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Thyroid Hormones and Methylmercury Toxicity

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Abstract

Thyroid hormones are essential for cellular metabolism, growth, and development. In particular, an adequate supply of thyroid hormones is critical for fetal neurodevelopment. Thyroid hormone tissue activation and inactivation in brain, liver, and other tissues is controlled by the deiodinases through the removal of iodine atoms. Selenium, an essential element critical for deiodinase activity, is sensitive to mercury and, therefore, when its availability is reduced, brain development might be altered. This review addresses the possibility that high exposures to the organometal, methylmercury (MeHg), may perturb neurodevelopmental processes by selectively affecting thyroid hormone homeostasis and function.

Keywords

Selenium; Selenoenzymes; Deiodinase; Pathophysiology; Thyroxine; Triiodothyronine; Mercury; Neurodevelopment

Thyroid Hormones and Deiodinases during Neurodevelopment

The thyroid hormone, 3,5,3'-triiodothyronine (T3) and its precursor, the "prohormone" thyroxine (T4), are iodinated compounds synthesized by the thyroid gland. Thyroid hormones play a vital role in cellular metabolism, normal central nervous system (CNS) development, and early growth and development and influence gene expression in virtually every vertebrate tissue.

Thyroid hormone signaling is mediated by the interaction of nuclear thyroid hormone receptors (TRs) with specific target gene promoters, repressing or enhancing transcription. Thyroid hormone action is primarily dependent upon intracellular concentrations of free T3 and TR-bound T3 [1]. These intracellular T3 levels are regulated by the supply of circulating

T4 and T3, the conversion of T4 by enzymatic outer (phenolic) ring deiodination to T3, and the degradation of T4 and T3 by inner (tyrosil) ring deiodination to the inactive reverse T3 (rT3) and the inactive 3,3'-diiodothyronine (T2), respectively by deiodinase enzymes [2]. Accordingly, due to the deiodination of thyroid hormones at the tissue level, thyroid hormone signaling can be aberrant even when serum hormone concentrations are constant [3]. Consequently, there is a delicate balance between thyroid hormone synthesis, transporting binding proteins, circulating T4 and T3 concentrations, pituitary–hypothalamic–thyroid axis, and deiodinase activity.

Monoiodothyronine deiodinase type I (D1; iodothyronine deiodinase), type II (D2; 5'-iodothyronine deiodinase), and type III (D3; 5-iodothyronine deiodinase; EC 1.97.1.10) are located in specific tissues that catalyze outer ring and/or inner ring deiodination in mammals [4] and thus play a critical role in the regulation of intracellular T3 levels (Fig. 1). T4 is converted to T3 by deiodinase D1 in the liver and kidney, contributing to the maintenance of circulating T3 (Table 1). This conversion of T4 to the active hormone T3 through the removal of an iodine atom on the outer phenolic ring (5'-deiodination) leads to activation of thyroid hormone.

D2 is the major T3-activating enzyme within target cells in the brain. In the anterior pituitary, more than 50% of TR-bound T3 is locally produced by D2-mediated T4 deiodination [5, 6] (Table 1). D2 activity is increased in hypothyroidism and decreased in hyperthyroidism [7].

D3 removes an iodine atom from the tyrosil ring which converts either T4 to the inactive reverse triiodothyronine or T3 to the inactive diiodothyronine (T2) [8]. The specific activities of the three iodothyronine deiodinases are summarized in Table 1.

Neurodevelopmental Deficits and Thyroid Hormones

Thyroid hormone signaling is vital for normal human brain development and has been implicated in the survival, proliferation, migration, arborization, and expression of specific phenotypic markers of neurons [9–12]. Additionally, thyroid hormones exert indirect effects on neurodevelopment which are mediated by astrocytic secretion of growth factors [13–15]. Deficiency in thyroid hormones during perinatal development leads to irreversible motor and intellectual deficits [16] with underlying cytoarchitectural changes [17]. Also, untreated congenital hypothyroidism results in marked neurological deficits and, in extreme cases, can lead to mental retardation and cretinism [18].

Deiodinase activity plays a critical role in maintaining adequate T3 levels during neurodevelopment. For example, it has been demonstrated that maternal T₄ (and not T₃) is effective in elevating the T₃ content of the hypothyroid brain of rat embryos [19], suggesting that local T₃ production is important in the maintenance of T₃ levels in the brain. Moreover, 5'-deiodination plays an important role in the rapid response of the cerebral cortex to hypothyroidism in adult rats [20]. In contrast to the rat brain, which expresses higher levels of D1 activity than D2 in the cerebrum [21], D2 is the only activating deiodinase in the human brain [22]. D2 expression in the rat brain is observed mostly in glial cells and is highly concentrated in tanycytes of the mediobasal hypothalamus [23–25].

More than 80% of brain T₃ is produced by conversion of T₄ to T₃ within the target cells by D2 and not by direct T₃ synthesis by the thyroid gland [5, 26–28]. This deiodination activity is tightly controlled at the early developmental stages because T₃ can initiate cellular differentiation possibly through the regulation of an internal clock mechanism [29].

The Role of Selenium in Neurodevelopment

Selenium (Se) is a vital micronutrient in humans and a component of selenocysteine—the 21st essential amino acid [30]. Selenocysteine is an integral component of the enzymes glutathione peroxidase (GPX), as well as the iodothyronine deiodinases. While GPXs protect organisms from oxidative damage, reduce lipid hydroperoxides to their corresponding alcohols, and reduce free hydrogen peroxide to water, the deiodinases, as mentioned, are important in the activation and deactivation of thyroid hormones.

All three types of deiodinases (D1, D2, and D3) are selenocysteine-containing enzymes. These residues are located in the enzyme active sites, where they play a critical role in the catalysis of the reductive cleavage of the carbon–iodine bonds in both the phenolic and tyrosil rings of the iodothyronines. Expression of the deiodinases is significantly decreased during severe selenium deficiency, resulting in the subsequent change in thyroid hormone homeostasis and in serum thyroid hormone concentrations. The substitution of the active site selenocysteine residues with recombinant sulfur-containing cysteine mutants decreases the catalytic efficiency of deiodinases by three orders of magnitude [31].

Since selenium is an essential element in animals, meat and seafood are reliable dietary sources of selenoproteins. Dietary selenium content varies depending on selenium soil content affecting the amounts of selenium uptake by the plants and by the animals feeding on these plants. Most of the selenium in plants is in the form of selenomethionine, selenocysteine, or selenocysteine metabolites. Selenium metabolism by plants occurs through sulfur pathways in which selenium substitutes for sulfur. Other organic forms of the element are known to exist, including some that have not yet been identified. Selenium concentrations in organ meats and seafood can vary from 0.4 to 1.5 µg/g; muscle meats, 0.1 to 0.4 µg/g; cereals and grains, less than 0.1 to greater than 0.8 µg/g; dairy products, less than 0.1 to 0.3 µg/g; and fruits and vegetables, less than 0.1 µg/g [32].

The recommended selenium intake values for infants, children, and adults are detailed in Table 2. The recommendations for selenium intake are based on an Adequate Intake (AI) that reflects the observed mean selenium intake of infants fed principally with human milk. In the absence of additional information, Estimated Average Requirement and Recommended Dietary Allowances for children and adolescents have been estimated by extrapolating from adult values.

Human milk is recognized as the optimal source for infants for at least the first year of life and is recommended as the sole nutritional milk source for infants during the first 4 to 6 months of life [33]. Therefore, determination of the AI for selenium for infants is based on data from breastfed infants where human milk is the principal fluid during the first year of life (periods 0 through 6 and 7 through 12 months of age, Table 2).

Several studies provide information about selenium requirements during pregnancy. However, during pregnancy, selenium requirement should allow accumulation of enough selenium by the fetus to saturate its selenoproteins. Based on an estimated selenium content of 250 µg (3.2 µmol)/kg body weight [34], a 4-kg fetus would contain 1,000 µg (12.6 µmol) of selenium. This need could be met by consumption of 4 µg (0.05 µmol) selenium/day throughout pregnancy. Pregnant women on a high-selenium diet (150 µg (1.9 µmol)/day] retain approximately 21 µg selenium (0.27 µmol)/day in early pregnancy and 34 µg (0.43 µmol)/day in late pregnancy compared to 11 µg (0.14 µmol)/day in non-pregnant women [35]. The low selenium retention may be a problem for pregnant women in the USA who are reported to consume on average only 73 µg (0.92 µmol)/day [36].

Methylmercury and its Inhibitory Effects on Neurodevelopment

Methylmercury (MeHg) is an organometallic cation (CH_3Hg^+) and a known neurotoxin. It is formed in aquatic systems where methylation of inorganic mercury by methanogenic bacteria leads to its release into water and bioaccumulation in the food chain. When ingested, MeHg readily binds to cysteine, forming a methylmercuric–cysteinyl complex. This complex is recognized by amino acid-transporting proteins, such as the neutral amino acid transporter (LAT1), which allows it to be transported freely throughout the body. The mobility of the methylmercuric–cysteinyl complex allows it to cross not only the blood–brain barrier but also the placenta.

Several studies have addressed the effects of MeHg on thyroid function and thyroid hormone synthesis and activity (see below). In mice, MeHg specifically binds to Sulfhydryl (-SH)-containing ligands in the thyroid gland, which may account for its effects on thyroid function [37]. However, different Hg species have been shown to exert dissimilar effects on thyroid function. MeHg interferes with the production of thyroid stimulating hormone (TSH, thyrotropin), thus lowering production of thyroid hormones [38]. Conversely, inorganic Hg inhibits the production of thyroid peroxidase, thyroidal enzyme that liberates iodine for addition onto tyrosine residues on thyroglobulin for the production of T4 and T3 [38]. Yet, both inorganic and MeHg dose-dependently inhibit the iodination of thyroglobulin [39]. This decreases thyroidal T4 and T3 synthesis, in turn increasing production of thyroid hormone as a compensatory mechanism. Inorganic Hg shows greater potency in inhibiting the iodination than MeHg, which may lead to more severe hypothyroidism.

Chronic exposure to low levels of MeHg during pregnancy is of concern since MeHg can readily reach the fetus. In general, MeHg levels in the fetus exceed maternal levels, reflecting an incomplete blood–brain barrier and lack of MeHg excretion in the fetus [40]. The most significant difference in organ retention (neonates > adults) is associated with MeHg brain concentrations [41, 42]. The developing fetus is five to ten times more sensitive to MeHg than the adult [43] due, in part, to the high sensitivity of developmental processes (i.e., cellular division, differentiation, and migration) to disruption by MeHg [44–45], as well as increased MeHg concentrations in fetal brains (referred to as a “sink” for MeHg). The developmental sequelae of human exposure to MeHg have been characterized in two epidemics in Japan and Iraq [46–49], where infants gestationally exposed to MeHg developed severe neurological delays, while their mothers experienced little or no overt signs of toxicity.

Mechanism of MeHg Toxicity

The exact mechanism of MeHg toxicity remains unknown. Hg is covalently bound to the carbon moiety in MeHg ($\text{CH}_3\text{–Hg}^+$). The carbon–Hg bond is chemically stable because of the low affinity of Hg for oxygen. MeHg does not exist as a free, unbound cation in biological systems (except an infinitesimal amount as governed by the law of mass action), and the chloride form is highly soluble in organic solvents and lipids. As mentioned previously, MeHg is found to bind to protein–SH groups of amino acids, such as cysteine, which is also present in glutathione [50]. This affinity for sulfur and sulfhydryl groups (SH) is a major factor underlying the biochemical and toxic properties of MeHg and its interference with optimal cell function. Notably, MeHg will however dissociate and move freely between –SH groups. A large body of research aimed at deciphering the cellular and molecular mechanisms of MeHg-induced neurotoxicity points at several critical features, namely (1) inhibition of macromolecule synthesis (DNA, RNA, and protein), (2) microtubule disruption, (3) increase in intracellular Ca^{2+} with disturbance of neurotransmitter function, (4) oxidative stress, and (5) excitotoxicity, secondary to altered

glutamate homeostasis and activation of *N*-methyl D-aspartate (NMDA) receptors. Nonetheless, its primary site of action and the genetic bases of its neurotoxicity have yet to be identified.

Mercury–Selenium Interactions

The interaction between mercury and selenium has been characterized in a number of studies. Given its antioxidant effects, selenium was proposed to protect against the toxicity of mercury. However, paradoxically, it increases tissue mercury concentrations, likely due to decreased excretion and higher retention of MeHg. Several early studies have shown that selenium exerts a protective effect against MeHg poisoning [51–53]. The mechanisms associated with this protective effect are not well understood, but are likely associated with diversion of mercury from target molecules to high molecular weight mercury–selenium-containing proteins found in plasma [54] and other tissues [55, 56]. Ralston et al. [57] examined the effect of dietary selenium on toxicity in weanling male rats exposed to MeHg. Growth of rats fed high-MeHg and adequate-Se diets was impaired by approximately 14% relative to their control group, whereas rats fed high-MeHg, rich-Se diets were indistinguishable from controls. The authors emphasized that the Hg-to-Se molar ratios provide a reliable criterion for evaluating risks associated with MeHg exposure. In their study, Ralston et al. [57] demonstrated that low-MeHg exposure did not affect rat growth at any dietary Se level. Hg toxicity directly correlated to the Hg-to-Se molar ratios. These authors are the first to provide data in support of the hypothesis that Hg-dependent sequestration of Se is a primary mechanism of Hg toxicity and that the Se molar ratios provide a more reliable and comprehensive criteria for evaluating risks associated with MeHg exposure. Others have also shown the protective properties of Se. For example, high Se concentrations in fresh lake trout (in Argentina) were associated with low Hg content in tissue (muscle), suggesting detoxification of Hg by a Se-rich diet [58].

Notably, dietary selenium levels affect Hg concentrations in the fetal brain [59], and both Se and MeHg have significant effects on the Se concentration and GPX activity in fetal brain. That Hg levels are unaffected in the pups is not surprising, given that the fetal brain lacks a functional blood–brain barrier and that mechanisms associated with MeHg efflux from tissues are not functional in this stage of development. When exposures to MeHg occur in utero or at early age, the damage to the CNS is ubiquitous. Generally, the earlier the exposure, the more generalized the damage. It has, thus, been hypothesized that these differences are caused by an immature blood–brain barrier leading to a more generalized distribution of MeHg in the developing brain. The activity of this enzyme was significantly depressed by MeHg in brain and when the dams were reared on a selenium-deficient diet. Watanabe et al. [59] argue that functional selenium deficiency caused by MeHg exposure may partly account for the neurobehavioral toxicity of MeHg that is seen in the pups assessed by reflex and motor development, thermal preference, and open-field activity.

Notably, ocean fish are Se-enriched; however, the availability of environmental Se will influence Hg's availability in fresh water fish. As suggested by Ralston, the Hg/Se ratio in waterways may therefore determine the risk associated with exposure to Hg in fish (<http://epa.gov/waterscience/fish/forum/2005/presentations/Monday%20Slides%200919/afternoon/Ralston%20Presentation.ppt>).

Selenoproteins

Thyroid hormone synthesis, metabolism and action require adequate availability of Se [31]. In the face of Se deficiency, its levels as well as those of deiodinase expression are conserved to maintain normal levels in the thyroid gland and the brain, assuring optimal T3 concentrations and function [31]. The functions of selenium are mediated by selenoproteins,

where selenium is specifically incorporated as the amino acid selenocysteine. Several selenoproteins are expressed in brain cells. One class is represented by the antioxidant GPX enzymes, which remove reactive oxygen species. GPX1 is a beneficial but non-essential selenoenzyme, while GPX 4 is required for protection of phospholipids in brain and endocrine tissues. Other selenoenzymes of significance in prevention and reversal of oxidative damage in tissues include thioredoxin reductases and selenium-dependent methionine sulfoxide reductase.

Selenoprotein P has been reported to possess antioxidant activities and the ability to promote neuronal cell survival. Gene knockout studies support its function in the delivery of selenium to the brain. Selenoprotein P is mainly produced in the liver as well as in small amounts in other tissues, including the CNS [60]. Interestingly, deletion of the mouse *Sepp1* gene (*Sepp1*) markedly reduces the levels of brain selenium content [61], and *Sepp1*^{-/-} knockout mice results show severe neurologic dysfunction even when they were fed normal selenium diets [62–66]. Messenger RNAs for other selenoproteins, including selenoprotein W, thioredoxin reductases, 15-kDa selenoprotein, and type 2 iodothyronine deiodinase, are also detected in the brain.

Selenoprotein W levels in animals that are Se-deficient are decreased in all tissues but not in the brain. Interestingly, GPX activities in Se-deficient animals increased in various brain regions. The same authors have also suggested that there are “mobile” and “immobile” GPX fractions in the brain as GPX activity was significantly lower in several brain regions from first-generation rats fed the Se-deficient diet vs. rats fed a Se-supplemented diet. Notably, selenoprotein W (SeW) in cortex, cerebellum, and thalamus were unchanged by Se depletion, but increased SeW levels occurred only in thalamus with Se supplementation [67]. The study confirms earlier observations by the same group, establishing that in the rat the regulation of SeW by Se is markedly different in various tissues [68].

Congruence Between the Effects of Thyroid Hormone Deficiency and the Outcome of MeHg Exposure During Gestation

Deiodinases involved in thyroid hormone metabolism in fetuses and neonates might be a potential target of MeHg [69]. This was demonstrated by perinatal exposure of metallothionein I and II (MT-I/II) null or wild-type neonatal mice to low doses of MeHg, inducing changes in brain deiodinase activities. Exposure to MeHg resulted in a decrease in brain D3 activity, resulting in limited transfer of T4 from the maternal to fetal circulation [66]. D3 activity is also important in the deactivation of T4 to rT3 and to T2. Thus, MeHg toxicity can be illustrated by the fact that levels of T4 in the fetal plasma remained constant, resulting in a harmful excess of T3 in the fetal brain tissue.

Due to the extremely high affinity between mercury and selenium, selenium sequesters mercury and reduces its biological availability, and the reverse is also true depending on concentrations. Therefore, selenium–MeHg interactions have protective as well as toxic consequences when either of these elements is present in abnormal concentrations. Hg-dependent sequestration of selenium and the latter’s inability to maintain optimal function of selenoenzymes may potentially contribute to MeHg toxicity. Previous studies have demonstrated that inorganic mercury inhibits deiodinase activity in adult rat liver [63–66], but future studies on the ability of MeHg to affect deiodinase have yet to be carried out.

The activity of selenoenzymes, including GPX, 5′-DI, and 5-DI were also studied in mice gestationally exposed to inorganic or organic mercury (MeHg). MeHg did not affect the concentration of Se in the brain, while it significantly inhibited the activity of GPX in the fetal brain but not in the maternal brain [69]. 5-DI decreased and 5′-DI increased in the fetal

brain, as if they had responded to hypothyroidism, despite the fact that maternal and fetal thyroid hormone plasma concentrations were unaffected. Because the level of T4 in the fetal plasma was not affected by MeHg, the authors posited that these changes in enzymatic activities may reflect a harmful excess of T3 in the fetal brain [69].

Finally, it has been demonstrated that Hg interferes with thyroidal function, both by interfering with the conversion of T4 to T3 as well as with the production of thyroidal hormones [70]. There are a number of sites where MeHg may directly affect thyroid function. Several studies have demonstrated that MeHg can accumulate in mouse thyroid gland [59] and cause a decrease in thyroidal radioactive iodine uptake and thyroid hormone synthesis [37]. Similarly, mercury was also shown to deposit in thyrotrophs of rats administered MeHg [71]. MeHg has also been shown to cause a transient decrease in serum T4 levels (followed by an increase in serum TSH levels) [72].

Similarities Between Hypothyroidism and MeHg Poisoning

Notable changes in circulating amounts of thyroid hormones develop in association with selenium deficiency in lambs [73] and other animal models. It has been hypothesized that MeHg toxicity may be associated in a similar effect, resulting from sequestration of selenium by excess MeHg [57]. Accordingly, it is intriguing that selenium deficiency, thyroid deficiency, and excessive MeHg can lead to similar neurodevelopmental effects.

Using tracing techniques such as BrdU immunocytochemistry, several studies have established that aberrant neocortical cell migration is defective in the progeny of severely hypothyroid dams [74]. In rats maintained on a low iodine uptake, cell migration and cytoarchitecture in the somatosensory cortex and hippocampus of 40-day-old progeny show mislocalization of cells for their developmental age. Somatosensory cortex layering was blurred, and in the cortex, normal barrel receptor field were absent emphasizing that histogenesis and cytoarchitecture are significantly perturbed in conditions associated with maternal hypothyroxinemia [17, 75, 76]. Thus, early maternal thyroid hormone deficiency, and even hypothyroxinemia, may lead to cytoarchitectural changes and altered migratory cortical cell patterns. Mechanisms associated with this effect may reflect a decrease in the availability of the hormones to the developing brain or indirectly via poor placental function associated with maternal hypothyroidism.

Similarly, neuropathological sequela of human exposure to MeHg in full-term newborn infants is also characterized by disturbances in the development of the brain cytoarchitecture, consisting of abnormal migration of neurons to the cerebellar and cerebral cortices and deranged cortical organization of the cerebrum. The effect of MeHg is characterized by heterotopic neurons in the white matter of cerebrum and cerebellum [44]. In animal models, where these effects can be more clearly defined, similar techniques established abnormally widespread distribution of the labeled cells throughout cortical layers II–VI of offspring exposed to MeHg on embryonic days 16 (E16) and E21, indicating disruption of the inside–out pattern of neuronal migration [77]. Unfortunately, selenium levels in either study were not evaluated.

In summary, while it is yet to be determined whether these effects are directly related to altered maternal thyroid hormone homeostasis, the phenotypes of hypothyroidism and MeHg exposure clearly share multiple common features. Taken together, these studies establish an inhibitory effect of MeHg on thyroid hormone synthesis, secretion, and metabolism. The implications of these combined effects are that thyroid hormone metabolism imbalances resulting from Hg exposure might directly lead to deficits in neurodevelopment.

Future considerations need to be directed at the possibility that interactions between MeHg and selenium result in altered selenoenzyme activity and loss of optimal control over thyroid hormone synthesis, metabolism, and deactivation, which directly contribute to the neurodevelopmental effects associated with gestational MeHg exposure. MeHg readily accumulates in the fetal brain, its concentrations exceeding the corresponding dams' brain levels. Thus, the possibility of subtle changes in selenoenzyme function and perturbed neurodevelopment as a result of altered thyroid hormone status seems a worthy experimental pursuit.

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Fig. 1.
Deiodinase activity: activation of T4 by D1 and D2 to T3 and deactivation to rT3 and T2

Table 1**The Deiodinases: Tissue Localization and Activity**

Type	Location	Function
D1 (iodothyronine deiodinase)	Liver, kidney, muscle tissue and thyroid gland	Able to deiodinate both phenolic and tyrosil rings
D2 (5'-iodothyronine deiodinase)	Brain, some in testis and thyroid gland	It is the major activating enzyme; generates the active form of thyroid hormone T3 via deiodination of T4 phenolic ring or rT3
D3 (5-iodothyronine deiodinase)	Fetal tissue and the placenta	It is the major inactivating enzyme; deiodinates T4 to rT3, rT3 to T2, or deiodinates the T3 tyrosil ring to T2

Table 2

Recommended Selenium Intake Values

Dietary reference intakes (DRIs)	
Age	Males and females (3g/day)
0–6 months	15 ^a
7–12 months	20 ^a
1–3 years	20
4–8 years	30
9–13 years	40
14–18 years	55
19+ years	55
Pregnant women	60
Lactating women ^b	70

Adapted from: Institute of Medicine, 2000. The AI is the mean value of observed intakes as calculated from data on the selenium content of human milk and other studies which estimated the volume typically consumed as determined by test weighing of infants in the age category. In the age group 7 through 12 months, an amount is added for the contribution to intake of selenium obtained from weaning foods

^aDenotes adequate intake; all other values are the recommended DRIs

^bHuman milk selenium concentration appears to be about 18 µg (0.23 µmol)/l in Canada and the USA [36]