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Modulating effects of dietary fats on methylmercury toxicity and distribution in rats

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Abstract

Fish consumption is the most important source of human exposure to methylmercury (MeHg). Since fish is also a rich source of $n-3$ polyunsaturated fatty acids, this study was conducted to examine the effects of dietary fats on MeHg-induced acute toxicity in rats. Weanling male Sprague Dawley rats were administered semi-purified casein-based isocaloric diet containing soy oil, seal oil, docosahexaenoic acid (DHA), fish oil, or lard for 28 days. Rats were then gavaged with 0, 1, or 3 mg MeHg/kg body weight (BW) per day and fed the same diet for 14 consecutive days. On 43rd day of the experiment, rats were sacrificed and blood samples were collected and analyzed for hematology. Liver and spleen were removed, fixed, and examined for pathological changes. Blood, feces, liver, and brain were analyzed for total mercury and/or MeHg contents. Serum samples were analyzed for clinical markers of hepatic injury and immunoglobulin. Total mercury contents in all tissues measured increased with dose. Mercury excretion in feces increased with dose and duration of MeHg treatment. Both diets and MeHg showed significant effects and interacted significantly on many of the toxicological endpoints measured. Many of the effects of MeHg were diet-dependent. For example, in the rats fed the lard diet, 3 mg MeHg/kg BW significantly increased relative liver and spleen weight as compared with vehicle control; whereas in rats fed the fish oil, soy oil, seal oil, or DHA, this effect of MeHg was less obvious or absent, suggesting a protective effect of these diets. MeHg at 3 mg/kg BW significantly decreased serum albumin level in all except DHA dietary groups, implying a protection by the DHA diet on this parameter. Only in the lard dietary group, did 3 mg MeHg/kg BW significantly increase serum bilirubin level, indicating an enhancing effect of this diet on MeHg toxicity. MeHg suppressed the adaptive immune system and stimulated the innate immune system in rats in a diet-dependent fashion. The seal oil diet provided more resistance, while the fish oil diet rendered greater sensitivity to these effects of MeHg on the immune system. These results imply significant modulating effects of dietary fats on MeHg toxicity which may translate into more severe or protective clinical outcomes. Therefore, dietary fats are important factors to be considered in the risk assessment of MeHg exposure.

Keywords: Methylmercury; Acute toxicity; Diets; Dietary fats; Serum biochemistry; Hematology; Immune system; Pathology

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1. Introduction

Regular consumption of fish (one to two meals per week) is associated with substantial reduction in the risk of death from heart attacks, and is thus recommended by the American Heart Association (Anderson et al., 2004). Unfortunately, fish consumption is the most important source of human exposure to methylmercury (MeHg). In the Canadian North, levels of mercury (Hg) in the terrestrial freshwater and marine biota, especially ringed seal, have been reported to exceed the Health Canada consumer guideline (0.5 μg/g wet weight) (Jensen, 1997; Chan et al., 1995; Chan, 1998). One to two meals per week of some species can result in mercury ingestion exceeding the reference dose (0.1 μg/kg body weight) set by the United States Environmental Protection Agency (EPA) (Hightower, 2004). MeHg at high doses is neurotoxic to both humans and many animal species, including non-human primates (Mahaffey, 2004). At lower doses, MeHg produces neurodevelopmental toxicity in children, particularly when exposure occurs *in utero* (Harada, 1995; Mahaffey, 2004). An increasing number of studies also suggest that the cardiovascular system may be adversely affected by lower MeHg exposures than those currently associated with neurological and neurodevelopmental deficits (Mahaffey, 2004; Stern, 2005). Epidemiological studies in Finland suggest that mercury exposure increases the risk of myocardial infarction (Rissanen et al., 2000), and increased Hg levels accelerate the progression of atherosclerosis in the carotid artery (Salonen et al., 2000). In addition, prenatal exposure to MeHg as a result of maternal fish intake has been correlated with significant blood pressure elevations in 7-year-old children (Patrick, 2002). In light of these findings, the risks and benefits to human health of fish and marine mammal consumption have become a controversial issue.

Fish and marine mammals are important components of the Northern traditional diet, containing high concentrations of protein, selenium, and ω-3 fatty acids essential to human health. Dietary factors, such as selenium, zinc, cysteine, proteins, fats, fibers, and vitamins have been shown to modulate mercury toxicity (Chapman and Chan, 2000). It was reported that increased coconut oil in the diet increased whole-body retention of mercury in mice receiving a single oral dose of 5 μmol MeHgCl, whereas increased cod-liver oil in the diet did not (Højbjerg et al., 1992). An increase in dietary linoleic acid resulted in increased mortality in Japanese quail treated with 15 ppm MeHgCl (Kling and Soares, 1981). Japanese quail fed a tuna fish diet containing MeHg showed more prolonged survival than those fed a corn and soy diet containing similar levels of MeHg (Ganther and Sunde, 1974). Berntssen et al. (2004) found a higher fecal excretion, and lower tissue accumulation of MeHg and metallothionein induction in rats following exposure to MeHg-containing fish in comparison to MeHg added to the same matrix. These observations provide evidence for the importance of dietary proteins and fats in modulating MeHg toxicity. Fish oil, an important source of $n-3$ polyunsaturated fatty acid (PUFA) for Inuit and other fish consumers, is known to have anti-cancer (Li, 2003), anti-inflammatory (Simophoulos, 2002), and cardiovascular-protective (Carroll and Roth, 2002) effects. Randomized clinical trails have shown reduced mortality after myocardial infarction among patients assigned to diet rich in fatty fish or to fish oil supplements (Guallar et al., 2002). Lard, on the other hand, which is used in Inuit traditional cooking, has been associated with cancer and heart disease (Kesteloot et al., 1991; Reddy, 1987; Menotti et al., 1999). It is not clear, however, if, how, and why different types of dietary fats such as fish oil and lard, may have protective or enhancing effects on MeHg toxicity. It would be of significant health value for people at risk of MeHg intoxication to be able to make an informed choice in selecting a diet that would minimize MeHg toxicity. MeHg has been extensively studied for its renal, hepatic, neurological, and immunological toxicities (Bellinger et al., 2000). However, there is a lack of knowledge as to how these multi-targeted toxicities of MeHg can be alleviated or aggravated by dietary fats such as fish oil, lard, soy oil, and seal oil. We have therefore conducted a feeding study in rats to examine the effects of these fats on MeHg-mediated toxicity in potential target organs using a comprehensive set of toxicological parameters.

2. Materials and methods

2.1. Animals, diets, and treatments

All animal care and handling procedures conformed to the guidelines of the Canadian Council on Animal Care, and the experimental protocol was reviewed and approved by the Health Canada Ottawa Animal Care Committee prior to the initiation of the study. Male Sprague Dawley rats at ages of 42–45 days (Charles River Canada, St. Constant, Quebec, Canada) were acclimatized on a starch-based, semi-purified basal diet containing corn starch and casein for 5–10 days. Rats were housed in pairs in disposable cages contained in glove box style Isotec units (Harlan Sprague Dawley Inc., Indiana) maintained under negative pressure with exhausted ventilation. After acclimatization, rats (207–254 g) were randomly assigned to five different diet groups of 18 animals per diet. Throughout the study, each group of rats was fed