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Review

Thyroid effects of endocrine disrupting chemicals

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ABSTRACT

In recent years, many studies of thyroid-disrupting effects of environmental chemicals have been published. Of special concern is the exposure of pregnant women and infants, as thyroid disruption of the developing organism may have deleterious effects on neurological outcome. Chemicals may exert thyroid effects through a variety of mechanisms of action, and some animal experiments and in vitro studies have focused on elucidating the mode of action of specific chemical compounds. Long-term human studies on effects of environmental chemicals on thyroid related outcomes such as growth and development are still lacking. The human exposure scenario with life long exposure to a vast mixture of chemicals in low doses and the large physiological variation in thyroid hormone levels between individuals render human studies very difficult. However, there is now reasonably firm evidence that PCBs have thyroid-disrupting effects, and there is emerging evidence that also phthalates, bisphenol A, brominated flame retardants and perfluorinated chemicals may have thyroid disrupting properties.

Contents

Abbreviations: BP2, benzophenone 2; BP3, benzophenone 3; BPA, bisphenol A; DBP, di-*n*-butyl phthalate; DDT, dichlorodiphenyltrichloroethane; DEHP, di(2-ethylhexyl) phthalate; HCB, hexachlorobenzene; 4-MBC, 4-methylbenzylidene-camphor; MBP, mono-*n*-butyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate; NIS, sodium iodide symporter; NP, nonyl phenol; OMC, octyl-methoxycinnamate; PBB, polybrominated biphenyls; PBDE, polybrominated diphenyl ethers; PCB, polychlorinated biphenyls; PCDD, polychlorinated dibenzo-*p*-dioxin; PFC, perfluorinated chemicals; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; T3, triiodothyronine; T4, thyroxine; TBBPA, tetrabromobisphenol A; TBG, thyroxin-binding globulin; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TPO, thyroid peroxidase enzyme; TR, thyroid receptor; TRE, thyroid response element; TSH, thyroid-stimulating hormone; TTR, transthyretin.

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1. Introduction

The abundant industrial use of chemicals in a wide variety of products causes a constant exposure of humans and wildlife to synthetic chemicals with the potential of interfering with biological systems. Numerous chemicals are suspected to be detrimental to human health, ranging from effects on the immune system, the brain and general body growth and composition to the reproductive system and disturbances of pancreatic function. Some environmental chemicals are specifically suspected to have thyroid-disrupting properties.

Thyroid hormones are involved in numerous physiological processes as regulators of metabolism, bone remodeling, cardiac function and mental status. Thus, maintenance of normal thyroid function is essential for psychological and physiological well-being. However, thyroid hormones are of special importance in fetal development, as development of the brain is dependent on normal levels of thyroid hormones. Absence of thyroid hormones reduces neuronal growth and differentiation in the cerebral cortex, hippocampus, and cerebellum (Auso et al., 2004; Lavado-Autric et al., 2003; Nicholson and Altman, 1972). During the first part of pregnancy, the fetus relies entirely on transplacental transfer of maternal thyroid hormones and thus on a normal maternal thyroid function, but maternal thyroid homeostasis is also contributing substantially to fetal development during the remaining part of pregnancy.

In recent years, the presence of subclinical hypothyroidism in large populations, especially if iodine-insufficient, and the long-term health consequences and the need of treatment have been much debated. Epidemiological studies have indicated that even a marginally low thyroxine level in a pregnant woman may give rise to reduction of cognitive functions of the offspring (Berbel et al., 2009; Haddow et al., 1999; Pop et al., 2003). Thus, even minor changes in the thyroid homeostasis may affect fetal neurological development.

Exposure to thyroid-disrupting chemicals may potentially result in such subtle reductions of serum hormone levels, which in turn may have significant consequences for public health.

In this review, we will give an overview of the current knowledge about the human effects of potentially thyroid-disrupting chemicals. Wildlife observations and experimental animal and in vitro studies are referred to if they serve to explain potential modes of action.

2. Thyroid-disrupting chemicals – mechanisms of action

Thyroid function is regulated by a finely tuned negative feedback mechanism of circulating thyroid hormones at the hypothalamic and pituitary levels, maintaining relatively stable serum levels of thyroid hormones with each individual having his or her specific set point (Feldt-Rasmussen et al., 1980). Alterations in the thyroid gland, binding proteins, peripheral metabolism and clearance also affect thyroid function. The mechanisms involved in thyroid homeostasis are thus numerous and complex, and environmental chemicals may interfere at all levels.

The large physiological range of TSH and peripheral thyroid hormones in human, resulting in a large variation of measurements between individuals makes studies of human populations very difficult. In addition, human exposure is constant, cumulative for persistent chemicals, and involves a vast number of chemicals.

At the level of the thyroid gland itself, chemicals may disturb the overall activity of the gland by interference with the TSH-receptor, as thyroid-stimulating hormone (TSH) stimulates all steps of the hormone production. The function of the sodium iodide symporter (NIS) or thyroid peroxidase (TPO) can be affected by chemicals through stimulation or inhibition. Chemicals may also interfere with other receptors on the thyrocyte whereby interference with intracellular mechanisms (e.g. cytokine actions) may occur.

Thyroid hormones are in humans mainly bound to thyroid binding globulin (TBG), whereas transthyretin (TTR), being the most important carrier protein in rodents, binds only a minor proportion of the hormones. However, TTR has been proposed to be of importance by transferring thyroid hormones over the blood–brain barrier as well as over placenta to the fetal compartment. In contrast to TTR, to which hydroxylated PCBs can competitively bind, no EDCs have been demonstrated to compete with thyroid hormones for binding to TBG or albumin with significant strength (Lans et al., 1994; van den Berg, 1990). Competitive binding of environmental chemicals to transport proteins may result in increased bioavailibility of endogenous thyroid hormones, but feedback regulation via TSH may compensate for this change in binding capacity of the transport proteins. Displacement of T4 from TTR by EDCs is not believed to be a major health hazard in humans (Purkey et al., 2004). Another potential effect of binding of EDCs to natural transport proteins may facilitate their transport to thyroid dependent tissues such as the brain or the fetus.

At target cells, thyroid hormones are probably actively transported across the cell surface via membrane bound transporters. Interference of EDCs with these proteins may compromise the bioavailibity of thyroid hormones to the nuclear thyroid hormone receptors (TR). Several chemicals have been shown to interact with the TR, either directly as agonists or antagonists, or by regulating expression of the TR genes.

In the brain, thyroid hormones are involved in oligodendrocyte development and myelination as well as extension of Purkinje cell dendrites, which is essential for normal neuronal circuit formation (synaptogenesis) and subsequent behavioral functions. Alterations in TR-expression or thyroid hormone receptor binding may disturb the normal development of the central nervous system.

Thyroid hormones are metabolised in peripheral tissues by the iodothyronine deiodinases, thus regulating the levels of the biologically active T3 by activation of T4 and inactivation of T4 and T3. Furthermore, thyroid hormones are metabolised in the liver by sulphation and conjugation by UDPGTs, and stimulation of these enzymes by EDCs may lead to faster clearance of the thyroid hormones.

Due to the physiological feedback regulation between TSH and peripheral hormones, the effects of EDCs are not easily predictable or detectable, as no ‘exposure free’ state exists in humans. Unfortunately, very few human studies include long term health effects of thyroid related outcomes such as neurological development or growth in their outcomes. Despite the compensating capacity of the thyroid gland the combined long-term effects of numerous EDCs, some of which accumulate with time, may potentially result in hypothyroidism.

3. Endocrine disrupting chemicals and thyroid effects

3.1. Polychlorinated biphenyls (PCBs) and dioxins

Polychlorinated biphenyls (PCBs) and dioxins (PCDD) comprise a group of highly persistent lipophilic chemicals deriving from industrial production, such as pesticides or combustion processes. They are accumulated through the food chain and are, despite being banned for decades, widely detectable in human, wildlife and environmental samples. Many of these compounds, especially the hydroxylated metabolites, which are also biologically active, have a high degree of structural resemblance to thyroxine (T4).