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Neurotoxicity of mercury: an old issue with contemporary significance

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Abstract

Mercury exerts a variety of toxic effects, depending on the specific compound and route of exposure. However, neurotoxicity in virtue of its consequence to health causes the greatest concern for toxicologists. This is particularly true regarding fetal development, where neurotoxic effects are much more severe than in adults, and the toxicity threshold is lower.

Here, we review the major concepts regarding the neurotoxicity of mercury compounds (mercury vapor; methylmercury and ethylmercury), from exposure routes to toxicokinetic particularities leading to brain deposition and the development of neurotoxic effects.

Albeit research on the neurotoxicity of mercury compounds has significantly advanced from the second half of the twentieth century onwards, several grey areas regarding the mechanism of toxicity still exist. Thus, we emphasize research advances during the last two decades concerning the molecular interactions of mercury which cause neurotoxic effects. Highlights include the disruption of glutamate signaling and excitotoxicity resulting from exposure to mercury and the interaction with redox active residues such as cysteines and selenocysteines which are the premise accounting for the disruption of redox homeostasis caused by mercurials. We also address how immunotoxic effects at the CNS, namely microglia and astrocyte activation modulate developmental neurotoxicity, a major topic in contemporary research.

1. Mercury exposure and neurotoxicity

Contact between human populations and mercury (Hg) dates back to the early days of civilization. Given this long standing contact, Hg toxicity and its effects over human behavior and mood have been known for centuries (Clarkson and Magos 2006).

However, it was only in the second half of the twentieth century, following the poisoning outbreaks in Minamata Bay and Iraq, that research on mercury toxicity gained steam. Particularly in the last two decades, research on the toxicity of mercury compounds, namely on its neurotoxicity, has produced more than 1000 research papers (Pubmed search for

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"mercury neurotoxicity") leading to an improved understanding of the mechanisms of its toxicity.

The interest of researchers in mercury toxicity is not surprising since the main source of exposure of human populations to Hg, particularly to methylmercury (MeHg), is fish consumption which has a global importance as a protein source.

Exposure to elemental mercury (Hg^0), namely in the form of mercury vapor (hereafter $vapHg^0$) was until recently a common issue related to the widespread use of mercury dental amalgam fillings. The clinical substitution of mercury amalgams with other materials (Broadbent et al. 2020) has largely reduced the significance of this exposure to human populations, but in occupational settings, in particular in Artisanal Small Scale Gold Mining, neurotoxicity related to exposure to $vapHg^0$ is still a major health concern (Gibb and O'Leary 2014).

Similarly, the medical use of mercury-based preservatives such as thimerosal (ethylmercury thiosalicilate) has been rapidly declining and although exposure doses are generally below the toxicity threshold, remains a cause of concern, especially in populations already exposed to Hg via other sources (Dórea, Farina, and Rocha 2013; Dórea, Marques, and Abreu 2014).

In this review, we highlight the main findings concerning the neurotoxicity of vapHg0 and of the organomercurials MeHg and ethylmercury (EtHg), with special emphasis on evidence concerning cellular and molecular neurotoxicity and detoxification mechanisms.

2. Sources and human exposure

2.1 Mercury vapor

Mercury vapor in ambient air generally posses no threat to human populations since its concentrations is low, in the range of 2 to 20 ng/m^3 (WHO, 2003). In fact, the majority of individuals is exposed to $vapHg^0$ via its release from dental amalgam surfaces (Rooney 2007; Clarkson 2002), which contain 50% of the elemental mercury (Dye et al. 2005). Several studies (Woods et al. 2009; DeRouen et al. 2006; Dye et al. 2005) have shown a positive association between the number of amalgam fillings and the body's Hg burden, although levels excreted in urine (0–4 $\mu g\ L^{-1}$) are normally below toxic levels. Despite evidence for increased Hg body levels and excretion, there is no substantial evidence showing neurotoxic effects of mercury arising from mercury amalgam fillings (Mackert and Berglund 1997). Nevertheless, its contribution to total body Hg should be taken into account in total exposure and risk estimates (Richardson et al. 2011).

Presently, the biggest concerns regarding $vapHg^0$ neurotoxicity arise due to occupational exposure to elemental mercury. Workers in industries where mercury enters the manufacturing process (e.g. chloro-alkali plants) or in mines have long been addressed (Neal 1938; Buckell et al. 1993) as an at risk population, with current health guidelines setting the limit of occupational exposure to $vapHg^0$ at 0.02 mg $mercury/m^3$ for an 8h work-journey (SCOEL 2007). Although in the northern hemisphere the industrial use of Hg is subsiding, in the southern hemisphere it is still used namely in gold mining (UN Environment 2017).

Indeed, in Artisanal Small Scale Gold Mining scenarios, the level of vapHg^0 greatly exceeds safe limits. Measurements in mining camps (Drake et al. 2001; Malm 1998) frequently report ambient air levels well above the recommended (up to 100 fold), and biomarker measurements in individuals involved in the mining process frequently exceeded the LOEL for neurotoxicity (Bose-O'Reilly et al. 2017). Furthermore, people living in communities surrounding the mining camps may also be exposed to toxic Hg levels, including pregnant women and children (Armah et al. 2016; Bose-O'Reilly et al. 2016; Castilhos et al. 2015; Kristensen, Thomsen, and Mikkelsen 2014), and the number of humans exposed to this element is still high (Gibb and O'Leary 2014).

Because vapHg^0 is secreted in breast milk, breast fed children might be exposed to dangerous amounts if the mother lives near a mining area (Bose-O'Reilly et al. 2008).

1.2 Methylmercury

Methylmercury (MeHg) forms in the aquatic environment as a result of microbial action existing in pg/L (10^{-15}) levels (Gworek et al. 2016). Following its entry at the basis of the food chain MeHg undergoes up to 10^9 fold biomagnification, reaching mg/kg (10^{-6}) levels in fish. Since fish ingest MeHg from food and absorption outweighs elimination, it bioaccumulates and its levels increase throughout lifespan, constituting more than 90% (Branco et al. 2007) of the Hg in fish muscle where it is bound to thiol groups in cysteine (Cys) residues of proteins (Harris, Pickering, and George 2003). The consequence of these two processes is that apex marine predators, such as bluefin tuna, swordfish and sharks accumulate large quantities of MeHg, and humans sitting on the top of the food chain may be exposed to potentially toxic levels (Clarkson and Magos 2006).

The Minamata outbreak put to evidence the neurotoxic potential of ingesting fish containing high levels of MeHg. Values of MeHg in the seafood of Minamata were exceptionally high (>20 μg g^{-1}) due to the direct discharge of industrial effluents loaded with MeHg to the Minamata bay water (Clarkson and Magos 2006), but it brought to the attention of the scientific community and general public the fact that fish consumption was a major route by which humans are exposed to this compound. The contribution of other food sources for exposure of humans to MeHg is generally low, albeit in some particular polluted areas, cereals such as rice can accumulate considerable amounts of mercury in the edible part (Meng et al. 2011).

Over the last several years, several experimental and epidemiological studies have shown that fetal development and early infancy are the life-stages most sensitive to MeHg toxicity, and therefore pregnant and breastfeeding women (MeHg is secreted in breast milk) represent the highest risk groups. This has prompted regulatory agencies worldwide to establish advisory guidelines for the intake of mercury by human populations, in particularly pregnant women to protect fetal development.

The caveat is that fish, in addition to MeHg, also have many nutrients which play an important role in neurodevelopment. Particularly, fish are rich in long-chain-3 polyunsaturated fatty acids (PUFA), such as decosohexanoic (22:6) acid (DHA) and eicosapentanoic (20:5) acid (EPA) (Budtz-Jørgensen et al., 2007; Dorea, 2003; Ström et al.,

2011) and several micronutrients, namely selenium in the form of selenomethionine (SeMet), selenocyteine (Sec) (Ralston, Kaneko, and Raymond 2019; Budtz-Jørgensen, Grandjean, and Weihe 2007; Ström et al. 2011). Therefore, the risk-benefit relationship related to fish consumption has to be considered when communciating risk to fish-consuming populations (Budtz-Jørgensen, Grandjean, and Weihe 2007).

1.3 Ethylmercury

Exposure to ethylmercury (EtHg) occurs via thimerosal-containing vaccines (TCV). The typical dose of EtHg in a TCV inoculation (0.5 mL) is approximately 25 μg (Source: www.fda.gov), which is considerable less Hg than the contained in an average meal of high mercury fish (e.g. swordfish). The concern for thimerosal arises, therefore, from potential exposures during early infancy and in countries where the vaccine schedule requires several TCV inoculations. In fact, studies have shown that EtHg levels in hair are positively correlated with the number of TCV inoculations (Dórea et al. 2011). Although the time-frame between vaccinations allows for a decrease in EtHg levels, this additional mercury source may potentially contribute to aggravate neurotoxic effects in populations already exposed to other Hg sources and species (e.g. consumption of fish with high MeHg) (Dórea, Marques, and Isejima 2012).

2. Brain deposition of Hg compounds

2.1 Mercury vapor (vapHg^0)

The lungs are the route by which vapHg^0 enters the body, with about 80% reaching the blood stream (Magos 1997). Once in the blood, vapHg^0 can be oxidized to mercury (II) (Hg^{2+}) by catalase present in red blood cells (RBC) (Clarkson 2007).

This process is sufficiently slow eough to allow vapHg^0 to readily reach the brain (Magos 1997). Since it is an uncharged monoatomic gas, it diffuses through cell membranes but it may in part be transported across through specific transporters of uncharged gaseous molecules such as ammonia (Clarkson 2007). Therefore, vapHg^0 can easily cross the blood-brain barrier (BBB) and reach the central nervous system (CNS) (Beate, Stephan, and Gustav 2010), and accumulate in the cerebral cortex and cerebellum (Warfvinge 1995).

Mercury vapor can also cross the placental barrier, reaching the developing fetus. Because vapHg^0 is partially oxidized in fetal liver, Hg levels following exposure to mercury vapor are lower in the brain of the fetus that in the brain of the mother (Clarkson 2007). However, animal studies have shown that following birth, Hg accumulated in fetal liver bound to metallothioneins is redistributed to the brain (Yoshida, 2002).

Once inside cells, vapHg^0 has to be oxidized to Hg^{2+} to interact with molecular targets. Indeed, Hg^{2+} is directly responsible for toxic effects associated to vapHg^0 exposure. Since Hg^{2+} cannot diffuse back across the BBB, it is retained and accumulates in the CNS (Mottet et al. 1997; Rooney 2007).

2.2 Methylmercury

Once ingested, fish protein is hydrolyzed and the MeHg-Cys complex is absorbed in the intestinal wall. This is an highly efficient process, with more than 95% of MeHg being absorbed in the GI tract (Clarkson and Magos 2006). This occurs because the MeHg-Cys complex has a similar structure to the amino acid methionine (Met), which enables it, by molecular homology/mimicry, to use the neutral amino acid carrier (LAT) (Roos et al. 2010; Simmons-Willis et al. 2002).

The systemic distribution of MeHg is fast, and only about 5% of the absorbed amount remains in the blood-stream after 30 to 40 hours, mostly bound to hemoglobin in red-blood cells (Berglund et al. 2005) and to a smaller extent in the plasma bound to albumin (Yasutake, Hirayama, and Inoue 1989). From the blood compartment, MeHg is distributed to all protein-rich tissues including the brain, kidney, liver, muscle, hair and nails (Clarkson 2007; Mottet et al. 1997).

The MeHg-Cys complex can rapidly cross the BBB by the same molecular mimicry mechanism described above, penetrating endothelial cells and subsequently the CNS. Transport back across the BBB is limited and therefore MeHg accumulates and causes toxicity, the cerebellum and calcarine cortex in adults, being the primary site of deposition (Clarkson and Magos 2006).

A common observation in MeHg toxicology both in epidemiological (Weiss, Clarkson, and Simon 2002) and animal studies (Branco et al. 2011) is that neurotoxicity takes place sometime after exposure. This lag time, referred to as the latent phase, results from the distribution time necessary for MeHg to reach the CNS and accumulate above the threshold of toxicity. Most interestingly, experiments with non-human primates (Mottet et al. 1997; Vahter et al. 1995) have shown that following chronic exposure to MeHg, Hg^{2+} levels increase, indicating that demethylation takes place in the CNS (Figure 1). Therefore, individuals chronically exposed to MeHg will accumulate both Hg species in the CNS. The site of this demethylation, has yet to be fully characterized, but may take place in astrocytes.

The molecular mimicry mechanism also facilitates the crossing of the placental barrier by MeHg-Cys complexes (Hong, Kim, and Lee 2012; Antunes dos Santos et al. 2016). Since fetal blood has a higher hematocrit and plasma albumin concentration, it accumulates 30–70% more MeHg than maternal blood (Unuvar et al. 2007; Stern and Smith 2003). Besides the higher exposure to MeHg, the immaturity of the BBB and the developing CNS make neurotoxicity much more serious during fetal development. Indeed, the NOAEL for neurodevelopmental effects is set a 10 mg/kg of MeHg in maternal hair, a level that is approximately 5-fold lower than the amount of MeHg causing effects in adults (Clarkson and Magos 2006).

2.3 Ethylmercury

Thimerosal is dissociated into thiosalicilate and EtHg upon inoculation (Dórea, Farina, and Rocha 2013). Much of the assumptions on EtHg neurotoxicology were based on the similarities with MeHg but, even though evidence points to EtHg entering neural cells by the

same molecular mimicry mechanism as MeHg (Zimmermann et al. 2013), toxicokinetic studies have pointed important differences between the two organomercurials.

Results with infant *Macaca fascicularis* monkeys receiving a vaccine schedule equivalent to human infants (Burbacher et al. 2005) showed that EtHg has a shorter half-live than MeHg (6.9 vs 19.1 days), reaching a lower blood peak concentration following repeated exposure. Most importantly, for an equivalent exposure dose, the total level of Hg in the brain was 3–4 times lower for monkeys exposed to TCV than monkeys receiving MeHg, and the elimination from the brain was also faster (24 days for EtHg and 60 days for MeHg).

Other studies in rodents have confirmed these findings, noting differences in toxicokinetics between MeHg and EtHg (Rodrigues et al. 2010; Barregard et al. 2011).

One of the most significant findings of these toxicokinetic studies is that following thimerosal/EtHg exposure, the accumulation of Hg^{2+} in the brain is greater than upon MeHg exposure (Figure 1) (Burbacher et al. 2005; Rodrigues et al. 2010). Indeed, in the brain of *Macaca fascicularis* the proportion of Hg^{2+} to total Hg was 71 and 10% in animals exposed to thimerosal and MeHg, respectively, with absolute levels of Hg^{2+} being twice as high in the case of thimerosal exposure (Burbacher et al. 2005). The toxicological significance of this difference is not clear, but, since Hg^{2+} is highly electrophilic with a greater affinity for thiols and selenols, this rapid dealkylation could explain observations on the higher toxicity of EtHg compared to MeHg (Branco et al. 2017).

3. Neurotoxic effects

3.1 Mercury vapor

Chronic exposure to mercury vapor results in a well-defined clinical pictures known as mercurialism. Symptoms include tremors, behavioral alterations and disturbances such as extreme shyness, loss of memory, irritability and persistent insomnia (Magos 1997). Studies with workers formerly exposed to $vapHg^0$ showed symptoms may last until several years after cessation of exposure due to Hg^{2+} retention in brain (Ellingsen et al. 1993; Kishi et al. 1994; Steckling et al. 2014).

Apart from case reports, systematic data concerning developmental effects of $vapHg^0$ in humans are lacking. However, experiments with pregnant rats showed that exposure to $vapHg^0$ above threshold limits causes significant adverse effects both in dams and in offspring (Morgan et al. 2002). These include behavioral alterations and impaired coordination (Yoshida 2002).

3.2 Methylmercury

Patient analysis of the large-scale MeHg poisoning events of Minamata and Iraq provided critical evidence on the sequence of symptoms associated to MeHg's neurotoxicity (Clarkson and Magos 2006). Numbness of the extremities (paresthesia) and loss of coordination (ataxia) are the first symptoms, reflecting impairment of cerebellar function. As exposure progresses, speech becomes slurred, mobility and sensory ability are severely affected and eventually death may ensue (Weiss, Clarkson, and Simon 2002).

Symptoms are considerably more serious during *in utero* exposure even at relatively low levels of MeHg (i.e. compared to the Minamata and Iraq cases) may insidiously affect neurodevelopment (Clarkson and Magos 2006). Indeed, large-scale cohort epidemiological studies in the Faroe Islands and New Zealand studies pointed that the regular consumption of high mercury food - such as whale (Faroe) and shark meat (New Zealand) - by pregnant women translated in lower performance results by their children when tested for several neurodevelopmental endpoints (cognitive and motor skills) in the years following birth (Grump et al. 1998; Grandjean et al. 1997, 2004). Likewise, some studies with indigenous populations of the Amazon showed decreased performance in neurobehavioral outcomes by adults and children with high hair mercury (Cordier et al. 2002; Lebel et al. 1998; Yokoo et al. 2003).

On the other hand, in another large cohort epidemiological study in the Seychelle islands, where MeHg exposure results from frequent consumption of low MeHg fish, results consistently showed no association between MeHg exposure and neurodevelopmental test results (Myers et al. 2003; Davidson et al. 2011; Orlando et al. 2014; van Wijngaarden et al. 2013).

The hypothesis explaining such differences in neurotoxicity is that the high nutritional value of a fish-based diet may protect neurodevelopment from the chronic effects of MeHg exposure (Ralston, Kaneko, and Raymond 2019). Data from riverine fish eating populations in the Amazon where hair mercury can be higher than 30 μg/g, but with no apparent symptoms seem to back this hypothesis (Dorea 2003). However, this interpretation is not straightforward since many confounding factors are involved in these epidemiological assessments (Esben, Philippe, and Pal 2007), including consumption of essential long-chain fatty acids (Choi et al. 2014).

3.3 Ethylmercury

Experimental evidence for EtHg neurotoxicity is limited. Studies in animals have shown a multitude of effects in animals treated with EtHg/thimerosal, ranging from altered social behavior, hormone regulation, growth brain histology and neurochemistry (Li et al. 2014; Olczak et al. 2009). A study by Horning and co-workers, showed that EtHg-related neurodevelopmental effects in mice were strain-dependent, suggesting a genetic susceptibility to EtHg-induced neurodevelopmental effects (Hornig, Chian, and Lipkin 2004).

Attempting to translate data from rodent studies concerning EtHg toxicity to human biology is challenging for several reasons. In some studies (Olczak et al. 2009; Li et al. 2014) the doses used far exceed the dose to which a child is exposed in a regular vaccination schedule. Even results from studies properly encompassing dose-adjustment to mimic human exposure (Berman et al. 2008) are hard to translate due to the obvious differences in CNS neurodevelopment between rodents and humans, both in terms of time-frame and complexity (Semple et al. 2013). Moreover, the interval between inoculations in rodent pups (2 days) might not be sufficient to allow for clearance of EtHg from the organism prior to the following inoculations, which introduces a bias to the results since in humans the inter-inoculation period is larger.

Data in human populations are scarce, possibly because the significance of EtHg exposure is less of a concern than exposure to MeHg, with a tendency for further reduction due to the phasing-out of most TCV (Kalkbrenner, Schmidt, and Penlesky 2014). Still, much has been written on the link between TCVs and neurodevelopmental disorders in humans, namely Autism Spectrum Disorders (ASD). Despite the controversy, several retrospective and prospective epidemiological studies (Verstraeten et al. 2003; Taylor, Swerdfeger, and Eslick 2014; Uno et al. 2015; Stehr-Green et al. 2003; Madsen et al. 2003; Hviid et al. 2003; Heron and Golding 2004; Fombonne et al. 2006; Andrews et al. 2004) have found no positive association between TCVs and impaired neurodevelopmental outcomes in children. Nevertheless, given a context of multi-source exposure to Hg compounds, a reduction in exposure to EtHg in the early neurodevelopmental period is certainly desirable (Marques et al. 2007).

4. Molecular and cellular mechanisms of neurotoxicity

The last fifty years evidenced the detrimental effects of mercury for the CNS for both human and animal populations. The risk of neurotoxicity is diverse among different age groups being the developing brain highly sensitive and sometimes irreversibly affected. Some molecular mechanisms of mercury toxicity have been elucidated, however, their sequence, range and interdependence are still a matter of study.

4.1 Neuronal signaling

One of the important mechanisms for MeHg neurotoxicity is related with the disruption of glutamate transport, which in mammalians is the main excitatory neurotransmitter (Fonfría et al. 2005). When released into the synaptic cleft glutamate stimulates Ca^{2+} influx through NMDA receptors in the post-synaptic terminal. In a normal physiological scenario, the glutamate in the synaptic cleft is taken up by astrocytes through Na+/K+ transporters, allowing for the signal transmission to terminate (Fonfría et al. 2005). Both MeHg and Hg^{2+} affect glutamate mediated excitatory signaling by simultaneously enhancing its release from the pre-synaptic terminal and by hindering their uptake by astrocytes and creating neuronal excitotoxicity and dysfunction (Aschner et al. 1990; Aschner et al. 1998; Yuan and Atchison 2003). Indeed, by accumulating preferentially in astrocytes, MeHg hinders their critical functions, which are important in protecting neurons from neurotoxic effects. These include coordination of the extracellular microenvironment for instance by removing neurotransmitters such as glutamate and providing precursors for glutathione synthesis, and the buffering of extracellulat K+, to name a few (Shanker, Syversen, and Aschner 2003).

Increased levels of glutamate in the synaptic cleft promote an increased calcium influx to the post synaptic terminal (Sarafian 1993). In turn, excessive Ca^{2+} will affect the mitochondria by increasing nitric oxide synthase (iNOS) activity and NO production (Farina, Aschner, and Rocha 2011).

4.2. Cellular energetics

(mitochondria) to be completed

MeHg knowingly affects mitochondrial function causing K+ accumulation and H+ efflux, decreasing inner membrane potential and increasing ROS such as superoxide anion and H2O2 production (Mori et al. 2007). Additionally, MeHg inhibits the electron transport chain (ETC) activity, which induces Cyt c release leading to cell death (Mori et al. 2011).

4.3 Oxidative stress

Mercury targets antioxidant enzymes as well as glutathione and additionally increases ROS production. MeHg has a high affinity for protein sulfhydryl groups (for a review see (Ajsuvakova et al. 2020) and a much greater affinity for selenothiol groups and therefore proteins and specially selenoproteins such as thioredoxin reductase (TrxR) and glutathione peroxidase (GPx) are targets of outmost importance (Branco et al. 2012; Carvalho et al. 2008, 2011). Down-regulation of redox enzyme's activity is at the basis of increased reactive oxygen species (ROS) levels during Hg exposure.

Oxidative stress has a crucial role in cell lineage fate of neural stem cells, with higher levels of ROS and mitochondrial damage resulting in astrogliogenesis rather than neurogenesis (Xavier et al. 2014). Indeed, adding to the complexity of MeHg's neurodevelopmental effects, sub-cytotoxic concentrations were also shown to block rat neural stem cell differentiation into neurons (Tamm et al. 2008), promoting astrogliogenesis via STAT-3 signaling. However, as MeHg exposure rises, signaling is blocked and astrogliogenesis arrested (Jebbett et al. 2013). Higher concentrations, also limit neuronal migration leading to a distorted CNS architecture (Clarkson and Magos 2006).

In this context, redox active systems such as the glutathione and thioredoxin systems, appear as key players controlling redox signal transduction and regulating ROS production (Ostrakhovitch and Semenikhin 2013). The glutaredoxin/glutathione system includes glutathione (GSH) and related enzymes like seleno-dependent GPx and glutaredoxins (Grx), whereas the thioredoxin system comprises, thioredoxin (Trx) and TrxR. Along with the glutathione/glutaredoxin system, the thioredoxin system keeps the intracellular environment reduced preventing oxidative and nitrosative stress (Branco and Carvalho 2019). Since both systems are established targets for Hg compounds in the CNS, the disruption of redox signaling pathways is likely at the basis of neurodevelopmental effects (Ren et al. 2017).

MeHg affects mitochondrial function causing K^+ accumulation and H^+ efflux, decreasing inner membrane potential and increasing ROS such as superoxide anion and H_2O_2 production (Mori et al. 2007). Additionally, MeHg inhibits the electron transport chain activity, which induces cytochrome C (Cyt c) release leading to cell death (Mori et al. 2011).

The glucocorticoid receptor (GCR) has been considered central in neuroendocrine integration and it contributes to stress response. Thus, implication in brain disorders is gaining considerable attention The GCR and has been shown to be inhibited by mercurials (Baxter and Tomkins 1971). Although the implications for mercury toxicology were unclear at the time, more recently, the GCR signaling pathway has been related to developmental disorders promoted by heavy metals, such as arsenic (Ahir et al. 2013), linking it to neurodevelopment alterations resulting from metal exposure. MeHg in particular binds to a

redox active Cys residue in GCR leading to conformational changes in the protein and loss of function (Spulber et al. 2018).

Since GCR is ubiquitous in almost every cell type and it regulates genes controlling development, metabolism and immune response, its inhibition by MeHg as shown in HeLa AZ-GR cell line may play a role in the developmental neurotoxic effects of MeHg (Spulber et al. 2018). Of significance is also the fact that regulation of GCR depends on its association with Trx (Makino et al. 1999) and this enzyme strongly interacts either with Hg^{2+} or MeHg (Carvalho et al. 2008).

As discussed above, MeHg affects mitochondrial function causing K^+ accumulation and H^+ efflux, decreasing inner membrane potential and contributing to the ROS increase, namely superoxide anion and H_2O_2 production (Mori et al. 2007).

4.4 Neuroinflammation

Immunotoxic events are triggered by non-cytotoxic MeHg exposure and are considered the critical toxic effect (Vas and Monestier 2008). Thus, it is reasonable to hypothesize that it may precede the neurotoxic effects observed during in utero exposure.

In this sense, microglia, the major representative of the innate immune system in the CNS, could be key in modulating MeHg neurotoxicity, since these cells are known to be highly sensitive to MeHg with some reports showing activation at MeHg <1 μM (Ni et al. 2011). On the other hand, astrocytes also become reactive at low MeHg levels releasing IL6 which modulates microglia activity contributing instead neuroprotection (Noguchi et al. 2013; Eskes et al. 2002). Which cells that are first activated, microglia or astrocytes, and how activation fluctuates during exposure to MeHg still needs clarification.

Notably, the molecular pathways inherent to microglia/ astrocyte activation (e.g. NF-kB, STAT-3) and cell death (e.g. ASK-1) rely on cysteine switches for activation of signaling cascades and therefore these events should be interpreted in the light of the interaction between mercurial compounds with redox systems (Ostrakhovitch and Semenikhin 2013; Vilhardt et al. 2017). In fact, preliminary results from our group, show that sub-cytotoxic levels of Hg^{2+} cause GSH depletion, which triggers activation of p38 signaling and up-regulation of pro-inflammatory cytokines in microglia cells [unpublished data].

5. Conclusion and Future prospects

Despite the neurotoxicity of mercury compounds has long been known, recent decades have seen growth in the understanding of their underlying molecular mechanisms. Mercury neurotoxicity appears to be a multifactorial process (Figure 2) that however has its basis on the interaction between mercurials - which are chemically soft electrophiles - and nucleophilic residues of proteins namely thiols and selenols. Of special significance is that this interaction occurs at very low levels of exposure and could trigger cellular events (e.g. microglia activation) well before neurotoxic symptoms manifest themselves.

Accordingly, future research should focus on the effects of low levels of exposure namely which are at the basis of neurodevelopmental toxicity, i.e activation of immune cells at the

CNS and neurodifferentiation. Most importantly, attention should be given to how nutritional factors (e.g PUFAs, selenium) mitigate or mosulate these low level effects. This is essential to better understand the etiology of mercury neurotoxicity and refine risk assessment strategies.

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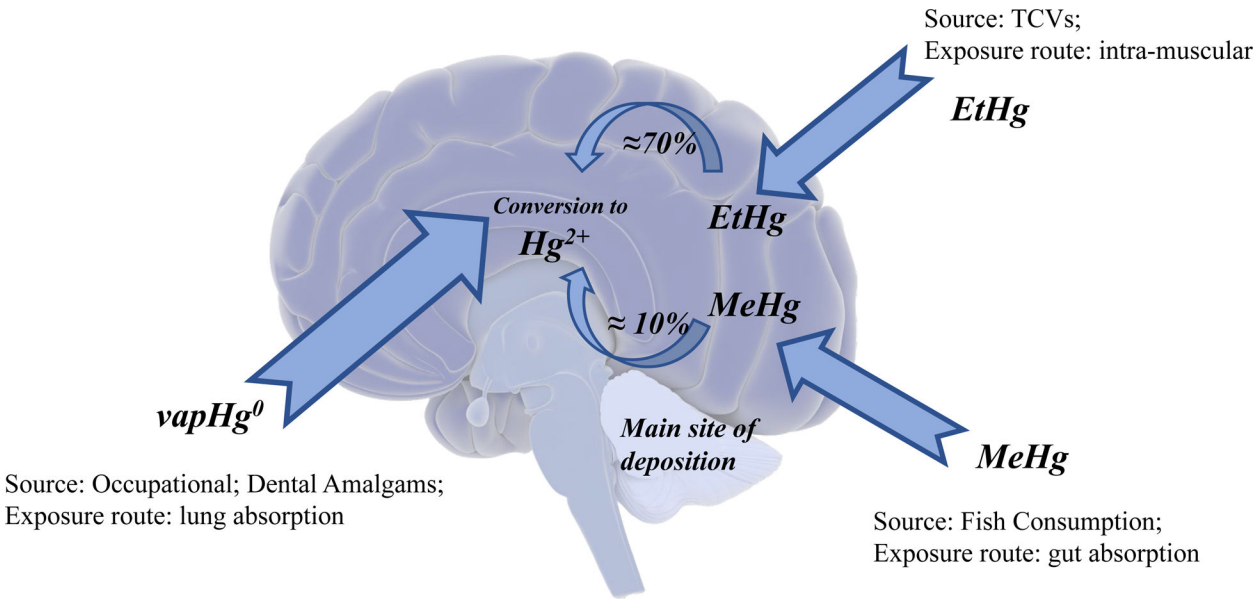

Figure 1-

Sources, exposure route and accumulation of mercury compounds in the Brain. All mercury compounds accumulate in the brain and cause toxicity. Mercury vapor ($vapHg^0$) resulting from occupational settings or released from dental amalgams enters circulation via the lungs and crosses the blood brain barrier (BBB) reaching the brain where it is oxidized to Hg^{2+}. Methylmercury (MeHg) from fish crosses the BBB by molecular mimicry and accumulates in the brain, with a small fraction (≈ 10%) being converted to Hg^{2+}.Ethylmercury (EtHg) resulting from the breakdown of thimerosal following TCV inoculation crosses the BBB similarly to MeHg. Albeit its elimination is faster than MeHg's, it is more rapidly converted to Hg^{2+} (≈ 70% of EtHg reaching the brain). The cerebellum is the main site of deposition of mercury compounds.

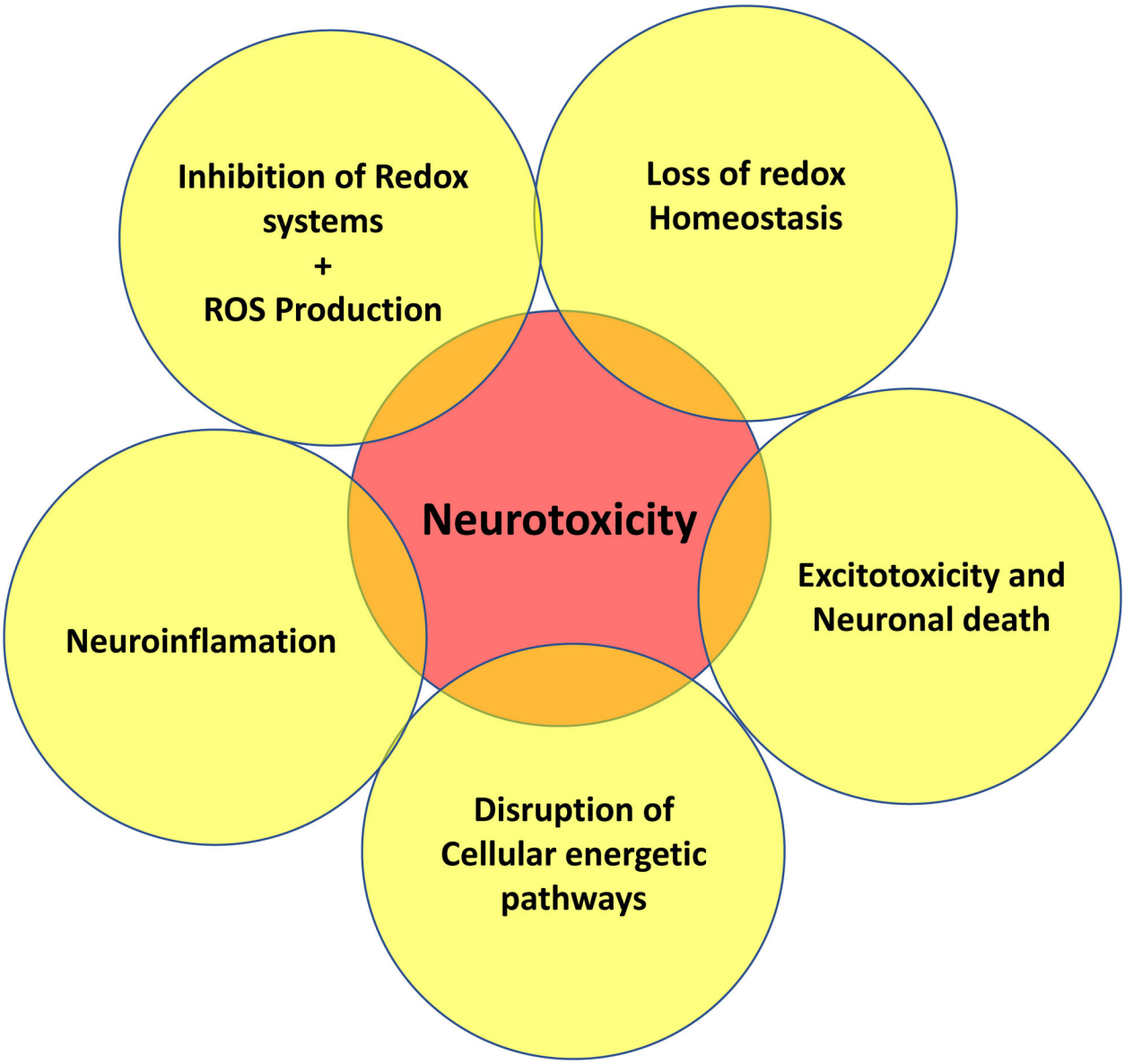

Figure 2-
Neurotoxicity of mercury is a multifactorial process which encompasses disruption of regular signalling pathways on a molecular and cellular level.