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Induction of Thyroid Hormones Disruption by Exposure of Dioxins and Phthalates: A Comprehensive Review

Abdul Qader[1], Zahira Batool[2], Hamza Tariq[3]

[1] Drugs Testing Laboratory Faisalabad, Punjab, Pakistan
[2] Department of Pharmacy, Quaid-e-Azam University, Islamabad, Pakistan
[3] Department of Pharmacy, Lyallpur Institute of Advance Studies, Faisalabad, Pakistan

Abstract

The main objective of this study is to elaborate the crucial effect of dioxins and phthalates on thyroid hormones such as tetraiodothyronine (T4) and tri-iodothyronine (T3) in body fluids. The literature evidences have been collected from Google Scholar, PubMed and Medline by using different key words. All literature evidences showed a drastic effect of dioxins and phthalates on the status of thyroid hormones. Hexachlorobenzene (HCB) is an environmental pollutant that increases activity of malic enzyme (ME) by increasing ME gene transcription. ME interact with aryl hydrocarbon receptors (AhR) and modulate the expression of genes with specific xenobiotic or DRE in their promoters that respond to dioxin. HCB increases activity of thyroid enzymes whose induction depends on thyroid hormone (TH) levels. Dioxin decreases T4 levels and increases TSH levels in neonatal plasma. Dioxin and HCB also causes various disorders in infants. Phthalates disrupt the thyroid hormones levels especially in pregnant women and infants through various mechanisms. Phthalates mainly decrease T4 levels and further studies are in process to describe exact mechanism.

Keywords: Dioxins, Phthalates, Thyroid hormones.

***Corresponding author:**
Abdul Qader
Drugs Testing Laboratory Faisalabad, Punjab, Pakistan
Email: pharmacistqader316@gmail.com

INTRODUCTION

Several review studies have evaluated the literature evidences on adverse human health effects due to environmental exposure of toxic chemical compounds [1, 2, 3]. In this study, there is discussion about epidemiological literature findings relevant to the examination of toxic impact of different environmental chemicals on thyroid function. Polychlorinated dibenzo dioxins are very toxic environmental pollutants. These pollutants are generated during synthesis of herbicides in industry. In a study of Air-force Vietnam-war vetrans, the exposure of tetrachlorodibenzopara dioxin revealed a remarkably high level of thyroid stimulating hormone in body fluids which represents a clear picture of reduction in thyroid hormones [4]. The exposure tetrachlorodibenzopara dioxin in dam during gestation period lead towards an increase in the level of thyroid stimulating hormone while decrease in thyroid hormones [5]. In rats, the exposure of tetrachlorodibenzopara dioxin also showed similar results [6]. A very important point is that the reduction in tetra-iodothyronine and elevation in thyroid stimulating hormone levels depend upon administered doses of tetrachlorodibenzopara dioxin [7]. According to in-vivo and in-vitro investigations the phthalates exert determinantal effects on thyroid hormone activity. When rats fed on 2-ethylhexa phthalate, a most commonly used compound, the levels of tetraiodothyronine and tri-iodothyronine decreased in plasma. On the other hand, the rats receiving 2-ethylhexa phthalate intravenously revealed an increase in concentration of tetraiodothyronine and tri-iodothyronine. Furthermore, the exposure of another commonly used phthalate such as dibutyl phthalate to male rats induced a dose dependent reduction in plasma tri-iodothyronine and tetraiodothyronine levels [8].

DIOXINS

Hexachlorobenzene

Hexachlorobenzene (HCB) is a widespread environmental pollutant and an important fungicide. It is also obtained as a by-product from other poly-halogenated chemical compounds. The chronic induction of HCB in animals exhibits various effects, such as reproductive, porphyria induction, immunosuppression, reduction of T4 levels, reproductive dysfunction, thyroid and liver carcinogenesis. HCB is classified as a dioxin-type chemical, and its vast toxic effects are due to its interaction with the aryl hydrocarbon receptor (AhR) [24]. This receptor is a ligand-dependent transcription factor belonging to the loop-helix

family of DNA-binding proteins. It is supposed that HCB enters the cell and attaches with Ah-receptor complex, consisting of AhR, heat shock proteins and aSrc-protein kinase. After binding, the AhR moves into the nucleus and modify the genes expression while forming a heterodimer. Furthermore, the AhR complex protein kinase can also stimulate a phosphorylation cascade. In the case of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD), activation of the activating protein-1 (AP-1) complex, phosphorylation of epidermal growth factor receptor, mitogen-activating protein kinase pathway and induction of Ras have been described. No ligand-induced receptor interaction with XRE sequences is necessary for the second pathway [7].

HCB induced modification of malic enzyme transcription

HCB affects the malic enzyme (ME) through the aryl hydrocarbon receptor. Chronic exposure to HCB results in an increase in ME activity as well as an induction of ME messenger RNA (mRNA) levels, with the marked effect occurring after 9 days of intoxication. This effect is distinctive for ME, as other liver enzymes are not affected by HCB. Transient transfection experiments in H35 cells demonstrate that this effect is accompanied by an increase in ME promoter activity [23]. Cis-regulatory elements responsible for the HCB effect have been localized between positions 2315 and 2177, although neither xenobiotic response elements nor activating protein-1 elements are present in this region. Instead, a thyroid hormone response element (TRE) is located between 2281 to 2261, and mutations of this element eliminate the induced response to HCB. Scatchard analysis signifies that neither T3 receptor binding nor T3R mRNA levels are affected by HCB, however, gel shift assays show that protein/DNA complexes formed on the TRE element of the ME promoter are induced by HCB. This proposes that HCB increases ME gene transcription by modulating the levels of still unidentified nuclear proteins that bind to the TRE element of the ME promoter [9].

HCB induced modification of lipogenic-genes

It is of interest to analyze how dioxin-type chemicals can modify the expression of metabolic genes and how this may interfere with the HCB signaling pathway and the transcriptional machinery that controls those genes. The literature evidences have shown that HCB can enhance the activity of various enzymes, such as glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase and cytosolic malic enzyme in the liver, with no influence on the activity of the mitochondrial dehydrogenases. Further, it was found that the enzyme induction was totally dependent on thyroid hormone levels [5].

Relationship between dioxin and maternal thyroid hormone status

In human populations, when maternal thyroid function is not regulated properly, it causesmotor and cognitive disorders in their offspring. Studies on animals have shown that dioxins can interfere with thyroid function, and exposure to dioxins has been documented to alter thyroid function in humans. The epidemiologic evidence indicates that dioxins could cause adverse effects on thyroid function even at standard exposure levels. Since fetal thyroid hormone production does not begin until after 20 weeks of gestation, changes in maternal thyroid hormone levels due to environmental toxins during the first and second trimesters could profoundly impact fetal neurodevelopment. However, no studies have been conducted in human populations that assess the correlation between maternal thyroid hormone status and dioxin exposure during this stage of pregnancy [21]. The thyroid hormone levels of mothers and infants were linked to exposure to PCB and dioxin during the perinatal period. Infants who were exposed to higher levels of dioxin-TEQ had higher TSH and lower T4 levels in their plasma two weeks after being born. Their thyroid hormone levels were also connected to their neurological examination at the time of birth [10]. The primary way in which dioxin affects the body is by binding to a protein called aryl hydrocarbon receptor (AhR), located in the cytoplasm. AhR is a transcription factor that becomes activated when it forms a heterodimer with an aryl hydrocarbon receptor nuclear translocator (ARNT) and interacts with specific DNA enhancer elements and this leads to the activation of these genes [22].

Tetrachlorodibenzo-p-dioxin

Recent studies have shown that the most potent form of dioxin, 2,3,7,8, -tetrachlorodibenzo-p-dioxin (TCDD), can also alter the functions of multiple proteins. Dioxin's effects are characteristic of hormones, growth factors, and cytokines since the action mechanism is receptor-mediated. Dioxin can induce amplification of Ah receptor-mediated responses accomplished through hormones and growth factors [10]. Developmental processes involve precise incorporation of the endocrine system, accompanying various hormones. The environmental toxic compounds that inhibit, mimic or modulate endogenous chemical messengers that can affect development. Dioxin alters cell differentiation and growth by affecting hormonal balance and homeostasis such as modulation of growth factors, enzyme induction and receptors. TCDD can act as an anti-estrogenic or estrogenic way depending on developmental and tissues stage. It can also increase or decrease levels as well as transform growth factor α (TGFα), depending on the type of tissue. The effects of TCDD on glucocorticoid and epidermal growth factor (EGF) receptors can be either suppressed or enhanced, depending on the type of cells, tissue, and developmental stage. Considering that TCDD is an endocrine disruptor can help to better understand its tissue-specific and developmental stage-specific actions [20]. TCDD, a harmful environmental contaminant that is persistent and lipophilic, is acknowledged to be a human carcinogen and endocrine disruptor. Research on animals indicates that TCDD might contribute to reduced levels of total and free thyroxine (T4), while some studies imply that it might lead to an increase in thyroid-stimulating hormone (TSH) levels. Research into the link between serum the level of thyroid hormones and TCDD concentrations in adults has been limited to only few human studies, with mixed results. According to Ott et al. there was positive association between TCDD concentrations and T4 in 131 trichlorophenol plant workers who were consistently exposed to TCDD over 45 years ago. Notably, chloracne status and TCDD levels estimated through backward extrapolation to the time of the accident were also positively correlated with T4 levels [11].

Impact of dioxins on nervous system

Exposure to dioxinduring the perinatal period can lead to neurological disorders in children and animals, such as memory disorders, learning, delayed acquisition of auditory startle and hyperactivity, and delayed acquisition of auditory startle (19). These effects are like those observed in infants exposed to thyroid hormone deficiency in the womb or in the early stages of life. Therefore, even a small amount of exposure to dioxin or PCBs during this period can have a significant impact on the development of the nervous system through the effects of the chemicals on thyroid levels during brain development [10].

PHTHALATES

Impact of Phthalates and related derivatives on thyroid hormones status

Earlier research has found that phthalate exposure can impact thyroid hormones in the final trimester of pregnancy. Given the importance of these hormones for fetal development in the first trimester, we gathered amniotic fluid and urine samples from expectant mothers to investigate 11 metabolites, such as MEP, MECPP, MEHP, and MnBP from nine phthalates by leveraging liquid chromatography and tandem mass spectrometry [18]. Serum thyroid hormones, including T4, free T4, and TBG, were analyzed from blood samples collected from each participant. Our results indicate that there may be a change in thyroid hormone levels during the initial stages of pregnancy among expectant mothers exposed to DnBP. Further analysis is vital to establish these

linkages [12]. Epidemiological studies have shown that phthalates could potentiallydisturb thyroid hormones, especially in susceptible populations such as pregnant women. Experimental studies have confirmed this by demonstrating that certain phthalates, including DEHP and DnBP, possess anti-thyroid activity that affects various mechanisms, such as the up-regulation of thyroid-related genes and sodium-iodide symporter. It is crucial to note that maternal thyroid hormones play a critical role in early fetal development, and exposure to varying levels of phthalates during different stages of pregnancy could affect fetal development during critical periods. A study was also conducted to assess the impact of phthalate on thyroid hormones during early pregnancy while analyzing the levels of phthalates in pregnant mothers following the 2011 Taiwan DEHP scandal in amniotic fluid and urine samples [17].

Phthalates induced thyroid hormones disruption and other health hazards

After adjusting urinary creatinine, TBG, gestational age and exposure to other phthalates, we observed a significant negative correlation between T4 and urinary MnBP levels in pregnant women during early pregnancy. TBG is regarded as a major factor in the evaluation of thyroid hormones status. The findings suggest that changes in T4 levels during early pregnancy could potentially pose a risk to development of fetus. Therefore, it is crucial to prioritize strategies that reduce phthalate exposure in pregnant women [12]. Experimental studies have suggested that phthalates can disrupt thyroid function through various mechanisms, such as interfering with the binding of T3 to transport proteins, interacting with active T3 uptake at the plasma membrane, or exerting antagonistic activity at thyroid receptors. Children are potentially more vulnerable to adverse health effects from exposure to environmental chemicals than adults. This is in part because exposure to phthalates and other chemicals may be higher relative to body weight. Additionally, appropriate levels of insulin-like growth factor (IGF-I) and thyroid hormones are crucial for a child's neurological development and growth. Our study aimed to assess exposure to six different phthalates in a large cohort of children by measuring their metabolites in urine samples. The previous studies have also reported there is an associations between phthalate exposure and growth that is indirectly associated with, thyroid hormones and, IGF-I. Although there is not a lot of available evidence from animal studies, rats that have been exposed to DBP and DEHP have shown reductions in peripheral thyroid hormones [13].

Recently, there has been a growing focus on various health hazard impacts, particularly in vulnerable populations such as infants and pregnant women. Numerous studies have suggested that phthalates could affect the hormonal system, potentially leading to an antagonistic effect on the functions of thyroid glands both in-vitro and in-vivo. Phthalates have the potential to down-regulate the human sodium/iodide symporter (NIS) promoter, which can have negative implications given the well-known risk of neural defects resulting from thyroid hormone deficiency during early pregnancy. In addition, there is evidence to suggest that either high or low maternal free thyroxine (FT4) concentrations during early pregnancy affect IQ and decrease grey matter and cortex volume in children. Given the potential for phthalate exposure to reduce fetal thyroid hormone availability through maternal thyroid hormone signaling, these findings are of significant concern [14]. Maintaining proper thyroid function during pregnancy is critical to ensure proper fetal development and growth. A slight imbalancement in thyroid status can have negative effects on both the developing fetus and postnatal health. Prevalence of environmental toxic compounds, particularly endocrine disruptors such as synthetic phthalates and phenols, may contribute to the dysregulation of thyroid hormone levels in addition to iodine deficiency and pre-existing thyroid disease. In-vivo and in-vitro studies indicate that these compounds can interfere with thyroid hormone signaling by affecting feedback mechanisms, metabolic inactivation/ activation and biosynthesis linked with the central pituitary-hypothalamic thyroid axis [15]. Several studies investigating the relationship between exposures of phthalates and phenols with thyroid hormone in pregnant women. However, the exact conclusions from these studies are challenging due to the variations of results. For instance, while urinary DEHP metabolites were associated with lowered TSH and higher thyroxine (T4) levels in 2,521 pregnant mothers, contrasting outcomes (increased TSH and lowered T4) were reported elsewhere by 439 participants. Study design discrepancies like differences in the trimester of urine and blood samples, participant characteristics like iodine levels, and variation in exposures could partly explain the disparities observed in the results of these studies [16].

CONCLUSION

HCB is a potent promoter of ME that increases the gene expression by binding to AhR, and hence the enzyme concentration in the plasma when the studies have been performed. HCB also enhances response to dioxin. TCDD is the potent form of dioxin that interferes with the activity of HCB signaling pathway and modulate T4 levels and TGF-α. Phthalates also interact with thyroid hormones and possess anti-thyroxin activity by down regulating of NIS promoter which caused is by thyroid deficiency in early pregnancy causing various complications in newborns. Moreover, case studies shown that there is decrease of TSH and increase of T4 levels in infants exposed to phthalates.

Conflicts of interest

None declared.

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