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INVITED REVIEW

Environmental chemicals and thyroid function

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Abstract

There is growing evidence that environmental chemicals can disrupt endocrine systems. Most evidence originates from studies on reproductive organs. However, there is also suspicion that thyroid homeostasis may be disrupted. Several groups of chemicals have potential for thyroid disruption. There is substantial evidence that polychlorinated biphenyls, dioxins and furans cause hypothyroidism in exposed animals and that environmentally occurring doses affect human thyroid homeostasis. Similarly, flame retardants reduce peripheral thyroid hormone (TH) levels in rodents, but human studies are scarce. Studies also indicate thyroid-disruptive properties of phthalates, but the effect of certain phthalates seems to be stimulative on TH production, contrary to most other groups of chemicals. Thyroid disruption may be caused by a variety of mechanisms, as different chemicals interfere with the hypothalamic–pituitary–thyroid axis at different levels. Mechanisms of action may involve the sodium–iodide symporter, thyroid peroxidase enzyme, receptors for THs or TSH, transport proteins or cellular uptake mechanisms. The peripheral metabolism of the THs can be affected through effects on iodothyronine deiodinases or hepatic enzymes. Even small changes in thyroid homeostasis may adversely affect human health, and especially fetal neurological development may be vulnerable. It is therefore urgent to clarify whether the animal data showing effects of chemicals on thyroid function can be extended to humans.

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Introduction

Over the past decade there has been an increasing focus on the effects of synthetic chemicals on human endocrine systems – especially on effects related to androgen and estrogen homeostasis. However, there is increasing evidence from animal and *in vitro* studies that also the thyroid is vulnerable to endocrine-disrupting effects.

Environmental chemicals may interfere with thyroid homeostasis through many mechanisms of action, i.e. at the receptor level, in binding to transport proteins, in cellular uptake mechanisms or in modifying the metabolism of thyroid hormones (THs) (Fig. 1). Several environmental chemicals have a high degree of structural resemblance to the THs thyroxine (T4) and triiodothyronine (T3), and therefore interfere with binding of THs to receptors or transport proteins. This, in turn, may lead to subclinical hypothyroidism, which in adults is often diagnosed only by chance because of subtle symptoms. However, growth and development in fetal life and childhood is highly dependent on normal levels of THs. Particularly during gestation, normal levels of THs are crucial for the development of the central nervous system. This critical phase may be vulnerable to even subtle effects of synthetic chemicals on fetal and maternal TH levels. Such developmental deficiencies may not be identifiable until later in life (1).

Perchlorate is an example of a chemical with well known antithyroidal effects, which has been exploited in diagnosis and treatment of thyrotoxicosis (2). It has therefore been of concern that perchlorate is found in drinking water (3). A study of workers in an ammonium perchlorate production plant found a significant decrease in thyroid gland iodine uptake related to presence at work (4). However, human studies are contradictory concerning the effect of environmentally occurring levels of perchlorate on neonatal thyroid function (5–7).

Here we present a review of the literature on the impact of endocrine disrupters on thyroid function – with a focus on human health and especially fetal vulnerability.

Industrial chemicals

Polychlorinated biphenyls (PCBs)

PCBs comprise 209 highly persistent, distinct congeners that accumulate in lipid tissues. Their hydroxylated

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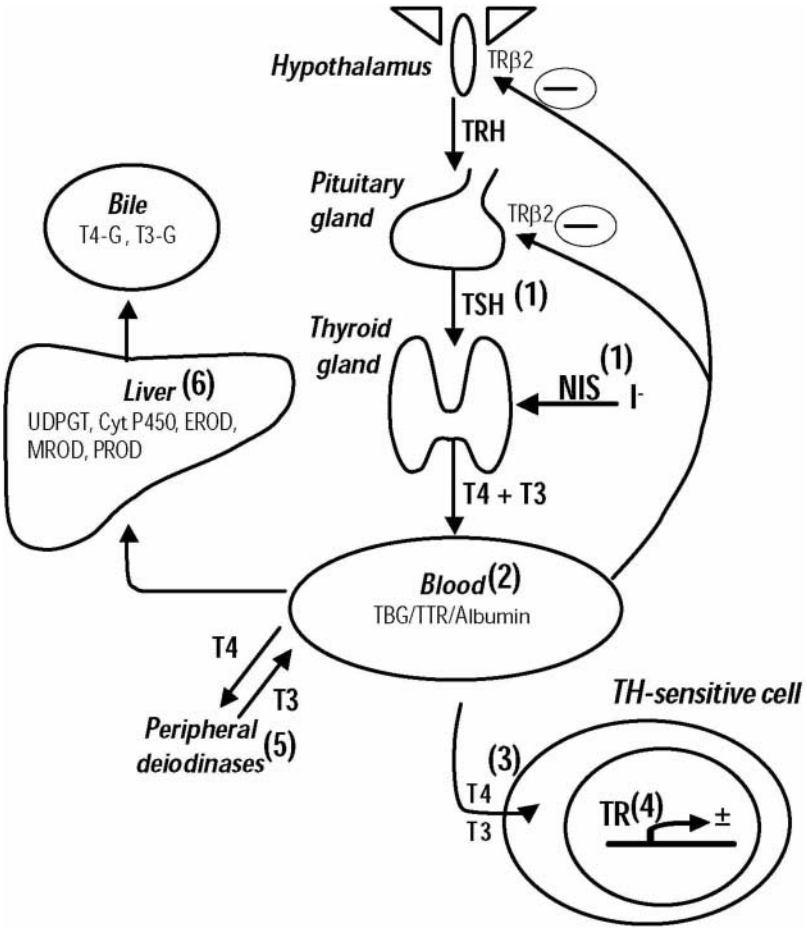

Figure 1 Possible mechanisms of action of environmental chemicals on the hypothalamic–pituitary–thyroid axis. (1) Synthesis of THs: interference with NIS, TPO or TSH receptor. (2) Transport proteins. (3) Cellular uptake mechanisms. (4) The TH receptor. (5) Iodothyronine deiodinases. (6) Metabolism of THs in the liver. TRH, thyrotropin-releasing hormone.

metabolites are also biologically active. PCBs and especially the hydroxylated metabolites have a high degree of structural resemblance to T4. The effect of PCB exposure on peripheral TH levels is well documented by studies in laboratory animals. One of the most consistent findings is that PCB exposure decreases the levels of circulating THs, especially T4 (8–10). Histopathological changes of the thyroid indicative of hyperactivity were found after both oral and s.c. exposure (10, 11). Monkeys exposed orally to PCB for 18-23 weeks showed significant dose-dependent reduction of T4, free T4 (FT4), total T3 (TT3) and increase in thyroid-stimulating hormone (TSH) as well as histopathological changes of the thyroid compatible with induced hypothyroidism (12). There is substantial evidence that perinatal PCB exposure decreases THs in rat pups (13–21). Also injection of PCBs into chicken eggs from early gestation resulted in a severe decrease of the TH peak late in gestation, accompanied by a considerable delay in the timing of hatching (22, 23).

PCBs are metabolized to hydroxylated PCB compounds (OH-PCBs), which in rodents can accumulate in the fetal compartment. In pregnant rats exposed to 4-OH-CB107, accumulation of the metabolite was found in fetal liver, brain and plasma, and total T4 (TT4) in both maternal and fetal blood samples was decreased. Furthermore, FT4 was significantly decreased and TSH increased in the fetus. The levels of T4 in fetal forebrain were similarly decreased and deiodination of T4 to T3 was increased (18). A study of PCB77 showed a similar reduction of fetal peripheral THs and an accumulation of the hydroxylated metabolite of this congener in the fetal compartment in mice (15). Similar relationships between thyroid function and the concentration of PCBs in plasma are reported from wildlife animals. Significant decreases of T3 and/or T4 were found in sea lions (24), polar bears (25) and seals (26, 27), and histopathological changes of thyroid glands related to exposure level were found in jungle crows (28) and cormorants (29).

Multiple studies of PCB exposure and effects have been carried out in human populations, the majority of which raise concern that environmental levels of PCBs may alter thyroid homeostasis. In adults, adolescents and children (Table 1) from highly PCB-exposed areas the concentration of PCB in blood samples correlated negatively to levels of circulating peripheral THs (30, 31). A few studies also demonstrated a positive

Table 1 Human studies of thyroid effects of PCB. PCBs were measured in blood if not otherwise stated.

Author	Year	No. of subjects	Effect	Reference
Hsu *et al.*	2005	60 boys	No effects	43
Takser *et al.*	2005	101 mothers 92 cord blood	Mothers: ↓ TT3, ↑ TSH Cord blood: No significant correlations	39
Schell *et al.*	2004	115 adults	↓ FT4, ↓ T4, ↑ TSH	33
Bloom *et al.*	2003	66 adults	No effects	35
Ribas-Fito *et al.*	2003	98 infants	No significant effects (trend toward ↑ TSH)	38
Langer *et al.*	2003	101 adults	Higher thyroid volume in highly exposed subjects	36
Persky *et al.*	2001	229 adults	↓ T4, FTI (females); ↑ T3-uptake (men)	31
Matsuura *et al.*	2001	337 breastfed infants[a]	No effects	42
Sala *et al.*	2001	192 (608) adults	No significant effects (trend toward ↑ TSH)	105
Hagmar *et al.*	2001	110 adults (men)	No effects	34
Hagmar *et al.*	2001	182 adults (women)	↓ TT3	30
Steuerwald *et al.*	2000	182 children	No effects	37
Longnecker *et al.*	2000	160 cord blood	No effects	41
Osius *et al.*	1999	320 children	↓ FT3, ↑ TSH	32
Koopman-Esseboom *et al.*	1994	105 mothers and Infants[a]	Mothers: ↓ TT3, ↓ TT4 Infants: ↑ TSH (2 weeks and 3 months age)	40

[a]PCB measured in breast milk.

correlation between PCB exposure and TSH (32, 33). In contrast, other studies found no associations between PCBs and THs in serum (34, 35). The thyroid volume is another endpoint for thyroid function, which is rarely used in human toxicological studies. In adults from a PCB-polluted area the thyroid volume assessed by ultrasound was found to be significantly larger than in 'non-exposed' subjects. The highest thyroid volumes were clustered among 5% of subjects ($n = 23$) with PCB levels above 10 000 ng/g lipids (36).

Perinatal exposure to PCBs may be the most important for chronic effects. Measurements of PCBs in cord blood were not associated with infant THs (37–39). However, measurements of PCBs in maternal blood during pregnancy showed negative correlations to peripheral maternal THs and positive correlations to TSH (39). Similarly, most studies of PCB content in breast milk did not demonstrate significant associations with infant peripheral TH levels (40–42), although one study found significant positive correlation to TSH in the infants as well as significant negative correlations to maternal TT3 and TT4 (40). These changes in THs were within normal reference ranges. A study of boys prenatally exposed to high doses of PCBs and polychlorinated dibenzo-*p*-furans (PCDFs) showed no differences in thyroid function compared with a control group (43). In conclusion, human and wildlife observations point towards subtle, but significant, effects of low-dose PCB exposure on human thyroid function.

Dioxins

Polychlorinated dibenzo-*p*-dioxins (PCDDs) and furans (PCDFs) are widespread, persistent and highly toxic environmental pollutants from industrial burning processes or production of herbicides. 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin (TCDD) is the prototype for this class of chemicals and the most toxic among PCDD/F congeners.

TCDD given to pregnant rats is transferred to their offspring via transplacental and lactational routes (44). A single dose of TCDD in rats dose-dependently decreased T4 and FT4 (45) and increased TSH (46). In offspring a single dose of TCDD to the dam during gestation was correlated to decreased T4 and to a 2-fold increase in TSH (in male offspring) as well as hyperplasia of the thyroid gland (47). Human studies are scarce, but in a large study of Vietnam war veterans, the group with the highest exposure to TCDD showed a significant increase in TSH levels (48).

Flame retardants

The group of flame retardants contains different chemicals such as tetrabromobisphenol A (TBBPA), polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls. TBBPA and PBDEs show even closer structural relationship to T4 than PCBs. PBDEs are extensively used as flame retardants in plastics, paints, electrical components and synthetic textiles. TBBPA is a halogenated derivative of bisphenol A (BPA) and is widely used as a flame retardant in electrical equipment such as televisions, computers, copying machines, video displays and laser printers. TBBPA is generally regarded a safe flame retardant because it is not readily accumulated in the environment, nor is it highly toxic.

In rodent studies, PBDEs reduced the circulating levels of THs. The commercial PBDE mixture DE-71 decreased the levels of circulating THs and induced the activity of the hepatic enzymes uridinediphosphate-glucuronosyltransferase (UDPGT), ethoxyresorufin-*o*-deethylase (EROD) and pentoxyresorufin-*o*-deethylase (PROD)

(49–51). High doses of DE-71 also resulted in histopathological changes such as increased follicular epithelial height and colloid depletion, indicative of a hypothyroid state. Another commercial mixture, Bromkal, as well as the pure congener DE-47 decreased FT4 and TT4 levels and induced microsomal enzyme activities (EROD, methoxyresorufin-*o*-deethylase (MROD), PROD) (9), whereas the pure pentabrominated congener BDE-99 was a less potent reducer of TH levels when administered at equimolar doses (52). No histopathological changes were observed after treatment with DE-47, but plasma binding of T4 was significantly reduced after high dose of DE-47 (10). Lower-brominated BDE congeners were more potent plasma T4 reducers than mixtures containing higher-brominated congeners (50). In fish, TT4 was decreased after exposure to PBDE (53). Perinatal maternal exposure of rats to different mixtures and congeners of PBDE reduced THs pre- and postnatally in both dams and fetuses (54). Similarly, exposure of kestrels before and after hatching to different PBDE congeners decreased T4 levels in the offspring (55). TBBPA exhibited antithyroidal effects by decreasing the rate of tail shortening in tadpole metamorphosis (56). Further studies of TBBPA are mainly *in vitro* and described in details below.

Few human studies exist regarding flame retardants and thyroid function. Eleven workers in an electronic recycling facility were followed over 1.5 years. Levels of PBDE were fluctuating during the study and there was a trend towards increasing T4 over time. Changes were small and not significant, and as such not conclusive (57). In 110 men exposed through Baltic fish consumption, plasma levels of persistent organohalogens were measured and showed among multiple correlations a significant negative association between TSH and the PBDE BDE-47 (34). In a study of perinatal exposure levels, THs and six congeners of PBDE were measured in 12 pairs of maternal and cord blood. There was no apparent correlation between serum PBDEs and TH levels, which may be due to a very small sample size (58).

Thus, our current knowledge on the effect of flame retardants on human thyroid function is very limited.

Phenols: nonylphenol (NP), pentachlorophenol (PCP) and BPA

NP and octaphenol are industrial additives used in a wide variety of detergents, plastics and pesticides. NP may be one of the more critical compounds due to its toxicity, persistence and estrogenic effects. PCP has been extensively used as a biocide and wood preservative in the timber industry and as an antifungal agent in the leather industry. Furthermore, PCP is the primary metabolite of the pesticide hexachlorobenzene (HCB), which is described in detail below. BPA is used to manufacture polycarbonate and numerous plastic products including compact discs, foodcan linings, adhesives, powder paints and dental sealants. BPA is rapidly glucuronidated in rats and humans.

Exposure of rats to NP increased TSH dose-dependently (59), but no consistent effects on peripheral hormones were found (59, 60). Another rat study showed increased levels of T3 and T4, but no change in TSH in ovariectomized rats. This pattern was not consistent with *in vitro* studies of protein extracts showing NP to inhibit thyroperoxidase (TPO) activity (61). PCP also decreased T4 levels in ewes (62, 63). In fish and tadpoles, NP may have an impact on development as TH levels were clearly decreased (64) as well as the rate of metamorphic progression and tail resorption in bullfrog tadpoles (65).

Rats exposed to BPA exhibited increased weight of the thyroid, but no histopathological changes (66). No significant effects on TH levels were found in either polecats (67) or field voles (68) after BPA exposure. However, a positive correlation between increasing BPA and activity of UDPGT was found – UDPGT catalyzes the conjugation of various substances to glucuronic acid, and an increasing activity may lead to faster metabolism of THs. BPA blocked T3-induced resorption of tail segments in larvae *in vitro* and decelerated T4-induced metamorphic changes of tadpoles *in vivo* (69). BPA fed to pregnant rats was associated with significant increase of TT4 at postnatal day 15 in the pups (70).

Human literature on these compounds is very sparse. In human newborns, PCP in cord plasma was negatively correlated to T3, FT4 and T4-binding globulin (TBG) (71). These results suggest that PCP may alter TH levels in newborns and consequently may lead to adverse neurodevelopmental defects.

Phthalates

Phthalates are widely used as plastic emollients and the amount used globally is rising. Exposure to phthalates is inevitable, but for certain groups such as hospitalized neonates exposure may be massive. The exposure to phthalates through necessary medical devices such as feeding tubes is correlated to the urinary content of mono(2-ethylexyl)phthalate (72), and such intensive exposure at a potentially vulnerable point of development may cause permanent damage, despite the fast metabolism of phthalates. Expert panel reports reviewed reproductive and developmental effects of five di-phthalates (di-isodecyl phthalate (DIDP), di-*n*-octyl phthalate (DnOP), di-*n*-hexyl phthalate (DnHP), di-isononyl phthalate and di(2-ethylhexyl) phthalate (DEHP)). As relatively few studies have been focusing on thyroid-disrupting effects, firm conclusions on this aspect could not be drawn (73–79).

Rodent studies found histopathological changes in the thyroid of rats after exposure to DEHP, DnOP and DnHP, corresponding to hyperactivity of the thyroid (80–84). Long-term treatment with high doses of

DEHP resulted in basophilic deposits in the colloid and enlargement of the lysosomes (80). The levels of circulating THs were not affected after oral exposure of rats to DEHP (85), whereas i.v. exposure in doses corresponding to levels of DEHP solubilized in blood bags for human transfusions resulted in a significant increase in serum T3 and T4, which returned to normal after 7 days (86). The thyroid glands examined in this study showed initial reactive hyperplasia. In contrast di-*n*-butyl phthalate (DBP) decreased T3 and T4 in rats in a dose-dependent manner (87).

Only few studies exist on the effects of phthalates on human thyroid function. A follow-up examination of 19 adolescents, who were exposed to large amounts of DEHP due to invasive treatment in the neonatal period (extra-corporeal membrane oxygenation (ECMO)), showed normal levels of THs (88). These results may not be representative, as DEHP exposure through ECMO treatment is extremely high (89), but of short duration. Furthermore, changes in TH levels as a result of exposure to environmental chemicals may be transient. They may nonetheless have permanent effects on the development of the central nervous system, if changes occur in a critical developmental phase.

Other chemicals

Other groups of chemicals with potential effects on the thyroid are parabens and pesticides, of which the latter are a large and inhomogeneous group of compounds.

Parabens are widely used as preservatives in food, cosmetics and pharmaceutical products. Recent studies suggest that parabens possess estrogenic potential, but no studies have focused on thyroid toxicity (90). Methylparaben seemed to have a weak intrinsic antithyroid activity *in vitro* by dose-dependently inhibiting iodide organification (91).

Among many different pesticides, the thyroid-disrupting effects of dichlorodiphenyltrichloroethane (DDT) and HCB are the most studied. DDT exposure of birds decreased T4 (92) or increased thyroid weight and reduced colloid content of the follicles (93). However, other studies found no measurable thyroid effects (94). Blubber concentration of DDT correlated negatively to TT3 and free T3 in seals (26, 27), whereas a study of sea-gulls showed no correlations with THs (95).

HCB is metabolized to PCP, which has endocrine-disrupting abilities. Multiple studies in laboratory animals confirm the negative correlation between HCB and T4 (96–100), and in some studies also T3 (101, 102). The metabolites of HCB, PCP and tetrachlorohydroquinone, had even stronger effects than the parent compounds (103). Prenatal HCB exposure of rats reduced serum levels of T4 and FT4 in pups and increased T4-UDPGT and type II 5′deiodinase (5′DII) in the brain (98). This indicated an increased peripheral T4 metabolism, which may represent local hypothyroidism in the fetal brain, where 5′DII is responsible for deiodination of T4 to the biologically active T3. Wildlife observations of HCB exposure showed negative correlations to the ratio TT4/FT4 in polar bears (25), and to T4 and T4/T3 ratio in gulls (95). A study of seals found no associations of THs to HCB (27). An excess ratio of enlarged thyroid was found among people accidentally exposed to high levels of HCB (104), and several studies of adults have shown negative associations between HCB and serum levels of T4 (33, 35, 105) or T3 (39), but not TSH or free hormones (105). In infants, no correlations between the concentration of HCB and THs in cord blood were found (39). Thus, evidence of thyroid-disruptive properties of DDT and HCB is concerning.

Many other pesticides are currently used, and reports on their thyroid-disrupting effects are emerging, e.g. methoxychlor (106, 107), chlordane (26, 108) and endosulfan (109). Humans may be exposed to mixtures of these compounds and numerous others, which makes a prediction of expected health effects very difficult. Chemicals may have different effects on the thyroid axis or act synergistically as has been shown in rats exposed to a mixture of PCBs, PCDDs and PBDEs, which resulted in a dose-dependent decrease of TT4 (110).

Mechanisms of action

Until recent years the estimation of antithyroidal effects of environmental chemicals has mainly relied on measures of circulating hormone levels, thyroid size or histopathology, but over the last 10 years, additional endpoints have been developed. Intra-thyroidal T4 content, gene transcription activity and cellular growth appear to be more sensitive endpoints when assessing the significance of endocrine disruption from various chemicals. A well established example is perchlorate, which in small amounts does not alter plasma hormone levels, but diminishes thyroid gland T4 content (111–113), supporting the observation from *in vitro* studies of an inhibition of sodium–iodide symporter (NIS) (114). Thus, endocrine-disrupting chemicals present in small amounts in the environment may not cause overt changes of hormone levels in animals and humans, but may nonetheless alter the hormonal homeostasis.

The mechanisms involved in thyroid homeostasis are numerous and complex. As a consequence environmental chemicals can act at many levels in the thyroid system (Table 2).

Synthesis of THs: interference with the NIS, TPO or TSH receptor (Fig. 1, point 1)

Perchlorate compromises iodine uptake to the thyroid follicular cells by inhibiting the NIS (114) (Fig. 2). In contrast, phthalates such as DIDP, butyl benzyl

Table 2 Mechanisms of action of thyroid-disrupting chemicals.

Mechanisms of action	Group of chemicals	References
Inhibition of the iodide uptake	Perchlorate, phthalates	114, 115
Thyroperoxidase	NP	61
Inhibition of the function of the TSH receptor	DDT, PCB	116
Binding to transport proteins	PCB, phthalates, phenols, flame retardants, HCB	18, 117–123
Cellular uptake of thyroid hormones	Phthalates, chlordanes	125
Binding to thyroid hormone receptor and gene expression	PCB, phenols, flame retardants, BPA, HCB	56, 70, 126, 129, 130, 132–137
Iodothyronine deiodinases	Methoxychlor, MBC	61, 142, 143
Excretion/clearance of thyroid hormones	PCB, dioxin, phenols, flame retardants, HCB, BPA	45–47,67,68,144–146

phthalate (BBP) and DnOP increased the activity of the NIS and enhanced NIS mRNA expression (115). TPO activity was inhibited *in vitro* by NP (61). The activity of the thyroid gland is stimulated by TSH and may thus be altered by environmental chemicals affecting the function of the TSH receptor. DDT and the PCB mixture Aroclor 1254 interfered *in vitro* with post-receptor signaling by inhibition of the adenylate cyclase activity and cAMP production (116).

Transport proteins (Fig. 1, point 2)

Halogenated aromatic hydrocarbons structurally resemble THs and may therefore compete with binding to the TH receptors and transport proteins, possibly interfering with TH transport and metabolism. PCBs (18, 117), flame retardants (118), phenol compounds (119, 120) and phthalates (121) competitively bound to transthyretin (TTR). Metabolites and derivatives of PCBs, several brominated flame retardants and phenol compounds had remarkably stronger binding affinity than their parent compounds, indicating an important role for hydroxylation and halogenation in thyroid toxicity (118). In contrast to the interference with TTR, no environmental chemicals have been demonstrated to compete with THs for binding to TBG or albumin with significant strength (122, 123).

Competitive binding of environmental chemicals to TH transport proteins may result in increased bioavailibility of endogenous THs. The investigation of this mechanism of action is restrained by interspecies differences, as TTR is the principal transport protein in rodents and TBG in humans. It is unlikely that enough T4 could be displaced from TTR to be toxic in adult humans (117). However, TTR is the major TH transport protein in the human brain, presumably playing an essential role in the determination of FT4 levels in the extracellular compartment, which is independent of the T4 homeostasis in the body. Furthermore, TTR may mediate the delivery of T4 across the blood–brain barrier and the maternal to fetal transport through the placenta. Thus, environmental chemicals bound to TTR may be transported to the fetal compartment and fetal brain, and be able to decrease fetal brain T4 levels (124).

Cellular uptake mechanisms (Fig. 1, point 3)

Bioavailibility of THs to the nuclear TH receptors may become compromised as THs are probably actively

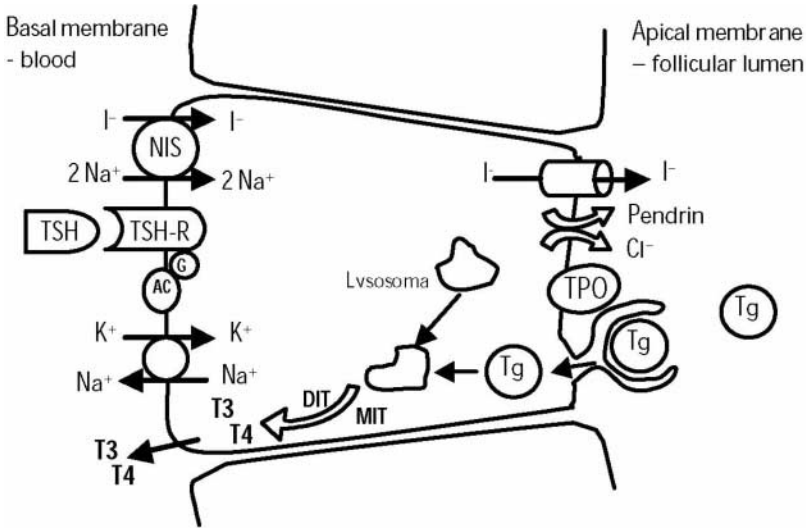

Figure 2 The thyroid follicle cell. AC, adenylate cyclase; DIT, di-iodotyrosine; G, G-protein; MIT, mono-iodotyrosine; Tg, thyroglobulin.

transported across the cell surface via membrane bound transporters. Several environmental chemicals, including DBP and BBP inhibited [^{125}I]T3 uptake in red blood cells from bullfrog tadpoles (125).

The TH receptor (Fig. 1, point 4)

Environmental chemicals can change TH-stimulated gene transcription, but it is still not clear through which mechanisms these changes are induced.

T3-mediated gene activation through thyroid receptor alfa-1 (TRalfa1) and TRbeta was dose-dependently suppressed by BPA and expression of T3-suppressed genes was upregulated by BPA. Thus, BPA acted as an antagonist to T3 (126). Maternal exposure to BPA in rats increased the expression of TH-responsive gene neurogranin in the hippocampus of the pups. This led to speculations that BPA may antagonize the feedback through TRbeta, but act as an agonist at TRalfa and thus upregulate TH-responsive genes (70). However, other studies found no effect of BPA on expression of T3-mediated reporter genes in a hamster ovary cell line (127) and pituitary cell line (128). BPA was a weak ligand for the TR (126), but the derivatives TBBPA and tetrachlorobisphenol competed for binding to the receptor (56).

PCBs also alter the expression of TH-responsive genes. PCBs acted as antagonists by partial dissociation of TR/retinoid X receptor heterodimer complex from the TH response element (TRE) (129). OH-PCBs inhibited the binding of T3 to the TR (130), but other studies found that the human TRbeta had very low affinity for OH-PCBs, DDT and its metabolites and that other organochlorine pesticides did not compete for the receptor (131). Thus, the competitive binding of some environmental chemicals appears to be both receptor-specific and compound-specific. Increased gene expression in the fetal rat brain after maternal exposure to PCBs included neuroendocrine-specific protein A, neurogranin, myelin basic protein, and the transcription factors oct-1 and hairy enhancer of split (132–134), RC3/neurogranin and myelin basic protein in pups of PCB-treated dams (134). In a study of brain protein extracts from PCB-treated chicken embryos 17 of 109 differentially expressed proteins differed with PCB treatment (135). Malic enzyme (ME) gene expression is regulated mainly by THs and was increased by exposure to HCB, probably through still unidentified nuclear proteins that bind to the TRE of the ME promoter (136).

Expression of TR genes (Fig. 1, point 4)

Seiwa *et al.* examined the effect of BPA on oligodendrocyte precursor cell (OPC) differentiation on myelin basic protein, which is a major myelin component, and 2,3-cyclic nucleotide 3-phosphodiesterase expression. TRbeta1-levels in OPCs and oligodendrocytes decreased significantly after BPA treatment for 48 h, suggesting a suppression of T3-induced differentiation of OPCs. Expression of TRalfa1 was not affected (137). Dicyclohexyl phthalate, BBP and PCP inhibited the expression of the TRbeta gene (138).

Neural growth

Oligodendrocyte development and myelination are under TH control, as well as the extension of Purkinje cell dendrites, which is essential for normal neuronal circuit formation (synaptogenesis) and subsequent behavioral functions. In a study of perinatal exposure, PCB affected the development of white matter in rat pups by mimicking some, but not all, of the effects of hypothyroidism on white matter, indicating that PCB may partly affect the neurological development through thyroid disruption (139). These effects may be congener-specific as another study showed a single PCB congener to enhance the effect of T3 by increasing the formation of oligodendrocytes (140). PCBs also caused abnormal development of Purkinje cell dendrites (141).

Metabolism of circulating THs (Fig. 1, points 5 and 6)

Peripheral iodothyronine deiodinases control the conversion of THs in different organs and are thus essential in the regulation of levels of the biologically active T3 by activation of T4 and inactivation of T4 and T3. Type I 5′deiodinase (5′DI) in the liver was decreased *in vitro* by several environmental chemicals: octyl-methoxycinnamate, 4-methylbenzylidene-camphor (MBC) (61), methoxychlor (142), and a mixture of organochlorines, lead and cadmium (143).

OH-PCBs inhibited TH sulfation (144–146).The sulfotransferase isozymes were also target proteins for inhibition by hydroxylated polyhalogenated aromatic hydrocarbons (PHAHs). OH-PCBs, PCDDs, PCDFs and other halogenated compounds were potent inhibitors of *in vitro* T2 sulfation (144). TCDD induced UDPGT activity in a dose-dependent manner in both exposed adult rats (46) and in the offspring (47), and decreased the activity of 5′DI in liver and kidney (45). Exposure doses of BPA in polecats (67) and field voles (68) were significantly correlated to the activity of UDPGT. UDPGTs catalyze the conjugation of various substances to glucuronic acid and increasing activity may lead to faster metabolism of the THs. However, in these studies, no significant effects on TH levels were found.

Significance and perspectives

Humans are exposed continuously to a large number of man-made chemicals, many of which are persistent in

the environment. Many studies of exposure to various environmental chemicals point towards a subtle disruption of the thyroid axis within normal reference values. The T4/TSH relationship is very unique for each human, and the intra-individual variation of THs is small compared with the population-based reference intervals (147–149). Thus, small changes in thyroid function within the normal reference range may have negative health consequences for the individual. In particular, the human fetus may be vulnerable to subtle changes in the T4 and TSH homeostasis as the fetal turnover of the thyroid store of T4 is very rapid (150). Thus, the fetus may become depleted of T4 more rapidly than adults. Even mild hypothyroidism in the mother or the fetus can result in neonatal neurological and cognitive deficiencies, which may not be measurable until adulthood.

There is evidence that exposure to PHAHs such as PCBs and dioxin may cause cognitive damage in humans (151–153). This effect may be mediated by induction of hypothyroidism, which is known to cause cognitive deficiencies in the fetus/infant.

The literature on thyroid-disrupting effects of individual chemicals is rapidly increasing, as animal exposure studies and *in vitro* tests reveal a multitude of potential mechanisms of action. For some persistent compounds, such as PCBs, the available evidence is much stronger than for some of the rapidly metabolized chemicals such as phthalates. Although interspecies differences in thyroid homeostasis need to be kept in mind, the evidence from animals should raise concern, especially about exposure of the human infant and fetus to chemicals.

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