegenerative diseases or neurobiological diseases with multiple mechanistic pathway like mitochondrial dysfunction, Ca^{++} signaling, ROS generation, apoptosis, autophagy, interrupted anti-oxidant enzymes activity and crucial signaling pathway. Arsenic (As) phosphorylates the *tau* protein, (a microtubule associated protein of neurons), where this phosphorylation makes aggregation of *tau* proteins, deregulate the function of tau protein and causes neurodegeneration (Alizadeh-Ghodsi et al. 2018). Arsenic also cause the inflammation and degeneration of neural cells by ROS production and inhibition of antioxidant

activity in neural stem cells, reasoned for multiple sclerosis (MS) and impaired neural activity (Sun et al. 2017; Alizadeh-Ghodsi et al. 2018). Arsenic induces the inflammatory process in the cerebrum; cerebellum, thalamus and brain stem by modifying the inflammatory genes. Inflammation instigates the myelin reduction in nerve cells into the central nervous system, which hindered the electric signal in between neurons and cause neurodegenerative diseases and multiple sclerosis. Other inflammatory mechanism activates the microglial cells, cytokine interleukin-6 (IL-6), and IFN-γ (released from astrocyte), which causes the injury of neurons, inhibition of regeneration, death of neurons and oligodendrocyte implicated in neurodegenerative diseases as PD, AD, HD and traumatic brain injury on different parts of the brain (Alizadeh-Ghodsi et al. 2018; Sun et al. 2017; Ashok et al. 2015).

Mixed metal effects also analyzed in animal to disclose the severity of metal on neurodegenerative diseases. Al, Pb, Hg may cause the neurotoxicity with deregulation of Ca^{++} homeostasis in the brain microsomes (Andrade et al. 2017). Changes in the flux of Ca^{++} has been presented as indexing of heavy metal neurotoxicity in brain (Bostanci and Bagirici 2013). Al, Pb, Hg neurotoxicity implemented by IP3 mediated calcium release (Pb > Hg > Al) and inhibition of calcium uptake by microsomes in brain (Pb > HG > Al) (Pentyala et al. 2010). Cd and Pb have combined effects of Na^+/K^+ATPase, where Pb made the reaction more potent and imbalance the Na^+/K^+, Ca^{++} intracellular manner. Pb, Cd and Arsenic elicits ROS, and stimulate the signaling pathway of ERK, JNK, MEPK to induce neurotoxicity inside the brain and seeding of neurodegeneration diseases (Nori et al. 1996). Every metal has their different pathways to react and generate its effect, so the cumulative effect is always more detrimental than a single metal. Further study of mixed metal, Pb, Cd, MeHg, Arsenics acts individually differently, such as Pb binds to NMDA receptors, Cd inhibits the Na^+/K^+ ATPase pump, MeHg inhibits the glutamate uptake, where all are responsible for Ca^{++} deregulation in neurons (Ahlskog et al. 1995). This instigate the mechanism to ROS generation, inhibition of antioxidant, reduced BDNF, induced apoptosis, mitochondrial deregulation, and causing the neural cell death (Wang and Du 2013; Stackelberg et al. 2013).

5 Signaling Mechanism to Brain Cancer

Abnormal growth of a cell inside the brain causes a brain tumor. Brain tumor is very rare (2%) in human, and it has been found in two forms, benign and cancerous (or malignant). Cancerous form is divided in two, primary tumors (within a brain), and malignant (spread from other organs) (metastasis). Till now, the cause of cancer is unknown and only few mechanisms speculates the brain cancer, which found in glial cell (glioblastoma) and meningioma (benign) (Lathia et al. 2015). Glioblastoma can developed in astrocytes, oligodendrocytes and neural stem cells, which have metastatic activities, known as cancer stem cells (Omuro and DeAngelis 2013). Contrary occupational studies showed that metals have no role in brain cancer, as it has not been detected in brain cancer patients (Wesseling et al. 2002). Mechanism

behind the glioblastoma development, further reflected same in heavy metal mechanism, as comparable mechanism thought to be reason behind the initiation of brain cancer. In glioblastoma, the mechanism of calcium ion imbalance or irregular calcium signaling, mitochondrial dysfunction, increase in apoptotic pathway, restriction in autophagy, irregular cell cycle, JNK, ERK, MAPK signaling, Na^+/K^+ ATPase plays very prominent role, which are reprise by metals. Pb, Cd, As and Hg may induce the calcium ion deregulation in neural cells (Vu et al. 2018), which disrupts the mitochondrial dysfunction (Gugnani et al. 2018), disrupts the energy source and make cells glucose dependent (founds mostly in glioblastoma cells) (Singh et al. 2005). Heavy metals induced ROS formation may initiate DNA damage, lipid peroxidation, disruption in protein activities, free radical generation and correlate with epigenetic of brain tumors (Zhang et al. 2017). Metals produced oxidative stress causes the DNA mutation, strand breakage, and DNA methylation, histone alteration. In heavy metal, arsenic hypermethylate the DNA in the promoter of CDKN2A, Ras associated domain family protein 1A and serine protease 3 (Cui et al. 2006). Explanatory study of mechanism induced by metal was obscure but some occupational studies reveals that metals presents in individual patients with brain cancer. There is elevated risk of low-grade glioblastoma in worker of metal industry (Van Wijngaarden and Dosemeci 2006). Pb also has carcinogenic activity (Arslan et al. 2011). Several other studies also indicated that Pb causes the high risk of cerebral tumor (Cocco et al. 1998, 1999).

6 Conclusions and Future Recommendation

Heavy metal, As, Pb, Cd, Hg, Al has been known for their toxic effects in all aquatic and mammalian species. Toxicity of these metals are susceptible for the brain and cause neurotoxicity, which impacts neurodegenerative diseases like, Alzheimer disease, Parkinson's disease, Amyotrophic lateral Sclerosis, Multiple sclerosis etc. Every individual metal has their own mechanism to cross the blood brain barrier and reach the brain; some make complexes with proteins and some transported by specific transporter receptors to CNS. Choroid plexus is also playing an important role into crossing the metal to CNS, from where they reach different brain parts and induce neurotoxicity, including changes in the memory and cognitive functions of the brain. Pb, Cd, Hg and Arsenic have a separate mechanisms in diverse part of the brain to affect neural activity such as Pb bind to the NMDA receptor and prevents taking glutamate, which affects cognitive disability, memory and LTP. Cd induces the ROS formation, mitochondrial dysfunctions, imbalance of Ca^{++}, oxidative stress in neuronal cells, causes the death of neurons in ALS diseases. Metal induced oxidative stress initiate the signaling process of ERK, JNK, and MEPK, which activate the glial cells to produce immunogenic response. Activated glial cells persuade the immune system, release cytokine IL-6, IFN-γ which may cause damage to neurons and degenerate neurons of the nervous system. There is not much evidences of metal

in a sample of the brain cancer patients; however, the possibility is high in workers of metal industry to get neurological diseases with lowered level of glioblastoma.

It's evident from the studies that the lucid mechanism caused by the metal is obscure. Prolonged exposure of the metal and induction of brain cancer mechanism and neurodegenerative diseases at molecular level is completely ambiguous. Future research is represented as an innovation of molecular mechanism which might be able to explain the association of heavy metals and different types of brain tumors such as glioblastoma, meningitis.

References

Agnihotri SK, Agrawal U, Ghosh I (2015) Brain most susceptible to cadmium induced oxidative stress in mice. J Trace Elem Med Biol 30:184–193

Ahlskog JE, Waring SC, Kurland LT, Petersen RC, Moyer TP, Harmsen WS, Bush V (1995) Guamanian neurodegenerative disease: investigation of the calcium metabolism/heavy metal hypothesis. Neurology 45(7):1340–1344

Alizadeh-Ghodsi M, Zavvari A, Ebrahimi-Kalan A, Shiri-Shahsavar MR, Yousefi B (2018) The hypothetical roles of arsenic in multiple sclerosis by induction of inflammation and aggregation of tau protein: a commentary. Nutr Neurosci 21(2):92–96

Andrade VM, Aschner M, Marreilha Dos Santos AP (2017) Neurotoxicity of Metal Mixtures. Adv Neurobiol 18:227–265

Ankley GT, Bennett RS, Erickson RJ, Hoff DJ, Hornung MW, Johnson RD, Mount DR, Nichols JW, Russom CL, Schmieder PK, Serrrano JA, Tietge JE, Villeneuve DL (2010) Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment. Environ Toxicol Chem 29(3):730–741

Arini A, Gourves PY, Gonzalez P, Baudrimont M (2015) Metal detoxification and gene expression regulation after a Cd and Zn contamination: an experimental study on Danio rerio. Chemosphere 128:125–133

Arslan M, Demir H, Arslan H, Gokalp AS, Demir C (2011) Trace elements, heavy metals and other biochemical parameters in malignant glioma patients. Asian Pac J Cancer Prev 12(2):447–451

Aschner M (2007) Manganese: recent advances in understanding its transport and neurotoxicity. Toxicol Appl Pharmacol 221:131–147

Aschner M, Clarkson TW (1989) Methyl mercury uptake across bovine brain capillary endothelial cells in vitro: the role of amino acids. Pharmacol Toxicol 64:293–297

Ashok A, Rai NK, Tripathi S, Bandyopadhyay S (2015) Exposure to As-, Cd-, and Pb-mixture induces Abeta, amyloidogenic APP processing and cognitive impairments via oxidative stress-dependent neuroinflammation in young rats. Toxicol Sci 143(1):64–80

Ashok BS, Ajith TA, Sivanesan S (2017) Hypoxia-inducible factors as neuroprotective agent in Alzheimer's disease. Clin Exp Pharmacol Physiol 44(3):327–334

Baker EL, Feldman RG, White RF (1983) The role of occupational lead exposure in the genesis of psychiatric and behavioral disturbances. Acta Psychiatr Scand Suppl 303:38–48

Baranowska-Bosiacka I, Gutowska I, Rybicka M, Nowacki P, Chlubek D (2012) Neurotoxicity of lead hypothetical molecular mechanisms of synaptic function disorders. Neurol Neurochir Pol 46(6):569–578

Bélanger M, Allaman I, Magistretti PJ (2011) Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. Cell Metab 14(6):724–738

Bishak YK, Payahoo L, Osatdrahimi A (2015) Mechanisms of cadmium carcinogenicity in the gastrointestinal tract. Asian Pac J Cancer Prev 16(1):9–21

Bostanci MÖ, Bagirici F (2013) Blocking of L-type calcium channels protects hippocampal and nigral neurons against iron neurotoxicity. The role of L-type calcium channels in iron-induced neurotoxicity. Int J Neurosci 123(12):876–882
Caffo M, Caruso G, Fata GL, Barresi V, Visalli M, Venza M, Venza I (2014) Heavy metals and epigenetic alterations in brain tumors. Curr Genomics 15(6):457–463
Caito S, Aschner M (2015) Neurotoxicity of metals. Handb Clin Neurol 131:169–189
Camandola S, Mattson MP (2017) Brain metabolism in health, aging, and neurodegeneration. EMBO J 36(11):1474–1492
Carocci A, Rovito N, Sinicropi MS, Genchi G (2014) Mercury toxicity and neurodegenerative effects. Rev Environ Contam Toxicol 229:1–18
Carpenter RL, Jiang BH (2013) Roles of EGFR, PI3 K, AKT, and mTOR in heavy metal-induced cancer. Curr Cancer Drug Targets 13(3):252–266
Caserta D, Graziano A, Monte G, Lo Bordi G, Moscarini M (2013) Heavy metals and placental fetal maternal barrier: a mini review on the major concerns. Eur Rev Med Pharmacol Sci 17(16):2198–2206
Chang SH, Lee HJ, Kang B (2013) Methylmercury induces caspase-dependent apoptosis and autophagy in human neural stem cells. J Toxicol Sci 38(6):823–831
Cherry JD, Olschowka JA, O'Banion MK (2014) Neuroinflammation and M2 microglia: the good, the bad, and the inflamed. J Neuroinflam 11:15
Chow ES, Hui MN, Lin CC, Cheng SH (2008) Cadmium inhibits neurogenesis in zebrafish embryonic brain development. Aquat Toxicol 87(3):157–169
Chowanadisai W, Kelleher SL, Lonnerdal B (2005) Zinc deficiency is associated with increased brain zinc import and LIV-1 expression and decreased ZnT-1 expression in neonatal rats. J Nutr 135:1002–1007
Christie KJ, Emery B, Denham M, Bujalka H, Cate HS, Turnley AM (2013) Transcriptional regulation and specification of neural stem cells. Adv Exp Med Biol 786:129–155
Clauberg M, Joshi JG (1993) Regulation of serine protease activity by aluminum: implications for Alzheimer disease. Proc Natl Acad Sci USA 90:1009–1012
Cocco P, Dosemeci M, Heineman EF (1998) Brain cancer and occupational exposure to lead. J Occup Environ Med 40(11):937–942
Cocco P, Heineman EF, Dosemeci M (1999) Occupational risk factors for cancer of the central nervous system (CNS) among US women. Am J Ind Med 36(1):70–74
Cui X, Wakai T, Shirai Y, Hatakeyama K, Hirano S (2006) Chronic oral exposure to inorganic arsenate interferes with methylation status of p16INK4a and RASSF1A and induces lung cancer in A/J mice. Toxicol Sci 91(2):372–381
Cvjetko P, Cvjetko I, Pavlica M (2010) Thallium toxicity in humans. Arh Hig Rada Toksikol 61(1):111–119
Davis LE, Kornfeld M, Mooney HS (1994) Methylmercury poisoning: long-term clinical, radiological, toxicological, and pathological studies of an affected family. Ann Neurol 35(6):680–688
Davson H, Welch K, Segal MB (1987) The Secretion of the Cerebrospinal Fluid. The physiology and pathophysiology of the cerebrospinal fluid. Churchill Livingstone, New York, pp 218–221
Desai V, Kaler SG (2008) Role of copper in human neurological disorders. Am J Clin Nutr 88(3):855S–858S
Diaz RS, Monreal J (1994) Thallium mediates a rapid chloride/hydroxyl ion exchange through myelin lipid bilayers. Mol Pharmacol 46(6):1210–1216
Doorn JM, Kruer MC (2013) Newly characterized forms of neurodegeneration with brain iron accumulation. Curr Neurol Neurosci Rep 13(12):413
Dorman DC, Brenneman KA, McElveen AM, Lynch SE, Roberts KC, Wong BA (2002) Olfactory transport: a direct route of delivery of inhaled manganese phosphate to the rat brain. J Toxicol Environ Health A 65:1493–1511
Dusek P, Litwin T, Czlonkowska A (2015) Wilson disease and other neurodegenerations with metal accumulations. Neurol Clin 33(1):175–204

Evans J, Hastings L (1992) Accumulation of Cd(II) in the CNS depending on the route of administration: intraperitoneal, intratracheal, or intranasal. Fundam Appl Toxicol 19(2):275–278
Farina M, Avila DS, Da Rocha JB (2013) Metals, oxidative stress and neurodegeneration: a focus on iron, manganese and mercury. Neurochem Int 62(5):575–594
Fondell E, O'Reilly EJ, Fitzgerald KC, Falcone GJ, McCullough ML, Park Y, Kolonel LN, Ascherio A (2013) Magnesium intake and risk of amyotrophic lateral sclerosis: results from five large cohort studies. Amyotroph Lateral Scler Frontotemporal Degener 14(5–6):356–361
Galván-Arzate S, Santamaría A (1998) Thallium toxicity. Toxicol Lett 99(1):1–13
Gassowska M, Baranowska-Bosiacka I, Moczydlowska J, Frontczak-Baniewicz M, Gewartowska M, Struzynska L, Adamczyk A (2016) Perinatal exposure to lead (Pb) induces ultrastructural and molecular alterations in synapses of rat offspring. Toxicology 373:13–29
Giacoppo S, Galuppo M, Calabrò RS, D'Aleo G, Marra A, Sessa E, Bua DG, Potortì AG, Dugo G, Bramanti P, Mazzon E (2014) Heavy metals and neurodegenerative diseases: an observational study. Biol Trace Elem Res 161(2):151–160
Giasson BI, Sampathu DM, Wilson CA, Vogelsberg-Ragaglia V, Mushynski WE, Lee VMY (2002) The environmental toxin arsenite induces tau hyperphosphorylation. Biochemistry 41(51):15376–15387
Gibon J, Tu P, Frazzini V, Sensi SL, Bouron A (2010) The thiol-modifying agent N-ethylmaleimide elevates the cytosolic concentration of free $Zn(2^+)$ but not of $Ca(2^+)$ in murine cortical neurons. Cell Calcium 48(1):37–43
Giralt M, Molinero A, Carrasco J, Hidalgo J (2000) Effect of dietary zinc deficiency on brain metallothionein-I and -III mRNA levels during stress and inflammation. Neurochem Int 36(6):555–562
Gorojod RM, Alaimo A, Porte Alcon S (2015) The autophagic-lysosomal pathway determines the fate of glial cells under manganese- induced oxidative stress conditions. Free Radic Biol Med 87:237–251
Gottofrey J, Tjalve H (1991) Axonal transport of cadmium in the olfactory nerve of the pike. Pharmacol Toxicol 69(4):242–252
Graves AB, Rosner D, Echeverria D, Mortimer JA, Larson EB (1998) Occupational exposures to solvents and aluminium and estimated risk of Alzheimer's disease. Occup Environ Med 55:627–633
Greenough MA, Camakaris J, Bush AI (2013) Metal dyshomeostasis and oxidative stress in Alzheimer's disease. Neurochem Int 62(5):540–555
Greter M, Merad M (2013) Regulation of microglia development and homeostasis. Glia 61:121–127
Grubman A, Pollari E, Duncan C, Caragounis A, Blom T, Volitakis I, Kanninen KM (2014) Deregulation of biometal homeostasis: the missing link for neuronal ceroid lipofuscinoses? Metallomics 6(4):932–943
Gugnani KS, Vu N, Rondon-Ortiz AN, Bohlke M, Maher TJ, Pino-Figueroa AJ (2018) Neuroprotective activity of macamides on manganese-induced mitochondrial disruption in U-87 MG glioblastoma cells. Toxicol Appl Pharmacol 340:67–76
Guilarte TR, McGlothan JL, Nihei MK (2000) Hippocampal expression of N-methyl-d-aspartate receptor (NMDAR1) subunit splice variant mRNA is altered by developmental exposure to Pb2+. Mol Brain Res 76(2):299–305
Halliwell B, Gutteridge JMC (2007) Free radicals in biology and medicine, 4th edn. Oxford University Press
Han J, Yang X, Chen X, Li Z, Fang M, Bai B, Tan D (2017) Hydrogen sulfide may attenuate methylmercury-induced neurotoxicity via mitochondrial preservation. Chem Biol Interact 263:66–73
Harris WR (1983) Thermodynamic binding constants of the zinchuman serum transferrin complex. Biochemistry 22:3920–3926
Hart MP, Gitler AD (2012) ALS-associated ataxin 2 polyQ expansions enhance stress-induced caspase 3 activation and increase TDP-43 pathological modifications. J Neurosci 32(27):9133–9142
Heppner FL, Ransohoff RM, Becher B (2015) Immune attack: the role of inflammation in Alzheimer disease. Nat Rev Neurosci 16:358–372

Hosovski E, Mastelica Z, Sunderic D, Radulovic D (1990) Mental abilities of workers exposed to aluminium. Med Lav 81:119–123
Hossain S, Liu HN, Nguyen M, Shore G, Almazan G (2009) Cadmium exposure induces mitochondria-dependent apoptosis in oligodendrocytes. Neurotoxicology 30(4):544–554
Hussien HM, Abd-Elmegied A, Ghareeb DA, Hafez HS, Ahmed HEA, El-Moneam NA (2018) Neuroprotective effect of berberine against environmental heavy metals-induced neurotoxicity and Alzheimer's-like disease in rats. Food Chem Toxicol 111:432–444
Hyder F, Patel AB, Gjedde A, Rothman DL, Behar KL, Shulman RG (2006) Neuronal-glial glucose oxidation and glutamatergic-GABAergic function. J Cereb Blood Flow Metab 26:865–877
Jarup L (2003) Hazards of heavy metal contamination. Br Med Bull 68:167–182
Jett DA, Kuhlmann AC, Farmer SJ, Guilarte TR (1997) Age dependent effects of developmental lead exposure on performance in the morris water maze. Pharmacol Biochem Behav 57(1–2):271–279
Jiang LF, Yao TM, Zhu ZL (2007) Impacts of Cd(II) on the conformation and self-aggregation of Alzheimer's tau fragment corresponding to the third repeat of microtubule-binding domain. Biochim Biophys Acta 1774(11):1414–1421
Joana S, Cristóvão RS, Cláudio MG (2016) Metals and neuronal metal binding proteins implicated in Alzheimer's Disease. Oxid Med Cell Long 17–47
Johansson C, Castoldi AF, Onishchenko N, Manzo L, Vahter M, Ceccatelli S (2007) Neurobehavioural and molecular changes induced by methylmercury exposure during development. Neurotox Res 11(3–4):241–260
Jung YS, Jeong EM, Park EK, Kim YM, Sohn S, Lee SH, Moon CH (2008) Cadmium induces apoptotic cell death through p38 MAPK in brain microvessel endothelial cells. Eur J Pharmacol 578(1):11–18
Kawahara M, Muramoto K, Kobayashi K, Mori H, Kuroda Y (1994) Aluminum promotes the aggregation of Alzheimer's amyloid beta-protein in vitro. Biochim Biophys Res Commun 198:531–535
Killin LO, Starr JM, Shiue IJ, Russ TC (2016) Environmental risk factors for dementia: a systematic review. BMC Geriatr 16(1):175
Kim MJ, Dunah AW, Wang YT, Sheng M (2005) Differential roles of NR2A- and NR2B-containing NMDA receptors in Ras-ERK signaling and AMPA receptor trafficking. Neuron 46(5):745–760
Kinoshita PF, Yshii LM, Vasconcelos AR, Orellana AM, Lima Lde S, Davel AP, Scavone C (2014) Signaling function of Na, K-ATPase induced by ouabain against LPS as an inflammation model in hippocampus. J Neuroinflam 11:218
Koppenal C, Finefrock AE, Bush AI, Doraiswamy PM (2004) Copper, iron and zinc as therapeutic targets in Alzheimer's disease. Res Prac Alzheimer's Dis 9:250–255
Kumar P, Sannadi S, Reddy R (2013) Alterations in apoptotic caspases and antioxidant enzymes in arsenic exposed rat brain regions: reversal effect of essential metals and a chelating agent 6(3):1150–1166
Kumudini N, Uma A, Devi YP, Naushad SM, Mridula R, Borgohain R, Kutala VK (2014) Association of Parkinson's disease with altered serum levels of lead and transition metals among South Indian subjects. Indian J Biochem Biophys 51(2):121–126
Lafon Cazal M, Pietri S, Culcasi M, Bockaert J (1993) NMDA dependent superoxide production and neurotoxicity. Nature 364(3):535–537
Lathia JD, Mack SC, Mulkearns-Hubert EE, Valentim CL, Rich JN (2015) Cancer stem cells in glioblastoma. Genes Dev 29(12):1203–1217
LeBel CP, Ali SF, McKee M, Bondy SC (1990) Organometal induced increases in oxygen reactive species: the potential of 2′,7′-dichlorofluorescin diacetate as an index of neurotoxic damage. Toxicol Appl Pharmacol 104(1):17–24
Lemercier V, Millot X, Ansoborlo E, Menetrier F, Flury-Herard A, Rousselle C, Scherrmann JM (2003) Study of uranium transfer across the blood-brain barrier. Radiat Prot Dosimetry 105(1–4):243–245
Li W, Garringer HJ, Goodwin CB, Richine B, Acton A, VanDuyn N, Vidal R (2015) Systemic and cerebral iron homeostasis in ferritin knock-out mice. PLoS One 10(1):e0117435

Liu Y, Wu H, Kou L, Liu X, Zhang J, Guo Y, Ma E, (2014) Two metallothionein genes in Oxya chinensis: molecular characteristics, expression patterns and roles in heavy metal stress. PLoS One 12:9(11)

Loef M, Walach H (2015) Iron and copper in alzheimer's disease: a review micronutrients in dementia and cognitive decline, pp 563–571

Lohren H, Blagojevic L, Fitkau R, Ebert F, Schildknecht S, Leist M, Schwerdtle T (2015) Toxicity of organic and inorganic mercury species in differentiated human neurons and human astrocytes. J Trace Elem Med Biol 32:200–208

Lopez GC, Varea E, Palop JJ, Nacher J, Ramirez C, Ponsoda X, Molowny A (2002) Cytochemical techniques for zinc and heavy metals localization in nerve cells. Microsc Res Tech 56(5):318–331

Lynam DR, Roos JW, Pfeifer GD, Fort BF, Pullin TG (1999) Environmental effects and exposures to manganese from use of methylcyclopentadienyl manganese tricarbonyl (MMT) in gasoline. Neurotoxicol 20:145–150

Mantyh PW, Ghilardi JR, Rogers S, DeMaster E, Allen CJ, Stimson ER, Maggio JE (1993) Aluminum, iron, and zinc ions promote aggregation of physiological concentrations of beta-amyloid peptide. J Neurochem 61:1171–1174

Martinez EJ, Kolb BL, Bell A, Savage DD, Allan AM (2008) Moderate perinatal arsenic exposure alters neuroendocrine markers associated with depression and increases depressive-like behaviors in adult mouse offspring. Neurotoxicology 29(4):647–655

Martinez-Finley EJ, Gavin CE, Aschner M (2013) Manganese neurotoxicity and the role of reactive oxygen species. Free Radic Biol Med 62:65–75

Mason LH, Harp JP, Han DY (2014) Pb neurotoxicity: neuropsychological effects of lead toxicity. Biomed Res Int 2014:840547

McCarthy RC, Sosa JC, Gardeck AM, Baez AS, Lee CH, Resnick MW (2018) Inflammation-induced iron transport and metabolism by brain microglia. J Biol Chem RA118.001949. https://doi.org/10.1074/jbc.ra118.001949

Mergenthaler P, Lindauer U, Dienel GA, Meisel A (2013) Sugar for the brain: the role of glucose in physiological and pathological brain function. Trends Neurosci 36(10):587–597

Meyer E, Kurian MA, Hayflick SJ (2015) Neurodegeneration with brain iron accumulation: genetic diversity and pathophysiological mechanisms. Annu Rev Genomics Hum Genet 16:257–279

Modabbernia A, Velthorst E, Gennings C, De Haan L, Austin C, Sutterland A, Reichenberg A (2016) Early-life metal exposure and schizophrenia: a proof-of-concept study using novel tooth-matrix biomarkers. Eur Psychiatry 36:1–6

Mohamed Fel B, Zaky EA, El-Sayed AB, Elhossieny RM, Zahra SS, Salah Eldin W, Youssef WY, Khaled RA, Youssef AM (2015) Assessment of hair aluminum, lead, and mercury in a sample of autistic Egyptian children: environmental risk factors of heavy metals in Autism. Behav Neurol 2015:545674

Mohandas B, Colvin RA (2004) The role of zinc in Alzheimer's disease. Recent Res Devel Physiol 2:225–245

Moretto MB, Funchal C, Santos AQ, Gottfried C, Boff B, Zeni G, Rocha JB (2005) Ebselen protects glutamate uptake inhibition caused by methyl mercury but does not by Hg2+. Toxicology 214(1–2):57–66

Murakami M, Hirano T (2008) Intracellular zinc homeostasis and zinc signaling. Cancer Sci 99(8):1515–1522

Nathanson D, Mischel PS (2011) Charting the course across the blood-brain barrier. J Clin Invest 121(1):31–33

Neal AP, Worley PF, Guilarte TR (2011) Lead exposure during synaptogenesis alters NMDA receptor targeting via NMDA receptor inhibition. Neurotoxicology 32(2):281–289

Nelson N (1999) Metal ion transporters and homeostasis. EMBO J 18:4361–4371

Nori A, Fulceri R, Gamberucci A, Benedetti A, Volpe P (1996) Biochemical and functional heterogeneity of rat cerebrum microsomal membranes in relation to SERCA Ca(2 +)-ATPases and Ca2 + release channels. Cell Calcium 19(5):375–381

Notarachille G, Arnesano F, Calo V, Meleleo D (2014) Heavy metals toxicity: effect of cadmium ions on amyloid beta protein 1-42. Possible implications for Alzheimer's disease. Biometals 27(2):371–388

Okuda B, Iwamoto Y, Tachibana H (1997) Parkinsonism after acute cadmium poisoning. Clin Neurol Neurosurg 99(4):263–265

Oliver KR, Fazakerley JK (1998) Transneuronal spread of Semliki Forest virus in the developing mouse olfactory system is determined by neuronal maturity. Neurosci 82:867–877

Omuro A, DeAngelis LM (2013) Glioblastoma and other malignant gliomas: a clinical review. JAMA. 310(17):1842–1850

Orrenius S, Nicotera P (1994a) The calcium ion and cell death. J Neural Transm Suppl 43:1–11

Orrenius S, Nicotera P (1994b) The calcium ion and cell death. J Neural Transm Suppl 43:1–11

Osorio-Rico L, Santamaria A, Galvan-Arzate S (2017) Thallium toxicity: general issues, neurological symptoms, and neurotoxic mechanisms. Adv Neurobiol 18:345–353

Pal R, Nath R, Gill KD (1993) Influence of ethanol on cadmium accumulation and its impact on lipid peroxidation and membrane bound functional enzymes (Na + , K + -ATPase and acetylcholinesterase) in various regions of adult rat brain. Neurochem Int 23(5):451–458

Pamphlett R, Kum Jew S (2016) Locus ceruleus neurons in people with autism contain no histochemically-detectable mercury. Biometals 29(1):171–175

Parkinson DK, Ryan C, Bromet EJ (1986) A psychiatric epidemiologic study of occupational lead exposure. Am J Epidemiol 123(2):261–269

Parks JM, Johs A, Podar M (2013) The genetic basis for bacterial mercury methylation. Science 339(6125):1332–1335

Pelclová D, Urban P, Ridzon P (2009) Two-year follow-up of two patients after severe thallium intoxication. Hum Exp Toxicol 28(5):263–272

Pentyala S, Ruggeri J, Veerraju A, Yu Z, Bhatia A, Desaiah D, Vig P (2010) Microsomal Ca2 + flux modulation as an indicator of heavy metal toxicity. Indian J Exp Biol 48(7):737–743

Peres TV, Schettinger MR, Chen P, Carvalho F, Avila DS, Bowman AB, Aschner M (2016) Manganese-induced neurotoxicity: a review of its behavioral consequences and neuroprotective strategies. BMC Pharmacol Toxicol 17(1):57

Perl DP (2001) The association of aluminum and neurofibrillary degeneration in Alzheimer's disease, a personal perspective. In Exley C (ed) Aluminum and Alzheimer's disease. Elsevier, pp 133–146

Prakash C, Soni M, Kumar V (2016) Mitochondrial oxidative stress and dysfunction in arsenic neurotoxicity: A review. J Appl Toxicol 36(2):179–188

Quadri M, Federico A, Zhao T (2012) Mutations in SLC30A10 cause parkinsonism and dystonia with hypermanganesemia, polycythemia, and chronic liver disease. Am J Hum Genet 90(3):467–477

Rai A, Maurya SK, Khare P, Srivastava A, Bandyopadhyay S (2010) Characterization of developmental neurotoxicity of As, Cd, and Pb mixture: synergistic action of metal mixture in glial and neuronal functions. Toxicol Sci 118(2):586–601

Rao DB, Wong BA, McManus BE, McElveen AM, James AR, Dorman DC (2003) Inhaled iron, unlike manganese, is not transported to the rat brain via the olfactory pathway. Toxicol Appl Pharmacol 193:116–126

Reinholz MM, Bertics PJ, Miletic V (1999) Chronic exposure to lead acetate affects the development of protein kinase C activity and the distribution of the PKCgamma isozyme in the rat hippocampus. Neurotoxicology 20(4):609–617

Riihimaki V, Hanninen H, Akila R, Kovala T, Kuosma E, Paakkulainen H, Valkonen S, Engstrom B (2000) Body burden of aluminum in relation to central nervous system function among metal inert-gas welders. Scand J Work Environ Health 26:118–130

Ríos C, Galván-Arzate S, Tapia R (1989) Brain regional thallium distribution in rats acutely intoxicated with Tl2SO4. Arch Toxicol 63(1):34–37

Robison G, Sullivan B, Cannon JR (2015) Identifcation of dopaminergic neurons of the substantia nigra pars compacta as a target of manganese accumulation. Metallomics 7(5):748–755

Roos PM, Vesterberg O, Nordberg M (2006) Metals in motor neuron diseases. Exp Biol Med (Maywood) 231(9):1481–1487

Rudgalvyte M, Peltonen J, Lakso M (2016) RNA-seq reveals acute manganese exposure increases endoplasmic reticulum related and lipocalin mRNAs in caenorhabditis elegans. J Biochem Mol Toxicol 30(2):97–105

Saha A (2005) Thallium toxicity: a growing concern. Indian J Occup Environ Med 9(2):53–56

Salvador GA, Uranga RM, Giusto NM (2010) Iron and mechanisms of neurotoxicity. Int J Alzheimers Dis 2011:720658

Serlin Y, Shelef I, Knyazer B, Friedman A (2015) Anatomy and physiology of the blood-brain barrier. Semin Cell Dev Biol 38:2–6

Shaw CA, Tomljenovic L (2013) Aluminum in the central nervous system (CNS): toxicity in humans and animals, vaccine adjuvants, and autoimmunity. Immunol Res 56(2–3):304–316

Sheehan MC, Burke TA, Navas-Acien A (2014) Global methylmercury exposure from seafood consumption and risk of developmental neurotoxicity: a systematic review. Bull World Health Organ 92(4):254–269F

Shen XM, Dryhurst G (1998) Iron- and manganese-catalyzed autoxidation of dopamine in the presence of l-cysteine: possible insights into iron- and manganesemediated dopaminergic neurotoxicity. Chem Res Toxicol 11(7):824–837

Simmons-Willis TA, Koh AS, Clarkson TW, Ballatori N (2002) Transport of a neurotoxicant by molecular mimicry: the methylmercury-L-cysteine complex is a substrate for human L-type large neutral amino acid transporter (LAT) 1 and LAT2. Biochem J 367(Pt 1):239–246

Singh D, Banerji AK, Dwarakanath BS, Tripathi RP, Gupta JP, Mathew TL, Jain V (2005) Optimizing cancer radiotherapy with 2-deoxy-d-glucose dose escalation studies in patients with glioblastoma multiforme. Strahlenther Onkol 181(8):507–514

Sparks DL, Schreurs BG (2003) Trace amounts of copper in water induce beta-amyloid plaques and learning deficits in a rabbit model of Alzheimer's disease. Proc Natl Acad Sci USA 100:11065–11069

Stackelberg KV, Elizabeth G, Tian C, Birgit CH (2013) Mixtures, metals, genes and pathways: a systematic review. Working Paper prepared for: methods for research synthesis: a cross-disciplinary workshop. Harvard Center for Risk Analysis, 3 Oct 2013

Straka E, Ellinger I, Balthasar C, Scheinast M, Schatz J, Szattler T, Gundacker C (2016) Mercury toxicokinetics of the healthy human term placenta involve amino acid transporters and ABC transporters. Toxicology 340:34–42

Sun X, He Y, Guo Y, Li S, Zhao H, Wang Y, Xing M (2017) Arsenic affects inflammatory cytokine expression in Gallus gallus brain tissues. BMC Vet Res 13(1):157

Suzuki T, Shishido S, Ishihara N (1976) Different behaviour of inorganic and organic mercury in renal excretion with reference to effects of D-penicillamine. Br J Ind Med 33(2):88–91

Szabo ST, Harry GJ, Hayden KM, Szabo DT, Birnbaum L (2016) Comparison of Metal Levels between Postmortem Brain and Ventricular Fluid in Alzheimer's Disease and Nondemented Elderly Controls. Toxicol Sci 150(2):292–300

Takeda A, Suzuki M, Okada S, Oku N (2000) Zn localization in rat brain after intracerebroventricular injection of 65Zn-histidine. Brain Res 863:241–244

Tuschl K, Clayton PT, Gospe SM Jr (2012) Syndrome of hepatic cirrhosis, dystonia, polycythemia, and hypermanganesemia caused by mutations in SLC30A10, a manganese transporter in man. Am J Hum Genet 90(3):457–466

Tykwinska K, Lauster R, Knaus P, Rosowski M (2013) Growth and differentiation factor 3 induces expression of genes related to differentiation in a model of cancer stem cells and protects them from retinoic acid-induced apoptosis. PLoS One 8(8):e70612

Van Wijngaarden E, Dosemeci M (2006) Brain cancer mortality and potential occupational exposure to lead: findings from the national longitudinal mortality study, 1979–1989. Int J Cancer 119:1136–1144

Vu HT, Kobayashi M, Hegazy AM, Tadokoro Y, Ueno M, Kasahara A, Hirao A (2018) Autophagy inhibition synergizes with calcium mobilization to achieve efficient therapy of malignant gliomas. Cancer Sci. (https://doi.org/10.1111/cas.13695 (Epub ahead of print)

Waly M, Power-Charnitsky VA, Hodgson N, Sharma A, Audhya T, Zhang Y, Deth R (2016) Alternatively spliced methionine synthase in SH-SY5Y neuroblastoma cells: cobalamin and GSH dependence and inhibitory effects of neurotoxic metals and thimerosal. Oxid Med Cell Longev 6143753

Wang B, Du Y (2013) Cadmium and its neurotoxic effects. Oxid Med Cell Longev 2013:898034

Wegst USR, Mullin EJ, Ding D, Manohar S, Salvi R, Aga DS, Roth JA (2015) Endogenous concentrations of biologically relevant metals in rat brain and cochlea determined by inductively coupled plasma mass spectrometry. Biometals 28(1):187–196

Wesseling C, Pukkala E, Neuvonen K, Kauppinen T, Boffetta P, Partanen T (2002) Cancer of the brain and nervous system and occupational exposures in Finnish women. J Occup Environ Med 4(7):663–668

White DM, Longstreth WT, JrL Rosenstock, Claypoole KH, Brodkin CA, Townes BD (1992) Neurologic syndrome in 25 workers from an aluminum smelting plant. Arch Intern Med 152:1443–1448

Wu MJ, Hu HH, Siao CZ, Liao YM, Chen JH, Li MY, Chen YF (2018) All Organic Label-like Copper(II) Ions Fluorescent Film Sensors with High Sensitivity and Stretchability. ACS Sens 3(1):99–105

Yang H, Wu J, Guo R, Peng Y, Zheng W, Liu D, Song Z (2013) Glycolysis in energy metabolism during seizures. Neural Regen Res 8(14):1316–1326

Yang T, Xu Z, Liu W, Feng S, Li H, Guo M, Xu B (2017) Alpha-lipoic acid reduces methylmercury-induced neuronal injury in rat cerebral cortex via antioxidation pathways. Environ Toxicol 32(3):931–943

Yassa HA (2014) Autism: a form of lead and mercury toxicity. Environ Toxicol Pharmacol 38(3):1016–1024

Yin JC, Wallach JS, Del Vecchio M, Wilder EL, Zhou H, Quinn WG, Tully T (1994) Induction of a dominant negative CREB transgene specifically blocks long term memory in drosophila. Cell 79(1):49–58

Yokel RA (2006) Blood brain barrier flux of aluminum, manganese, iron and other metals suspected to contribute to metal induced neurodegeneration. J Alzheimers Dis 10(2–3):223–253

Yokel RA, Florence RL (2006) Aluminum bioavailability from the approved food additive leavening agent acidic sodium aluminum phosphate, incorporated into a baked good, is lower than from water. Toxicology 227(1–2):86–93

Yuntao F, Chenjia G, Panpan Z (2016) Role of autophagy in methylmercury-induced neurotoxicity in rat primary astrocytes. Arch Toxicol 90(2):333–345

Zeineh MM, Chen Y, Kitzler HH, Hammond R, Vogel H, Rutt BK (2015) Activated iron-containing microglia in the human hippocampus identified by magnetic resonance imaging in Alzheimer disease. Neurobiol Aging 36:2483–2500

Zevin S, Benowitz NL (1999) Drug interactions with tobacco smoking. An update. Clin Pharmacokinet 36(6):425–438

Zhang Z, Miah M, Culbreth M, Aschner M (2016) Autophagy in neurodegenerative diseases and metal neurotoxicity. Neurochem Res 41(1–2):409–422

Zhang C, Jiang H, Wang P, Liu H, Sun X (2017) Transcription factor NF-kappa B represses ANT1 transcription and leads to mitochondrial dysfunctions. Sci Rep 7:44708

Zhao G, Ding M, Zhang B (2008) Clinical manifestations and management of acute thallium poisoning. Eur Neurol 60(6):292–297

Zheng W, Aschner M, Ghersi-Egea JF (2003) Brain barrier systems: a new frontier in metal neurotoxicological research. Toxicol Appl Pharmacol 192(1):1–11

Zucca FA, Segura-Aguilar J, Ferrari E, Muñoz P, Paris I, Sulzer D, Sarna T, Casella L, Zecca L (2017) Interactions of iron, dopamine and neuromelanin pathways in brain aging and Parkinson's disease. Prog Neurobiol 155:96–119