Environmental Chemicals Impacting the Thyroid: Targets and Consequences

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Thyroid hormone (TH) is essential for normal brain development, but the specific actions of TH differ across developmental time and brain region. These actions of TH are mediated largely by a combination of thyroid hormone receptor (TR) isoforms that exhibit specific temporal and spatial patterns of expression during animal and human brain development. In addition, TR action is influenced by different cofactors, proteins that directly link the TR protein to functional changes in gene expression. Considering the importance of TH signaling in development, it is important to consider environmental chemicals that may interfere with this signaling. Recent research indicates that environmental chemicals can interfere with thyroid function and with TH signaling. The key issues are to understand the mechanism by which these chemicals act and the dose at which they act, and whether adaptive responses intrinsic to the thyroid system can ameliorate potential adverse consequences (i.e., compensate). In addition, several recent studies show that TRs may be unintended targets of chemicals manufactured for industrial purposes to which humans and wildlife are routinely exposed. Polychlorinated biphenyls, polybrominated diphenyl ethers, bisphenol-A, and specific halogenated derivatives and metabolites of these compounds have been shown to bind to TRs and perhaps have selective effects on TR functions. A number of common chemicals, including polybrominated biphenyls and phthalates, may also exert such effects. When we consider the importance of TH in brain development, it will be important to pursue the possibilities that these chemicals—or interactions among chemical classes—are affecting children’s health by influencing TH signaling in the developing brain.

Introduction

THYROID HORMONE (TH) IS ESSENTIAL FOR normal brain development in both humans and animals (1), but the mechanisms by which TH exerts its actions are only partly understood (2). Likewise, the influence of environmental factors, such as iodine availability, is well recognized (3), but our ability to identify environmental factors that exert direct effects on TH action during brain development may be limited by the complexity of TH receptor (TR) function during brain development and potential selective impacts of environmental factors impacting TR function. The goal of this review is to briefly place new information about the effects of environmental contaminants on TR function within the context of TH action during brain development (Fig. 1).

Mechanisms by Which Chemicals May Interfere with Thyroid Function

All chemicals currently classified as thyroid toxicants have been defined by their ability to reduce circulating levels of TH (4). Thus, these chemicals alter the relationship between TH biosynthesis and elimination, such that the steady-state levels of hormones are reduced. The modes of action by which these chemicals can influence circulating levels of TH are directed at TH biosynthesis or at TH metabolism (Table 1).

Changes in Serum Hormone Levels

Changes in serum concentrations of THs [thyroxine (T4), triiodothyronine (T3), and thyroid-stimulating hormone (TSH)] can be caused by chemicals that inhibit TH synthesis, release, and serum transport, and by chemicals that increase metabolism of various THs [e.g., deiodinases, uridine diphosphate glucuronyltransferase (UDPGTs)]. If a chemical decreases serum hormone concentrations, specific assays can be used to determine the mechanism by which these hormone concentrations are decreased. Moreover, the specific profile of changes in hormone concentrations may be informative. For example, mice carrying targeted deletions of type 2 deiodinase have elevated circulating levels of both T4 and TSH with no change in serum T3 (5). In contrast, mice carrying a targeted...
deletion of the type 1 deiodinase have elevated circulating levels of T4 and reverse T3 (rT3), but no change in serum T3 or TSH (6). Iodine deficiency can result in a reduction in serum T4 with no change or even an increase in serum T3 (7). Chemicals that inhibit thyroid peroxidase activity can produce a "stereotypical" hormone profile with decreased levels of serum T4 and T3 and an increase in serum TSH (8,9). Finally, a targeted deletion of the T3 transporter MCT8 can produce elevated levels of T3 (10). Therefore, it is possible that environmental factors interfering with the hypothalamic-pituitary-thyroid (HPT) axis at specific points of regulation may produce a hormonal profile that is indicative of the mechanism of action.

The mechanisms by which environmental chemicals can alter circulating levels of TH are many (4). Halogenated aryl hydrocarbons can induce the expression of UDPGT enzymes in the liver by activation of either the aryl hydrocarbon receptor (11) or Pregnane X receptor (PXR)/Constitutive Androstrate receptor (CAR) (12,13). In addition, hydroxylated compounds [e.g., polychlorinated biphenyls (PCBs)] can displace T4 from the serum-binding protein transthyretin (14–16). Thus, environmental contaminants may exert actions at a number of sites of regulation to cause a reduction in circulating levels of THs.

**Table 1. Examples of Chemicals That Can Interfere with the Thyroid System**

<table>
<thead>
<tr>
<th>Function</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibit iodide uptake</td>
<td>ClO₄, ClO₃, NO₃, thiocyanate</td>
</tr>
<tr>
<td>Inhibit TPO activity</td>
<td>PTU, methimazole, isoflavones</td>
</tr>
<tr>
<td>Inhibit deiodinase</td>
<td>PCBs, iapanoic acid, thiouracils</td>
</tr>
<tr>
<td>Displace T4 from TTR</td>
<td>Hydroxylated PCBs, PBDEs</td>
</tr>
<tr>
<td>Activate liver UDPGTs</td>
<td>AhR agonists, agonists of PXR/CAR</td>
</tr>
<tr>
<td>Direct action on TR</td>
<td>PCBs, PBDEs(?) , BPA, triclosan</td>
</tr>
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</table>

**Chemicals That Interfere with TRs: PCBs**

Several authors speculated early that environmental chemicals may act as imperfect TH analogs (17,18). Now, several recent reports show that a broad range of chemicals to which humans are routinely and inadvertently exposed can bind to TRs and may produce complex effects on TH signaling. Perhaps the best example is that of PCBs—industrial chemicals consisting of paired phenyl rings with various degrees of chlorination (19). Although the production of PCBs was banned in the mid 1970s, these contaminants are routinely detected in the environment (20) and in human tissues (21) at high concentrations. Of particular concern is the observation that PCBs become concentrated in fatty tissues such as brain. For example, a recent study by Lackmann et al. (22) has found that 6-week-old breast-fed infants had serum PCB levels of 1.19 µg/L, which was significantly higher than the 0.29 µg/L found in serum of bottle-fed infants. Kalantzi et al. (23) reported that in the United Kingdom, total PCB levels in breast milk ranged from 26 to 530 ng/g lipid, translating to a daily infant intake of 6.24–2067 ng/kg. Thus, when we consider the importance of TH signaling in the neonate [e.g., (24–26)], the relatively high exposure to PCBs during lactation suggests that early postnatal development may be particularly vulnerable to thyroid disruption by PCBs.

Epidemiological studies have indicated that developmental exposure to PCBs is associated with neuropsychological deficits, such as a lower full-scale IQ, reduced visual recognition memory, attention deficits, and motor deficits (27–32). Recently, Stewart et al. (33) have reported a negative association between PCB body burden and response inhibition in 3-year-old children, and a negative association between PCB body burden and size of the corpus callosum (splenium). In addition, the association between PCB body burden and response inhibition was stronger in those children with the smallest splenium. This association was retained at 9 years of age (34). Several investigators have speculated that PCBs may impact brain development by interfering with TH signaling (35–37). This concept was derived, in part, from the apparent structural similarity between PCBs and TH (17). Several studies have shown that PCBs, or specific PCB congeners, in maternal and cord blood, are associated with lower TH levels in both the mother and infant (38,39). For example, Wang et al. (40) have recently shown that PCB levels in cord blood are negatively associated with free T4 and with the product of free T4×TSH (as a measure of impacts on the negative feedback system).

Although several studies have failed to identify an association between PCB body burden and thyroid function (41–45), experimental studies uniformly find that PCB exposure decreases circulating levels of T4 in rats (46–48), and some authors propose that PCBs exert neurotoxic effects on the developing brain by causing a state of relative hypothyroidism (49–51). This concept is supported by the experimental observations that the ototoxic effect of PCB exposure can be partially ameliorated by T4 replacement (52); that the cerebellum, a tissue highly sensitive to TH insufficiency (53–55), is targeted by PCB exposure; and that the effect of PCBs on ovarian development can be partially ameliorated by T4 administration (56). PCB exposure also alters motor behavior associated with cerebellar function (57,58), as well as cerebellar anatomy (58). Interestingly, PCB exposure is associated...
with an increase in expression of glial fibrillary acidic protein (58), which is also increased by TH insufficiency (59).

However, experimental studies do not provide uniform support for the hypothesis that PCB exposure injures brain development by causing a relative state of TH insufficiency. For example, PCB exposure causes a severe reduction in circulating levels of T4, but PCB-exposed pups do not exhibit reduced body weight or body weight gain (60–62); they exhibit elevated levels of expression of several TH-responsive genes in the brain (60,63), and they do not exhibit elevated serum TSH levels (64). These observations are consistent with the hypothesis that at least some individual PCB congeners, or their metabolites, can act as TR agonists (or possibly antagonists) in vivo. Recently, Kitamura et al. (65) have reported that nine separate hydroxylated PCB congeners can bind to the rat TR with a “half-maximal binding” as low as 5 µM. In addition, using a human neuroprogenitor cell line, Fritsche et al. (66) found that a specific PCB congener could mimic the ability of T3 to enhance oligodendrocyte differentiation and that this effect was blocked by the selective TR antagonist NH3. Finally, Arulmozhiraja and Morita (67) have identified several PCB congeners that exhibit weak TH activity in an yeast-two hybrid assay optimized to identify such activity.

Not all reports indicate that PCBs act as agonists on the TR. Kimura-Kuroda et al. (68) reported that two separate hydroxylated PCBs interfere with T3-dependent neurite outgrowth in mouse cerebellar granule cell primary cultures. In addition, Bogazzi et al. (69) found that a commercial mixture of PCBs (Aroclor 1254) exhibited specific binding to the rat TRβ at approximately 10 µM. This concentration inhibited TR action on the malic enzyme promoter in a chloramphenicol acetyl transferase (CAT) assay, and this effect required an intact thyroid hormone response element (TRE). However, the PCB mixture did not alter the ability of TR to bind to the malic enzyme TRE in a gel shift assay. In contrast, Iwasaki et al. (70) found that a specific hydroxylated PCB congener inhibits TR-mediated transcriptional activation in a luciferase assay at concentrations as low as 10⁻⁶ M. This effect was observed in several cell lines, but was not observed using a glucocorticoid response element. Miyazaki et al. (71) followed this report by showing that PCBs can dissociate TR·RXR heterodimers from a TRE. Thus, some PCB congeners may be agonists, while others are antagonists. Or perhaps more likely, individual PCB congeners may be mixed agonists/antagonists—their specific actions depending on the conditions of the assay used to study it.

**Bisphenol-A**

Bisphenol-A (BPA, 4,4’-isopropylidenediphenol) is produced at a rate of over 800 million kg annually in the United States alone (72), and is used primarily in the manufacture of plastics, including polycarbonate plastics, epoxy resins that coat food cans, and in dental sealants (73,74). Howe et al. (73) estimated human consumption of BPA from epoxy-lined food cans alone to be about 6.6 µg/(person day). BPA has been reported in concentrations of 1–10 ng/mL in serum of pregnant women, in the amniotic fluid of their fetus, and in cord serum taken at birth (75,76). Moreover, BPA concentrations of up to 100 ng/g were reported in placenta (75). BPA is also halogenated (brominated or chlorinated) to produce flame retardants. Tetrabromobisphenol-A (TBBPA) is the most commonly used, with over 60,000 tons produced annually (77,78). Thomsen et al. (79) have recently reported that brominated flame retardants, including TBBPA, increased in human serum from 1977 to 1999 with concentrations in adults ranging from 0.4 to 3.3 ng/g serum lipids. However, infants (0–4 years) exhibited serum concentrations that ranged from 1.6 to 3.5 times higher (79).

When we consider this pattern of human exposure, it is potentially important that BPA has been shown to bind to the TR (80). Best characterized as a weak estrogen (81), binding to the estrogen receptor with a Kᵦ of approximately 10⁻¹⁰ M (82,83), BPA binds to and antagonizes T3 activation of the TR (84,85) with a Kᵦ of approximately 10⁻¹⁴ M, but as little as 10⁻⁶ M BPA significantly inhibits TR-mediated gene activation (85). Moreover, Moriyama et al. (80) found that BPA reduced T3-mediated gene expression in culture by enhancing the interaction with the corepressor N-CoR. Interestingly, we have found that developmental exposure to BPA in rats produces an endocrine profile similar to that observed in thyroid resistance syndrome (86). Specifically, T4 levels were elevated during development in the pups of BPA-treated animals, but TSH levels were not different from controls (87). This profile is consistent with BPA inhibition of TR/β-mediated negative feedback. However, the TR-response gene RC3 was elevated in the dentate gyrus of these BPA-treated animals (87). Because the TRβ isoform is expressed in the dentate gyrus, we concluded that BPA may be a selective TRβ antagonist in vivo.

If BPA acts as a TR antagonist in vivo, it is predictable that specific developmental events and behaviors would be affected by developmental exposure to BPA. In this regard, Seiwa et al. (88) have shown that BPA blocks T3-induced oligodendrocyte development from precursor cells (OPCs). In addition, there may be an association between the thyroid resistance syndrome and attention-deficit hyperactivity disorder (ADHD) in humans (89–91) and in rats (89); therefore, it is potentially important that BPA-exposed rats exhibit ADHD-like symptoms (92). In addition, BPA exposure alters neocortical histogenesis in the mouse (93). Although no specific link was made to TH action in this study, it is possible that BPA alters early development of the cortex by interfering with TH signaling.

Despite the antagonistic effects of BPA on the TRβ, halogenated BPAs appear to act as TR agonists (84). Both TBBPA and tetrachlorobisphenol A can bind to the TR and induce GH3 cell proliferation and growth hormone production (84). Thus, these compounds may exert agonistic effects on the TR and this could be important during early brain development. For example, TH of maternal origin can regulate gene expression in the fetal brain (94–96); one of these genes codes for Hes1 (63). Considering the role of HES proteins in fate specification in the early cortex (97–99), the observation that industrial chemicals can activate the TR and increase HES expression (63) may indicate that these chemicals can exert subtle effects on early differentiative events.

**Emerging chemicals**

Polybrominated diphenyl ethers (PBDEs) are used as flame retardants and are becoming common contaminants in human tissues (100–104). A few studies have focused on their
ability to influence thyroid function (105–109), but this has not included an evaluation of their ability to interact directly with the TR. Another common compound with a structure similar to PBDEs, triclosan, has also been shown to interfere directly with TR function in frog metamorphosis (110). Triclosan is a hydroxylated, polychloro-diphenylether used as an antibacterial agent in hand soaps and creams, and has been identified as a contaminant in human blood (111).

**Conclusion**

The human population is exposed to a large number of specific polychlorinated aromatic hydrocarbons, and biomonitoring studies now detect these chemicals in adults, children, pregnant women, and in the fetal compartment (112). Increasing numbers of reports are revealing that a broad array of compounds can bind to the TR and affect TH-regulated gene expression, both in vivo and in vitro. However, considering the tremendously pleiotropic effects of TH, it is predictable that these synthetic compounds may have very complex effects on the TR. In addition, these studies suggest that chemicals may interact with other important TH-binding proteins, such as deiodinase enzymes, which appear to control the sensitivity of different brain regions to TH exposure during development (113). Therefore, if exogenous chemicals alter the activity of these enzymes, it may influence the sequence of TH-sensitive developmental events. Likewise, specific transporters appear to control the availability of T3 to cells in the brain (114,115); thus, if environmental chemicals interfere with tissue uptake of TH, adverse human health effects could result. Our ability to identify chemical effects on TR function in vitro far exceeds our ability to identify chemical effects on TR function in vivo, in part because the mechanisms of TH action in the developing brain are less well understood. However, it will be important to define the role of TH in brain development and to identify the mechanisms by which TH exerts these actions if we are to understand the potential human health effects of persistent exposure to these bioaccumulative compounds.

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EFFECTS OF ENVIRONMENTAL CHEMICALS ON THYROID FUNCTION


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