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Methyl Mercury Injury to CNS: Mitochondria at the Core of the Matter?

Maria Rosaria Carratù[1]* and Anna Signorile[2]

[1]*Department of Biomedical Sciences and Human Oncology, University of Bari, Italy*
[2]*Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari, Italy*

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***Corresponding author:** Prof. Maria Rosaria Carratù, MD, Department of Biomedical Sciences and Human Oncology, University of Bari, Policlinico, Piazza Giulio Cesare 11, 70124 Bari, Italy, Tel. no: ++39 080 5478455; Email: mariarosaria.carratu@uniba.it

Abstract

Methyl-mercury (MeHg) is one of the most hazardous environmental pollutants of great concern to public health and regulatory agencies because of its primary toxicity to the human central nervous system. The major source of MeHg exposure to the general population is through consumption of contaminated fish and other food products. MeHg, absorbed from the gastrointestinal tract, is easily transported across the blood-brain barrier (BBB). Cysteine-facilitated transport of MeHg into the brain has been demonstrated, and in particular a neutral amino acid transport system capable of mediating MeHg-cysteine uptake has been identified in astrocytes where MeHg accumulation induces cell swelling and inhibition of glutamate uptake. Elevation of glutamate levels in the extracellular space may, in turn, trigger or accelerate processes of excitotoxic neuro degeneration. The rising of extracellular glutamate levels is responsible for the sustained activation of glutamate receptors, hence enhancing Na^+ influx and Ca^{2+} release from intracellular organelles that may trigger a biochemical cascade which promotes the reactive oxygen species (ROS) production. In this scenario, mitochondria may play a crucial role, as these organelles act as a buffer against cytosolic calcium and mediate ROS formation in cells. Herein, we summarize studies providing insights into the molecular and cellular mechanisms involved in MeHg-induced neuro degeneration with particular focus on the role of astrocytes and mitochondria. Indeed, mitochondria may be supposed to lie at the crossroads of a network of events (microtubule disorganization, Ca^{2+} dyshomeostasis, ROS generation) leading to neuro degeneration, although it is difficult to establish the upstream mechanisms and downstream effectors in this cascade of events.

Keywords: Methyl-mercury; Astrocytes; Neuronal Degeneration; Ca^{2+} homeostasis; Oxidative stress; Mitochondria

Abbreviations: BAPTA: 1,2-bis(o-aminophenoxy)ethane-N,N,N',N'-tetra acetic acid; BBB: Blood Brain Barrier; CNS: Central Nervous System; GPx: Glutathione Peroxidase; GSH: Glutathione; MeHg: Methyl Mercury; MPTP: Mitochondrial Permeability Transition Pore; NMDA: N-methyl-D-aspartate; OTC: L-2-oxothiazolidine-4-carboxylic acid; ROS: Reactive Oxygen Species

Introduction

MeHg is a bio accumulative environmental toxicant, which has very high affinity for sulphur-containing anions, the sulfhydryl (-SH) groups on the amino acid cysteine and hence for proteins containing cysteine, forming a covalent bond. The high affinity of MeHg for thiol groups makes proteins and peptides bearing cysteines susceptible to structural and functional modification by MeHg in all sub cellular compartments, thus causing a range of effects at many locations throughout the body. The majority of environmental MeHg contamination occurs through the biotransformation of inorganic mercury to organic mercury in a process termed methylation. During methylation, inorganic mercury is converted into MeHg by microbial action, primarily in sediments of fresh and ocean waters. Thus, MeHg enters the aquatic food chain and is biomagnified as it accumulates in predatory fish such as swordfish, pike, and ocean tuna. Therefore, MeHg contamination in fish can be significant, and fish consumption represents an important route of human exposure [1]. MeHg, absorbed from the gastrointestinal tract, is easily transported across BBB. Once it is demethylated in the brain, elemental mercury bio accumulates in the brain tissue. Cysteine-facilitated transport of MeHg into the brain has been demonstrated, and in particular the L-type large neutral amino acid transporter [2,3] capable of mediating MeHg-cysteine uptake has been identified in astrocytes. Therefore, it has been proposed that MeHg-cysteine conjugate is the pathway whereby MeHg exerts its toxicity [4-6]. Neuronal degeneration upon MeHg exposure has been reported to occur either by necrosis [7-10] or apoptosis [11-15] two modes of cell death

characterized by distinct morphological and molecular features. Several morphological and biochemical parameter hallmarks of apoptosis have been described after the acute MeHg treatment of different cell lines: neuro epithelial cells [16,17] dorsal root ganglion neurons [18], cerebellar granule cells [7,19,20], cerebrocortical neurons [12] and hippocampal cells [10]. MeHg has been shown to possess high affinity for tubulin sulfhydryl groups, to depolymerize cerebral microtubules *in vitro* and to inhibit microtubule assembly [21]. Microtubule fragmentation and neuronal network dissolution have been observed in cultured primary cerebellar granule neurons exposed to MeHg [22]. Micro tubular disruption induced by MeHg binding to sulfhydryl groups of peptides and resulting in the accumulation of cells in G2/M has been proposed as an important event in the development of apoptosis by MeHg in neuronal cell lines [8,14]. In the present review, we summarize studies providing insights into the molecular and cellular mechanisms involved in MeHg-induced neuronal degeneration with particular focus on the role of astrocytes and mitochondria.

MeHg accumulation in astrocytes: glutamate excitotoxicity, calcium overload, ROS production

MeHg preferentially accumulates in astrocytes where it induces cell swelling and specifically inhibits excitatory amino acid uptake [23]. In neonatal rat cortical primary astrocyte cultures, uptake of both L-glutamate and D-aspartate is significantly reduced and efflux of both glutamate and aspartate from preloaded astrocytes are increased by MeHg in a dose- and time-dependent fashion [24]. The consequent elevation of glutamate levels in the extracellular space may trigger or accelerate processes of excitotoxic neuro degeneration [25]. Accordingly, the co-application of non-toxic concentrations of MeHg and glutamate leads to the appearance of neuronal lesions typical of excitotoxic damage [23]. In this context, the excitatory amino acid receptors (N-methyl D-aspartate (NMDA) and non-NMDA-types) mediated pathways have been indicated as the main routes responsible for Ca^{2+} entry into cells following MeHg exposure [26]. This view is supported, at least in part, by the finding that antagonists of the NMDA receptor, including MK-801 (a non-competitive NMDA antagonist), D-2-amino-5-phosphonovaleric acid (a competitive NMDA antagonist), and 7-chlorokynurenic acid (an antagonist at the glycine site associated with the NMDA receptor) can block MeHg-induced toxic effects in cerebral neuron culture [2,27,28]. The rising of extracellular glutamate levels is responsible for the sustained activation of glutamate receptors thus enhancing Na^{+} influx and Ca^{2+} release from intracellular organelles that may trigger a biochemical cascade which promotes the ROS production [29]. Oxidative stress by itself inhibits, however, the astrocytic glutamate uptake through a direct action on the transporter proteins [27,30]. Endogenous glutathione (GSH) is one of the most abundant and essential thiol tripeptide for scavenging ROS [31]. The excessive formation of ROS induced by MeHg exposure is associated with the depleted intracellular GSH levels and can be reverted under treatment with L-2-oxothiazolidine-4-carboxylic acid (OTC) [32,33]. Indeed, MeHg also inhibits astrocytic uptake of cystine and cysteine, the key precursors of GSH biosynthesis [34]. Thus, neuronal damage in response to MeHg most likely represents aberrant control of the extracellular milieu by astrocytes [34,35,36].

Mitochondria at the crossroads of a network of events leading to neuronal degeneration?

Calcium overload

The calcium ion is known to play a critical role in cell loss in the central nervous system (CNS), and Ca^{2+} overload has been shown to trigger either necrotic or apoptotic cell death [29]. The biochemical mechanisms by which sustained increases in intracellular Ca^{2+} cause neuronal cell death include the activation of degradative enzymes, such as phospholipases, proteases and endonucleases, mitochondrial dysfunction, and perturbation of cytoskeleton organization [29]. MeHg, at low micromolar concentrations, disrupts calcium homeostasis and causes elevations in intracellular calcium in cerebellar neurons [37-40]. The Ca^{2+} channel blockers ω-conotoxin MVIIC and nifedipine, which significantly delay MeHg-induced elevation in Ca^{2+} levels in this *in vitro* model, and the Ca^{2+} chelator BAPTA protect granule cells and human neuroblastoma cells from MeHg-induced cell death [38,41].

Reactive oxygen species and antioxidant defenses

ROS, such as superoxide anion, hydrogen peroxide, and hydroxyl radical are considered to be initiators of peroxidative damage. The brain is sensitive to oxidative/free radical injury and a number of studies have suggested the implication of such mechanism in the MeHg neurotoxicity [42-45]. Of particular interest, the scientific literature suggest that the targeting of thiol- and selenol-containing proteins or peptides, including GSH, can be the primary molecular events that trigger secondary and tertiary processes that ultimately culminate in MeHg-induced oxidative stress [2]. Indeed, antioxidants/oxygen radical scavengers, *e.g.* vitamin E, GSH, and catalase provide some degree of protection against MeHg deleterious effects either *in vitro* or *in vivo* [26,27,46-49]. In rat cerebellar P2 preparations, both *in vitro* and *in vivo* MeHg exposures increase the rate of ROS formation which is prevented by the iron chelator deferoxamine [42]. MeHg-induced generation of ROS seems to be a crucial event in determining progression towards damage and cell death in different cell types, including human monocytes [50], human T cells [51] and neurons [43,52]. The selective vulnerability of neurons to mercury has been linked to the absence or limited presence of inherent protective mechanisms such as metallothionein, GSH, heme oxygenase and other stress proteins [8] . This would explain why in adult animals, at moderate dosage of MeHg, the primary target is the CNS, although the MeHg concentration may be considerably higher in other tissues, such as liver and kidney. Thus, most cells have a capacity

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for resisting or repairing the damage inflicted by MeHg. If so, the targets of MeHg would be cells that cannot meet the metabolic challenge of damaged proteins and/or do not have the ability to sequester mercury via the synthesis of metallothionein or other proteins and peptides. Thus, disruption of calcium homeostasis and free radicals generation are among the detrimental effects associated with MeHg-induced toxicity [2,8,26]. In this scenario, mitochondria may well play a crucial role, as these organelles can act as a buffer against cytosolic calcium and mediate reactive species formation in cells [53,54]. Importance of mitochondria for MeHg toxicity [26,55] has emerged from studies performed both *in vivo* [56,57] and *in vitro* [58,59]. *In vivo* exposure to MeHg causes its accumulation inside mitochondria followed by a series of biochemical changes in these organelles [60]. These effects are similar to those observed in studies of mitochondria respiratory chain inhibition [61].

Mitochondrial dysfunctions induced by MeHg include the failure of energy metabolism, the disruption of calcium homeostasis and the dissipation of the mitochondrial membrane potential, effects which lead to a mitochondrial burst of ROS production [62-64]. ROS are important mediators of damage to cell structures, including lipids and membranes, as well as proteins and nucleic acids [65]. The detrimental effects of ROS are balanced by the antioxidant action of non-enzymatic antioxidants in addition to antioxidant enzymes [65]. *In vivo* and *in vitro* experimental observations have shown that the toxic effects of MeHg are accompanied by a significant deficit of antioxidant defenses, such as the depletion of GSH and the inhibition of GSH peroxidase (GPx) activity [58,66,67]. Thus, oxidative stress is remarkably involved in MeHg-induced cytotoxicity, and the benefit of the antioxidant properties of organoselenium compounds, guanosine and flavonoids (myricetin, myricitrin, rutin) against MeHg-induced ROS generation and mitochondrial dysfunction has been demonstrated [68,69].

Relationship between microtubule disorganization, Ca^{2+} overload and mitochondria dysfunctions

A crucial role in cellular injury induced by MeHg has the close relationship between Ca^{2+} overload and mitochondria dysfunctions [26]. It is well recognized that at physiological concentration, Ca^{2+} is a powerful regulator of organelle metabolic activity, which acts primarily promoting ATP synthesis by stimulating crucial enzymes of Krebs cycle. On the other hand, mitochondrial changes that occur in most instances of cell death (apoptosis and necrosis) require an elevated influx of Ca^{2+} into matrix [70,71]. A series of works indicates a spectrum of mitochondrial effects, either directly or indirectly via Ca^{2+} overload, of MeHg both *in vivo* and *in vitro*, including alterations in complex III of the mitochondrial electron transport chain, depression of respiration and ATP production, swelling of the mitochondrial matrix, and loss of $\Delta\Psi m$ with subsequent release of cytochrome c [72-74]. In myogenic cell lines, MeHg causes apoptosis via both mitochondria- and endoplasmic reticulum-generated processes through activation of stress-activated protein kinase/c-Jun N-terminal kinase [75]. Moreover, there is a close relationship between microtubules and mitochondrial function, such as mitochondrial permeability transition pore (MPTP), thus microtubule disorganization would play an important role in mitochondrial dysfunction. In particular, stabilization and disruption of microtubule opens MPTP and depolarizes $\Delta\Psi m$ in cardiac myocytes [76]. Thus, in this scenario mitochondria may be supposed to lie at the crossroads of a network of events (microtubule disorganization, Ca^{2+} dyshomeostasis, ROS generation) ultimately leading to neuronal degeneration, even it is difficult to establish the upstream mechanisms and downstream effectors in this cascade of events.

Conclusion

Exposure to MeHg can cause profound damage to the CNS. A number of molecular and cellular mechanisms have been identified as being the primary targets of MeHg cytotoxicity. MeHg preferentially accumulates in astrocytes where it induces cell swelling and specifically inhibits excitatory amino acid uptake, hence the consequent elevation of glutamate levels in the extracellular space may trigger or accelerate processes of excitotoxic neuro degeneration. MeHg exhibit high affinity for tubulin sulfhydryl groups, hence depolymerizes cerebral microtubules and inhibits microtubule assembly. Thus, micro tubular disruption has been proposed as an important event in the development of apoptosis by MeHg in neuronal cell lines. Disruption of calcium homeostasis and free radicals generation are among the detrimental effects associated with MeHg-induced toxicity. In this scenario, mitochondria may play a crucial role, as these organelles can act as a buffer against cytosolic calcium and mediate reactive species formation in cells. Mitochondrial dysfunctions induced by MeHg include the failure of energy metabolism, the disruption of calcium homeostasis and the dissipation of the mitochondrial membrane potential, effects which lead to a mitochondrial burst of ROS production. Remarkably, the toxic effects of MeHg are accompanied by a significant deficit of antioxidant defenses, such as the depletion of GSH and the inhibition of GPx activity. In conclusion, mitochondria are plausible active players in the network of events occurring in astrocytes and ultimately leading to neuronal degeneration.

Conflict of interest

The authors declare no conflict of interest

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