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Accumulation of Methylmercury and Inorganic Mercury in the Brain

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ABSTRACT

Differences in metabolism between different mercury species are well recognized. Conclusions that only a minor demethylation of methylmercury takes place in the brain are based primarily on results from short term studies. Results from a number of studies on humans exposed for many years to methylmercury have shown high concentrations of inorganic mercury in the brain in relation to total mercury. Similar evidence is available from studies on monkeys exposed for several years to methylmercury. The results indicate that a significant accumulation of inorganic mercury takes place with time despite the fact that the demethylation rate is slow. Differences in biological halftimes between different mercury species will explain the results. Some data do still need confirmation using different analytical methods. There is reason to believe that the one-compartment model for methyl mercury cannot be used without reservations. Inorganic mercury has a complicated metabolism. After exposure to metallic mercury vapor, inorganic mercury, probably bound to selenium, accumulates in the brain. A fraction of the mercury is excreted, with a long biological halftime. Studies on rats and monkeys indicate that inorganic mercury penetrates the blood-brain barrier only to a very limited extent.

Index Entries: Methylmercury; inorganic mercury; demethylation; biotransformation; biological halftime; brain.

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INTRODUCTION

After absorption, both metallic mercury vapor and methylmercury easily penetrate the blood-brain barrier; however, this is not the case for divalent inorganic mercury. Metallic mercury vapor is rapidly oxidized to ionic mercury but it remains as vapor in the blood for a short time, long enough for part of it to penetrate the blood-brain barrier and then, after oxidation, accumulate in the brain. In the WHO criteria document of 1976 (*1*) it was concluded that methylmercury could be partly converted to inorganic mercury in mammals. The fraction of total mercury present in tissues as inorganic mercury depends on the duration of exposure to methylmercury and the time after cessation of exposure.

Clarkson et al. (*2*) have reviewed available data, including those from the Iraqi outbreak. The kidneys usually contained the highest fraction of Hg^{++}. In the victims of the Iraq epidemic, where the people had been exposed for about 2 mo to high oral doses, the percentage of inorganic mercury in whole blood was 7%, in plasma 22%, in breast milk 39%, in liver 16–40%, and in urine 73%. Quantitative data from human brains were not available. In studies over some weeks on squirrel monkeys, Berlin et al. (*3*) found more than 95% of mercury in the brain in the form of MeHg. He found it unlikely (*4*) for biotransformation to occur in the brain. Clarkson et al. (*1*) do not exclude that a slow demethylation rate may produce a relatively high concentration of inorganic mercury in the brain in people with low exposures.

The accumulation and excretion of methylmercury has been considered to follow a one-compartment model (*1,2,5*). We will discuss and present data indicating that the situation is not so simple.

EPIDEMIOLOGICAL AND CLINICAL EVIDENCE

The evidence from the Iraqi outbreak, referred to above, indicates the possibility of a rather complicated metabolism owing to biotransformation in several organs. This is now supported by data from brain tissues from a number of fatal cases following the Minamata outbreak in 1956. Takizawa, in 1986 (*6*), reported total mercury and methylmercury concentrations in brain of about 30 human autopsy cases who had died from 20–100 d to 18 y after onset of symptoms of methylmercury poisoning. Total mercury content was measured by flameless atomic absorption spectrophotometry, and methylmercury by electron capture gas-liquid chromatography (*6,7*). The total mercury content in what they classified as "acute" cases (autopsy < 100 d after onset of symptoms) was 8.8–21.4 mg/kg and the concentrations of methylmercury was 1.85–8.42 mg Hg/kg wet weight. The corresponding brain concentrations for the "chronic" cases were 0.35–5.29 mg Hg/kg for total mercury and 0.31–1.02 mg Hg/kg for methylmercury. On average, only 28% of the mercury was reported

present as MeHg in the acute cases and 17% in the chronic cases. If it is assumed that the difference is inorganic mercury, the concentrations are very high, similar to what has been observed after toxic exposure to metallic mercury vapor (4). Data were also presented on residents near Minamata Bay and a nonpolluted area. Our best estimate from these data shows that only 16% and 12%, respectively, of the total mercury was present as methylmercury.

The apparent difference between acute and chronic cases is of great interest. The fraction that remained as methylmercury was lower in the chronic cases than in the acute cases. Such a difference would be expected if there was an ongoing demethylation of methylmercury and if methylmercury is eliminated from the brain at a higher rate than inorganic mercury. Even if we still lack a detailed knowledge concerning the metabolism of inorganic mercury, there is accumulating evidence that part of the inorganic mercury in brain, endocrine organs, and the kidneys has a very long biological halftime, probably several years. This is in contrast to the short halftime, days or weeks, for the bulk of the mercury that has been demonstrated in tracer studies on humans (*8,9*).

From the early seventies there are reports of very high concentrations of mercury in different parts of the brain (*10–12*) several years after retirement. In a report by Kosta et al. 1975 (*12*) average levels of 0.70 mg Hg/kg wet wt were reported in brain tissue (6 cases), 27.1 mg Hg/kg in the pituitary gland (7 cases), 35.2 mg Hg/kg in the thyroid (8 cases), and 8.4 mg Hg/kg in the kidneys (8 cases). Nonexposed controls showed average levels of 0.0042 mg Hg/kg in brain tissue (5 cases), 0.040 mg Hg/kg in the pituitary gland (6 cases), 0.030 mg Hg/kg in the thyroid (16 cases), and 0.14 mg Hg/kg in the kidneys (7 cases). Evidence is also given that the fraction of mercury with a long biological halftime could be present as a mercury–selenium compound. Selenium and mercury concentrations in the brain were observed with a molar ratio 1:1.

A recent Swedish study of 7 dentists and one dental nurse by Nylander et al. (*Swedish Dental J.*, in press) found increased concentrations of mercury in pituitary gland, occipital lobe cortex, kidney cortex, and thyroid. Values of up to 4.0 mg/kg wet wt were observed in the pituitary gland, up to 0.3 mg/kg in the occipital lobe cortex, and up to 2.1 mg/kg in the kidney cortex. The two cases with the highest levels of Hg in the pituitary and occipital lobe cortex were 80 y old and had not been professionally active for about 15 y. In one of these cases levels of Hg in kidney and thyroid was analyzed and was 2.1 and 28.0 mg Hg/kg, respectively.

There are data from studies of the general population suggesting a substantial demethylation of MeHg in the brain. Kitamura et al. (*13*) found a ratio of MeHg/total Hg of only 15% examining 20 Japanese subjects from the general population where the average level of total mercury was about 100 μg/kg wet wt. In a Swedish study of 6 cases from the general population (*14*), Nylander et al. found that on an average 80% of

the mercury in the occipital lobe cortex was inorganic. In this study, the method of Magos was used. Total mercury was checked against neutron activation, and included the use of reference samples. One has to assume that part of the inorganic mercury was from mercury amalgam fillings, since there was a correlation between amalgam load and total mercury concentrations in the occipital lobe cortex within a group of 34 examined autopsies (*14*). Two out of the 6 cases on which speciation was carried out had no amalgam fillings, however. As for the Japanese data, amalgam could not possibly explain the inorganic fraction of mercury in the CNS, since the mercury levels were on an average 10 times higher than the Swedish (about 100 μg/kg wet wt compared to 10 μg/kg), probably owing to a higher consumption of fish contaminated with MeHg.

There are problems in interpreting some of the studies. In the important Japanese studies from Minamata the possibility of continued exposure has not been ruled out. No quality control data are presented. For example, it is possible that the recovery of methylmercury was incomplete even if the official Japanese methods were used and the recovery is reported to be complete after addition of MeHg. In the studies from Minamata, the tissues were stored in formaldehyde for a prolonged time. The lack of formal quality control is something that is not unique for the Japanese studies, but it may be more critical because completely different methods were used for analyzing total and organic mercury.

EVIDENCE FROM ANIMAL STUDIES

In studies on squirrel monkeys given oral doses of MeHg weekly for a number of weeks (*3*) the biotransformation to inorganic mercury was as follows: in the liver about 20% of the total mercury was inorganic, in the kidney 50%, in the bile 30–85%, but in the brain less than 5%. We now have data from long term studies on monkeys showing a different picture. Mottet and Burbacher (*15*) have summarized a long series of studies on the metabolism and toxicity of MeHg on monkeys (Macaca Fascicularies). The animals had been orally exposed daily to high but usually subtoxic levels of MeHg for a period of 2–3 y and sacrificed during the ongoing exposure. At the end of the exposure period we found on an average 18% (range: 10–33%) of the mercury in the brain cortex in inorganic form (*16*). The total mercury concentration varied between about 5,000–7,000 μg/kg wet wt. In monkeys that had been without mercury exposure for 0.5–2 y after the same treatment, the relative concentration of inorganic mercury was still higher, about 90% (range: 79–98%). The total mercury concentration was on an average 179 μg/kg (range: 52–314). A general model could not be established in the absence of data on the concentrations of inorganic and organic mercury in the brain at different time intervals during the accumulation and clearance phases. The long halftime of inorganic mercury in the brain is obvious, however.

The MeHg used for feeding the monkeys contained a 5% impurity of inorganic Hg, but this could not account for the high inorganic content found in the brains. The absorption of inorganic mercury via the gastrointestinal tract is low, approximately only about 5% (*17*). In rats given daily subcutaneous doses of mercuric chloride for six wk, only 0.01% of the absorbed dose of mercury was found in the brain, whereas about 3% of the absorbed dose was retained in the kidneys (*18*). A much higher penetration into the brain tissues has to be assumed to explain the high fraction of inorganic mercury observed in the monkey studies. This has been discussed in detail in the paper by Lind et al. (*16*). We have confirmed the low penetration into the CNS in studies where three Macaca monkeys have been given pure inorganic mercury. We have given mercuric chloride P.O. to one monkey for 3 mo. The occipital pole of the brain had a total mercury concentration of only 58 μg/kg wet wt (49 μg were inorganic mercury) despite high blood levels, 0.1–0.2 ppm total mercury and very high concentrations in the kidneys, 90,000 μg Hg/kg (about three times the concentration of total mercury in the MeHg experiments). In two other experiments, mercuric chloride was administered intravenously daily during 3 mo. The total mercury blood levels averaged from 0.7–1.0 ppm throughout the exposure period. Occipital pole total mercury levels were 45 and 52 μg/kg wet wt. Kidney cortex levels were 273,000 and 259,000 μg/kg wet wt.

CONCLUDING REMARKS

There are a number of questions that need to be answered. It would be important to carry out analyses of some of the CNS samples from Japan using other analytical methods and with stringent quality control. We plan to expose new series of monkeys to pure methylmercury and inorganic mercury, respectively, for different time periods and study the accumulation and clearance of the different forms of mercury at different time intervals after beginning and end of exposure. However, already there is good reason to believe that a one-compartment model does not adequately describe the metabolism of methylmercury. Its implications for interpreting dose-response relationships and for risk assessment are important. Further identification of the short and long term proximate toxic form of mercury and the specific sites of brain injury are basic to the investigation of the toxic mechanisms.

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