Environmental Health Perspectives
Vol. 25, pp. 71-76, 1978

Modification of Methylmercury Toxicity and Metabolism by Selenium and Vitamin E: Possible Mechanisms

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Selenium and vitamin E exert powerful effects in reducing acute or chronic methylmercury toxicity. Levels of selenium normally found in foods (below 1 ppm) delay the onset of toxic signs caused by much higher levels of methylmercury. Tissue levels of mercury in selenium-supplemented animals equal or exceed those found in animals given methylmercury alone. Selenium does not appear to act by simply modifying intake, absorption, excretion, or distribution of methylmercury, and direct effects of both selenium and vitamin E have been observed *in vitro* when methylmercury was added to cultured nervous tissue cells. The only established functions for selenium and vitamin E in animals are related to the prevention of oxidative damage in tissues. To encompass the protective effects of selenium and vitamin E and to explain other toxicological aspects of methylmercury and other alkylmetals, a new hypothesis is proposed: The toxicity of the alkylmetals is not caused solely by the intact molecule, but also involves free radicals formed by homolytic fission of the carbon-metal bond.

Introduction

The purpose of this paper is to develop a new hypothesis regarding the basic mechanism for the toxicity of methylmercury, including a mechanism for the protective effects of selenium and vitamin E which would encompass the known functions of these substances as essential nutrients. The effects of selenium and vitamin E on methylmercury toxicity will first be briefly summarized, followed first by an account of present theories of methylmercury toxicity and then by an alternative theory based on present knowledge.

Mercury and Selenium

Selenium was first reported to counteract acute mercuric chloride toxicity a decade ago by Parizek and Ostadalova (*1*). In 1972, selenium was shown to be highly effective in delaying chronic methylmercury toxicity in rats (*2*). An important aspect of the latter discovery was that the level of dietary selenium (0.5 ppm) used to obtain significant protection was in the range of the nutritional requirement for this essential trace element, and far below the level of methylmercury used to induce toxicity. Moreover, it was shown that tuna contained enough selenium to modify methylmercury toxicity, that tuna diets reduced methylmercury toxicity in Japanese quail more so than did diets based on plant sources of protein, and that tuna, having a high content of mercury, tended to accumulate selenium with mercury in a 1:1 molar ratio (*2, 3*). The biological antagonism between mercury and selenium has been confirmed in many laboratories (*4*). A protective effect of marine fish against methylmercury toxicity, compared to casein as the protein source, has been confirmed in the rat by two laboratories (*5, 6*), and some degree of protection could even be demonstrated in cats fed tuna compared to cats fed pike, which correlated with the higher level of selenium present in the marine fish compared to the freshwater fish (Ganther et al., unpublished data). Thus selenium has been established as a naturally occurring substance in foods at levels capable of modifying methylmercury toxicity that may be involved in the protective effect obtained by feeding marine fish. However, there may well be other protective factors in marine fish as well, such as arsenic (*7, 8*), and no one has actually isolated the protective factor(s) from fish.

The mechanism of action of selenium in modifying methylmercury toxicity is not known, but it

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does not appear to involve a decrease in tissue mercury concentration. Brain mercury levels are not decreased by selenium at the time selenium is exerting a protective effect (*6, 9*). Selenite increased the uptake of methylmercury in rat brain (*10*). In some cases where methylmercury is fed for long periods together with high levels of selenium, the mercury levels are well above the level (about 10 ppm) normally considered to cause obvious signs of central nervous system toxicity. For example, Stoewsand, Bache, and Lisk (*11*) noted high methylmercury levels (up to 40 ppm) and absence of toxic signs in Japanese quail fed 20 ppm Hg as methylmercury and 5 ppm Se as sodium selenite for 9 weeks. Similarly, El-Begearmi, Sunde, and Ganther (*12*) fed quail 6 ppm Se and 5, 10, or 15 ppm Hg as methylmercury for 20 weeks; total mercury levels in brain averaged 14, 33, and 58 ppm, respectively, but these animals were alive and showed no signs of mercury poisoning. Brain selenium levels were much higher than normal (about 0.2 ppm in the absence of methylmercury) but were insufficient to complex more than a fraction of the total mercury. (The highest level found was 4.1 ppm Se, which is capable of complexing a little over 10 ppm Hg on an equimolar basis; even if 2:1 or 3:1 Hg:Se complexes were formed, a large part of the 58 ppm Hg in brain of such animals is not bound to Se.) It is apparent that the concentration of either total mercury or methylmercury in brain is not always indicative of toxicity when selenium is administered. Selenium must do more than just bind mercury in a less toxic form, although this effect is probably involved in some aspects of the Hg:Se interaction, particularly when inorganic mercury is involved.

Another mechanism that has been considered is that some of the toxic effects of mercury result from complexing of essential, biologically active forms of selenium (*12*). The only functional form of selenium thus far identified in animals is the selenoenzyme glutathione peroxidase (*13, 14*); a deficiency of this enzyme is induced by feeding silver (*15*). In such a case, supplementation with additional selenium permits more of the biologically active selenium compound to be synthesized (*16*), thus overcoming a conditioned nutritional deficiency of selenium induced by the metal. Although there is some evidence that methylmercury may induce signs of selenium deficiency (*17, 18*), it was not found to be particularly effective in decreasing glutathione peroxidase levels when fed in the diet of rats (*16*) or cats (Ganther, et al., unpublished data), in contrast to silver, and in some tissues such as liver, methylmercury tended to elevate the activity of this enzyme in rats (*16*). Injection of a subacute dose of methylmercury caused a slight decrease in rat brain glutathione peroxidase activity (*10*).

The possibility that selenium might alter the distribution of mercury in brain and thereby protect some critical site has also been investigated (*10, 19*), with negative results. Injection of ^{75}Se-selenite did not alter the subcellular distribution of ^{203}Hg administered as ^{203}Hg-methylmercury, nor did ^{203}Hg and ^{75}Se tend to concentrate in any particular fraction of cytosol fractionated by gel filtration. When rats labeled at 7 days of age with a physiological dose of ^{75}Se-selenite were later injected with ^{203}Hg-methylmercury, there was some shift of ^{75}Se from the cytosol to the mitochondrial fraction of brain (*10*); both ^{203}Hg and ^{75}Se tended to follow the protein concentration in fractions of cytosol separated by gel filtration chromatography, but no evidence for cochromatography of the isotopes in a particular fraction was observed, unlike the case for mercuric chloride plus equimolar selenite (*19–21*).

Mercury and Vitamin E

In 1974, a protective effect of vitamin E against methylmercury toxicity in fowl was discovered by Welsh (*18*). Welsh and Soares (*22*) showed that a high level (about 500 ppm) of vitamin E decreased mortality in Japanese quail fed 30 ppm of methylmercury. These findings have been confirmed in Japanese quail (*23*) and in rats (*23, 24*). Vitamin E was found to have a direct protective effect on the toxic effects of methylmercury and ethylmercury on nervous tissue cells in culture (*25*). Selenium was also found to be protective, and at lower levels than vitamin E (*26*). Although a rather high level of vitamin E is required for protection, in contrast to selenium, the ability of this substance to prolong survival of animals given methylmercury may be a significant finding in terms of understanding the mechanism of the neurotoxicity of methylmercury. There are apparently no studies concerning the effect of vitamin E on inorganic mercury toxicity. We have recently reported some preliminary studies with Japanese quail fed 450 ppm of Hg as $HgCl_2$ with or without 500 ppm vitamin E, which showed that vitamin E was effective in reducing mortality; the growth depression observed with $HgCl_2$, however, was not affected (*27*).

Present Theories of the Mechanism of Methylmercury Toxicity

The basic cause of methylmercury toxicity has never been elucidated. Most toxicologists believe the intact molecule is responsible and that the mer-

cury atom interacts with sulfhydryl groups of proteins to bring about the toxic effects, but this is not established. There is a characteristic lag period of a least one week before the appearance of the signs of poisoning with alkyl mercurials (*28*). This lag period is present regardless of whether a single dose or continuous dosing is involved. No mechanism for this lag period has been established.

In the absence of a definitive mechanism for the action of methylmercury, alternative hypotheses to the intact molecule theory need to be considered. In particular, an explanation is needed for the lag period, and for the protective effects of selenium and vitamin E. Nearly 10 years ago, Clarkson (*29*) briefly alluded to the question of whether the toxicity of organomercurials was due at least in part to inorganic mercury released from them, in view of the latency period before signs of central nervous system damage and the slow metabolism of methylmercury to Hg^{2+}. He noted that at that time there was no basis to decide whether or not the intact mercurial was responsible. Since that time the "intact molecule" hypothesis appears to have gained the upper hand (*28*). Norseth and Clarkson (*30*) felt that biotransformation did not account for the delay in symptoms and summarized various supportive data: (a) most of the mercury in mouse brain was present as intact methylmercury up to 28 days after injection, and inorganic mercury never exceeded 4% of the total brain mercury; (b) the disturbances of the central nervous system elicited by inorganic mercury differ from those elicited by the alkyl mercurials; (c) other organomercurials that are known to penetrate the brain and rapidly release inorganic mercury have not been reported to produce central nervous system damage. These arguments in favor of the intact molecule theory, and alternative interpretations, will now be considered in more detail.

In regard to point (a) above, if the percentage of inorganic mercury in brain is taken as a measure of how much methylmercury has been transformed to inorganic mercury in brain, the necessary assumption is that all of the mercury thus degraded was retained in the brain. It is possible, however, that methylmercury breakdown may generate volatile products such as Hg^0, not all of which is retained. The breakdown of alkyl mercurials by radical mechanisms produces both Hg^0 and Hg^{2+}, and the proportions of Hg^0 and Hg^{2+} may vary depending on conditions (*31*). The diffusion of metallic mercury between brain and blood is rapid, and the oxidation of Hg^0 in blood is not instantaneous, so that a substantial portion of injected Hg^0 is exhaled (*32*). Thus the low percentage of inorganic mercury in brain may not reflect the true extent of methylmercury breakdown. It might also be noted that in chronic methylmercury poisoning in various species fed contaminated pike, methylmercury accounted for a lower percentage of the total brain mercury compared to the 28 day study by Norseth and Clarkson (*30*). In cats, this percentage varied from 77% (*33*) to 91% (*34*), and in mink it was 81% (*35*). Moreover, in other studies where inorganic mercury has been measured by direct volatilization with $SnCl_2$, there is the possibility that inorganic mercury present as HgSe might not be released completely from the tissue sample (Church and Ganther, unpublished data) and therefore could be underestimated. Also, the concentration of inorganic mercury necessary to cause damage is not known, so the presence of a low level of inorganic mercury relative to methylmercury may not rule out its toxicological significance (*28*).

Regarding point (b), that mercury vapor is oxidized to Hg^{2+} after penetrating the brain but produces different symptoms from those produced by methylmercury, it could be said that this is not necessarily surprising, considering the possibilities for differences in distribution and binding of the two forms of mercury to various binding sites on membranes, enzymes, and other brain components. Beyond that, there are two assumptions implicit in all the theories regarding the mode of action of mercurials, namely that the mercury atom itself is the responsible agent, and that the mercury atom must bind to its target(s) and remain bound to cause toxic effects. As obvious and attractive as these assumptions may be, it could also be that the organic moiety plays some role in the toxic process as well and is not simply serving as a carrier for the mercury atom to affect its mobility and binding characteristics. Viewed in this light, one can turn both arguments (b) and (c) around and say that neither inorganic mercury nor organic mercurials such as the aryl mercury compounds should be expected to duplicate the effect of alkyl mercurials, since they either lack the organic moiety or have an entirely different one. The assumption that mercury must bind to a substrate to be toxic is obviated by an alternative hypothesis (below).

Possible Role of Free Radicals in Methylmercury Toxicity

A new theory of methylmercury toxicity is presented for consideration. Stated in simplest form, the hypothesis is that the neurotoxicity of methylmercury may involve free radicals formed by breakdown of methylmercury and does not necessarily result solely from the intact molecule. The

starting point for this hypothesis was the idea that the toxicity of methylmercury might be due at least in part to methyl radicals ($CH_3 \cdot$) formed by the breakdown of methylmercury. The net formation of free radicals generally involves the homolytic fission of covalent bonds so that each product retains one of the shared electrons:

$$CH_3{:}H \xrightarrow{\text{homolysis}} CH_3\cdot + H\cdot \qquad (1)$$

There is an abundance of chemical literature documentating the homolytic decomposition of alkyl mercurials and other organometallic compounds (*36*). It is interesting in this context to note (*37*) that the earliest demonstration of the highly reactive properties of free radicals involved the thermal decomposition of tetramethyl lead in a horizontal tube to form gaseous free radicals. The alkyl metal decomposed, depositing a metallic mirror, and producing alkyl radicals which reacted further along the tube. Once a free radical has been formed, a new free radical may arise by the interaction of the free radical with some other molecule:

$$A\cdot + BC \longrightarrow A\text{-}B + C\cdot \qquad (2)$$

Compounds having covalent bonds that dissociate easily, such as the O-O bond in peroxides, can be used to initiate the homolytic cleavage of other compounds. Free radicals also are produced by the interaction of a substrate (such as ascorbic acid) with a metal ion that can undergo a univalent change in oxidation state.

Gage (*31*) has reported some experiments indicating that the demethylation of methylmercury hydroxide and other organomercurials can be induced with ascorbate plus low concentrations of copper. The breakdown formed Hg^{2+} and Hg^0 in various proportions, depending on the mercury compound and the experimental conditions. Breakdown of the organomercurials was minimal in the absence of air unless the ascorbate was first exposed to air in the presence of copper. It appeared that an unstable product of the Cu^{2+}-mediated autooxidation of ascorbate was involved. The monodehydroascorbate radical and other radicals are known to be formed by the oxidation of ascorbate in air in the presence of metal ions (*37*). Gage (*31*) was concerned with the mechanism for *in vivo* breakdown of organomercurials and he made no attempt to relate his findings to methylmercury toxicity, but his results suggest that radicals might induce methylmercury breakdown, and radicals may be products of its breakdown. Methyl radicals are formed by the photolysis of methylmercuric iodide and add to aromatic nuclei (*38*).

Assuming that free radicals are involved in the breakdown of methylmercury, it is envisaged that methylmercury, owing to its physical properties, would be taken up by membranes in target tissues such as brain in close proximity to lipids. It would then initiate a chain reaction peroxidation of various lipid constituents as a result of its chemical tendency to undergo homolytic fission, perhaps initiated by radicals produced by oxygen-dependent metabolic reactions. The onset of neuropathologic changes would be preceded by a lag phase, during which the various systems defending against lipid peroxidation (see below) would be overcome, followed by a rapid and progressive degeneration of the tissue.

Vitamin E would modify methylmercury metabolism by acting as a radical scavenger. It might be more efficient than other antioxidants because of its location in membranes, in turn a result of its physicochemical properties, and because of its ability to stabilize membranes by interacting with unsaturated fatty acid chains (*4*). Vitamin E could thus scavenge radicals that would otherwise initiate methylmercury breakdown, but would also be capable of reacting with methyl radicals that might be formed in the breakdown. A recent study (*39*) has shown that the methyl radical, generated by addition of ferrous sulfate to dimethyl sulfoxide, reacts with tocopherol to form stable methylated products.

Selenium, as a component of glutathione peroxidase, would slow the process of methylmercury breakdown by decomposing peroxides that would otherwise initiate methylmercury breakdown; this enzyme catalyzes the reduction of hydrogen peroxide and a large variety of organic hydroperoxides to products of greater stability (*40*):

$$ROOH + 2\,GSH \xrightarrow{\text{glutathione peroxidase}} R\text{—}OH + HOH + GSSG$$

In addition, certain metabolites of selenium formed in tissues, such as H_2Se (*41*), might also complex with the inorganic mercury formed by methylmercury breakdown, making it unavailable for binding to ligands, and also preventing the mercury from functioning as a radical initiator by undergoing univalent redox changes.

There is some evidence that selenium may retard the conversion of alkylmercurials to inorganic mercury. Fang (*42*) looked for an effect of excess dietary selenium on C-Hg bond cleavage (in alkylmercurials) by rat liver homogenates. For ethylmercury chloride, his data show that selenium supplementation (0.5 or 5 ppm as selenite in the drinking water) tended to cause a slight decrease in cleavage of the mercurial compared to what happened in rats fed a stock diet. No cleavage of methylmercury chloride was observed. Only in the case of phenylmercuric acetate was a definitely enhanced rate of cleavage observed, and this effect was only obtained with the 5 ppm

level, which is far above the physiological range of selenium intake. *In vitro* addition of 1–10 μmole/l. selenite reduced the apparent production of inorganic mercury from phenylmercuric acetate. It should be noted that differences in glutathione peroxidase activities for the rats fed the various diets would not be expected to be a factor in these studies because all animals received at least 0.5 ppm Se, a level adequate for synthesizing normal levels of this enzyme (*40*).

In regard to the effects of selenium or vitamin E on the toxicity of inorganic elements *per se*, where no organic moiety is involved, it might appear that a radical theory could not be involved. However, rats fed diets deficient in vitamin E are more susceptible to silver nitrate toxicity (*43*), and silver induces the characteristic signs of vitamin E and selenium deficiency in rats and chicks fed diets low in vitamin E and selenium (*44*). Such diets do not cause the appearance of deficiency signs in the absence of silver. The signs induced by silver can be overcome by supplementation with low levels of selenium, vitamin E, or antioxidants (*44*). The growth depression observed in rats given large amounts of $AgNO_3$ is prevented by nutritional levels of selenium and is also prevented by vitamin E (*15, 16*). Silver appears to induce a conditioned deficiency of selenium in animals fed an otherwise adequate level of dietary selenium, as shown by effects on tissue selenium and glutathione peroxidase levels (*15*).

The ability of selenium to counteract both acute and chronic $HgCl_2$ toxicity is well established. However, the levels of dietary selenium used to protect against chronic $HgCl_2$ toxicity (3–40 ppm) have in all cases been well above the nutritional range (*45, 46*). This is in contrast to methylmercury toxicity, where a dramatic effect is obtained with 0.5 ppm selenium (*2*). The action of selenium against $HgCl_2$ may involve a variety of mechanisms, such as direct stoichiometric complexing of mercury to reduce its availability (*47*). Mercuric chloride administered to mice inhibits kidney glutathione peroxidase substantially, provided mercury levels in the tissue are sufficiently in excess of selenium on a molar basis (*48*). $HgCl_2$ may therefore act to some extent to promote tissue oxidative damage, by inhibiting the glutathione peroxidase-linked defensive system and possibly by serving as an initiator of radical processes.

The possibility that free-radical damage might be involved in the effects of other environmental toxicants must be considered. Alkyl lead compounds, for example, are of great interest in regard to environmental pollution because of their use in gasoline. The main organ affected in alkyl lead poisoning is the central nervous system (*49*), just as for alkylmercurials, but the mechanism is not known. Tetraethyllead is converted in tissues to various metabolites, including triethyllead (*49*), which involves the loss of methyl groups. Selenium has a limited degree of effectiveness against Pb^{2+} in rats (*50*) but has not yet been tested against alkyl lead derivatives. Neither has vitamin E, although it does protect against some effects of Pb^{2+} toxicity (*51*). For reasons considered here, vitamin E and selenium might be expected to be more effective against alkyl lead toxicity than against inorganic lead toxicity.

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