

Pathophysiological Mechanisms of Mercury's Effect on Thyroid Gland

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Abstract

With acute exposure, mercury has high affinity for thyroid tissue causing atrophic changes in thyroid gland. Inhibition of coupling, antagonism of deiodinases and induction of autoimmune reactions are the three fundamental pathophysiologic mechanisms that have been documented as it relates to mercury's effect on thyroid. Mercury inhibits the coupling process through inhibition of iodide incorporation into iodothyronine fraction. Thyroid hormone has an inverse relationship with body mercury levels as measured by the three primary biomarkers, however, this relationship was found to be independent of the HPT axis. Mercury also decreases production of the potent form of thyroid hormone, i.e. triiodothyronine (T3), through its antagonizing effect on deiodinases through selenium and selenoproteins. Selenium plays a dichotomic role by decreasing affinity of mercury towards biological tissue while causing retention and saturation of mercury by attaching it to selenoproteins. Reduction of anti-TPO and anti-Tg antibodies has also been observed after the removal of source of mercury exposure in a statistically significant study. Further research is required to clinically analyze these thyro-toxic mechanisms of mercury.

Keywords: Mercury; Toxicity; Thyroid; Thyroxine; Triiodothyronine; Selenium; Amalgam; Deiodinases; Autoimmunity;

Abbreviations

Mercury (Hg), Triiodothyronine (T3), Thyroxine (T4), World Health Organization (WHO), Hypothalamic-Pituitary-Thyroid Axis (HPT), Antinuclear Antibodies (ANA), Glutathione Peroxidase (GPX), Diiodotyrosine (DIT), Anti-Thyroid Peroxidase (Anti-TPO), Anti-Thyroglobulin (Anti-Tg).

Introduction

Mercury, also known by its Latin name hydrargyrum (Hg), is considered one of the top 10 public health contaminants by WHO and its toxicity has been documented since 19th century [1-3]. Mercury is primarily seen in three forms including elemental, inorganic and organic [4] and has been found to be associated with various pathologies including thyroid disorders [5,6]. One of the earliest studies on mercury's effect on thyroid tissue was carried out in Nishida, et al. [5] to analyze for multiple variables

causing toxicity in mice models. Nishida, et al. [5] examined the toxicity of organic and inorganic mercury in mice with inoculation of radio-isotopically labeled $\text{CH}_3^{203}\text{HgCl}$ and $^{203}\text{HgCl}_2$ [5]. The data were analyzed for changes in growth, body and thyroid weight as well as the affinity of mercury for thyroid. The study concluded mercury having "moderate to high" affinity for thyroid [5] and since then various studies have highlighted the pathophysiologic mechanisms causing the toxicity of mercury on thyroid function. These studies have also underlined the mechanisms involved in direct and indirect inhibitory effects of mercury through deiodinases and selenium resulting in peripheral conversion of thyroxine (T4) to triiodothyronine (T3), structural inhibition of coupling process of thyroid hormone synthesis and possible induction of autoimmunity [5,6].

Method

This literature review compiles documented pathophysiologic mechanisms of mercury's toxicity on thyroid tissue from clinically and statistically relevant studies. The information is derived from peer-reviewed studies searched on PubMed, science direct and Google scholar. Statistically significant data were analyzed and replotted in form of figures from previous peer-reviewed literature. Other numerical data were gathered from Center for Disease Control and Prevention, World Health Organization, Environmental Protection Agency and Agency for Toxic Substances and Disease Registry.

Pathophysiology of Hg Toxicity on Thyroid Tissue

Deiodinases and selenium

Soldin et al. examined the effect of methyl mercury (organic mercury) on thyroid as it relates to deiodinases, which are selenium dependent enzymes responsible for conversion of thyroxine (T4) to triiodothyronine (T3) [6]. T3 is biologically active and more potent form of thyroid hormone, as it is able to induce gene expression on the nuclear thyroid receptors [7]. and is primarily derived by deiodinase driven conversion of T4 in brain, liver, kidney and peripheral tissue [6]. Selenium plays a critical role in deiodinases as it is not only a part of 25 selenoproteins identified in the human protein complement but also is

a part of selenocysteine, which is now considered to be the 21st essential amino acid [8]. Selenocysteine itself is found in enzymes such as glutathione peroxidase (GPX) as well as the iodothyronine deiodinases [6]. While deiodinases convert T4 to T3, (Figure 1) the more potent and biologically active form of thyroid hormone, glutathione peroxidase also plays an important role in protecting against oxidative stress and damage from free radicals [6,7].

Hence, selenocysteine not only plays an endocrinologically vital role in peripheral conversion of T4 to T3 but also plays a protective role against free radicals. All deiodinases utilize selenocysteines in their structure, making them selenium dependent enzymes. The substitution of selenocysteines by "sulfur-containing cysteine mutants" [6], decreases the efficacy of deiodinases, hence making selenium a crucial part of the thyroid work machinery.

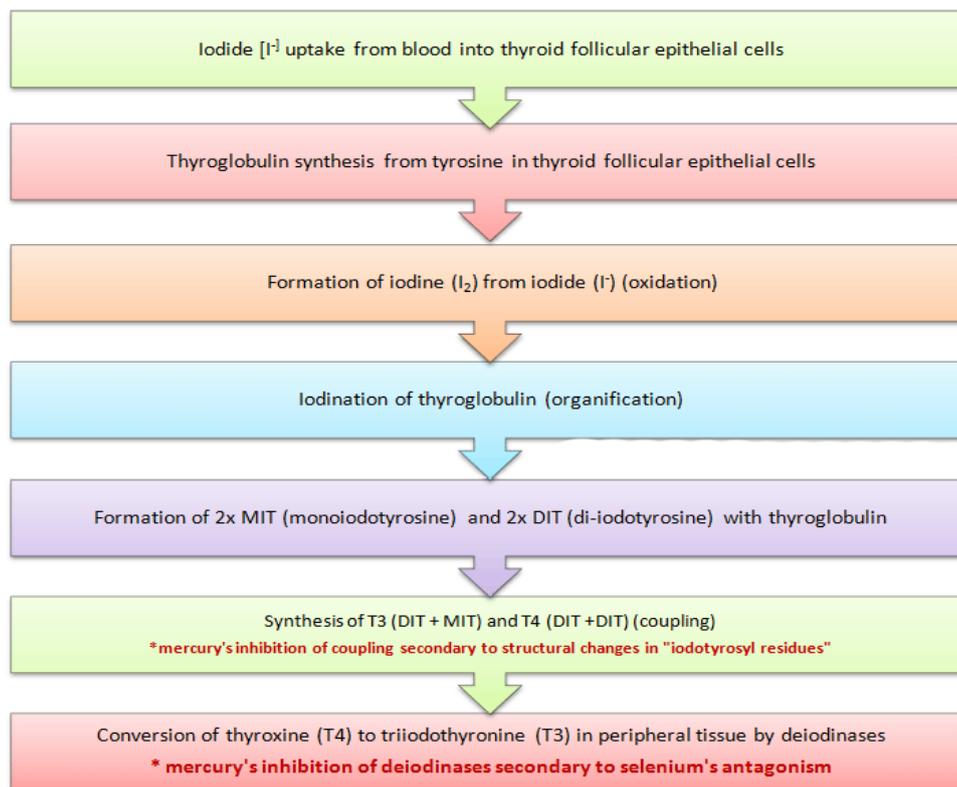


Figure 1: Inhibitory effect of Hg on pathways of thyroid hormone synthesis and peripheral conversion of thyroxine to triiodothyronine Ref [5,6,16]
*inhibitory effect of Hg.

Selenium is known to have a protective effect against mercury toxicity, however, its effect on a molecular level is enigmatic. Selenium's role as an inhibitor of oxidative stress has a protective effect against mercury toxicity but ironically, selenium also decreases the excretion of mercury [9-12]. The exact mechanism of selenium's effect on mercury is unknown but it is postulated that selenium causes deviation of mercury from biological tissue towards selenium based proteins, [12]. which protects human tissue from mercury toxicity. However, selenium's non-excretory effect can cause chronic deposition of mercury. The enigmatic effect of selenium is overall protective, even though it can cause retention of mercury through selenoprotein attachment and saturation, it makes tissue toxicity unlikely. Of all the tissues, thyroid has the highest amount of selenium found in each gram of tissue [13]. making it a valuable thyro-protective and regulatory mineral in maintaining euthyroid status. Selenium's role in improving thyroid function was also examined by Drutel et al. [13] it was found that selenium was responsible for decreasing

anti TPO antibodies in Hashimoto's with overall improvement in thyroid imaging results [13]. According to Soldin et al. there might be a pathophysiological similarity between mercury toxicity and hypothyroidism [6]. as selenium aids thyroid gland in its normal physiologic function while acting as a thyro-protective agent. Hypothyroidism can be directly related to dietary selenium deficiency or can be secondary to selenium deficiency caused by mercury toxicity. Since thyroid hormone synthesis is a selenium dependent process and even a minute amount of selenium can play a critical role in maintaining euthyroid status, the possible interrelation between the pathophysiologic and molecular patterns for both etiologies of thyroid dysfunction need to be evaluated further.

Individual pathways of thyroid hormone production are affected by environmental substances and carcinogens [14]. These xenobiotic substances suppress thyroid synthesis pathways, including competitive antagonism of iodine symporter;

inhibition of thyroid peroxidases, as well as up regulation and inhibition of thyroid deiodinases. Direct relation of heavy metals and environmental chemicals with various physiological and endocrinological functions was also evaluated by Chen et al. study, which analyzed the thyroid status of individuals with heavy metal exposure and if any direct relation exists between thyroid hormones and the HPT axis [15]. The study analyzed a sample group of 11to19 year old subjects as well as a sample of adults from the U.S. National Health and Nutrition Examination Survey (NHANES) 2007-2008. It was observed that as the body mercury levels go up, thyroid hormone levels go down [15]. The HPT axis and TSH levels were not affected by mercury levels. The direct relationship of mercury with thyroid hormone without the involvement of the HPT axis clearly demonstrated the lack of affinity of mercury with the pituitary gland and the hypothalamus, while creating uncertainty regarding the issue of mercury's permeability through blood brain barrier. Whether or not thyroid tissue has natural affinity for mercury or structural similarity to some form of mercury like it does to substances like gluten, or mercury's attachment to thyroid is indirectly related to its selenium content, is something that requires more in-depth research.

Coupling

Nishida et al. evaluated the toxicity of organic (methyl-mercuric chloride) and inorganic (mercuric chloride) mercury on thyroid tissue. Mice were inoculated with isotopically labeled mercury (CH₃HgCl or HgCl₂) with a single dose as well as continuous doses for a 30-day period. The mice that were injected with mercury showed transient growth delays after inoculation with highest concentration of either form of mercury as well as significant atrophic reduction in thyroid

weight when inoculation levels for either form of mercury reached 150 ug/d. The mercurials also suppressed coupling as they inhibited the incorporation of radioactive-iodide into the iodothyronine fraction [5]. Coupling of iodotyrosine is a major step in the thyroid synthesis pathway, however it is also one of the least studied pathways [17]. Coupling is the attachment of two iodinated tyrosine molecules (iodotyrosine) resulting in di-iodotyrosine (DIT) or in a single (mono) iodotyrosine molecule that further results in mono-iodotyrosine [18]. Combination of di-iodotyrosine + di-iodotyrosine produces thyroxine [tetra-iodothyrosine] (T4) and grouping of di-iodotyrosine + mono-iodotyrosine produces tri-iodothyrosine (T3) [18]. Coupling is a crucial step in producing and proportioning T4 and T3.

Ratio of both mercurials with reference to organ weight were measured and both mercurials showed "moderate to high" affinity for the thyroid gland; the ratios were obtained for all the organs tested, both with single dose as well as with 30-day administration [5]. The ratios were expressed with the values obtained for liver as a standard of comparison and the values were expressed as values of radioactivity (cpm)/tissue weight of the specific organ in (mg). The ratios obtained for liver to CH₃₂₀₃HgCl were 1:0.307 cpm/mg and 1:0.297 cpm/mg for a single dose and continuous doses of 30 days respectively. Ratios obtained for liver to ²⁰³HgCl₂ were 1:0.289 cpm/mg for single dose and 1:0.289 cpm/mg for continuous doses for 30 days. (Figure 2A) represents the ratio of mercurials after single dose administration in thyroid tissue as well as in other organs and it can safely be deduced that mercury has "high" affinity for thyroid after acute administration. (Figure 2B) represents the ratio of mercurials after continuous administration for 30 days in thyroid tissue as well as other organs and in this case, mercury represents "moderate" affinity for thyroid gland after chronic administration [5].

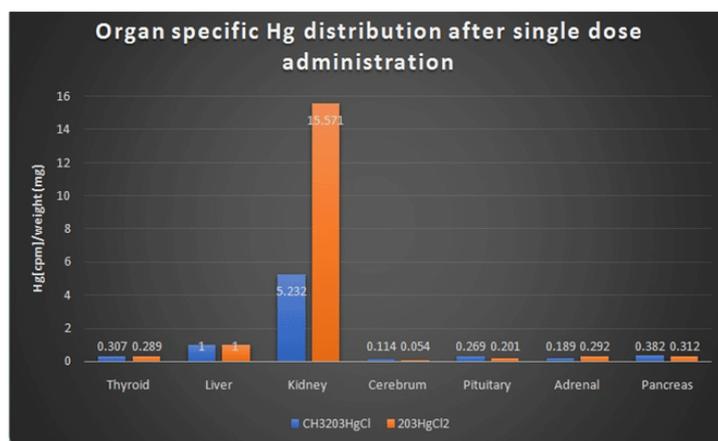


Figure 2A: Derived from data in Table 1 of reference 5. Figure represents the ratio of organic and inorganic mercury in various organs with isotopically labeled mercury with mean radioactivity (cpm)/tissue weight (mg) of the organ. Hepatic ratios were used as baseline with ratios of 119.79 + 18.13 and 96.59 + 20.31 for methyl and inorganic mercurial, respectively (0.2 > p > 0.1).

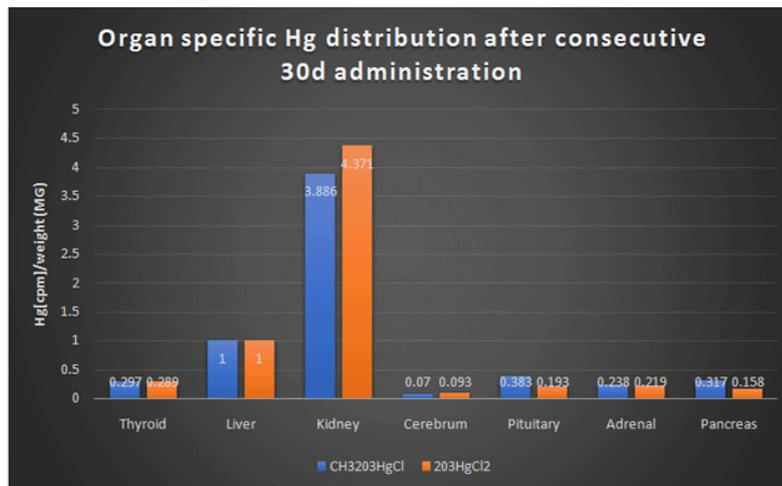


Figure 2B: Derived from data in Table 1 of reference 5. Figure represents the ratio of organic and inorganic mercury in various organs with isotopically labeled mercury with mean radioactivity (cpm)/tissue weight (mg) of the organ. Hepatic ratios were used as baseline with ratios of 74.74 ± 22.51 and 58.10 ± 9.18 for 30 d administration of methyl and inorganic mercurials, respectively ($0.2 > p > 0.1$).

Both mercurials were found to cross the epithelial layer and create “unfavorable” structural changes in “iodotyrosyl residues” after attaching to thyroglobulin and clearly hindering the coupling process [5]. At the same time mercurials showed “moderate to high affinity” for thyroid tissue based on acute and chronic administration with high affinity seen in acute administration and tolerance, and/or biotransformation playing a role in mercury having lower thyroid affinity after chronic administration.

Autoimmunity

With more than 100 million amalgam fillings placed annually in the United States alone, it represents a major source of thyroid toxicity [19]. Amalgam is a metal-based filling with silver appearance and primarily comprises of liquid mercury in elemental form in combination with metal alloy consisting of silver, tin and copper in proportions of 50%, 35%, 9% and 6% respectively [20]. Mercury is known to have significant association with autoimmune and allergic processes, hence representing a good starting point for thyroid disorders of autoimmune etiology. Amalgam fillings represent a major source of mercury exposure and its effect on autoimmune thyroid disorders has been examined by various studies in the past. In the past, studies have demonstrated mercury inducing an immune response in susceptible animals and humans based on the genetic and immunologic makeup of the species [21–24]. Sterzl et al. study was carried out to analyze the effect of amalgam removal on antibodies that are found in patients with autoimmune thyroiditis. The study demonstrated reduction of thyroid antibodies after removal of mercury exposure, in this case amalgam fillings [25]. The antibodies included anti-thyroid peroxidase (TPO) and anti-thyroglobulin (anti-Tg). There was a significant decrease in the antibodies level in patients who had hypersensitivity to mercury [25]. Reduction of anti-TPO and anti-Tg antibodies in patients with mercury hypersensitivity gives a strong indication of activation of autoimmune cascade by mercury. Those who are

hypersensitive to mercury have a pronounced immunological response to mercury and such population represents the same group which is more likely to develop autoimmune diseases in response to external instigators. Removal of amalgam fillings in patients who are hypersensitive or allergic to mercury would be beneficial as mercury represents a significant risk factor for those with autoimmune diseases [26].

The most common form of autoimmune thyroid disorder, Hashimoto thyroiditis causes infiltrating lymphocytes and T cells to cause cytotoxic effect on the thyroid resulting in hypothyroidism [27]. Previous studies in animals have shown mercury to cause autoimmune effects with T cell induced lymphocytosis and up regulation of immune mechanism as a result of (inorganic) mercury exposure [28]. A similar T cell induced process cannot be ruled out for autoimmune thyroiditis through amalgam fillings with taking into consideration the biotransformation of mercury from elemental to inorganic form. A good starting point for testing of autoimmune diseases is testing for antinuclear antibodies (ANA), which is positive in autoimmune disorders [29]. As a highly sensitive test for autoimmune disorders, a negative ANA is good for ruling out some of the autoimmune disorders with a substantially high negative predictive value (NPV), however a positive ANA can have multiple interpretations depending on the titers and patterns [29].

Somers et al. examined the association of positive ANA titers and mercury biomarkers in context of ANA pattern and titers. The study was based on U.S. National Health and Nutrition Examination Survey (NHANES) data from females in childbearing age. Data was gathered for 6 years (1999–2004) and was further divided into 2-year subgroups in sequential order. Participation for the survey was above 75 % in all subgroups and ANA was measured using indirect immunofluorescence with titer cutoff strength of $> 1:80$. Of all the subjects in the survey group, “16 % had ANA positivity with geometric mean (geometric SD)

mercury concentrations of 0.22 (0.03) ppm in hair, 0.92 (0.05) µg/L in blood, and 0.62 (0.04) µg/L in urine and association were strongest for high-titer ($\geq 1:1,280$) ANA: hair, OR = 11.41 (95% CI: 1.60, 81.23); blood, OR = 5.93 (95% CI: 1.57, 22.47)" [30]. It was found that hair and blood mercury levels have a positive correlative relationship with ANA positivity. ANA positivity does not represent a clinical pathology but a hyperactive autoimmune state which can be interpreted as "subclinical autoimmunity", or individuals who have the biomarker positivity without active clinical disease.

Amalgam driven elemental mercury's effect on thyroid can be through T cell-based immune response as it has been observed with inorganic mercury. Similar mechanism can be responsible for elemental mercury toxicity secondary to biotransformation to inorganic mercury since direct toxic effect of elemental mercury from amalgam has not been documented until now. With ANA having a statistically significant positive correlation with hair and blood mercury levels, ANA testing along with mercury serum and hair levels can give more insight on the origins and Pathophysiology of autoimmune thyroid disorders in those who have been exposed to toxic mercury levels though amalgam fillings.

Discussion

Nishida et al. [5] was one of the earliest studies to document the effect of mercury toxicity on thyroid tissue. Since Nishida et al. many Pathophysiology mechanisms have been outlined on mercury's effect on thyroid tissue. These studies have outlined various mechanisms specific to individual forms of mercury. This review is intended to compile all the pathophysiologic mechanisms of mercury's toxicity on thyroid tissue from studies with a statistically significant yield. First proposed mechanism described by Nishida et al. was through structural inhibition of coupling process through conformational changes in "iodotyrosyl residues", effecting the coupling mechanism of thyroid hormone synthesis. Iodide integration was affected to interfere with iodothyronine and the overall coupling process. The study also found that organic and inorganic mercury possess "moderate to high" affinity for thyroid gland depending on the duration of exposure [5]. After acute inoculation mercury was found to have high affinity for thyroid tissue when expressed as a ratio of radioisotopically labeled mercury/weight of the tissue with ratio of organ affinity for hepatic tissue as control. Chronic inoculation only yielded moderate affinity for thyroid tissue, whether or not this was secondary to mercury's tolerance or transformation was unknown. Growth delays were also observed with highest inoculation doses of both organic and inorganic mercurial's as well as atrophic changes in thyroid weight [5]. According to Nishida et al. mercury was found to have a more substantial effect on T4 concentration as compared to T3 concentration with taking in consideration T4 concentration as a direct reflection of measurable thyroid function since T4 is primarily produced by thyroid gland where as T3 is produced both by thyroid gland as well as sources of peripheral conversion. This also substantiates the inhibition of coupling process and the proportion with which thyroxine is produced in the thyroid tissue.

Indirect effect of mercury through deiodinases and selenium inhibition was highlighted by Soldin et al. Thyroid contains the highest concentration of selenium per gram of tissue of any organ in the human body and selenium plays as significant role in the optimal function of deiodinases, which are primarily responsible for converting T4 to T3. Mercury implants itself into deiodinases in place of selenium while directing mercury away from biological tissue towards seleno-proteins, hence playing a protective role towards thyroid and decreasing overall tissue toxicity caused by mercury. The thyro-protective role of selenium is concentration dependent and eventually with selenium saturation due to high concentration of mercury, this role would eventually diminish.

Documented autoimmune effect of inorganic mercury on thyroid tissue is primarily through T cell immune response. It has been strongly demonstrated by Sterzl et al. that removal of amalgam fillings resulted in improved thyroid function secondary to reduction in thyroid autoantibodies titers. The study was not able to analyze the mechanism of antibody reduction and whether or not elemental form of mercury was responsible for direct toxic effect or mercury had gone through biotransformation to induce a T cell response from inorganic form. It has been established that inorganic mercury induces a T cell response and serum mercury levels have also been found to have a positive correlation with ANA positivity, which is a strong reflection of autoimmunity. Likewise, Sterzl et al. also concluded that removal of amalgam fillings would decrease the pathogenesis of autoimmune diseases. It is evident that amalgam removal decreases thyroid antibody titers, and mercury titers are associated with ANA positivity and inorganic mercury causes T cell immune response. Further research is required to determine whether elemental mercury is playing the causative role behind thyroid autoimmunity or it is secondary to biotransformation to inorganic form, inducing T cell response.

Recommendations

With mercury exposure inhibiting various pathways of thyroid hormone synthesis, as well as peripheral conversion of T4 to T3, it is imperative that sensitive screening modalities are utilized in those who are exposed to mercury. Regular screening for euthyroid status in those who have amalgam fillings as well as potential of exposure from secondary environmental sources should be considered. Serum, hair and urine biomarkers can be used to establish mercury levels in susceptible subjects with known sources of mercury exposure.

Conclusion

Organic and inorganic mercury have been incriminated with thyroid dysfunction, but it is still not clear whether the role of elemental mercury on thyroid tissue is direct or secondary to biotransformation. With reported prevalence of hypothyroidism from 1 to 10% in the general population [31], the trifocal inhibitory effect of mercury on thyroid tissue in statistically significant studies need to be addressed and further research is required to analyze the possible role mercury might be playing in hypothyroidism.

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