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Invited review

The toxicology of mercury and its compounds

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ABSTRACT

A concentrated review on the toxicology of inorganic mercury together with an extensive review on the neurotoxicology of methylmercury is presented. The challenges of using inorganic mercury in dental amalgam are reviewed both regarding the occupational exposure and the possible health problems for the dental patients. The two remaining "mysteries" of methylmercury neurotoxicology are also being reviewed; the cellular selectivity and the delayed onset of symptoms. The relevant literature on these aspects has been discussed and some suggestions towards explaining these observations have been presented.

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Introduction

A search on PubMed using "mercury" as a search phrase will give almost 34,000 records in return including some 1700 reviews. The records in PubMed dates back to 1813 while the oldest review is from 1963. The literature covers a vast range of properties and applications of mercury and its compounds. Even if we limit our search to "mercury toxicity" we will find around 5000 papers and 600 reviews reported since 1926. Although many questions regarding the hazard and risk associated to mercury exposure have been addressed – there are still issues that deserve our scientific curiosity and examination. In the present review we will give a brief overview of mercury toxicology and bring some recent reviews to the attention of the reader. Some of the issues we think need future work are e.g.:

- The mechanism(s) of alkylmercury neurotoxicity
- The delay in the premier of symptoms after exposure to alkylmercury
- The beneficial effects of nutrients to risk assessment of alkylmercury neurotoxicity

Mercury is a highly toxic element, which we often see discussed together with cadmium and lead, which are prominent examples of toxic heavy elements. However, mercury differs from cadmium and lead as it is present in our environment in several different forms that exhibit a range of toxicological properties. Measuring the elemental concentrations of both cadmium and lead in the environment may provide us with exposure criteria that are meaningful for their toxicological assessment. This is not the situation for mercury where we would need to differentiate at least between:

- Elemental mercury (Hg^0)
- Inorganic mercury compounds (mercurous – Hg_2^{++} and mercuric – Hg^{2+})
- Organic mercury compounds (primarily alkyl mercury compounds)

The different species of mercury indicated above differ with respect to their behavior in the environment as well as with respect to their potential to interact with biological processes.

Mercury is present in the earth crust and we are all exposed to some form of mercury through the air we inhale, the water we drink and the food we eat. Adding to that, mercury has been used in a wide range of products ranging through seed treatment, consumer applications, dental fillings and preservatives in vaccines. Thus, we are all exposed to mercury in some form and at some concentration. These environmental and public health aspects of mercury have been extensively reviewed by Clarkson in 2002 [1]. The reader is referred to this review entitled "The three modern faces of mercury" which discusses, in an excellent way, all the major issues relating human exposure and the special characteristics of mercury chemistry.

There are numerous reviews available which address the mammalian and human toxicology of mercury and its compounds. A particularly comprehensive and thorough review has been presented by Clarkson and Magos [2]. This review includes the toxicology of both inorganic and organic mercury. The review highlights some "mysteries" which may still challenge our scientific curiosity. One such aspect is the delay of symptoms after exposure to alkyl mercury compounds. The latent period may last from weeks to several months after the exposure, while the onset of signs and symptoms, when they occur, escalates rather rapidly. The latency period does not decrease by increasing the dose and the mechanism behind the latency period is still not known. We do not even know the key mechanism by which alkyl mercury compounds causes their neurotoxicity, and a proposed prime mechanism should explain both the nature of the latency period as well as the cellular specificity of damage.

In the following text we will present a short review of the general toxicology of mercury. However, the main part of our presentation will address the toxicology of alkylmercury and make an attempt to evaluate the possible mechanisms, which are of practical importance, when considering the safe levels of mercury exposure e.g. through fish consumption.

Elemental mercury

Elemental mercury (Hg^0) is volatile at room temperature and the vapors may represent a hazard to humans. Such exposure may occur in laboratories, work places as well as in homes. In private homes, the broken thermometers containing mercury could become a source of exposure, as it can be very difficult to collect the spilled mercury. In many countries the use of mercury in thermometers has now been banned as a policy to reduce the risk to consumer and the release of mercury into nature. Work place exposure may occur in many types of industries, where major uses of elemental mercury include the chlorine-alkali manufacture, dental amalgams, electronic switches and fluorescent lamps. In countries with proper work environment monitoring and hazard containment procedures, such exposure is now at a minimum. However, the Western world has transferred hazardous industries to countries characterized by less developed economies and industrial regulations. In these countries processes including potential mercury release will continue to be a challenge to both man and the environment. In addition to dental amalgam (see below) mercury has been of considerable use in laboratory instruments, which during the last decades have been replaced by other technologies. Thus, the overall use of elemental mercury has been reduced, but is still reported as a grave environmental problem e.g. in gold mining regions in Brazil and the Philippines.

Toxicokinetics

Elemental mercury exposure from the air is readily taken up through the lungs and about 74% is retained in the human body [3]. From blood, the elemental mercury distributes throughout the body, as it easily passes through most cell membranes including the blood–brain barrier and the placenta. In blood, the elemental mercury is oxidized to mercuric mercury partly under the influence

of catalase [4] and this influence brain uptake of mercury [5]. This oxidation can be inhibited by alcohol [6]. Thus, over time the disposition of mercury from inhaled mercury vapor will reflect both the diffusion of elemental form as well as that of oxidized mercury. It has been shown that uptake of elemental mercury in the brain will decrease if the amount of catalase activity in the brain is inhibited [7]. The uptake of elemental mercury in brain tissue is also markedly dependent on brain glutathione (GSH) levels, as a 20% reduction in brain GSH content will result in a 66% increase in brain mercury content [8].

Toxic effects

Acute inhalation exposure, at high concentrations, may induce respiratory distress including dyspnea. Chronic exposure may induce symptoms from the central nervous system (CNS) including tremors, delusions, memory loss and neurocognitive disorders. Many of the signs and symptoms associated with slight poisonings will eventually disappear after the exposure ends. However, severe exposure may result in a lasting effect on brain function. Additionally, long-term exposure may also cause effects in kidney. An extensive review has been provided by Clarkson and Magos [2].

It is believed that the ultimate neurotoxic compound after mercury vapor exposure is Hg^{2+}. The evidence for this assumption is limited, but Warfvinge [9] have demonstrated that the cerebellar distribution of Hg^{2+} after vapor exposure is similar to that found after methylmercury (MeHg). As the neurotoxic effects of mercury vapor is quite different from that of MeHg, we extend this to support that MeHg itself and not Hg^{2+} is the ultimate toxic neurotoxic agent after exposure of MeHg (see extensive discussion later).

Dental amalgam

Dental amalgam has been used for more than 150 years for tooth fillings. The amalgam consists of approx. 50% metallic mercury together with silver and copper as well as small amounts of other metals such as zinc. The powdered metals are mixed with mercury shortly before the amalgam is used. This operation used to be done by hand which represented a source of mercury exposure to the dental personnel. Thus, the use of dental amalgam causes exposure both to dental personnel and to the patient who carries the amalgam tooth filling as mercury will be released from the filling over time. The last process may according to a review by WHO represent a significant source for mercury exposure [10].

The release of mercury from fillings is primarily determined by chewing and the temperature of food items as demonstrated by the use of nicotine-containing chewing gum [11]. It has further been shown that the urinary mercury reflects the number of amalgam fillings [12]. Allergic responses in the oral cavity can occur, although very seldom, as a result of amalgam fillings. Beyond that, the biological effects from amalgam fillings will be similar to mercury vapor or Hg^{2+}. There are numerous accounts in the literature of patients claiming to have a range of symptoms compatible with mercury vapor exposure. Some of these case stories include claims that removal of amalgam fillings improved the condition. It is very difficult to perform such studies and validation of the results is even more difficult. There have been claims that mercury may induce Alzheimer's disease [13] as brains from Alzheimer's disease patients contained elevated amounts of mercury [14]. However, this can be the result of membrane damage causing cells to accumulate more mercury than normal cells. This leaves us to speculate over what were the cause and the effect. The lack of correlation between amalgam dental fillings and Alzheimer's disease was also demonstrated in an epidemiological study [15]. A possible effect of dental amalgam on cognitive functions has also been addressed in epidemiological studies by Nitschke et al. [16] and Factor-Litvak et al. [17] without finding any association. We might assume that simultaneous exposure to MeHg from e.g. fish might potentiate any mercury induced fetal effects from amalgam. However, in a study by Watson et al. [18] such an effect was not found.

Dentists and dental assistants can become exposed to mercury while preparing and using mercury dental amalgam. The possible occupational hazard associated with this has been the object of several studies. There are concerns that exposure to metallic vapor causing urine concentrations above 500 nmol/L may cause chronic cognitive effects and these aspects have been examined in a meta-analysis [19]. Other studies by Langworth et al. [20] and Hilt et al. [21] have also raised concern that dental personnel may have an increased prevalence of cognitive malfunction as well as neuropsycological symptoms. Such an association was indicated in the study by Ritchie et al., but the functional differences could not be directly attributed to mercury exposure [22] and the need for further studies have been emphasized by e.g. Echeverria [23]. However, in two recent studies such long-term effects were not found [24,25]. Additionally, a potential risk to pregnancies and congenital malformations could not be found [26].

Inorganic mercury compounds

Inorganic mercury compounds have been used in a very extensive range of medical and cosmetic products; antiseptics, teething powders, skin-lightning creams. Accidental or intentional poisonings of mercuric chloride have not been uncommon. Inorganic mercury compounds can be either mercury in monovalent (mercurous – Hg_2^{++}) or divalent (mercuric – Hg^{2+}) form. Mercurous chloride (calomel) has very low solubility in water and is therefore regarded as non-hazardous. However, the use of teething powder containing mercurous mercury by infants led to a marked increased in their urinary mercury level [27]. It has also been speculated if Abraham Lincoln's sometimes erratic behavior could be the result of his regular intake of "blue pills" which consisted of mercurous mercury [28].

Toxicokinetics

Inorganic mercury accumulates primarily in the kidney, followed by its accumulation in the liver. The kinetics of mercuric mercury in humans have been reported by Rahola et al. [29] and Hattula and Rahola [30] demonstrating that about 1–16% of the initial dose was absorbed with a body half-time of about 41 days. No significant deposition of mercury was found in the head region for the first 58 days. Animal studies by Friberg et al. [31] have shown that 8% of the mercuric chloride applied to the skin can be absorbed in 5 h. In an experimental study on rats it was shown that there was an uneven distribution of mercury in the nervous system [32]. More mercury was found in the neurons compared to the glial cells, and the mercury had accumulated in lysosomes. The motor neurons contained more mercury than the sensory neurons and it was noted that mercury was present in the cerebellum, but not in the Purkinje cells.

Toxic effects

The organs primarily affected after acute poisoning of mercuric mercury are the intestine and kidneys. In the intestine the corrosive effects will dominate while in the kidneys renal failure may occur within 24 h due to necrosis of the tubular epithelium. As little as 1 g can prove fatal to an adult human. The most prominent effect of mercuric mercury is tubular necrosis in the kidney and after prolonged exposure glomerulonephritis can also be seen. Mercuric mercury may also cause autoimmune diseases – for a review, see Pollar and Hultman [33].

Organic mercury

Among the organic mercury compounds the prime interest of both epidemiological and experimental research has been methyl mercury. There are a range of excellent reviews available addressing the wider aspects of selective neurotoxicology [34–36] as well as methyl mercury neurotoxicity in particular [37–46].

Historical background

Organic mercury has a long history of toxicology in man and effects reported include neurotoxic effects. For MeHg the first case of fatal occupational poising was recorded in 1863 where laboratory personnel working on the synthesis of organic mercurials apparently did not realize the toxic properties of the compounds they were working with [47,48]. Later, the occupational hazards and toxicological properties of organic mercury were thoroughly described by Hunter et al. [49,50]. The early report included four human cases and experiments conducted on rodents and monkeys. Some key observations included in these reports were:

- A delay period before the onset of symptoms
- More intense and widespread morphological changes in monkey CNS even though it received a lesser dose of organic mercury when compared to the rat
- Substantial changes in cerebellar granule neurons and lack of any observable effects in Purkinje neurons.

The later report by Hunter and Russell [50] confirmed the findings in humans; where profound loss of granule neurons and the sparing of Purkinje neurons was observed. The observed constriction of the visual field was explained by the atrophy of granular neurons in the area striata. These early reports established some key elements in the toxicity of MeHg that still need to be explained:

- The delay period ("latent phase") in the occurrence of symptoms
- The cellular specificity of organic mercury neurotoxicity

The mechanisms associated with the latency periods have been discussed for both acute and chronic exposures by Weiss et al. [51]. These authors suggested that the latent period after MeHg exposure is characterized by an overwhelming compensatory mechanism that may last for weeks or months, followed by overt toxic symptoms as these mechanisms are exhausted. However, in case of MeHg poisoning, the latency period tends to lengthen with increasing blood levels. The authors suggest that such an effect might be attributed to nonmonotonic dose–response relationships where high-level exposures invoke compensatory processes more efficiently compared to exposure at lower levels.

Organomercury speciation

The organic mercury compounds include alkyl and phenyl groups as their organic molecular part. The phenyl mercury compounds are mainly used as preservatives in medicine and a recent edition of e.g. Goodman and Gilman [52] will provide an excellent introduction to pharmacology and toxicology of these compounds. Among the alkyl compounds we know, both the methyl and ethyl mercury compounds can be present in our environment. These compounds may exist as monoalkyl or dialkyl compounds. The dialkyl compounds are very volatile and difficult to handle for any practical purpose including toxicology studies [53,54]. Further, these compounds are readily absorbed both through the airways and intact skin, and are highly toxic even at very low exposure. Our experience with these dialkyl compounds in humans is very limited. However, there is one well-documented case, demonstrating the danger of handling these types of compounds [55]. It is believed that the dialkyl mercury compounds have an affect on the environmental distribution of organic mercury as they are highly volatile, insoluble in water and do not bind to sulfhydryl (SH) groups.

Although ethyl- and methylmercury compounds have very similar toxicological properties, there are some important differences that should be noted. Ethylmercury is more rapidly degraded to Hg^{2+} and for equivalent doses, less mercury will be found in the brain after ethylmercury exposure as compared to MeHg. Please consult Magos et al. [56] for further details on the differences between ethyl- and methyl Hg.

MeHg is readily absorbed by inhalation and about 80% is retained after vapor exposure. If MeHg is present in an aerosol, the absorption rate will depend on the particle size and characteristics. After oral exposure, the absorption from the intestine is virtually 100%, even though the MeHg found in the food is bound to SH-groups. MeHg can also be absorbed through intact skin [57].

Absorbed MeHg will bind to blood and tissue protein SH-groups and to lesser extent SH-groups of e.g. cysteine and GSH. It is transported through cell membranes mainly bound to cysteine by the large neutral amino acid transporter [58]. Other transport mechanisms are also active including passive diffusion [59]. The distribution from blood to tissue is slow and equilibrium is not reached until 4 days after exposure.

Approximately 10% of the body burden is found in the head region. The uptake into the brain is slower than for other organs. However, the brain has a stronger affinity for MeHg and the brain concentration has been shown to be 3–6 times higher that of the blood. About 20% of the MeHg present in brain is water soluble – and found mainly as MeHg–GSH complex. Throughout the rest of the body, MeHg is rather evenly distributed although some concentration dependent effects can be seen in the liver and the kidney. MeHg is transported through the placenta and will be deposited in the fetus. At equilibrium, fetal brain may have the same concentration as the mother's brain. However, the fetal blood concentration in humans can be higher than that of the mother. This can be due to differences in hemoglobin as this is the primary binding protein for MeHg in erythrocytes – and hemoglobin content is found to be different in mother and fetus.

Long term dosing of monkeys with MeHg has been shown to result in increased amounts of Hg^{2+} at a very slow rate [60]. The inorganic mercury accumulates mainly in astrocytes and microglial cells. The importance of this process towards the MeHg neurotoxicity will be discussed later.

The main excretion pathway of MeHg is through bile and kidney. Net daily excretion rate at 1% of body burden will give a body half-life of about 70 days. This estimate fits very well with the extensive database developed from the epidemic poisoning in Iraq [61]. The enterohepatic recirculation of MeHg is an important factor for the fecal excretion of MeHg. A SH-resin to be taken orally was developed by Clarkson et al., in order to break the enterohepatic circulation and thus increase the excretion rate of MeHg [62]. Intestinal demethylation may contribute significantly to increase fecal excretion, as Hg^{2+} is not reabsorbed via enterohepatic circulation to the same degree as MeHg.

Chemistry

Interaction with sulfhydryl groups

MeHg has a strong affinity for SH-groups and the log K is in the order of 15–23 [63]. Although the high affinity, there is a very rapid exchange of MeHg between SH-groups resulting in a very rapid redistribution of MeHg when new SH-groups become available

[64]. As SH-groups as well as disulfide bridges are abundant in proteins, MeHg will find molecular targets at many places throughout the body. These binding properties will contribute to the rather uniform distribution throughout the body that can be observed after long-term exposure.

Interaction with complexing agents

Chelating agents that can be clinically useful for mercury compounds contain one or two SH-groups. As mentioned before, mercury has a high affinity for SH-groups and mercury redistributes easily when new SH-groups become available. Thus, the efficiency of a SH-chelating agent depends on binding properties of the chelating agent compared to the biological SH-groups present. For clinical use the chelating agent needs to be water-soluble in order to facilitate excretion in urine. If the complex is lipid soluble it may cause a redistribution of mercury that is not beneficial to the patients. The possible use of chelating agents for the treatment of mercury intoxications has recently been reviewed by Guzzi and La Porta [43]. The first line drug suggested by WHO [10] for patients intoxicated with inorganic mercury is DMPS (2,3-dimercapto-1-propoane sulfonic acid). Other chelating compounds that can be used clinically are DMSA (2,3-dimercapto-succinic acid), D-penicillamine, BAL (British anti Lewisite) and NAC (N-acetyl cysteine). Questions have been raised as to the usefulness of DMSA as this compound may actually increase cellular uptake of MeHg – although without inflicting damage as measured by microtubule integrity [65].

Dietary selenium (Se)

Selenium (Se), is an essential trace element known to reduce and even prevent MeHg toxicity [66,67]. The mercury binding affinity for Se ($\log K$ 10^{45}) is a million times higher than its affinity for sulfur ($\log K$ 10^{39}) in analogous forms [68]. Several studies have shown that Se may offer protective effect towards mercury induced toxicity through several mechanisms including:

- Sequestration of Hg [69,70]
- Antioxidative effect [71,72]
- GSH synthesis [73]
- Increased GSH peroxidase (GPx) activity [74]
- High selenoprotein levels [75]
- Increased demethylation [76].

In addition, MeHg toxicity does not appear to occur when Se is present in molar excess of Hg in tissues [75].

Data from Ralston & Raymond indicates that Purkinje cells in the cerebellum and pyramidal cells of the hippocampus contain high concentration of selenoprotein W [77]. The presence of high selenoprotein content may therefore be an intracellular source of Se that in turn may contribute to sequestering of mercury and thus have a protective effect in Purkinje cells after MeHg-induced toxicity.

The toxic effects we observe on important biochemical processes are dependent on the effective concentration present at that site as well as the biochemical "capacity" available to the cell for that particular process. Then obviously, any difference in intracellular ability to bind mercury at sites where it does not cause any cellular harm will reduce the mercury dose present at the critical sites. Thus, the differences between cells e.g. in their content of selenoporteins may become a very important aspect for further understanding the issue of cellular specificity of MeHg neurotoxicity. It may also help us understand the delay in the onset of symptoms as this may occur when all the mercury binding capacity has been used.

Epidemiological studies

The Minamata and Iraqi epidemic poisonings

There have been two major human disasters of massive MeHg poisoning. The first took place in Japan from the late 1940-ies where a chemical factory released MeHg as a byproduct of their acetaldehyde production into the Minamata Bay. The release continued until 1968 and thus people were exposed for up to 20 years through the consumption of contaminated fish and other sea products. The estimated exposed population is around 200,000 people. Some 17,000 residents have claimed to be certified victims of the disaster and 2264 have so far been certified. Fish is the primary protein source in rural Japan. Adults were found to develop a range of neurological problems including blurred vision, hearing impairment, olfactory and gustatory disturbances, ataxic gait, and clumsiness of the hands, dysarthria as well as somatosensory and psychiatric disorders. In cases of fetal exposure, serious disturbances in mental and motor developments were observed. Patients had significant impairments in chewing, swallowing, speech, gait, other coordination and involuntary movement. These impairments were always bilateral. Pathological investigation of the affected brain, showed a loss of neurons in granular layer of cerebellum as well as loss of granular cells in affected parts of cortex like the somatosensory, visual and auditory area. In the affected fetal brains, the pathological changes were more widespread and diffused compared to the adult brain. The Minamata epidemic has recently been reviewed by Ekino et al. [78] as well as by Eto [79].

The second major disaster of epidemic MeHg poisoning occurred in rural Iraq during the winter of 1971–1972 and has been documented by Bakir et al. [61]. It has been estimated that at least 40,000 persons may have been poisoned while some 6000 cases were hospitalized. The cause of this outbreak was homemade bread made from seed grain treated with organic mercury compounds including methyl- and ethylmercury. Due to the latency period of MeHg neurotoxicity, the victims of the Iraqi disaster experienced no symptoms during the period of bread consumption. The first symptoms to occur were usually parasthesia, which was rapidly succeeded by more severe symptoms like ataxia, dysarthria and constriction of vision. These are clinical effects similar to that observed by Hunter et al. [49,50] and represent acute exposure at high dose. The University of Rochester (NY, USA) under the leadership of Professor T.W. Clarkson was able to undertake a large study of the Iraq epidemic and thanks to this effort we have a large body of data available on blood and hair samples. This has been an important basis in establishing the relation between biological indicators (mercury in blood/urine/hair) and the occurrence of symptoms. The Rochester group continued their work on populations with continuous and low exposure in other parts of the world. Their extensive studies have been summarized by Myers et al. [80].

Low level MeHg exposure through diet

The primary source of MeHg for long-term and low level exposure is fish. All forms of mercury may be converted to MeHg by bottom sediment microorganisms in the aquatic environment. MeHg is then accumulated in the food chain and by the rule of thumb; the larger and older species will contain the highest concentration of MeHg. The environmental levels of MeHg will depend on the local situation, as some aquatic environments are the recipients of mercury from the industrial waste while others reflects the global cycle of mercury, where we assume that roughly 50% is from natural sources [81]. Epidemiological studies in Canada, Peru, Samoa and the Mediterranean have failed to show any adverse effects related to MeHg consumption via seafood although increased blood or hair levels have been occasionally found as reviewed by WHO [10,82]. However, the main interest for MeHg in fish has been the possible developmental effects

caused by prenatal exposure. There are three large studies that have received most attention, as they have included a large number of mother–infant pairs:

- New Zealand study [83]
- The Faros Island in the North Sea [84]
- Seychelles Islands in the Indian Ocean [85]

These studies together with the data from Iraq have been used to determine safe levels for the critical population, pregnant women, towards exposure to MeHg via fish consumption. There are some significant differences between these studies, both in their design and outcome. The New Zealand study compared maternal hair levels of mercury during pregnancy with IQ, language development and motor skills at the age of 6 years. The poorer scores were associated with hair levels at 13–15 ppm during pregnancy. In the Faroe Islands, the main source of MeHg is from whale meat and there is a concomitant intake of poly-chlorinated biphenyls as well. Samples of cord blood and maternal hair were also collected and the offspring was examined during the first year of life as well as at the age of seven. At the age of 7 a comprehensive battery of neurological and neuropsychological tests was performed. In the Seychelles, maternal hair samples were collected during pregnancy and correlated to several tests of neurology, IQ and developmental milestones up to 9 years of age, without finding any convincing evidence of adverse effects on child development related to prenatal exposure to MeHg from ocean fish. A detailed discussion of the outcome of MeHg exposure via fish consumption is beyond the scope of this review and the reader is referred to the review of these studies by Clarkson and Magos [2].

Any restriction on the consumption of fish should only be done with due consideration of the beneficial effects that fish has on human health – in particular on the developing brain. Daniels et al. [86] studied more than 7000 children and was able to demonstrate that fish intake by the mother and the young child gave a higher developmental score. A panel organized by the Harvard Center for Risk Assessment reviewed the risk involved with MeHg in fish and determined that regulatory agencies should carefully consider the impact of any regulation on the fish intake by pregnant women and the population in general, as a decrease in fish consumption may cause a net negative effect on public health [87–89]. It should be noted that some of the nutrients present in fish, e.g. selenium and omega-3 fatty acids may enhance brain development whereas others may reduce the toxic effects of MeHg [44,90].

Patients with glutathione synthesis deficiency

With respect to GSH deficiency, there is remarkable report available on a patient from Oslo (Norway) with an inborn error of GSH synthesis. The patient had been mentally retarded since infancy including signs and symptoms similar to those found in the Minamata-disease patients [91]. The patient was diagnosed as having a generalized GSH deficiency and 5-oxoprolinuria and had been treated with bicarbonate in order to control his metabolic acidosis. Post mortem examination revealed selective atrophy of the cerebellar granule layer, focal lesions in the right frontoparietal cortex, visual cortex and thalamus. The major clinical symptoms as well as the brain lesions resembled MeHg intoxication as demonstrated e.g. in the Minamata patients. However, it is not likely that the patient was poisoned by MeHg as the brain mercury levels at the time of autopsy were in the normal range. It is a well established fact that MeHg can cause a reduction in brain GSH and neurological symptoms have been reported also for other patients with inborn errors of GSH synthetase. However, post mortem pathology has not been performed on other patients as reviewed by Njalsson and Norgren [92].

Pathological changes

The central nervous system is the critical organ in primates while in rodents, damage is seen in kidney and peripheral nerves, at lower doses than those that affect brain [93]. The first morphological changes seen in the rat and rabbit are located to the dorsal root ganglia and at higher concentrations, effects are also observed in the cerebellum and the brain stem [94–96]. In the cat, Charbonneau et al. [97] showed that changes are first observed in the cerebellum where granule cells degenerate followed by the degeneration of cerebellar Purkinje cells as well as changes in the occipital, parietal and temporal cortex. However, in primates – consistently across species – changes are observed in the cerebellar granule cells as well as in the visual cortex [98–100].

This issue of susceptibility of granule cells towards MeHg exposure has previously been reviewed by Fonnum and Lock [34]. The lack of MeHg effect in the Purkinje cells remains puzzling as these cells accumulate as much or more MeHg compared to the cerebellar granule cells [101–103]. However, we should keep in mind that there are considerable technical challenges in doing such studies of MeHg cellular distribution.

Mechanisms of action

For excellent reviews on possible mechanisms of cellular specificity of neurotoxic compounds the reader is referred to reviews by Fonnum and Lock [34] on cerebellum, Philbert et al. [36] on the central nervous system and Fonnum and Lock [35] on cerebellar granule cells.

Hg^{2+} as the ultimate toxic compound after MeHg exposure?

Before we examine the molecular and cellular effects of MeHg in nervous tissue there is one issue that should be addressed – can Hg^{2+} be the ultimate toxic compound responsible for the neurotoxicology of MeHg rather than MeHg itself?

Hargreaves et al. [104] suggested that Hg^{2+} may play such a role after MeHg exposure and that Hg^{2+} present in neurons is the result of MeHg overload in glial cells. Tiffany-Castiglioni and Qian have provided a review of this proposal [60]. Using the silver staining method described by Pihl [105], Hargreaves et al. [104] reported that mercury during the latent phase was observed in glial cells and during the symptomatic period in the neurons. This formed the basis for the proposal that MeHg was demethylated in glial cells and mercury was then transported to neurons with subsequent development of neurotoxicity. This way the selection of neurons to be become damaged could be ascribed to their neighboring glial cells being efficient in demethylating MeHg. The slow process of demethylation and transfer of mercury from glial to neuronal cells could explain the delay in the onset of symptoms.

Magos and Clarkson [106] presented a method by which total and inorganic mercury could be determined in the same biological sample. This method was used by Syversen [107] to determine total mercury and Hg^{2+} in subcellular fractions of rat brains after a single intravenous dose of ^{203}Hg labeled MeHgCl or $HgCl_2$. The data showed that Hg^{2+} in brain after MeHg was about 20 times higher compared to a similar dose of $HgCl_2$. This confirms that the demethylation process is active in brain tissue and that it produces more intracellular Hg^{2+} than what is taken up through the blood–brain barrier. The peak brain concentration of Hg^{2+} occurred one day after $HgCl_2$ exposure compared to 8 days after MeHg exposure.

Garman et al. [108] gave ^{203}Hg labeled MeHg by stomach tube to *Macacas* and examined the brains by histopathology and autoradiography. The autoradiography was performed by examining sections treated with a photographic silver emulsion. However, a note at the end of the paper reveals that the autoradiography does not show the

isotope but rather the Hg–Ag complex being formed in the emulsion. Such a complex can only be formed between Hg^{2+} and Ag, and not between MeHg and Ag. Most of the label (representing Hg^{2+}) observed was found in the glial cells and not in the neurons. Sakai et al. [109] carried out similar silver staining on brain sections from Minamata victims and found that the bulk of label was found in glial cells although Hg–Ag grains were found in most of the cerebellar neurons as well – again it should be pointed out that this represent inorganic mercury rather than total mercury.

Magos et al. [56] compared the neurotoxicology of MeHg and ethylmercury. The Hg^{2+} levels after ethylmercury were higher than after MeHg while granular layer damage was seen only after MeHg exposure and it was concluded that Hg^{2+} or the demethylation process could not be the primary agent responsible for alkyl-Hg neurotoxicity. Moreover, histochemical evidence of silver impregnated preparation did not show any staining over the granule cells. The authors point out that the silver impregnation methods will detect only the inorganic Hg^{2+} and not the alkyl compounds in these preparations.

Charleston et al. [110] performed a study where monkeys were exposed to low levels of MeHg for extended periods. The deposits of inorganic Hg were determined by the silver impregnation method as referred to above. The largest deposits were seen in astrocytes and microglia while very little, if any, deposits were observed in neurons after 6 months. In animals exposed for 12 months, some deposits were found in neurons and even more deposits were seen after 18 months. However, in all cases more deposits were found in glial cells compared to neurons. In a further report on the same animals [111], the authors suggest that the proximal toxic form of MeHg is Hg^{2+} acting through astrocyte or microglial populations.

Vahter et al. [112] suggested that latency periods associated with MeHg exposure might be due to the slow production and accumulation of Hg^{2+} in the brain over periods of months. However, as reported by Weiss et al. [113], one would expect the buildup of inorganic Hg to be faster at higher levels of MeHg exposure, resulting in a shorter latency period when the dose increases. Magos et al. [56] compared methyl- and ethylmercury toxicity including measuring the release of Hg^{2+} and found that ethylmercury produce more Hg^{2+} while being less toxic compared to MeHg. Thus, his conclusions does not support the key role of Hg^{2+} as suggested by Vahter et al. [112]. Burbacher et al. [114] reported on the disposition of mercury in infant monkeys injected intramuscularly with ethylmercury in the form of thimerosal in comparison with a second group of monkeys dosed orally with a MeHg compound. The study intended to mimic the immunization schedule in human neonates. Corroborating Magos's et al. [56] conclusions in the rat experimental model, Burbacher et al. [114] also reported that levels of organic Hg were lower in the brains of infant monkeys exposed to thimerosal compared to those exposed orally to MeHg. The brain half-times (defined as the time it takes for the brain level of Hg to decrease by half) also differed. The clearance half-times for organic Hg in the brain were 58 days on average after oral MeHg exposure versus 14 days after injection of ethylmercury.

Several studies by [110–112,115] in adult *Macaca fascicularis* monkeys addressed the pharmacokinetics of MeHg demethylation in the brain. Higher Hg^{2+} concentrations were noted in the brains of the monkeys 6 months after MeHg exposure had ended, whereas organic mercury had cleared from the brain. The estimated half-time of organic mercury of 37 days in the brain of these adult monkeys was consistent across various brain regions and was analogous to the brain half-time of MeHg in the infant monkeys reported by Burbacher et al. [114]. The estimated half-time of Hg^{2+} in the brain in the same adult monkeys varied greatly across brain regions, being in the range of 227–540 days. The concentrations of Hg^{2+} also varied significantly across brain regions, in some areas remaining unchanged (thalamus) while doubling in others (pituitary) 6 months after exposure to MeHg had ceased [112]. Stereologic and autometallographic studies indicated that Hg^{2+} persisted in the monkeys' brains and it was associated with a significant increase in the number of microglia and a decline in the number of astrocytes. It is noteworthy that these effects were seen 6 months after cessation of chronic exposure to MeHg [110,111,115], and that the effects in the adults were associated with brain Hg^{2+} levels approximately five times higher than those observed by Burbacher et al. [114] in the infant monkeys vaccinated with ethylmercury.

Several studies have shown equipotent toxicity for MeHg and ethylmercury in tissue culture experiments while Hg^{2+} has proven to be less toxic than MeHg in both vertebrate and invertebrate neuronal cell model systems. For example, MeHg is 6–40 times more toxic than Hg^{2+} in PC12 pheochromocytoma cells, as measured by viability [116,117]. While Hg^{2+} and MeHg show nearly equivalent cytotoxicity in a mosquito derived cell line, MeHg is approximately 20 times more potent than Hg^{2+} in inhibition of proliferation in these cells [118]. In addition, MeHg is 10 times more potent than Hg^{2+} in depressing nerve fiber growth in chick dorsal root ganglia explants [119]. Altogether, these studies refute the notion that Hg^{2+} in a number of model systems ranging from invertebrate animals to mammalian systems is the proximate source of damage associated with exposure to MeHg as well as ethylmercury. These studies should however be cautiously interpreted, as they all utilize the artificial conditions of tissue culture.

Thus, although there are several studies which may support the proposal that Hg^{2+} is the proximal toxic agent of MeHg, the literature also contain many reports using a range of biological models indicating that Hg^{2+} cannot play such a role. We therefore conclude that Hg^{2+} derived from demethylation of MeHg is not the mechanism for the development of neurological effects during the chronic latent phase of exposure. Clarkson and Magos [2] introduced the viewpoint that the demethylation of MeHg might be part of the defensive role of glial cells – again demonstrating the important intercellular dependence between neurons and glial cells.

Interaction with sulfhydryl groups

We have earlier pointed out the importance of SH-groups for the binding of mercury that in turn will reduce the "free" concentration of mercury available to interact with sensitive cellular binding sites. Purkinje cells are very rich in SH-groups [120] and these may act as inert sites and offer a quenching effect to Hg's action inside the cell, rendering a higher Hg tolerance [121,122]. In astrocytes, treatment with MeHg has been associated with greater depletion of GSH in cerebellum as compared to cortex [123]. The higher content of GSH in cortical astrocytes as compared to cerebellar astrocytes accounted for the increased ROS production in cerebellar astrocytes. However, no differences in the cellular distribution of GSH have been reported between granule and Purkinje cells [124].

After MeHg exposure, metallothionein (MT) was detected mainly in Bergmann glial cells, Purkinje cells, astrocytes and glial cells of white matter whereas it was not detected in granule cells [103]. Metallothioneins are composed of some 62 amino acids, of which 20 is cysteine, giving the protein a very high capacity for chelating metals that binds to SH-groups. Thus, metallothioneins represent an important factor in reducing the binding of mercury to functionally critical SH-groups.

These are important factors with respect to differential effects in neurons as well as the question of indirect effects on neurons as a result of effects initiated in glial cells. In summary, the content of SH-groups may influence the MeHg-induced toxicity, and partially explain the differential sensitivity between the cell types as demonstrated by the results on e.g. macromolecular synthesis [125–127].

Effects on DNA, RNA and protein synthesis

MeHg interferes with macromolcular synthesis of DNA, RNA and protein. The mechanism is not known, but we may assume that binding to important SH-groups plays an important part in these changes causing e.g. secondary changes in DNA and RNA, as well as conformational changes in ribosomal proteins [128]. Early studies of MeHg induced reduction of protein synthesis include in vivo studies by Yoshino et al. [129] and Cavanagh and Chen [130] as well as in vitro studies by Syversen [131]. Degenerative changes in rough endoplasmic reticulum were observed by Jacobs et al. [95] and Syversen et al. [132] and these morphological observations confirms the reported biochemical changes. The only report on an increased brain synthesis of DNA, RNA and protein is in a study from Brubaker et al. [133]. Syversen [125] was able to isolate neuron-enriched fractions from cerebellum and cerebral corticles from rats poisoned by MeHg. In vivo protein synthesis was reduced in cerebellar granule and Purkinje neurons as well as in cortical neurons. Interestingly, protein synthesis recovered in two cell types, but not in the cerebellar granule cells. These data suggest that there could be important macromolecular repair mechanisms present in some cells and not in others, and that the capacity for repair of the initial insult might be an important factor in selection of which cells would degenerate. The same principle of cellular selection due to limited repair capacity was advanced also by Jacobs et al. [95] and Sarafian et al. [134].

The importance of reactive oxygen species and glutathione

One of the major mechanisms behind MeHg-induced toxicity is via generation of reactive oxygen species (ROS) and depletion of GSH [135]. The balance between the oxidative and reductive cellular processes is critical for MeHg-induced neurotoxicity. Decreased GSH levels usually parallel increased ROS levels after MeHg exposure [136–139]. However, an epidemiological study associating oxidative stress and MeHg exposure [140] has shown both an increase and a decrease in GSH levels with increased total Hg levels. This suggests that MeHg can increase ROS that may either inhibit GSH levels or initiate an adaptive response to oxidative stress by increasing GSH levels.

Additionally, the induction of an increased synthesis of GSH [123,141,142] has been reported to be neuroprotective against MeHg-induced neurotoxicity. Important components available from seafood such as fatty acids, selenium and antioxidants have also been shown to protect against MeHg-induced ROS [71,143,144]. In the brain, the neuronal–glial interactions seem to play an important role in MeHg neurotoxicity. The astrocytes supply neurons with various factors e.g. cysteine, glycine and glutamine to neurons for GSH synthesis [145]. The increased amount of GSH in cortical, as compared to cerebellar astrocytes has been reported to account for the increased MeHg-induced ROS production in cerebellar astrocytes [123]. In summary, changes in intracellular MeHg content with GSH modulation may provide an explanation for the increased susceptibility of certain cell types towards MeHg-induced oxidative stress [123,142].

Interaction with microtubules

Neurons are highly specialized cells with unique cellular architecture including elongated processes; the axons and dendrites. Microtubules are part of the cytoskeleton that maintains the cellular three-dimensional structure and are prime structural components required for intracellular transport. Microtubules are polymers of tubulin and attached to their surface are a range of microtubule associated proteins or MAPs. Microtubules play a crucial role in a variety of cellular events, including axonal and dendritic transport [146,147], neuronal growth and differentiation [148,149], maintaining structure [150] and facilitating cellular migration [151]. Each tubulin monomer has at least 13 free SH-groups. When MeHg or Hg^{2+} binds to microtubular SH-groups the microtubules will depolymerize resulting in their disassembly, thereby causing neuronal degeneration [65,151–153]. Microtubules contain α and β-tubulin and exhibit micro heterogeneity and compartmentalization in neurons [154,155] for e.g. MAPs, which are distributed throughout the axons and dendrites. In the axonal region, Purkinje cells contain a high content of MAP1a and MAP1b. However, a low MAP2a and MAP2b content is found in Purkinje cell spiny dendrites [156]. The Purkinje cell dendritic tree is tightly packed and occupies a much smaller overall space when compared with a neocortical pyramidal cell. Such an arrangement allows the Purkinje cell to require a much small number of microtubules, which offers a metabolic advantage and may also be advantageous in case of MeHg toxicity that causes toxic effects via disruption of microtubule dynamics.

Mercury and membrane transport

Kerper et al. [157] used bovine brain capillary endothelial cells and was able to show that the uptake of MeHg was dependent (in part) on the MeHg-L-cysteine complex while the release of MeHg into brain interstitial space was mediated by GSH complex and that this transport was independent of ATP. MeHg-S-cysteine complex behaves as a mimic of the neutral amino acid, methionine, which is a substrate of the neutral amino acid transporter system L [157]. This mimicry has been reported to be responsible for a large part of MeHg uptake into the cells. The uptake for MeHg into the cells can be active, energy dependent (e.g. MeHg-cysteine) as well as passive (e.g. MeHgCl in cell cultures) depending on the Hg species [59,158,159]. Recently, it has been shown that MeHg inhibits ASCT2 neutral amino acid transporter [160]. The ASCT2 is an ASC (alanine-, serine-, cysteine-preferring) neutral amino acid exchanger which plays a physiological role in the transport of amino acid substrates such as L-serine, L-glutamine, L-cysteine and/or L-glutamate and D-serine [161], thereby playing an important role in regulating the intracellular GSH levels. In case of energy failure, ASCT2 takes on an important role of clearing excitotoxic L-glutamate levels [162]. The ASCT2 transporter is absent in astrocytes and in case of neurons, it is present only in dendrites and not neuronal cell bodies. However, in Purkinje cells it is also present in the cell body as well [161]. These properties of the neuronal ASCT2 firstly indicate that it may be an important regulator of neuronal antioxidant strength. Moreover, in case of MeHg poisoning, it can be speculated that ASCT2 may play an important role in clearing excitotoxic L-glutamate levels from the extracellular space more efficiently in Purkinje cells when compared to e.g. cerebellar granule cells. In fact, in case of MeHg toxicity, the inhibition of the glutamine/glutamine antiport catalyzed by the transporter has been reported [160].

Understanding how MeHg may cross biological membranes is important for our understanding of the protective capacity of both the placenta and the blood–brain barrier. Further, it may also have implications for the mechanism of mercury deposition in hair. Hair is a valuable, non-invasive, way to sample for biological monitoring. MeHg deposited in hair is the result of MeHg accumulated by the cells in the hair follicle, and if the transport mechanism into these cells is through MeHg-cysteine complex, then MeHg in hair reflects the transportable MeHg species in blood. It follows from this that MeHg in hair then would be a good indicator for MeHg being available for brain uptake. The usefulness of mercury in hair has been very well demonstrated in large scale poisonings incidents like Iraq [61] and with modern instruments available today, we can even do longitudinal trace element concentrations in a single strand of hair [163].

Methylmercury may induce exitotoxicity

Neuronal dysfunction has been proposed to be secondary to disturbances in astrocytes [164]. As referred to by Aschner and

Syversen [165], astrocytes accumulate MeHg, where among other effects it potently inhibits astrocytic glutamate uptake and stimulates its efflux [166,167]. This causes an increase in glutamate levels in the extracellular fluid, which may cause exitotoxic injury towards neurons. There are less astrocytes in the cerebellum than in the cerebral cortex, and this may imply two things. Firstly, in the cerebellum, a decreased ability to maintain the extracellular environment under stress would leave the neurons more vulnerable to MeHg's effects compared with neurons in the cerebral cortex. Secondly, if the mechanism of damage is associated with excitotoxicity due to astrocytic failure in maintaining the extracellular milieu, one would expect the damage to be most extensive in areas with higher astrocyte density. This does not appear to be the case. However, the sparing of Purkinje cells and the sensitivity of granule cells in the cerebellum cannot be attributed (solely) to the vulnerability of cerebellar astrocytes to MeHg, for under these circumstances, both Purkinje and granule cells would be expected to respond through the excitotoxicity induced by extracellular glutamate. These aspects may imply that the astrocytes may not be the primary target, but rather function as an aggravator of the primary effect on neurons. In addition, NMDA-type ionotropic receptors have been demonstrated only in neurons and are absent in glial cells [168]. In case of neurons, a heterogeneous regional and cellular expression has been observed with different subunits of the NMDA receptor. In human cerebellum, Purkinje cells are reported to exhibit significant higher expression of NMDAR1 subunit as compared to granule cells. The granule cells, on the other hand express higher NMDAR2C subunit expression when compared with Purkinje cells [169]. In general higher expression of NMDA-receptor subunits and a higher NMDAR1 to NMDAR2 ratio is observed in Purkinje cells as compared to granule cells. However, high levels of NMDA-sensitive [^{3}H]glutamate binding have been found in the granular layer and low levels in the Purkinje cell layer [170]. The question regarding the functional roles of these receptor subunits in both the cell types together with lower glutamate binding and higher receptor density found in Purkinje cells remains unresolved.

The cerebellum as a critical organ

We have made repeated comments on the differential effects of MeHg on granule cells compared the larger Purkinje cells in the cerebellum. We have also noted that in the cerebrum some of the major pathological changes occur in granule cells. Thus, it may seem that cytoplasmic volume might be one important factor in how cells become targets of permanent damage from MeHg. The other major issue is the relation between the neurons and the glial cells. For the sake of simplicity let us now use the background generated above on biochemistry and pathology and examine these questions using the cerebellum as our model area of the brain.

Cerebellar characteristics

The cerebellum is formed out of four main types of neurons: granule neurons, Purkinje neurons and two types of inhibitory interneurons; Golgi cells and the stellate/basket cells [171]. The cerebellum is divided into three major layers; the granular, Purkinje cell and molecular layers. The granular layer lies deepest and contains a very large number of densely packed inter-neurons known as granule cells. The Purkinje cell layer consists of a one-cell-thick layer of the cell bodies of the Purkinje cells. The molecular layer contains a very high density of unmyelinated axons, known as parallel fibers. The Purkinje cells are formed as one of the first neurons in the cerebellar plate whereas granule cells are derived from the external germinal layer. Granule cells migrate through first the molecular layer and then through the Purkinje cell layer to their adult location to form the internal granular layer. The information reaches the Purkinje cells via the granule cells where axons of the granule cells extended into the molecular layer form the parallel fibers, which make excitatory synapses onto the spines of the Purkinje cell dendrites.

Granule cells have a density of approximately 80 cells per 0.1 mm^3 and are extremely small cells (4–6 μm width) with astrocytes being rarely found in their vicinity. They have a high nuclear to cytoplasmic volume ratio. The total number of granule cells is reported to be 9.2×10^7 [172,173] and the number of Purkinje cells is reported to range from 2.78×10^5 [172] to 5.5×10^5 [174]. In addition, it has been reported that there are about 274 granule cells for each Purkinje cell [175].

Small size and scarce cytoplasm – lets make some speculations

Granule cells are smaller in size and their limited volume of cytoplasm might represent an important clue towards understanding their vulnerability towards MeHg-induced damage. It means that there is less binding sites for mercury and thus critical concentration at sensitive sites might be reached earlier during exposure. For the cytoskeletal proteins, primarily the microtubules, the distance between the outer cell membrane and the nucleus is very short and we may speculate that even limited depolymerization of the microtubules will have a profound effect on cellular metabolism and mitochondrial activity. During MeHg exposure, there will be an increased demand to replace proteins through protein synthesis that in turn require efficient mitochondrial processes while maintaining the appropriate balance of intracellular GSH. This requires not only enzymes but also adequate levels of intracellular selenium, as several of these enzymes are selenoproteins. As we have pointed out mercury has a much higher affinity for selenium compared to sulfur – and we may have a situation where selenium is extracted from the selenoproteins and used to sequester mercury instead. Thus, as illustrated here; there is not one mechanism of action for mercury but rather a range of simultaneous processes going on that in sum puts cells with a small volume cytoplasm at risk.

A mechanism or rather, a train of events, to explain the cellular selectivity of MeHg should also incorporate the observed delay period between exposure and the onset of symptoms. First of all, we know that there are a lot of granule cells in the cerebellum and we know that throughout the brain there is considerable redundancy which means that if damage to an important structure occurs, the system has some reserve capacity in order to ensure that critical neuronal network performance can be upheld. However, such redundancy has its limits and when that limit is reached there is a breakdown of the larger network. It takes time for the mercury to exhaust the intracellular defense mechanisms – even in small neurons – and this have to occur in some number of neurons in order for the network system to fail – but once that happen – the symptoms will develop very fast.

Conclusions and future research needs

The cellular specificity and the delay in onset of symptoms have been major mysteries of MeHg neurotoxicity. It this review we have tried to support the following ideas regarding these mysteries:

- Neurotoxicity is caused by MeHg itself and not demethylated Hg^{2+} although demethylation takes place in the brain.
- The selective damage in the brain reflects cellular defense mechanisms that become exhausted.
- Key elements in the cellular defense is the availability of selenium and SH-groups that can chelate mercury.
- Cells having a small cytoplasmic volume are more at risk for MeHg toxicity than larger cells.

- The delay in onset of symptoms may be a combination of cellular repair capacity of individual cells and neuronal network redundancy.

However, among the mysteries that still remain to be investigated is why the delay in onset of symptoms is independent of the dose.

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