REVIEW ARTICLE

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Impact of Thyroid Hormones Disrupting Potential of Environmental Polychlorinated Biphenyls and Heavy Metals on Brain Functions: A Review Article

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ABSTRACT

The normal functions of the brain depend upon thyroid hormones including tetraiodothyronine and tri-iodothyronine. The environmental polychlorinated biphenyls produce neurological deficiencies by disturbing the normal cascade of thyroid hormones in the brain. These chemicals mimic the structure of thyroid hormones. Like thyroid hormones, these toxic compounds also contain a biphenyl ring and halogen atoms in their basic structure. These toxic environmental chemicals mostly act at receptor levels and have the ability to attach to thyroid hormones binding proteins. The disturbance created by these environmental toxicants results in serious brain abnormalities. Furthermore, heavy metals like lead, mercury, and cadmium can also disturb the normal levels of thyroid hormones in plasma. The thyroid disrupting potential of these heavy metals creates a negative impact on the cognitive performance of the brain. The heavy metals act either by inhibiting the carrier and enzymatic (Deiodinases) proteins of thyroid hormones or by altering the morphological features of the thyroid gland. The developing fetus is more prone to develop serious abnormal brain functions due to the exposure of these toxicants because early brain development is dependent upon thyroid hormones coming from mother. The main objective of this study is to explore the indirect effect of polychlorinated biphenyls and heavy metals on brain functions. In our country, many cases of brain abnormalities arise due to these environmental toxicants but the reality is ignored due to lack of proper information about this fact.

Keywords: Thyroid hormones, polychlorinated biphenyls, heavy metals, brain functions

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INTRODUCTION

Thyroid hormones perform an essential role in brain development and functioning (1). The tetraiodothyronine, an active form of thyroid hormones, which is also known as thyroxin, has a crucial role in this matter because tri-iodothyronine, inactive form, cannot cross the blood-brain barrier. The fluctuations in the concentrations of thyroid hormones can occur due to the exposure of environmental polychlorinated biphenyls. The exposure of these chemicals leads to a reduction in tri-iodothyronine and tetraiodothyronine concentrations (2). The toxic polychlorinated biphenyls include a variety of lipophilic chemicals moieties whose presence has been investigated in samples taken from wildlife and the human population (3). These toxic chemical compounds consist of almost 209 individual congeners (4). These are industrial compounds comprising of a biphenyl ring which is chlorinated at various positions as shown in Figure-1. The chlorine

atoms may present at any position on the biphenyl ring. It depends upon a particular derivative of this chemical compound class. The preparation of polychlorinated biphenyls is prohibited because the concentration of these endocrine disruptors is increasing day by day in the surrounding environment (5). The heavy metals can also affect thyroid hormone status leading to abnormal brain functioning. In this scenario, the role of lead, cadmium, and mercury is very prominent. In this article, there is a discussion of some important literature studies. The results of these studies suggest a key role of environmental polychlorinated biphenyls and heavy metals in brain dysfunction.

Thyroid disrupting potential of toxic environmental polychlorinated biphenyl compounds

The experimental studies on the human population revealed a negative correlation between thyroid hormones and environmental polychlorinated biphenyls compounds (6) while some studies have shown a positive correlation between polychlorinated biphenyls and thyroid-stimulating hormones (7, 8). Not only human beings but also animal species such as seals (11), polar bears (10), and sea lions revealed a reduction in tetraiodothyronine and tri-iodothyronine levels due to exposure of toxic polychlorinated biphenyls (9). The experimental rat pups also revealed a reduction in thyroid hormone status due to these toxicants (12, 2). Furthermore, a study on newborns has revealed a negative correlation between these environmental toxicants and free tetraiodothyronine. However, some studies remained unsuccessful in finding such associations (3). The thyroid disrupting effect of some particular derivatives of toxic environmental Polychlorinated biphenyls has been given in Table-1.

Polychlorinated biphenyl toxicants and abnormal brain functions

The toxic environmental polychlorinated biphenyls can influence neuronal functioning by hindering THs cascade (13, 14). The epidemiological studies confirmed that the exposure of polychlorinated biphenyl chemicals could indirectly create neurological deficiencies of attention, memory, motor functions, and visual-recognition during developmental stages (5). These environmental compounds create hypothyroidism like situation in rat brain especially in white matter; therefore, these can reduce not only the total number but also the cellular density of oligodendrocyte (15). Furthermore, a derivative of polychlorinated-biphenyls i.e., polychlorinated biphenyls-118 (PCB-118) mimics the activity of tri-iodothyronine by triggering the differentiation of neural progenitor cells into oligodendrocyte and neurons (16). One thing of great concern is that if polychlorinated biphenyl chemical compounds cause the hindrance of thyroid hormones then the developmental processes mediated by these hormones should also be affected by polychlorinated biphenyl's exposure. However, replacement therapy can recover all these changes. In this scenario, one study has proposed that the administration of exogenous thyroxin can recover the hearing deficits (3) and choline acetyltransferase activity in the cerebral cortex (17).

Expected mechanisms of actions of polychlorinated biphenyl toxicants

According to literature studies, some expected mechanisms of actions of environmental polychlorinated biphenyls are mentioned below.

1. Both environmental polychlorinated-biphenyls and thyroid hormones have similar structures (5) as shown in figure-1. The toxic polychlorinated biphenyls undergo metabolic hydroxylation to produce hydroxyl derivatives having more resemblance with thyroid hormones which accumulate in various fetal body chambers. These chemical metabolites mostly detected in the liver, plasma, and brain (4). The level of these chemical metabolites in tissues was negatively correlated with thyroid hormones, particularly tetraiodothyronine (18, 19).
2. These chemicals can also attach with Thyroid hormones binding proteins such as transthyretin, a protein responsible for the transportation of thyroid hormones from one niche to another. However, limited studies have been conducted to elaborate this fact and still, there is no proper authentication about this aspect (20).
3. The environmental polychlorinated biphenyl toxicants may influence neuronal functions by hindering cascade of thyroid hormones as shown in Figure-3 (21). These toxicants act by changing the availability of deiodinase enzymes. These enzymes are involved in the production of different forms of thyroid hormones (49).

There are several types of deiodinase enzymes such as deiodinase-1, deiodinase-2, and deiodinase-3. However, there are two more types i.e. deiodinase-4 and deiodinase-5 but these are rare (1). These enzymes are distributed into different tissues in the human body as shown in Table-2.

Table 1: Showing thyroid disrupting effect of most common toxic derivatives of environmental polychlorinated biphenyls. Where Decrease: (↓) and T4: tetraiodothyronine

Environmental Toxicants	End Effect	References
Aroclor (1254)	T4 level (↓)	(41)
PCB (77)	T4 level (↓)	(2)
PCB (153)	T4 level (↓)	(44)

4. The researchers have elaborated that the metabolites can exert thyroid receptor agonist activity (22, 23). In contrast, many other experimental observations have revealed thyroid receptor antagonist activity (24). Perhaps at one time, the polychlorinated biphenyls can behave differently or it may depend on the circumstances of the assay which has been used during experimental study (5). The toxic polychlorinated biphenyls can inhibit the attachment of tri-iodothyronine with thyroid receptors to suppress the transcription process.
5. The toxicants may interfere with thyroid hormone function at the receptor level. These polychlorinated compounds may cause the detachment of the thyroid receptor by separating the heterodimer-complex. The polychlorinated biphenyl compounds can also induce a dose-dependent inhibition of thyroid-stimulating hormone by enhancing the production of cAMP and adenylate-cyclase activity (17). Some investigational studies reported the histopathological alterations due to oral administration of polychlorinated biphenyls by the oral route which are given below
    - Laminal obliteration
    - Follicular destruction
    - Edema
    - Intra follicular fibroblast proliferation
    - Hemorrhage
    - Hypertrophy (21, 25).

POLYCHLORINATED BI-PHENYL TOXICANTS AND PREGNANCY

During early pregnancy thyroid hormones come from mother because of immature thyroid axis as shown in Figure-3Up till now, we have understood very well that the thyroid hormones perform a significant role in brain development. The environmental polychlorinated biphenyls decreased the levels of thyroid hormones and thyroid-stimulating hormones in pregnant women in several experimental studies (26). A study on women's infants revealed a negative correlation between environmental polychlorinated biphenyls and maternal thyroid hormones at postpartum stages which is referred to as the last stage of pregnancy (27). However, some studies remained unsuccessful in finding such facts (28).

IMPACT OF HEAVY METALS ON THYROID HORMONES

LEAD

The exposure of lead can disrupt the levels of thyroid hormones in the body (29). Whether lead exposure alters thyroid functions or not? The available evidence is mixed because some investigators have reported fluctuations in serum thyroid hormones level but several other investigators do not provide such data (30). In this regard, the experimental studies on cows from lead polluted areas revealed a remarkably higher concentration of tetraiodothyronine and tri-iodothyronine (32). Lead exposure is also found to be associated with low levels of free tetraiodothyronine in pregnant women (31). The lead produces its toxic effect on brain functions by impairing the production of transthyretin, a protein responsible for the transportation of thyroid-hormones within the brain, in choroid plexus (33).

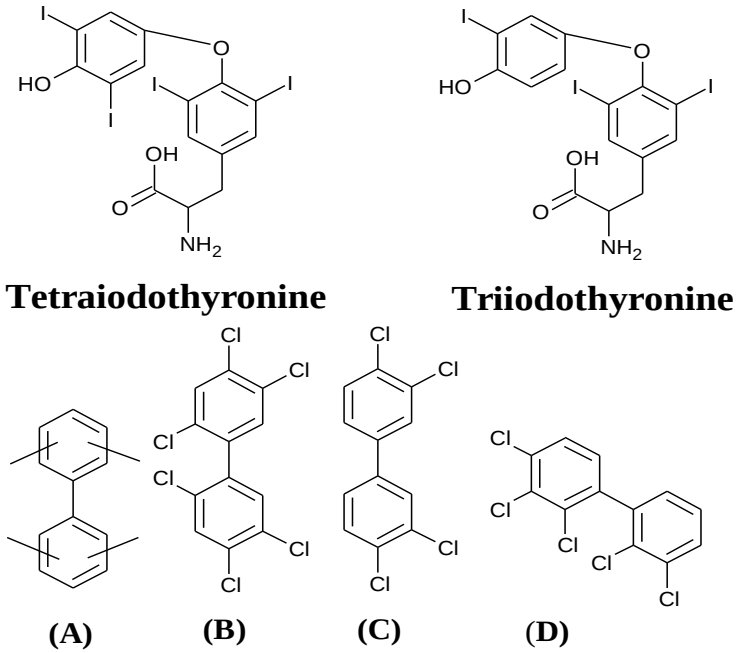

Figure 1: Showing the structures of tetraiodothyronine and tri-iodothyronine. Moreover, it is also showing the most common toxic derivatives of polychlorinated biphenyls as indicated by **(A)**, **(B)**, **(C)** and **(D)**. where **(A)** Common structure of polychlorinated biphenyls; **(B)** Polychlorinated Biphenyl-153; **(C)** polychlorinated biphenyl-77 and **(D)** Aroclor-1254. It is cleared from the figure that both thyroid hormones and polychlorinated biphenyls derivatives possess biphenyls rings which is a common structural feature. Besides, halogen atoms are also present at different positions in both thyroid hormones and polychlorinated derivatives which is another similarity. So, due to the presence of biphenyl ring and halogen atoms, these molecules show structural resemblance with each other. Therefore, the polychlorinated biphenyl toxicants may mimic the activity of thyroid hormones at the receptor level.

Mercury

The mercury is a cationic toxin that is found with several other environmental pollutants in the form of the complex. The human intakes these metallic cations mostly from
marine organisms, such as marine mammals and fishes.

Mercury cations form a complex with amino acids, such as cysteine, and distribute into different organs of the body. These cations can also get transfers across the brain and placental barriers (34, 35). According to researchers, the mercury is one of those pollutants which can alter thyroid gland functions by inhibiting the deiodination of thyroid hormones (30).

Cadmium

The chronic exposure of cadmium in female mice did not affect the tri-iodothyronine level while a reduction in serum tetraiodothyronine concentration was observed. However, this change was not remarkable (36). In one experimental study, the exposure of cadmium during the gestational period was associated with low levels of thyroid hormones (37). The exposure of cadmium can also cause a change in tetraiodothyronine producing follicle cells in the thyroid gland (36).

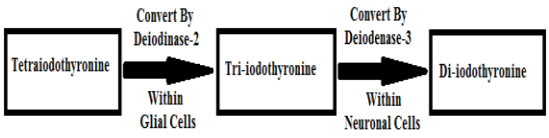

Figure 2: Showing how deiodinases are involved in the production of different forms of thyroid hormones. The polychlorinated compounds interfere with this enzyme catalytic cascade and destroy the normal functioning of the brain.

Table 2: Showing different types of deiodinases and their location inside the human body. Where TG; Thyroid gland, PG; Pituitary gland, SM; Skeletal muscles and CNS; Central nervous system

Deiodinases	Location	References
Deiodinase-1	Kidney, Liver, TG, PG	(45)
Deiodinase-2	Heart, Placenta, SM, Pituitary, TG, CNS	(46)
Deiodinase-3	Placenta, liver, CNS	(47) (48)

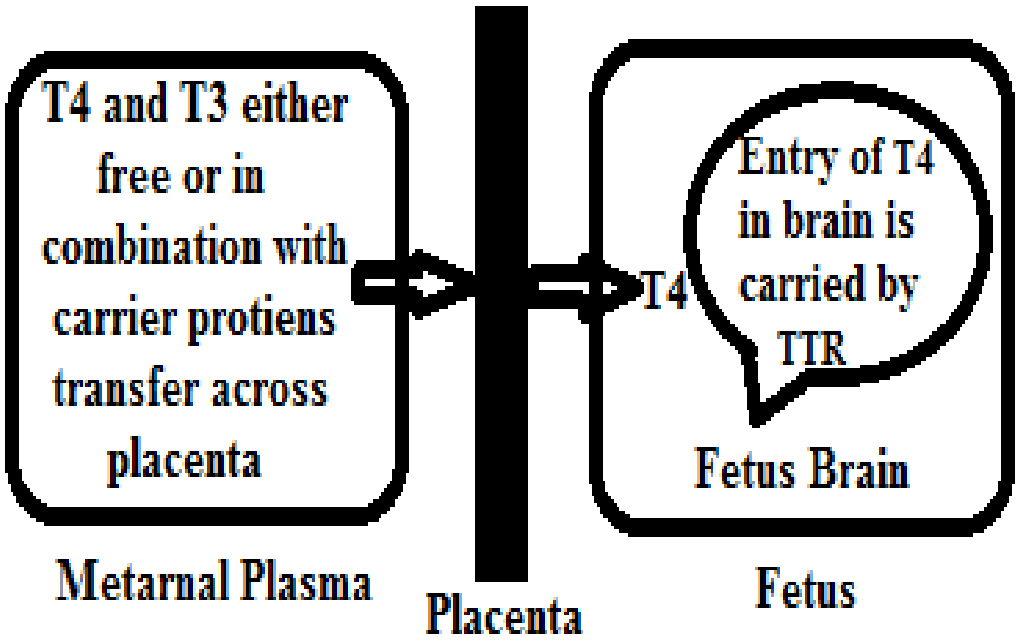

Figure 3: showing the transfer of thyroid hormones from mother to fetus during pregnancy. This diagram clearly illustrates that the early brain development in the fetus dependent upon thyroid hormones coming from maternal origin because the fetus thyroid axis is not properly organized during the early pregnancy stage. Therefore, any fluctuation in the mother's thyroid hormones can disturb normal brain development in the newborn child. Where T4: tetraiodothyronine, T3: tri-iodothyronine and TTR: transthyretin protein.

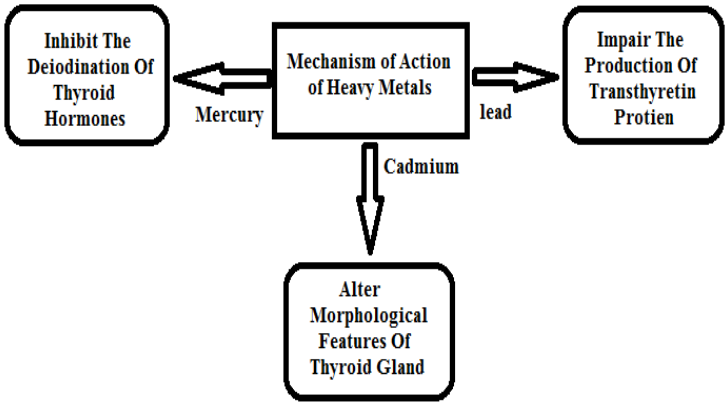

Figure 4: Showing the mechanism of actions of different heavy metals.

The combinational exposure of both de-cabrominated diphenyl-ether 209 (BDE-209) and cadmium in rats significantly reduced tri-iodothyronine, tetraiodothyronine, and free tetraiodothyronine levels (38). Furthermore, Baranski et al, found that the exposure of cadmium during and before the gestation period in female rats was associated with a reduction in postnatal growth (37)**.** In contrast, Chen et al suggested a positive correlation between thyroid hormones and cadmium in National-Health and Nutrition-Examination Survey (39). The exposure of cadmium can induce abnormal changes in tetraiodothyronine producing follicle cells in the thyroid gland. This exposure also induced some abnormalities in histomorphological features of the thyroid gland including the destruction of the rough-endoplasmic reticulum (RER) in the epithelium containing follicular cells, vacuolar swell up. Besides, the swelling of energy-producing organelles such as mitochondria was also observed (36).

DISCUSSION

Thyroid hormones play a very important role in the maintenance of brain functions. The levels of polychlorinated biphenyls and heavy metals are increasing day by day in the environment due to globalization. The brain functions are dependent upon thyroid hormones and these toxic environmental compounds can indirectly disturb the brain functions by altering the levels of circulating thyroid hormones in plasma. The exposure of these toxicants proved to be more dangerous during the early stages of pregnancy because of lacking mature thyroid axis. However, these toxic compounds can also disturb the levels of circulating thyroid hormones during later stages even at adolescence.

Table 3: Showing the end effect of heavy metals like lead, mercury, and cadmium on brain performance

. Metals	Effect on brain	References
Lead	Disturbs cognitive functions	(42)
Mercury	Neurotoxic effects	(42)
Cadmium	Goiter Disturb cognitive functions	(43) (44)

CONCLUSION

Thyroid hormones have a direct impact on brain functions. The polychlorinated biphenyls and heavy metals can indirectly create abnormalities in brain functions by altering the normal levels of thyroid hormones in body fluids.

CONFLICT OF INTEREST

The author declares no conflict of interest

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