Effects of Environmental Pollutants on Thyroid Hormone Functions

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Abstract

Many synthetic substances that are introduced into the environment are known to interfere with or are suspected of interfering with the proper function of thyroid hormone (TH) in humans. The command of development and growth, as well as the maintenance of metabolic homeostasis are crucial functions of THs. A increasing body of research demonstrates the environment pollutants can interfering with the endocrine system. The majority of the evidence comes from research on organs of reproduction. Additionally, there is concern that the thyroid's normal state of homeostasis may be disturbed.

There is a risk of thyroid disruption from several chemical categories, including some halogenated derivatives and metabolites of polychlorinated biphenyls, polybrominated diphenyl ethers, bisphenol-A, and other chemicals have been demonstrated to bind to TRs and potentially influence TR function selection. When given the importance of TH in brain development, it will be critical to investigate whether these chemicals, or chemical class interactions, affect Modulating TH signaling in the developing brain improves children's health. Because different drugs affect the in various ways, the hypothalamic-pituitary-thyroid axis, they can disturb the thyroid in a number of different ways.

Human health may be negatively impacted by even slight alterations in thyroid homeostasis, and developing fetal neurological systems may be particularly at risk.

Environmental influences on thyroid function should be further studied in the future as this information may help us comprehend the intricate background of gene-environment interactions underpin thyroid disease pathophysiology.

Key words: Environmental Pollutants, thyroid hormone (TH)

تاثير الملوثات البيئية على وظائف الهرمون الدرقي

الكلمات المفتاحية : الملوثات البيئية , الهرمون الدرقي

الخلاصة

من المعروف ان العديد من المواد الاصطناعية التي يتم ادخالها في البيئة تتداخل مع وظائف الغدة الدرقية لدى الانسان. ان التطور والنمو وكذلك الحفاظ على التوازن الأيضي هي وظائف حاسمة لهرمون الغدة الدرقية والكثير من الأبحاث بينت أن ملوثات البيئة يمكن أن تتداخل مع نظام الغدد الصماء , بالإضافة إلى دلك هناك خطر حدوث اضطراب في الغدة الدرقية من عدة فئات كيميائية تثمثل المشتقات المهجنة ومستقلبات ثنائي الفينيل متعدد الكلور ، وإيثرات ثنائي الفينيل متعدد البروم ، وثنائي الفينول أ والمواد الكيميائية الاخرى والتي توثر على وظائف الهرمونات الدرقية لدا سيكون من المهم التحقق فيما إذا كانت إذا كانت هذه المواد الكيميائية ، أو تفاعلات الطبقة الكيميائية ، تؤثر على تعديل إشارات الهرمون الدرقي لأن الأدوية المختلفة تؤثر بطرق مختلفة على محور الغدة النخامية والغدة الدرقية ويمكن أن تتاثر الغدة الدرقية بعدد من الطرق المختلفة. فيجب إجراء مزيد من الدراسات للتأثيرات البيئية على وظيفة الغدة الدرقية في المستقبل لأن هذه المعلومات قد تساعدنا على فهم الخلفية المعقدة للتفاعلات بين الجينات والبيئة التي تدعم الفيزيولوجيا المرضية لأمراض الغدة الدرقية.

Introduction

Synthetic chemicals' effects on human endocrine systems, particularly impacts linked to androgen and estrogen homeostasis, have gotten a lot of attention in the last decade. However, animal and in vitro evidence research suggests that the thyroid gland is similarly susceptible to endocrine-disrupting substances properties. [1]

Pollutants in the environment such as polychlorinated biphenyls (PCBs), bisphenol A (BPA), as well as brominated flame retardants (BFRs) demonstrated to alter endogenous hormones' normal function in wildlife and people, resulting in changes in hormone-mediated responses. It has the potential to disrupt thyroid homeostasis via a number of mechanisms, including receptor binding, transport protein binding, and cellular uptake processes , and thyroid hormone metabolism modification (THs) [2]

Many xenobiotics have been discovered the potential to alter thyroid system operation , according to growing research. [3] Homeostasis of thyroid hormone (TH) is required for the metabolism, expansion as well as the growth of vertebrates. [4] In the human fetus and newborn infant, TH is also required for optimal brain development, Several environmental pollutants are structurally comparable to the thyroid hormones thyroxine (T4) and triiodothyronine (T3), and hence obstruct the TH binds to receptors or transport proteins . Normal amounts of THs, on the other hand, are critical for fetal and childhood growth and development Normal TH levels are essential for central nervous system development, particularly during pregnancy. [5] This important period may be susceptible to even minor synthetic effects substances on maternal and fetal TH levels; developmental deficiencies may not be present obvious until a much later age. [6]

We present a literature review on the effects the effects of endocrine disruptors with a focus on human health and thyroid function safety, in particular, prenatal vulnerability.

Thyroid Hormone and TSH Levels are influenced by Environmental Factors

Chemicals

Many industrial chemicals and pesticides can interfere with thyroid function gland's natural work, and these chemicals are referred to as endocrine disruptors (EDCs) [7] Thyroid hormones are required for proper brain development., so any substance that may interfere with The thyroid gland's function should be thoroughly investigated. Pregnant women [9] infants [10] and young children have all been included in research into the effects on normal thyroid function of potential EDCs [11] Despite numerous studies on the effects of various substances in terms of TSH and thyroid hormone levels, the results are still highly variable. The majority of studies had insufficient power, with an average power of insufficient total number of participants. [12]. Furthermore, participants' exposure to various chemical Subtypes and doses both play a role to the disparities in the results. As a result, Drawing is difficult broad conclusions concerning whether or not a specific chemical has an effect regarding thyroid function

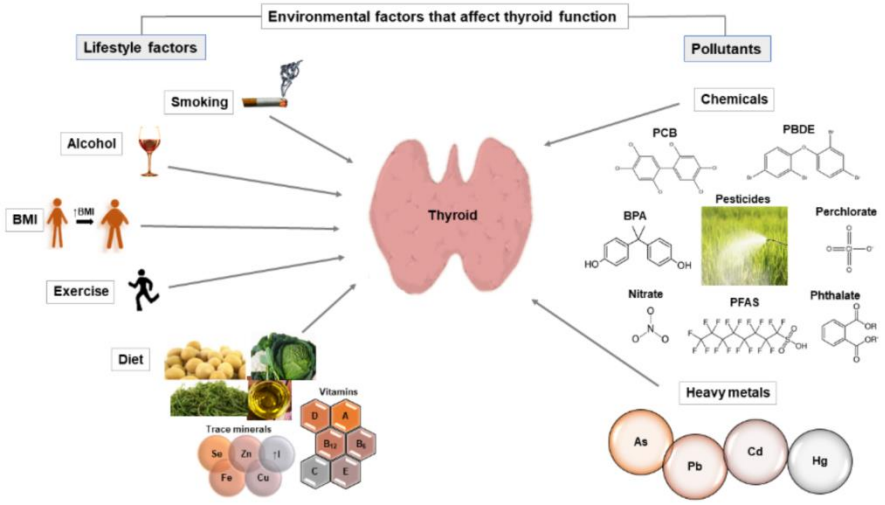

Figure 1: Environmental Factors Affecting Thyroid-Stimulating Hormone and Thyroid Hormone Levels

Polychlorinated biphenyls (PCBs)

EDCs are polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs). Because they have a similar structural design to thyroid hormones, they obstruct thyroid hormone signaling [13] PCBs bind to thyroid cells in an in vitro study. [14]
PCBs have long been used as electrical insulating fluids, as well as in carbonless copy paper, inks, paints, and a variety of other industrial and consumer products and PBBs may have an effect on thyroid iodide uptake. [15] These compounds, however, are POPs (persistent organic pollutants) that can build up in the environment and body fat, posing a health risk. [13]
PCB exposure has been shown in animal studies to affect peripheral TH levels. There has been significant research into the effects the effects PCBs' influence on thyroid hormone levels in healthy adults, there have been numerous inconsistencies. Some studies have found that PCBs have no effect on TSH [16] or Thyroid hormone concentrations [17].
PCB exposure is one of the most consistent findings lowers circulating TH levels, particularly T4 [18]. Both oral and s.c. dosing resulted in thyroid histopathological alterations indicative of hyperactivity [19]. Monkeys given PCB orally there was a significant dose-dependent relationship decrease in T4, free T4 (FT4), total T3 (TT3), and rise in thyroid-stimulating hormone for 18-23 weeks [20]. As well as thyroid histological alterations consistent with induced hypothyroidism [21].

Furthermore, PCBs can easily traverse the placenta and breast milk to embryos and babies. [**22**] PCBs have been shown to have an impact on thyroid function that is normal in Because of their structural similarity to TH, experimental animals. Thyroid hormones are reduced in developing and adult animals when they are exposed to PCBs and similar chemicals. [23].

The PCB metabolite 4-OH-2,3,3 ,4 ,5_ pentachlorobiphenyl (4-OH-CB107) has been found in human and wildlife blood plasma. [24] Female rats who are pregnant exposed to 4-OH-CB107 have a significant drop in TH levels in their descendants , implying that this drug has transgenerational effects. [25]

Other investigations, on the other hand, have found that PCB exposure causes an improvement [26]. as well as a decrease [27] in TSH, an increase [28] and a decrease [29] in T3, and an increase [30] and a decrease [31] in T4. Although prior research has looked into the impact the effects of PBBs on thyroid development problems, more research is needed [32].

To explain how PCBs are formed, the following processes have been proposed affect thyroid function. Because of their structural similarity, THs, PCBs and related substances bind TTR or TR and act as a TH agonist or antagonist **[**33**].** Co-planar and dioxin-type PCBs work by activating the aryl hydrocarbon receptor (AhR). These PCBs bind to AhR, causing hepatic uridine diphosphate glucuronyl transferases (UDPGTs) to be activated, resulting in biliary excretion and T4 elimination. [34] Furthermore, preliminary research indicates T3-induced Rana rugosa (R. rugosa) tadpole tail apoptosis is dose-dependently increased by 4-hydroxy-3,5,3,4-tetrachlorobiphenyl (4-OH-TCB). [35] . It was recently discovered that 4-OH-TCB causes MPT causes apoptosis when combined with ROS (reactive oxygen species) production. [36]

Phthalates

Phthalates are frequently utilized as plastic emollients, and their use is increasing rapidly. Phthalate exposure is unavoidable, although for some individuals, such as hospitalized infants, it can be severe. Despite the quick metabolism of phthalates, The urinary content of mono(2-ethylexyl)phthalate has been linked to Phthalate exposure can occur through medical devices such as feeding tubes. [37] Such prolonged exposure during a potentially vulnerable developmental stage may result in irreversible damage. [38]

In vitro and in vivo studies have revealed that phthalates have a negative impact on the subject of TH action. [39] . It was discovered DEHP and other phthalates have been shown in rats to increase Iodine uptake by thyroid follicular cells [40]. In rats that were fed Diets contaminated with DEHP , there was an increase in iodine uptake histological alterations and a drop in plasma T4 were seen, but T3 levels remained stable, whereas rats given DEHP intravenously had higher serum T4 and T3 concentrations[41]. DBP was also administered orally to male rats had lower T4 and T3 levels that are dose-dependent [42]. According to a recent human study , researchers discovered In adult men, there was an inverse relationship between T3 and free T4 (FT4) blood concentrations and mono(2-ethylhexyl) phthalate (MEHP, the hydrolytic metabolite of DEHP) . [43] IT discovered that urine mono butyl phthalate (MBP) concentrations were linked to lower T4 and FT4 levels in second trimester women who are pregnant [44]

There are few investigations regarding the effect of Phthalate Effects on Thyroid Function in humans. As a review of 19 adolescents who had been exposed to high levels of DEHP during their newborn period due to invasive treatment (extracorporeal Normal levels of THs were discovered using membrane oxygenation (ECMO) [45]. These findings may not be general, because DEHP exposure is extremely high when using ECMO.[46]. But only for a brief period of time.

Furthermore, increases in TH levels caused by environmental Chemical exposure may occur be temporary. If changes occur during an important developmental stage, they may have long-term impacts on the growth of the central nervous system [47].

Bisphenol A

Bisphenol A (BPA) is a widely In food packaging, a chemical is used , can lining, toys, tubes, and cosmetics , and other products. Due to the fact that Because BPA is not chemically linked to the material, it can easily seep into food or beverages after repeated use, physical manipulation, or high temperature exposure. [48]. BPA lowers thyroid iodide intake and TPO activity, as well as altering Proteins involved in thyroid hormone production have their genes expressed. [48] Furthermore, BPA inhibits thyroid hormone receptors. [50] The mechanism that negative effects of BPA and similar chemicals on TH action has been studied in vitro and in vivo. TMBPA and TCBPA have no antagonistic action against T3-induced growth hormone production [51]. Rats fed BPA throughout pregnancy and lactation had higher serum T4 levels as well as evidenced by activating the TH-responsive gene RC3/neurogranin was increased in the growing rat brain [52]. TH's ability to prevent mouse oligodendrocyte development was discovered to be limited by BPA. BPA reduced T3 binding to TR [53]. hepatoblastoma cells and human embryonic kidney cells , and transcriptional suppression was achieved in vitro Nuclear receptor corepressors (N-CoRs) recruit nuclear receptor corepressors to the promoter. [54] It was also discovered that BPA functions as a T3 antagonist in X. laevis tail tissue, reducing TR and TR gene expression.[55] BPA, TCBPA, and TMBPA all decreased this expression, implying that BPAs all operate as antagonists to inhibit T3 from binding to TR, resulting in gene expression regulation by TR. PDI can be found in a variety Endoplasmic reticulum, nuclear envelope, and plasma membranes are examples of organelles found in cell cytoplasm . [56] and its activity is governed by T3 binding to PDI. BPA reduces T3 binding to PDI, which has a negative impact on several cellular functions, according to [57].

Pesticides

Pesticides are classified as EDCs , and numerous There have been in vitro and in vivo studies pesticides, such as insecticides, fungicides, and herbicides, have been shown to interfere with normal thyroid function (reviewed in [58]. Thyroid hormone metabolism and synthesis are affected by pesticides (reviewed in) [59]. The impact of different the effect of pesticides on TSH and thyroid hormone levels in healthy adults was investigated. TSH and thyroid hormone levels have been measured using (phenoxybenzoic acid (3-PBA) (pyrethroid insecticide metabolite), trichloro-2-pyridinol (TCPY) (chlorpyrifos metabolite), cis and trans-3-2,2-dichlorovinyl-2,2-dimethylcyclopropane carboxylic acid (cis and trans-DCCA) (pyrethroid), paraquat in some studies between conventional (pesticide-using) and organic farmers [60]. The findings of studies have been mixed. TSH levels rose [61]. Fell [62] or remained unchanged [63] as a result of pesticide use. Following pesticide use, T4 levels either increased [64], decreased [65], or remained unchanged [60] T3 showed the same pattern: after pesticide usage, studies found a rise [62]. A decrease [60], or no change [61], because different types of pesticides were studied, such variances in outcomes are to be expected.

Mechanisms of action

Up until recently, measurements of thyroid size, circulating hormone levels, and histology were the primary endpoints used to estimate the antithyroidal effects of environmental pollutants. However, within the past ten years, new endpoints have been discovered. When evaluating the relevance of endocrine disruption caused by diverse substances, T4 content in the thyroid, gene transcription activity, and cellular growth seem endpoints that are more sensitive[66]. Perchlorate is a well-known example, which, although it does not affect plasma hormone levels in small doses, reduces T4 content of the thyroid gland [67]. Assisting the finding derived from in vitro investigations that sodium-iodide symporter (NIS) is inhibited [68]. Therefore, endocrine-disrupting substances that are present in minute concentrations may not exist in the environment directly impact levels of hormones in both animals and humans, but they may still affect the hormones' homeostasis.

Thyroxine (T4), triiodothyronine (T3), and thyroid-stimulating hormone (TSH) blood concentrations can change due to substances that block TH synthesis, release, and transport in the blood as well as substances that speed up the metabolism of different THs. Specific tests can be performed to identify the process by which blood hormone concentrations are lowered in response to a substance. Additionally, the precise profile of hormone concentration changes may be instructive. For instance, mice with type 2 targeted deletions deiodinase exhibit higher amounts of T4 and TSH in the blood, while serum T3 is unaffected [69]. However, mice with a specific the deletion of type 1 deiodinase has higher quantities of reverse T3 (rT3) and T4 in their blood, while their serum levels of T3 and TSH remain unaffected [70]. Iodine insufficiency may cause serum T4 levels to drop without changing or even elevate serum T3 levels [71]. Chemicals that block Thyroid peroxidase activity can be increased result in a "stereotypical" profile of hormones with lower serum T4 and T3 levels and higher serum TSH levels [72]. Last but not least, a targeted ablation MCT8, the T3 transporter, can result in increased T3 levels [73]. As a result, it's feasible that environmental elements that affect the HPT (hypothalamic-pituitary-thyroid) axis at particular moments in its control could result in a hormonal analysis indicative of There are numerous ways that environmental pollutants might change the levels of TH in the blood [74]. By activating either the Pregnane X receptor (PXR)/Constitutive Androstane receptor (CAR) or the aryl hydrocarbon receptor, halogenated aryl hydrocarbons can cause the expression of UDPGT enzymes in the liver [75]. Additionally, T4 can be displaced transthyretin, a serum-binding protein by hydroxylated substances [76] , such as polychlorinated biphenyls (PCBs) . As a result, environmental pollutants may operate at many sites of control to lower the amounts of THs in the blood.

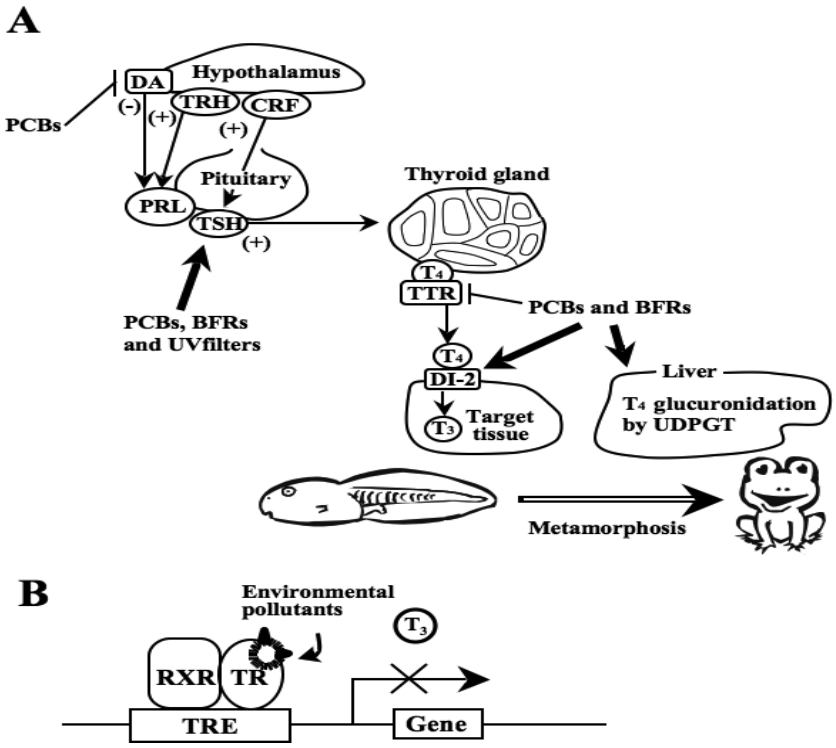

Figure 2:Possible Mechanisms for Thyroid Homeostasis Disruption by Environmental Pollutants

Conclusion

Numerous chemicals that are discharged into the environment are constantly being exposed to by both people and wildlife. Numerous investigations of various environmental contaminants point to a minor disturbance within normal reference values of the thyroid axis. Many of these pollutants have been discovered to disrupt thyroid homeostasis. a variety of methods. Each individual has a very distinct T4/TSH relationship, and intra-individual TH variance is minimal in comparison to reference intervals based on population. Small variations in thyroid function that are still within the normal range of reference could therefore be harmful to an individual's health As more and more possible thyroid-disrupting effects of certain chemicals are revealed by studies on animal exposure and in vitro experiments, the body of knowledge on these topics is expanding quickly

a system for action. The evidence is far greater for some persistent chemicals, like PCBs, than it is for some chemicals that are metabolized more quickly, like phthalates. Despite the fact that Thyroid homeostasis differs between species. must be considered, evidence from animals should raise concerns, particularly when it comes to the human vulnerability newborn as well as fetus to chemicals taken into consideration.

Future research should keep examining how environmental influences affect thyroid function. Large populations of people should participate in studies, and meta-analyses should also be carried out. More research in this field will give scientists the crucial knowledge they need to comprehend the intricate the history of gene-environment interactions that lead to thyroid disease.

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