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REVIEW ARTICLE

Mercury and Alzheimer's disease: a look at the links and evidence

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Abstract

This review paper investigates a specific environmental-disease interaction between mercury exposure and Alzheimer's disease hallmarks. Alzheimer's disease is a neurodegenerative disorder affecting predominantly the memory of the affected individual. It prevails mostly in the elderly, rendering many factors as possible causative agents, which potentially contribute to the disease pathogenicity cumulatively. Alzheimer's disease affects nearly 50 million people worldwide and is considered one the most devastating diseases not only for the patient, but also for their families and caregivers. Mercury is a common environmental toxin, found in the atmosphere mostly due to human activity, such as coal burning for heating and cooking. Natural release of mercury into the atmosphere occurs by volcanic eruptions, in the form of vapor, or weathering rocks. The most toxic form of mercury to humans is methylmercury, to which humans are exposed to by ingestion of fish. Methylmercury was found to exert its toxic effects on different parts of the human body, with predominance on the brain. There is no safe concentration for mercury in the atmosphere, even trace amounts can elicit harm to humans in the long term. Mercury's effect on Alzheimer's disease hallmarks formation, extracellular senile plaques and intracellular neurofibrillary tangles, has been widely studied. This review demonstrates the involvement of mercury, in its different forms, in the pathway of amyloid beta deposition and tau tangles formation. It aims to understand the link between mercury exposure and Alzheimer's disease so that, in the future, prevention strategies can be applied to halt the progression of this disease.

Keywords Alzheimer's · Neurodegenerative diseases · Environment-disease interaction · Methylmercury · Inorganic mercury

Abbreviations

AD	Alzheimer's disease
ApoE4	Apolipoproteins E4
APP	Amyloid precursor protein
BACE	Beta secretase or beta-site APP-cleaving enzyme
CSF	Cerebrospinal fluid
FAD	Familial Alzheimer's disease
FAT	Fast anterograde axonal transport
GIT	Gastrointestinal tract
GSH	Glutathione
GTP	Guanosine triphosphate
$HgCl_2$	Mercuric chloride
HgS	Cinnabar ore
ICOH	International commission on occupational health
IUPAC	The international union of pure and applied chemistry
LOAD	Late onset Alzheimer's disease
MAP	Microtubule associated protein
MCL	Maximum contaminant level
MCLG	Maximum contaminant level goal
MeHg	Methylmercury
MPL	Maximum permissible level
MT	Microtubules
NEP	Neprilysin
OSHA	Occupational safety and health administration
PTSD	Post-traumatic stress disorder
PTWI	The provisional tolerable weekly intake
RAGE	Receptor for advanced glycation end products
SAT	Slow anterograde axonal transport
sLRP	Soluble low-density lipoprotein receptor proteins bind
TBI	Traumatic brain injury
TRPM2	Transient receptor potential melastatin 2
TRPV1	The transient receptor potential cation channel subfamily V member 1

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US EPA Environmental Protection Agency
WHO World health organization

Introduction

Mercury is a common element in our environment. We are exposed to it throughout our lives in small amounts, therefore not aware of its effects on the long term. The toxicity of mercury was exhibited when the world witnessed big epidemics in Japan (Minamata) and Iraq. Individuals were accidentally exposed to very high doses of mercury which lead to mercury poisoning that had debilitating permanent consequences including death. Mercury toxicity depends on dose, form, and duration of exposure (Skerfving and Copplestone 1976; Harada 1995). Therefore, assessing the safety of mercury is paramount to prevent the unknown consequences to its exposure. One of these consequences is postulated to be neurodegeneration, which might lead to Alzheimer's dementia in the future. Dementia is a multifactorial, devastating disease affecting around 50 million people worldwide (Prince et al. 2016). It is most prevalent in the elderly population. As a result of the advancements in medicine, the proportion of the elderly population is increasing in parallel to the increase in the prevalence of dementia. In the year 2016, dementia was the second most common cause of death after ischemic heart disease in patients aged 70 and above, while it was the fifth most common cause of death regardless of age. In addition, it was the cause of 28.8 million DALYs (disability adjusted life years) globally, in 2016 (Vijayan and Reddy 2016). Age is by far the most well-known risk factor for dementia with women being slightly more affected than men (Nichols et al. 2019; Alzheimer's Association Report (106)). The most common form of dementia is Alzheimer's Disease (AD), a neurodegenerative disorder which is a product of gene, environment, socioeconomic status and lifestyle interactions (Alzheimer's Association Report (106)). In this review paper we explore the effect of mercury on the nervous system, particularly its implications on AD and we summarize the pathways by which mercury can affect the pathogenesis of this disease.

Alzheimer's disease

Background

AD is a neurodegenerative disease which is progressive, meaning that it worsens with time. It usually occurs in the elderly population above the age of 65, but some familial forms of AD occur earlier than that (Alzheimer's Association Report (105)). The most commonly known risk factors for AD are age, family history, and Apolipoprotein E 4 (ApoE4) allele (Alzheimer's Association Report (105)). Other risk factors include socioeconomic status, traumatic brain injury (TBI), cardiovascular disease risk factors, post-traumatic stress disorder (PTSD), education, exposure to pesticides and heavy metals and ischemic stroke (Alzheimer's Association Report (105)). It is still not clearly understood how these risk factors aid in the progression of AD as it is a heterogeneous disease, and is most probably a product of the interaction between all these factors. In familial AD, a specific gene called the presenilin (1 or 2) gene is mutated. Presenilin 1 gene is responsible for the catalytic function gamma secretase enzyme. It is also important for memory and neuronal survival. Mutations in the presenilin 1 gene, for example C410Y or L435F, put the function of gamma secretase to an end. This leads to a dramatic decrease in amyloid beta $_{40}$ production which increases the amyloid beta $_{42}$ to amyloid beta$_{40}$ ratio commonly seen in AD. This is a more probable explanation than stipulating an increase in amyloid beta$_{42}$ production (Xia et al. 2015; Kelleher and Shen 2017). The autosomal dominant mutation in amyloid precursor protein (APP) gene is another cause of familial AD (Arber et al. 2019). All the familial AD cases constitute less than 1% of all AD cases (Arber et al. 2019). ApoE4 allele is the gene with the strongest association with late onset AD (LOAD) (Alzheimer's Association Report (106)). ApoE4 is a lipoprotein primarily expressed in astrocytes and microglia. Therefore, the altered expression of this lipoprotein affects the function of glial cells. Having ApoE2 genotype reduces the risk of AD (Carocci et al. 2014; Fernandez et al. 2019). It is not clear how ApoE4 leads to AD, but the reduced clearance of amyloid beta (Amyloid beta) could be a potential mechanism (Fernandez et al. 2019).

Neuropathology

The hallmarks of AD are senile plaques and neurofibrillary tangles. They both start to form in different locations of the brain. Brain atrophy in AD generally starts with volumetric loss within the hippocampus, and with disease progression it extends to the anterior cingulate, the inferior and medial temporal lobes, the basal ganglia and amygdala (Feldman 2007). Senile plaques start to show in the basal, temporal, and orbitofrontal neocortex of the brain, progressing later on to the neocortex, hippocampus, amygdala, diencephalon, and basal ganglia. Neurofibrillary tangle formation is induced by amyloid beta deposition and is found primarily in the locus coeruleus and transentorhinal and entorhinal areas of the brain, and later on, in the hippocampus and neocortex (Tiwari et al. 2019).

Pathophysiology

The brain is composed of a network of neurons. Every neuron is composed of an axon, dendrites, synapses and the cell body.

Microtubules are an important structural component of the neuron, they are also the tracts for fast anterograde axonal transport (FAT) and slow anterograde axonal transport (SAT), which are responsible for the transport of membrane proteins, enzymes, neurotransmitters, neurofilaments, glycoproteins and more (Nogales 2001; Twelvetrees 2020). These transport tracts are important especially during the regeneration of the neurons, as they deliver the building units of the neuron (Salama et al. 2018). Microtubules (MT) are made of alpha and beta tubulin. Guanosine triphosphate (GTP) is required for the polymerization of tubulin dimers into microtubules. Tau proteins are microtubules associated proteins (MAPs) which provide support and shape to microtubules by anchoring them together and to the plasma membrane by binding to tubulin protein. MT form channels to supply the nerve cells with nutrients. Tau proteins when hyperphosphorylated can't function normally, and microtubules disassemble. Thus, depriving neurons of their nutrients leading to their death and degeneration (Del Alonso et al. 1996; Kapitein and Hoogenraad 2015; Bjørklund et al. 2019). These hyperphosphorylated tau proteins cluster together forming neurofibrillary tangles, which are the hallmark of AD. They are found intracellularly, primarily in the hippocampus early in the disease and later in the neocortex (Del Alonso et al. 1996; Bjørklund et al. 2019).

Amyloid precursor protein (APP) is a transmembrane protein. APP is under constant cleavage of two enzymes, alpha secretase and beta secretase. Beta secretase leads to the Amyloid beta protein formation. Two enzymes cleave the APP consequently to form Amyloid beta, the beta secretase or beta-site APP-cleaving enzyme (BACE1) and gamma secretase, creating different isoforms of Amyloid beta ranging from 36 to 43 amino acid residues. Amyloid beta$_{40}$ is the most commonly produced. Amyloid beta$_{42}$ (meaning 42 amino acids) is the more hydrophobic isoform that accumulates in AD patients' brains (Kelleher and Shen 2017). Usually our body has mechanisms to control the amounts of Amyloid beta produced. For example, degrading Amyloid beta by proteases, including neprilysin. Another mechanism is the transportation of Amyloid beta across the blood brain barrier out of the brain by low density lipoprotein receptor-related protein (LRP1). RAGE (receptor for advanced glycation end products) transports free Amyloid beta from the interstitial fluid into the brain. Soluble low-density lipoprotein receptor proteins bind (sLRP) bind to Amyloid beta in the plasma. sLRP levels in the plasma correlate to the deposition of Amyloid beta accumulation in the brain. Accumulation of Amyloid beta extracellularly in the brain form senile plaques, which is another hallmark of AD (Olivieri et al. 2000; Mawuenyega et al. 2013; Kim et al. 2014). Figure 1 summarizes the pathophysiology of AD.

Amyloid beta attacks the cell membrane of the neurons and forms channels which disrupt the ion balance or lead to the death of the neuron. Other studies suggest that Amyloid beta induces excitotoxic neurodegeneration or activates channels like the transient receptor potential melastatin 2 (TRPM2) or the transient receptor potential cation channel subfamily V member 1 (TRPV1), by decreasing glutathione (GSH) levels, which increases Ca2+ entry and mitochondrial oxidative stress leading to neuronal death (Balaban et al. 2017; Meleleo et al. 2019). TRPM2 is a Ca^{2+} permeable nonselective cation channel activated by oxidative stress (Sagare et al. 2012; Ostapchenko et al. 2015; Kelleher and Shen 2017).

Mercury

Sources and toxicity of mercury

Mercury is a product of nature. It is mainly found as cinnabar (HgS) in the earth's crust or in ocean sediments. It is released into the environment by either volcanic activity, weathering rocks or through anthropogenic influence. The main source of mercury pollution by far is human activity viz. combustion of fossil fuels, mining and various other industries. Mercury is used in sundry instruments such as thermometers. It is occasionally employed as a catalyst in chemical processes, and as a conductor in position-dependent electrical switching whereas its vapor is used in different forms of illumination. Liquid elemental mercury is the fundamental component in dental amalgams. According to the World Health Organization Factsheet on Mercury and Health, other forms of mercury are utilized as fungicides in agriculture, and in paints as preservatives or pigments (McNutt 2013).

Mercury is an element with the atomic number of 80. It is the only metal on earth that is liquid at room temperature. It is found in 3 chemical forms: Elemental mercury (Hg^0), also called *quicksilver*, which can be found as a liquid metal or in vapor form (odorless and unseen toxic vapor); inorganic mercury (Hg^+ and Hg^{2+}), and organic mercury (methylmercury or ethyl mercury) (Ye et al. 2016; US EPA 2020).

While mercury is a naturally occurring element, it is highly toxic and so are most of its compounds Depending on the duration and dose of exposure as well as the form of mercury and the condition of the individual exposed to it, mercury can exhibit significnt toxicity on the cardiovascular system, kidney, lungs and the CNS (Cariccio et al. 2019). The most common point of exposure for mercury is food (Ye et al. 2016). Depending on its physical form and characteristics, mercury can be absorbed through different routes. Figure 2 summarizes some of the sources that lead to mercury release into the environment.

Metallic mercury (Quicksilver) can be absorbed by inhalation, but is minimally absorbed through the gastrointestinal tract (GIT), due to the formation of globules (Ye et al. 2016). Being fat soluble and monoatomic, it easily penetrates the alveolar cell barrier and cell membranes and is then oxidized

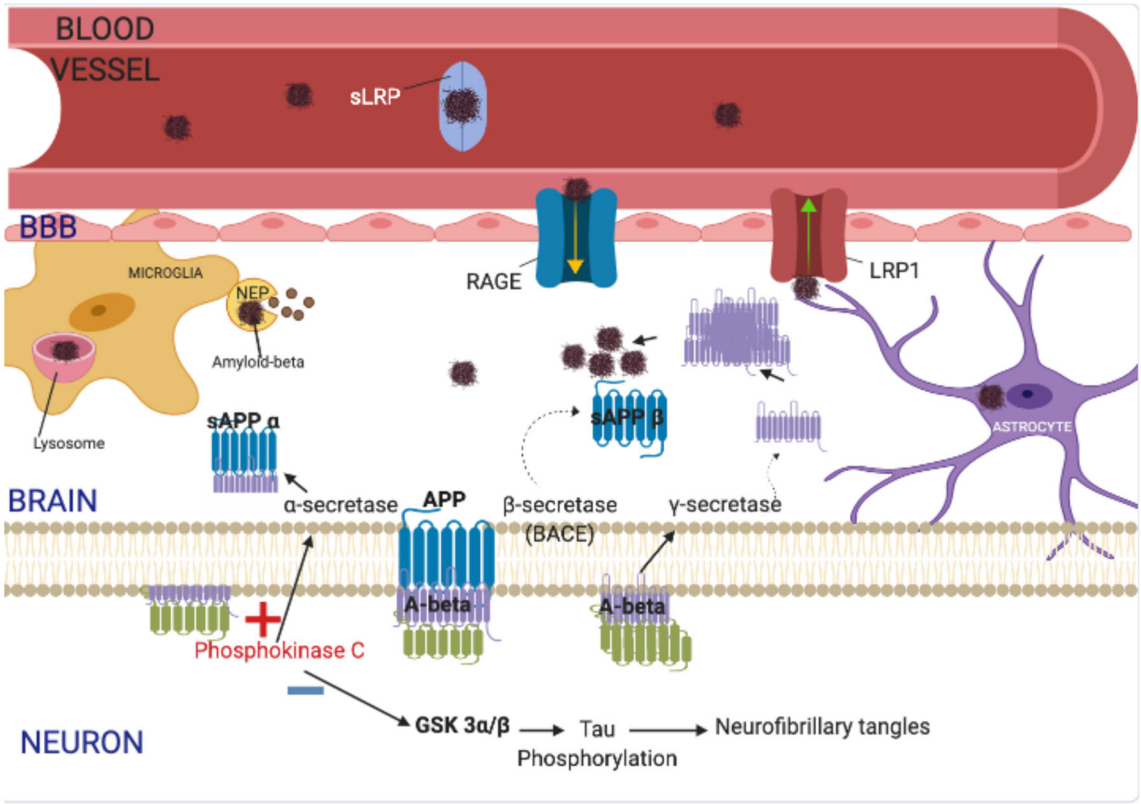

Fig. 1 The Neuropathology of Alzheimer's disease (AD). The figure shows the process of forming the two hallmarks of AD: Amyloid Beta (Amyloid beta) containing senile plaques and neurofibrillary tangles. A transmembrane protein, called amyloid precursor protein (APP) is cleaved by two enzymes called alpha secretase and beta secretase (BACE). In AD BACE is more active, forming senile plaques as an end product. These senile plaques are carried out of the brain by LDL-Receptor Protein 1(LRP1) and in the blood are carried by soluble Low-Density Receptor Protein (sLRP). Receptor for Advanced Glycation End Products (RAGE) carries senile plaques back into the brain and some of the senile plaques distribute to astrocytes or microglia, where they are digested by lysosomes. Neprilysin (NEP) degrades amyloid beta plaques. As for the neurofibrillary tangles, they are formed by Phosphokinase C inhibition of glycogen synthase kinase (GSK 3alpha/beta)

to inorganic mercury to combine with proteins (GSH, tubulin, ion channels or transporters). It also crosses the blood brain barrier and placenta by diffusion. Mercury is mainly distributed to the brain and kidneys. Its half-life is about 70 days (Ye et al. 2016; Cariccio et al. 2019). Vapor mercury is generated by the reduction of mercuric ions. Acute toxicity of vapor mercury presents as dyspnea, paroxysmal cough, chest pain or related lung conditions and nausea and vomiting. Chronic

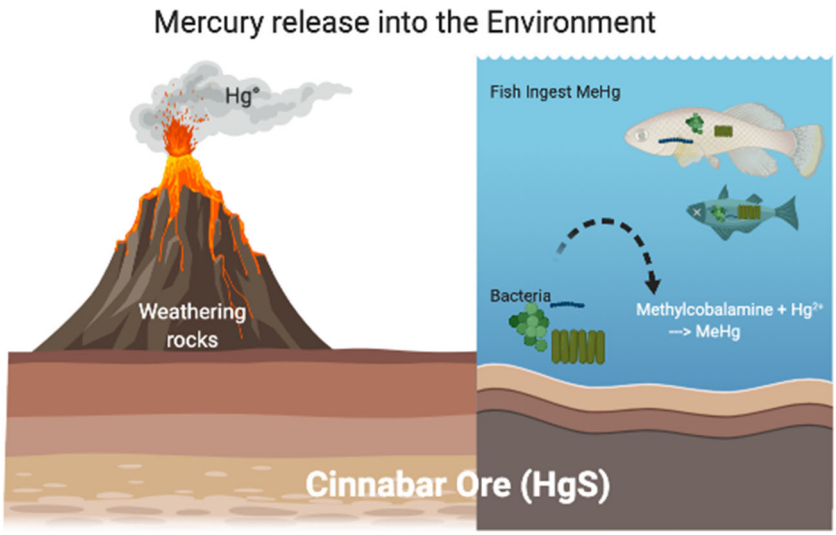

Fig. 2 Sources of Mercury. Mercury is released into the atmosphere naturally for example by weathering rocks or volcanic eruptions. Humans are exposed to mercury toxicity because of biomagnification. Bacteria in the sea convert inorganic mercury to methylmercury. Fish eat methylmercury and larger fish consume smaller fish, and we ingest the big fish carrying large doses of mercury

toxicity presents as tremors and psychological disturbances. Toxic effects on the kidneys and the central nervous system have also been reported. Mercury vapor establishes the entrance into the body, while long term effects are due to inorganic mercury deposition (Clarkson and Magos 2006).

Inorganic mercury is also mainly absorbed by inhalation, but could also be absorbed to a lesser extent by the skin (3–4%) and the GIT (2–10%). In contrast to metallic mercury, it cannot penetrate the blood brain barrier, but accumulates in the kidneys. Its half-life is about 2 months and it's mainly excreted in the urine and feces. Marine bacteria produce a compound called methylcobalamin, a derivative of vitamin B12, which reacts with inorganic mercury (Hg^{2+}) to convert it to methylmercury. Gut microbiota of fish and some animals also possess the ability to convert inorganic mercury to organic mercury, but to a lesser extent. Methylmercury accumulates in fish and shellfish before they are ingested by humans (Ye et al. 2016; Mutter et al. 2010; McNutt 2013). Mercuric chloride ($HgCl_2$), historically known as corrosive sublimate, is toxic when ingested in its water-soluble salt form. While minimally able to cross the blood brain barrier or the placenta, mercuric mercury accumulates in the kidney (Clarkson and Magos 2006), leading to a complete collapse of kidney function. Other sites of mercuric mercury toxicity include the mouth and lips, the lungs and the intestines.

Many reports have indicated that mercury, especially in the divalent inorganic form, is linked to autoimmune disease (Clarkson and Magos 2006). Mercurous chloride (Hg_2Cl_2) is an odorless yellowish white solid, also called calomel. It was previously used for medical purposes, especially in laxative formulae and teething powders. It is slowly absorbed when ingested due to its low solubility. It then dissociates to elemental mercury and inorganic mercury, both of which metabolize and disproportionate, respectively, to mercuric chloride. Elemental mercury persists long enough to pass the blood brain barrier (Clarkson and Magos 2006). Both mercuric mercury and mercurous mercury have been established as the cause of acrodynia ("pink disease") in children using teething powders and diaper washes containing these substances (Clarkson and Magos 2006). For the most part, inorganic mercury is thought to be responsible for the toxicities caused by inorganic forms of mercury (Clarkson and Magos 2006).

Organic mercury is the most toxic form of mercury. Methylmercury (mono- and di-methyl mercury) is the most commonly absorbed form through the GIT (>95%) and the respiratory tract (80%). It can also cross the blood brain barrier. Methylmercury is mostly excreted in the feces, and only 10% is eliminated in the urine. It takes 30 h for the absorbed mercury to distribute to the whole body. Its half-life ranges from 45 to 70 days (Ye et al. 2016; Cariccio et al. 2019). Methylmercury can be teratogenic, since it passes through the placenta (CDC 2017). Liver metabolism and the intestinal microflora also play a role in converting methylmercury and metallic mercury into inorganic forms (Meleleo et al. 2019).

The use of methylmercury as a fungicide for grains resulted in an epidemic in Iraq in the years 1971–72. The labels were written in a language unknown to the locals, causing farmers and their families in rural areas to consume these treated grains, leading to mercury poisoning (Skerfving and Copplestone 1976). A major epidemic due to the ingestion of fish containing methylmercury and subsequent poisoning erupted in Minamata Bay, Japan in 1956, killing thousands of people; the disaster resulted in the coinage of the "Minamata disease". Symptoms of mercury toxicity include: "sensory disturbances (glove and stocking type), ataxia, dysarthria, constriction of the visual field, auditory disturbances and tremors" (Harada 1995).

Amalgam fillings also contain mercury. Temperature of food and chewing can increase its release into the systemic circulation. Mercury in amalgams act in a similar way to mercury vapor or inorganic mercury (Syversen and Kaur 2012). A study by (Sun et al. 2015) showed that age, gender, residential region and income adjusted risk for AD in women with amalgam fillings was 1.132 times more likely than their unexposed counterparts. It is important to look at inorganic mercury when talking about amalgam fillings. A study by Björkman showed a correlation between amalgam fillings and inorganic mercury concentration in the autopsied brain (Björkman et al. 2007). Another study stated that the number of amalgam fillings (above 12) were associated with more mercury accumulation in the autopsied brains compared to the kidney and thyroid gland (Guzzi et al. 2006). Inorganic mercury in skin-whitening creams is still used widely in some countries (Weldon et al. 2000).

Neurotoxicity of organic mercury

Methylmercury is more neurotoxic than ethyl mercury due to the rapid degradation of latter to inorganic mercury (Hg^{2+}) (Magos et al. 1985). Methylmercury is excreted in the bile and through the kidney. The half-life of methylmercury is 70 days (Syversen and Kaur 2012). It should also be noted that inorganic mercury is not reabsorbed by the enterohepatic circulation, which is why demethylation increases fecal excretion of mercury (Syversen and Kaur 2012). Ethyl mercury is responsible for kidney damage, while methylmercury is more likely to damage the central nervous system. All organic mercurials are generally more bioavailable than inorganic mercury. Once inside the body, they are rapidly converted to inorganic mercury and exhibit the toxic effects asociated with it (Clarkson and Magos 2006).

Methylmercury binds thiol groups on proteins and amino acids (cysteine) and glutathione in the blood and tissues. Methylmercury is transported by amino acid transporters. Methylmercury resembles the amino acid methionine when binding to thiol groups on cysteine. This complex can use the L type neutral amino acid transporter to enter cells (Syversen and Kaur 2012). This process can be passive or active. Inside the cells, methylmercury binds to GSH (Syversen and Kaur 2012). Methylmercury in the brain is demethylated to inorganic mercury in glial cells and persists indefinitely. Vapor mercury (Hg^0) crosses the neuronal and glial membranes by diffusion and is oxidized intracellularly by the catalase hydrogen peroxide pathway to inorganic mercury. This oxidized compound readily binds to thiol-containing proteins (Bjørklund et al. 2017; Philbert et al. 2000). This process is summarized in Fig. 3.

Brain mercury concentrations are 3–6 times higher than blood mercury concentrations; this is shown after 4 days of exposure. In the brain, methylmercury is mainly found complexed with GSH, while the rest is water soluble (Syversen and Kaur 2012). Inorganic mercury is found to be in higher concentrations (20 times) in the brain after methylmercury exposure compared to mercuric chloride. Nevertheless, inorganic mercury peaks after one day after HgCl exposure, whereas Methylmercury needs 8 days. The time for demethylation and for mercury to be transferred from glial cells to the neurons might account for the long latency period (Syversen and Kaur 2012; Clarkson and Magos 2006). Mercury vapor can also cause damage to the central nervous system due to its ability to cross the blood–brain barrier (Clarkson and Magos 2006).

Mercury levels in biological fluids and the environment

Total blood mercury reflects methylmercury exposure. Whole blood mercury concentration below 10–20 mcg/L is considered normal. Chronic exposure to mercury vapor yields a blood concentration of 35 mcg/L at least (CDC 2009; Ye et al. 2016). The International Commission on Occupational Health (ICOH) and the International Union of Pure and Applied Chemistry (IUPAC) set the average blood mercury concentration level in those who do not eat fish at 2 mcg/L (Ye et al. 2016). While mercury in the urine is a measure of inorganic mercury exposure, neurological symptoms appear in patients when urinary concentrations are above 100 mcg/L. Levels at or above 800 mcg/L could be fatal (CDC 2009; Ye et al. 2016).

Keratin is a major constituent of hair, carrying many sulfhydryl groups that bind metals. There is a proportional relationship between methylmercury content in the blood and the hair. The hair-to-blood mercury concentration ratio set by the WHO is 250–300:1. The internationally recommended limit of hair mercury concentration is 1 mg/kg as proposed by the WHO. It generally doesn't exceed 10 mg/kg. Moderate mercury poisoning levels range between 200 and 800 mg/kg. In severe intoxications, it could reach about 2400 mg/kg. Nevertheless, hair mercury levels should not solely be used to make conclusions about mercury intoxication (Ye et al. 2016). The provisional tolerable weekly intake (PTWI) for inorganic mercury was set to be 4 mcg/kg body weight. However, for mercury exposure from fish, the PTWI is set at 5 mcg/kg (McNutt 2013). The FDA set an MPL (maximum

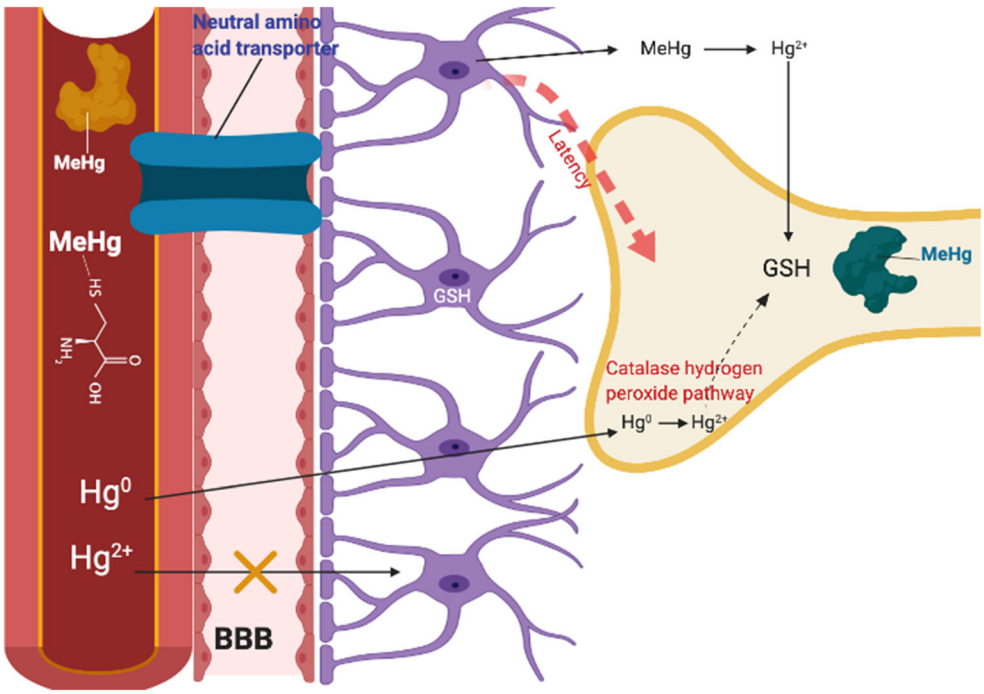

Fig. 3 Methylmercury (MeHg) binds to the thiol group on the amino acid cysteine in the blood. Resembling methionine, it uses the neutral amino acid transporter to cross the blood brain barrier. It then binds to glutathione in glial cells and is demethylated to inorganic mercury which persists lifelong. Vapor Mercury (Hg0) can travel across the blood brain barrier by diffusion. It is then oxidized by the catalase hydrogen peroxide pathway to inorganic Hg2+. Inorganic Mercury (Hg2+) cannot cross the blood brain barrier. Both inorganic mercury and MeHg can bind to reduced glutathione

permissible level) of 1 ppm of mercury in seafood. The U.S. and the Netherlands propose the PTWI (provisional tolerable weekly intake) of methylmercury to be 0.7 μg/kg body weight/week, whereas Japan suggests a higher methylmercury exposure limit, which is 2.0 μg/kg body weight/week (Ye et al. 2016). The Occupational Safety and Health Administration (OSHA) has set limits of 0.1 mg/m^3 of organic mercury in the workplace and 0.05 mg/m^3 of metallic mercury vapor for 8-h shifts and 40-h work weeks. The EPA has set a limit of 2 ppb of mercury in drinking water. According to The Water Quality Association, the Maximum Contaminant Level (MCL), which is the highest level of contamination (any kind of mercury) allowed in drinking water is 0.002 mg/L (2 mcg/L; equivalent to 2 ppb). So is the Maximum Contaminant Level Goal (MCLG).

Correlation between mercury levels and Alzheimer's disease

A study by Gerhardsson et al. showed no difference in the cerebrospinal fluid (CSF) mercury concentration between AD patients and their controls (Gerhardsson et al. 2008). Blood mercury concentrations in AD patients were higher than their controls, but there was an even higher level of mercury in early onset AD (Hock et al. 1998). However, the number of patients diagnosed early on was much less than the controls (13 vs. 110). Mutter et al. show a doubling of blood mercury concentration in AD patients compared to depressed and control individuals (Mutter et al. 2004). Other studies showed no difference between blood mercury levels of AD patients and the control group (Fung et al. 1995; Homme et al. 2014). Gerhardsson et al. demonstrated an elevation in plasma mercury levels, contrary to controls. Nevertheless, mercury levels in the serum of AD patients and their controls have shown contradictory results. While some showed an increased serum levels of mercury in AD patients, others show the exact opposite (Paglia et al. 2016; Gerhardsson et al. 2008). There was no difference in the levels of mercury in the urine between AD patients and their controls according to Chakraborty 2017; Pigatto et al. 2018. Studies have reported mixed results regarding mercury concentration in the autopsied brain. This may be due to the fact that mercury is volatile, leading to an underestimation of its concentration (Mutter et al. 2010). Fung showed no difference in mercury concentration between the autopsied brains of AD and multiple sclerosis patients when compared to controls (Fung et al. 1997).

Mercury exposure and Alzheimer's disease

A previous study in 2008 showed that the age adjusted dementia prevalence in India was 1–3%, which was lower than other countries (Kalaria et al. 2008). However, more recent studies show that India is third on the list after China and the USA when it comes to dementia prevalence (Chakraborty 2017). India also made the list for the highest mercury emission after China (Chakraborty 2017). Methylmercury in fish was reported to be three times as much as it used to be before anthropogenic activity in India (Chakraborty 2017). A clear cause-effect between mercury pollution in India and AD is still not established, but the association sheds light on mercury possibly being one of the risk factors for dementia (Chakraborty 2017). AD is a disease where cerebral oxidative stress is high, this can alter the functions of proteins due to oxidation, or reduced proteasomal degradation (Sagare et al. 2012; Kelleher and Shen 2017).

The most important property of mercury, which leads to its toxicity is its affinity to bind to thiol groups and selenium (Risher and Tucker 2017). Selenium is a protective element found in the brain, specifically the cortex. It is responsible for the protection of neurons against oxidative stress (Cardoso et al. 2017; Cariccio et al. 2019). Thiol groups are found in the amino acid cysteine, which is found throughout the body. When mercury binds to thiol groups on proteins and enzymes, they augment or diminish their activity (Hughes 1957). Most AD patients have at least one allele of apolipoprotein E4 (ApoE4). Having the ApoE2 genotype reduces the risk of AD. This is thought to be due to the fact that the ApoE2 has two cysteine groups, while the ApoE4 has 2 arginine groups instead. Both isoforms of ApoE are composed of 299 amino acids. This renders ApoE2 more capable of binding to mercury and detoxifying it (Carocci et al. 2014). The ApoE genotype is known to affect the neurodegeneration process in AD and therefore serves a potential biomarker to predict clinical diagnosis and assess treatment efficacy (Van Giau et al. 2015).

An example of a peptide containing a free thiol group is GSH, which provides protection against oxidative stress. GSH is predominantly found in the cytosol of the cell, 15% in the mitochondria and the rest in the endoplasmic reticulum. GSH in the brain is mainly found in non-neuronal cells like astrocytes (Rae and Williams 2017; Lu 2013; Dringen et al. 2000). Around 30% of glutathione was depleted in brain cells and neuroblastoma cells respectively by methylmercury and mercuric chloride exposure (Syversen and Kaur 2012; Olivieri et al. 2000). Methylmercury and inorganic mercury exposure increase free radicals and exacerbates oxidative stress in the brain (Syversen and Kaur 2012). This is further supported by Cariccio who found that methylmercury induces oxidative stress and free radical production, reduces glutathione concentration, and incites mitochondrial damage and abnormal intracellular protein aggregation (Cariccio et al. 2019). A study of inorganic mercury on rat kidney mitochondria revealed an increase in hydrogen peroxide level (Lund et al. 1993). While methylmercury is immunosuppressive, inorganic

mercury is an immunostimulant enhancing T cell response (Cariccio et al. 2019).

Among parts of the brain that are affected by Methylmercury poisoning include: the cerebellum, the granule cells of the cortex and the dorsal roots in the sensory ganglia (Philbert et al. 2000). A study showed that mercury was preferentially localized in neurons than in glial cells, and that it accumulated in lysosomes. This observation however would depend on the phase of mercury poisoning. Mercury was observed in glial cells during the latent phase and in the neurons during the symptomatic period (Hargreaves et al. 1985). Motor neurons were also more adversely affected by mercury versus sensory neurons, according to this study. Although mercury was found in the cerebellum, it was not the purkinje cells that were affected (Syversen and Kaur 2012). It is proposed that astrocytes have a higher cortical GSH content than the cerebellum. This could render the cerebellum more susceptible to methylmercury-induced oxidative stress (Syversen and Kaur 2012). The above is reflected in the symptoms that people manifest in response to mercury toxicity viz. ataxia (Harada 1995). Microcephaly was common in a group of Iraqi newborns, whose mothers were exposed to mercury (Davidson et al. 1998). Another study showed atropied cerebella compared to controls, which correlated with higher levels of mercury in the mother's hair (Cace et al. 2011).

Enzymatic activation was acutely aggravated in response to methylmercury to compensate for its cytotoxic effects. Later on, protein synthesis was inhibited, leading to cell death (Toimela and Tähti 2004). Mercuric chloride induced apoptosis in the same manner (Goering et al. 1999). Caspase 3 is an endoprotease, which is actively involved in apoptosis. It was reported to undergo a rise in catalysis in response to mercury exposure (Toimela and Tähti 2004).

Exposure to neuroblastoma and glioblastoma cell lines to methylmercury evinced that short exposure times activated cellular enzymes, while on the long run, inhibited protein synthesis and curbed cellular proliferation (Toimela and Tähti 2004).

Inside the cells, specifically mitochondria, methylmercury reacts with sulfhydryl groups of enzymes and other proteins, especially GSH. Mercury also inhibits the function of methionine synthase, which is an enzyme responsible for the generation of GSH, in vitro. This inhibits the antioxidant function of glutathione, and consequently, the generated reactive oxygen species damage nucleic acids, enzymes and lipids, leading to cell death. Nuclear DNA is protected from free radicals, because of the presence of histones, unlike mitochondrial DNA, which is unprotected (Toimela and Tähti 2004; Carocci et al. 2014).

Methylmercury inhibits the alanine, serine, glutamine, cysteine and glutamate transporter 2 (ASCT2), which plays an important role in intracellular GSH levels regulation (Syversen and Kaur 2012). ASCT2 is present in neuronal dendrites, and purkinje cell bodies. It is not found in astrocytes, though. It is thought to eliminate glutamate from the extracellular space, and the purkinje cells do so more efficiently. Methylmercury toxicity is reported to inhibit the glutamine/glutamine antiport catalyzed by the transporter (Syversen and Kaur 2012). Astrocytes play a role in methylmercury toxicity, owing to the fact that methylmercury accumulates in these cells. Astrocytes are then rendered unable to take up glutamate, and stimulate its efflux, causing injury to neurons due to excitotoxicity. The cerebellum has fewer astrocytes than the cortex. This could either leave it more or less susceptible to methylmercury poisoning. Were excitotoxicity the cause of damage, then the cortex would be the major part of the brain affected. Damage to the cortex is also seen in AD (Syversen and Kaur 2012).

Neuroinflammation is suggested to be part of AD's pathogenesis, contributing to its progression and chronicity (Heneka et al. 2010). A study showed that people who were occupationally exposed to mercury had more mercury accumulation in their autopsied brains (Falnoga et al. 2000). A study conducted on gold miners who were exposed to mercury, showed an increase of inflammatory cytokines,compared with diamond and emerald miners (Gardner et al. 2009). IL-6 and IL-8 were among the elevated cytokines in a study on Minamata disease patients' brains (Yamamoto et al. 2017). Microglia produce IL-1 eliciting an immune response. This inflammatory cytokine induces a cascade, ending in the up-regulation of APP and formation of neurofibrillary tangles as a result of neuroinflammation (Cai et al. 2014). Another study found an increase in IL-1 levels and TNF-α in response to mercuric chloride (Gardner et al. 2009). TNF-α was found to be elevated in AD patients' CSF (Dursun et al. 2015).

Mercury effects on amyloid Beta

APP (Amyloid Precursor Protein) is under constant cleavage of two enzymes, alpha secretase and beta secretase. Beta secretase is the pathway by which amyloid beta forms. Mercury was found to inhibit kinases in the alpha secretase pathway, shifting the reaction in favor of amyloid beta 40 and 42 production. This is further supported by a study where protein kinase C levels were reduced on mercury exposure in brain cells (Olivieri et al. 2000).

Methylmercury and mercuric chloride increased amyloid beta either through APP overproduction, neprilysin inhibition or increased release of amyloid beta (Olivieri et al. 2000; Song and Choi 2013). Fetal rat telencephalon exposed to methylmercury increased APP levels, ROS production and glia activation (Monnet-Tschudi et al. 2006). Studies on neprilysin are contradictory though. Some show no changes in neprilysin levels as (Kim et al. 2014) noted in male rats exposed to methylmercury of different doses for 4 weeks. The most

Table 1 Summary of the studies used in this review which showed the effect of mercury on amyloid beta

Type of mercury	Effect	Type of tissue/organism	Reference
MeHg	Reduced sLRP, increased RAGE, increased A-beta accumulation, reduced LRP1	Male adult rats	(Kim et al. 2014)
MeHg	Increased APP levels, glial activation and ROS production	Fetal rat telencephalon	(Monnet-Tschudi et al. 2006)
MeHg, Hg^{2+}	Reduced neprilysin, increased APP	Rat pheochromocytoma (PC12) cells	(Song and Choi 2013)
Hg	Reduction in neprilysin activity	Differentiated SH-SY5Y cells	(Chin-Chan et al. 2015)
Hg^{2+}	Increased IL-1, TNF-alpha	human peripheral blood mononuclear cells	(Gardner et al. 2009)

recent study showed that neprilysin mRNA levels did not manifest any changes on treatment with mercury. However, a reduction in neprilysin activity was noticed, which could be explained by mercury binding to its cysteine residues (Chin-Chan et al. 2015). Regardless of mercury exposure, reduced neprilysin levels in AD patients was established in one study (Yasojima et al. 2001), while another found an increased level of neprilysin in AD brain samples (Miners et al. 2009). A study by (Kim et al. 2014) showed that there is a negative correlation between sLRP and mercury levels in whole blood, and amyloid beta 42 ($A\beta_{42}$) levels in the hippocampus. Contrarily, it showed a positive correlation with Amyloid betamyloid beta in the CSF. Low levels of Amyloid betaamyloid beta in the CSF and high levels of $A\beta_{42}$ in the brain are commonly seen in AD patients (Rosén et al. 2012). In AD patients, an increase in oxidized sLRP in the plasma, which has a reduced affinity for binding Amyloid betaamyloid beta, leads to an increase in the level of free $A\beta_{40}$ and $A\beta_{42}$ which can reenter the brain. Another observation was that sLRP levels were 30% less in AD patients compared to controls. There from, AD patients show lower levels of sLRP that can bind Amyloid betaamyloid beta and lower binding affinity of sLRP, due to its oxidation (Sagare et al. 2007). Methylmercury was shown to reduce the LRP1 in animal models, thereby inhibiting the transport of Amyloid betaamyloid beta into the blood, capacitating its accumulation. Additionally, the upregulation of RAGE was demonstrated, which increased the influx of Amyloid betaamyloid beta into the brain. Kim et al. 2014 also showed a positive correlation between $A\beta_{42}$ in the hippocampus and mercury levels in the hippocampus and whole blood.

As mentioned above, LRP1 is one of the important transporters of Amyloid betaamyloid beta through the blood brain barrier, out of the brain. LRP1 is part of the LDL receptor family and contains many cysteine amino acids (Sagare et al. 2012). Mercury has a known affinity for sulfur (Hughes 1957), which leads to the presumption that by binding to the LRP1 transporter, it can either block or augment the effect of the transporter (Risher and Tucker 2017). As seen in the effect of mercury on the brain, it most likely blocks the effect.

All the studies above are summarized in Table 1.

Effect on tau

Neurofibrillary tangles are a distinctive hallmark of AD. The authors of this article summarized some of the effects of mercury on tau protein (Table 2), which is a microtubule associated protein (MAP) and the main component of neurofibrillary tangles.

Table 2 Summary of the studies used in this review to show the effect of mercury on tau protein

Type of mercury	Effect	Type of tissue/organism	Reference
MeHg	Increase in neurofibrillary tangle amounts due to tau hyperphosphorylation	Mice	(Fujimura et al. 2009)
Hg^{2+} in EDTA	Reduced GTP binding capacity to beta tubulin	Human brain tissue obtained at autopsy	(Duhr et al. 1993)
Hg Vapor	Reduced GTP binding capacity to beta tubulin	Brain rats	(Pendergrass et al. 1997)
	Increase phosphorylation of tau	Neuroblastoma cells	(Olivieri et al. 2000)
MeHg, Hg^{2+}	Bind thiol groups on alpha and beta tubulin	P19 murine embryonic carcinoma cells	(Hunter and Brown 2000) Yang et al. 2011)
Hg^{2+}	Bind tau fragments	P19 murine embryonic carcinoma cells	(Hunter and Brown 2000) (Yang et al. 2011)
Hg^{2+}	Reduced tau expression	SH-SY5Y cell line	(Chan et al. 2017)
Hg^{2+}	Overactivation of NMDA receptors	Rat cortical neurons	(Xu et al. 2012)

In a study, where male mice were exposed to methylmercury, increased aggregates of neurofibrillary tangles led to cell degeneration. Methylmercury-induced tau hyperphosphorylation through activation of the c-Jun-N-terminal kinase (c-JNK) signaling pathway in the cerebral cortex (Fujimura et al. 2009). Low mercury (Hg^{2+}) concentration, complexed with EDTA, was found to inhibit guanosine triphosphate (GTP) binding, which is necessary for tubulin dimer synthesis and neuronal function in healthy brains (Duhr et al. 1993; Carocci et al. 2014). GTP binding capacity to the beta tubulin was found to be reduced in AD brains, leading to abnormal microtubule aggregations. Exposing mice to mercury vapor reduced the GTP binding capacity as well (Bjørklund et al. 2019; Pendergrass et al. 1997). Mercury is reported to increase the phosphorylation of tau in vitro in neuroblastoma cells (Olivieri et al. 2000). Methylmercury or inorganic mercury can bind to thiol groups on alpha and beta tubulin causing microtubules to disassemble and degenerate (Cariccio et al. 2019; Bjørklund et al. 2019; Syversen and Kaur 2012; Yang et al. 2011; Hunter and Brown 2000). Inorganic mercury (Hg^{2+}) was found to bind tau fragments which further aggregated the microtubule disassembly (Bjørklund et al. 2019; Cariccio et al. 2019; Yang et al. 2011; Hunter and Brown 2000).

Another proposed mechanism of inorganic mercury-induced toxicity is the effect on MAP2 and tau expression. They both were less frequently expressed in differentiating neurons when exposed to mercury (Chan et al. 2017).

mercuric chloride exposure led to the overactivation of NMDA receptors in the cortical region of the brain in rats, which may have occurred through binding to the sulfhydryl groups on these receptors,, leading to an intracellular increase of Ca^{2+} ions via these receptors in rats. The above caused neuronal cytoskeletal protein disassembly and excitotoxicity, which eventually led to neuronal degeneration (Xu et al. 2012). The effects of mercury on tau and amyloid beta have been summarized in Fig. 4.

Prenatal and fetal basis of Alzheimer's disease

Given the sporadic nature of most cases of AD, the quest for an etiological factor, possibly during the vulnerable prenatal period, has been suggested. A review by the renowned behavioral neurotoxicologist Weiss (2011) draws attention to the

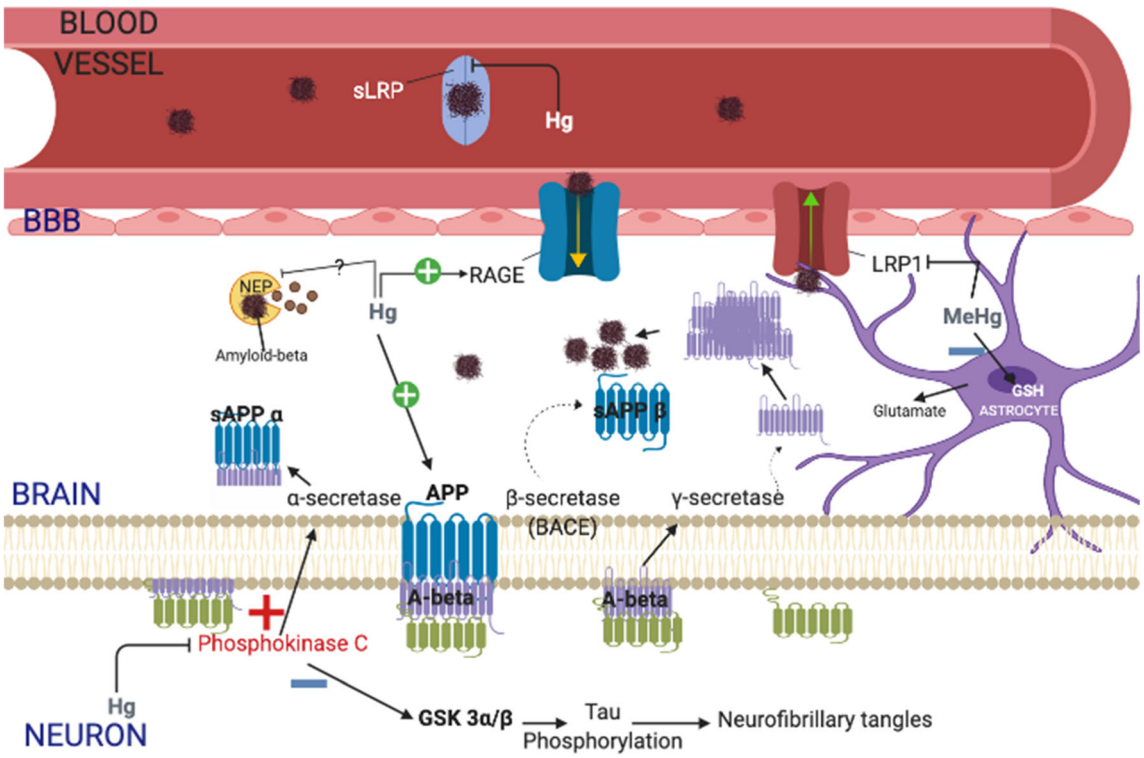

Fig. 4 The figure shows a close up of the neuron, blood brain barrier(BBB) and a blood vessel. Hg inhibits soluble Low-Density Receptor Protein (sLRP) from engulfing amyloid beta (Amyloid beta), increasing its concentration in the blood, and therefore increases the influx back to the brain interstitium by the Receptor for Advanced Glycation End Products (RAGE). RAGE is also upregulated by Hg. LDL-Receptor Protein 1 (LRP1) which carries Amyloid beta into the bloodstream, is inhibited by Hg. Amyloid precursor protein (APP) is upregulated by Hg, and therefore increases the substrate for beta secretase (BACE) enzyme which degrades APP to the end product which is Amyloid beta. Mercury also inhibits Phosphokinase C which eventually leads to neurofibrillary tangles formation. Methylmercury (MeHg) also affects astrocytes by inhibiting glutathione antioxidant activity and therefore increases the efflux of glutamate which is neurotoxic to the neurons. The effect of mercury on neprilysin (NEP) activity is still unknown

risks posed by prenatal exposures to environmental pollutants, such as heavy metals, including mercury, in the development of neurobehavioral deficits in advanced age. This is based, in part, on earlier studies by Rice who observed delayed neurotoxicity, years later, in monkeys. This was later confirmed in hundreds of Minimata cases (1996) in what Weiss calls Fetal Minamata Disease (2011). Indeed, the observation that pollutant exposure during the prenatal period can impact later brain metabolic function has been experimentally demonstrated for lead and suggests that environmental influences during brain development may predetermine the expression and regulation of protein chemistry (including APP) in later in life, potentially altering the course of amyloidogenesis (Basha et al. 2005). That mercury, specifically methylmercury, may have long term epigenetic effects, if that is what is being observed, has been a topic of intensive research in recent years (Culbreth and Aschner 2019).

Clinically, work by Grandjean and colleagues has followed a cohort of Faroese children with prenatal methylmercury exposure since the late 1980's, with periodic neurological, immunological and cardiovascular assessment (Grandjean et al. 1997; Debes et al. 2006, 2016) at 7, 14 and 22 years of age. According to these studies, mercury-related neuropsychological dysfunctions were most pronounced in the domains of language, attention, and memory, and to a lesser extent in visuospatial and motor functions at 7 and 14 years of age (Grandjean et al. 1997; Debes et al. 2006). At 22 years of age, cognitive deficits associated with prenatal methylmercury exposure remained detectable. However, while most deficits appeared to be less serious compared to those at ages 7 and 14 years, they significantly affected major domains of brain functions as well as general intelligence. The authors conclude that prenatal exposure to methylmercury is likely to cause permanent adverse effects on cognitive function (Debes et al. 2016).

An interesting caveat to this study originates from our laboratories in our quest for diagnostic and prognostic biomarkers. Sera of a subset of these children was used to detect autoantibodies of nervous system proteins (neuroantibodies; El-Fawal 2014). The children tested had both IgG and IgM titers against neuron-, astrocyte, and myelin specific proteins (Osuna et al. 2014). IgM levels, indicative of chronic insult, correlated with ongoing exposures to methylmercury and confirming earlier preclinical studies with methylmercury (El-Fawal et al. 1996). It is noteworthy that neuroantibodies have been reported in AD (Colasanti et al. 2010) and is undergoing further validation.

Conclusion

Mercury is a common environmental toxin and its effect on the nervous system is well established. More research efforts should be invested in decoding the etiological involvement of mercury toxicity in AD pathogenesis. AD is a progressive disease affecting too many people worldwide. Given the exceptional socioeconomic burden of AD, understanding the underlying neuropathology and hindering its progression has been steadily pursued and is supremely vital. Mercury is one of many converging components, the interplay of which gives to AD pathogenesis; it may well be more inculpated than we know. We suggest that it would definitely do well to lend more focus to studying individuals who are occupationally exposed to high levels of mercury. For future endeavors, we suggest to integrate mercury screening, during regular checkups, in serum and CSF levels of AD to retrieve more data in order to be able to interpret information. Difference in responses to mercury might also arise according to the duration of exposure, whether lifelong/chronic (as in pollution) or acute. This chronic effect could be assessed in a longitudinal study, in a country where the limit of mercury is above average like India or China. Some physiologic characteristics, like chronic diseases, sex, or pregnancy, will account for differences in response to mercury toxicity. These variables should also be assessed. Several venues of research are evident when one investigates the myriad aspects of mercury neurotoxicity and its potential contribution of neurodegenerative diseases. Recognizing the sporadic and chronic nature of AD development, one must recognize the long term, even prenatal, as well as the environmental milieu of pollutant mixtures, are major risk factors, targets of mitigation, but also avenues of exploration towards diagnostic and prognostic modalities.

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