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Mercury in Fish as a Potential Environmental Factor in the Development of Autoimmunity: A Mini-review with a Focus on Human Population Studies

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Abstract

Autoimmune diseases develop due to the interaction between genetic susceptibility and additional factors, such as environmental exposure to toxicants. Mercury (Hg), a well-established neurotoxin, has more recently been studied as an immunotoxin linked with biomarkers of autoimmunity, including the presence of antinuclear antibodies (ANA) and distinct cytokine profiles. Mercury (Hg) is virtually ubiquitous in the environment, and concerns about the potential health impacts of Hg exposure through fish consumption exist. A few studies have specifically examined the relationships among mercury, fish consumption, and autoimmune biomarkers in human populations. The findings of these studies are conflicting; this may be due to confounding exposures and opposing mechanisms of action. Additional studies are necessary to clarify the role of Hg through seafood consumption in autoimmunity.

Keywords: Autoimmune; Fish; Seafood; Mercury; Methyl mercury (MeHg); Antinuclear antibodies (ANA); Cytokines; N-3 PUFA; Selenium

Introduction

Autoimmune diseases develop due to interactions between genetic susceptibility and additional factors, including environmental exposure to toxicants [1]. Mercury (Hg) has been implicated as an environmental factor that contributes to the development and exacerbation of autoimmune disease [2]. Hg, a ubiquitous pollutant known to affect ecosystems and human health [3], exists in several chemical forms including inorganic mercury (iHg) and organic mercury (oHg). Microorganisms transform iHg present in sediment or water into oHg by methylation, yielding methyl mercury (MeHg). Plankton and algae absorb MeHg and are consumed by small fish, which are subsequently eaten by predators, ultimately resulting in bio-magnification of MeHg up the food chain [4]. Humans are thus exposed to Hg through ingestion when they consume seafood into which Hg has bio accumulated, particularly because the form of MeHg in fish tissue is not removed through cooking or cleaning processes [4]. This mini-review discusses the potential autoimmune effects of MeHg with a focus on human MeHg exposure through fish consumption. This question of dietary MeHg exposure is significant because Hg is a global toxicant [3], and billions of people worldwide risk increased exposure to MeHg through reliance on fish as a major source of dietary protein and nutrition [5,6].

MeHg Immune Effects in Animal and *in vitro* Studies

Animal models provide evidence for Hg's role in inducing autoimmune effects. Exposing genetically-susceptible mouse strains to Hg leads to the development and/or exacerbation of lupus-like symptoms [7-12], including increased antinuclear autoantibodies (ANA) [7,8]. MeHg exposure in mice led to an initial immunosuppression via reduction in T- and B-cell populations [13], followed by an increase in ANA and IL-4 mRNA expression [13-15]. *In vitro* studies in human peripheral blood mononuclear cells (PBMCs) treated with sub-toxic MeHg resulted in increased concentrations of cytokine IL-1β [16] and suppression of cytokines IL-2 and TGF-β [17]. These results support that MeHg, the form of Hg in human dietary sources, leads to immune dysregulation and autoimmunity. The preservation of food has several objectives [1].

MeHg, Fish Consumption, and Immune System Effects in Human Population Studies

Few human studies explicitly examine the role of Hg exposure through fish consumption with biomarkers of autoimmunity. Silva et al. [18] reports increased prevalence of ANA (10.7%) and antinucleolar antibodies (ANoA) (18%) in a population exposed to MeHg through fish consumption versus the reference site (ANA 7.1%, ANoA 2.0%), though the prevalence was not as elevated as those measured in occupationally exposed miners

(54.1% ANA, 40.8% ANoA). Another study of Amazonian communities [19] observed positive serum ANA more frequently in riverine who consumed fish daily (including species with confirmed high MeHg) than in controls (12.4% *vs.* 2.9%), and mean hair Hg of riverine (34.5 ppm) was significantly higher than controls (1.0 ppm). Despite the significant differences in both ANA and mean hair Hg in riverine versus control communities, there was no significant association between hair Hg and ANAs [19]. In a similar trend, our study [20-23] of participants residing on Cheyenne River Sioux Tribe (CRST) Lands, a known area of MeHg contamination, found a relationship between fish consumption and elevated levels of ANA and specific autoantibodies, yet blood Hg itself was not associated with autoantibodies. In both Amazonian Brazil and CRST studies, fish consumption, but not Hg measure in biological matrices, is associated with increased autoantibodies.

In seeming contrast, more recent studies published on Hg and autoimmune biomarkers in Hg-exposed populations in Columbia [24] and the Middle Atlantic Coast of the United States (Long Island) [25] show that fish consumption is significantly associated with increased levels of Hg in biological matrices, yet these Hg measures are not associated with altered levels of ANAs [24,25], rheumatoid factors (RF) [24], or cytokines [25]. It is difficult to isolate the effects of Hg exposure from eating fish with the effects of Hg exposure from other sources because Hg is an environmentally pervasive contaminant, and people who regularly consume Hg-contaminated local fish likely also encounter Hg through occupational or other environmental exposures. In the case of the studies in Amazonian Brazil [18,19] and Columbia [24], additional iHg exposures result from gold mining, while the studies of CRST [23] and Long Island [25] cite iHg exposures from emissions and industry. Although all studies discussed in this mini-review [18-25] show an increase in total Hg in biological blood and/or hair correlated specifically to reported fish consumption, only the Silva et al. Amazonian Brazil [18] implies a full linkage from fish consumption to increased concentration of bodily Hg, and Hg body burden with increased autoimmune markers.

Discussion

The fact that fish consumption is associated with autoimmune markers in Amazonian Brazil [18,19] and CRST [23] studies may be due to additional exposures to contaminants implicated in immune dysregulation. Fish consumption likely serves as an exposure surrogate or composite exposure predictor. Participants in these studies reside in environments impacted by mine wastes that include other metals (gold, cadmium, arsenic) known to play a role in autoimmunity [26-28]. Additionally, pesticide exposure was not adjusted for in the Amazonian Brazil [18,19] and CRST [23] studies. Like Hg, pesticides are persistent environmental contaminants capable of bio accumulating in fish and have been implicated in immune alterations [29]. The adjustment for pesticide exposure may explain the lack of autoantibody induction observed in the Columbia study [24] in spite of the fact that this population also resides in a gold mining setting.

Differences in genetic, metabolic, lifestyle and total environmental exposure across populations are also likely contributors to the discrepancies in findings. A notable difference among these human studies is the total body burden of Hg in the study populations. The CRST, Columbian, and Long Island population studies all measured low levels of total blood Hg in comparison to the Amazonian Brazil studies, and no significant associations between total Hg and autoimmune markers were observed. This suggests that chronically high total body burden of Hg, rather than MeHg from fish, is associated with increased autoimmune markers. This idea is supported by additional studies published on Amazonian Brazil mining communities without reported fish consumption that showed positive associations between high total hair Hg and ANA, ANoA, and cytokines (IL-1β, TNF-α, IFN-γ) [16-22]. An alternative possibility to a minimum total Hg exposure, or an additional requirement, may be that effective induction of autoimmune markers requires the presence of both iHg and MeHg. iHg and MeHg have been shown in mice [26] and human PBMCs [16] to elicit differential immune responses with iHg favouring a Th2 response whereas MeHg favours a Th1 response. Furthermore, studies of Amazonian Brazil populations reported a high prevalence of malaria [16-22], which has been shown in mouse models to lead to the generation of antibodies that react with nuclear antigens [27]. This suggests that a convergence of factors; iHg, MeHg, and specific immune challenge, such as malaria infection increases the probability of autoimmunity.

Other than exposures to additional environmental contaminants, selenium (Se), and fatty acids consumed alongside MeHg in fish may account for some of the uncertainty in the associations between Hg-contaminated fish consumption and autoimmunity. A study of Hg miners in China who had correlated elevated Hg and Se found increased selenoproteins and glutathione peroxidase (GSH-Px) [30], which may mitigate the adverse effects of Hg exposure contributing to the development of autoimmunity. The principle source of Se is through dietary animal protein [31], and some authors' state that Se, like MeHg, biomagnifies within predatory fish [32]. Others suggest that Se accumulates at the base of the food chain and that significant concentrations of Se may be ingested through plants grown in a Se-enriched environment [33]. A follow-up study in Amazonian Brazil found an inverse relationship between blood Hg and blood Se but no overall relationship between fish consumption and Se even though fish consumption was high [34]. Although the primary source of Se intake is unclear, Se and Hg are correlated in both the environment and the human body, and there is evidence that they have opposing mechanisms of action.

n-3 Poly-unsaturated fatty acids (n-3 PUFA) present in fish may also counteract the negative effects of Hg on the immune system. n-3 PUFAs are known to have the ability to regulate transcription factor activation and pro-inflammatory signalling pathways and may modulate pathways involved in autoimmune disorders [34-36]. This potentially explains why the Long Island study [25], the only one to measure n-3 PUFAs in participants, found correlations between n-3 PUFAs and detection of ANA only at lower titre concentrations.

Finally, it is worth mentioning that common markers of autoimmunity such as ANA and ANoA are generally observed at low frequency at the conservative titres (1:80 or more dilute) used in the human studies cited here, and many cytokine measurements lie below the limit of detection. This, and limited population sample size, pose additional obstacles to reaching a firm conclusion about the role of MeHg fish in the development of autoimmune biomarkers.

Conclusions and Future Avenues of Study

The findings of the few human studies incorporating MeHg exposures through fish consumption do not provide a conclusive answer as to whether or not these exposures significantly contribute to autoimmune development. In our study with the CRST [23], which exhibits elevated levels of certain autoimmune diseases, the main question from community members was, "Is it safe to eat local fish?" Reframed, the question is, "Does MeHg from fish consumption exacerbates the development autoimmunity?" Current studies do not provide a clear consensus. It appears that high total Hg body burden is necessary in order to observe significant changes in autoimmune biomarkers. A combination of both iHg and MeHg exposures may be required to exacerbate autoimmune development, since the various forms of Hg affect the immune system differently. Because Amazonian Brazil populations evidenced both relatively high total Hg and increased likelihood of exposure to malaria, it is possible that development of Hg-driven autoimmunity in humans depends upon a convergence of factors: iHg, MeHg, and specific immune challenge, such as malaria infection. It is likely that nutritional elements in fish, including Se and n-3 PUFAs, attenuate the immune effects of Hg exposures. The limited evidence in human populations about the role of fish MeHg in autoimmunity concurs with the current public health consensus to retain or increase fish consumption, especially of species with lower MeHg, for nutritional benefits while decreasing other exposures to Hg.

To elucidate the question of whether or not MeHg through fish consumption contributes significantly to alterations in autoimmune markers in humans, a larger, more robust set of human studies is needed. Autoimmune biomarkers could be measured in populations exposed to MeHg through fish consumption, beginning with the many communities world-wide in which Hg bio monitoring in fish tissue and/or human biological samples has already been done [37-48]. Estimated MeHg exposure, calculated from accurate species-specific tissue MeHg concentrations, should be modelled as a predictor alongside measures of iHg exposure with autoimmune biomarkers as the outcomes. This would help disentangle fish consumption's role in autoimmunity from that of other Hg exposures in order to inform public health recommendations.

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