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At the Cutting Edge

Environmental chemicals as thyroid hormone analogues: New studies indicate that thyroid hormone receptors are targets of industrial chemicals?

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Abstract

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 co-factors, proteins that directly link the TR protein to functional changes in gene expression. Several recent studies now show that TRs may be unintended targets of chemicals manufactured for industrial purposes, and to which humans and wildlife are routinely exposed. Polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), and bisphenol-A (BPA), 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 (PBBs) and phthalates may also exert such effects. Considering 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.
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Contents

It has long been recognized that thyroid hormone (TH) is essential for normal brain development in both humans and in animals (Dussault and Ruel, 1987), but the mechanisms by which TH exerts its actions are only partially understood (Bernal et al., 2003). Likewise, it has long been recognized that there are environmental influences on thyroid function (Gaitan, 1989), but our ability to identify environmental factors that affect thyroid hormone action during brain development may be limited by the lack of information about thyroid hormone action in the developing brain (Zoeller, 2003). Moreover, because all known "thyroid toxicants" have been identified solely by their ability to reduce circulating TH levels (Brucker-Davis, 1998), the default approach to identify such chemicals is by their effects on hormone levels and on thyroid histology (e.g., size of the colloid, qualitative appearance of hypertrophic or hyperplastic effects) (DeVito et al., 1999). However, chemicals that act directly on thyroid hormone receptors (TRs) may produce variable and perhaps unpredicted effects on hormone levels as well as to produce effects on brain development that incompletely mimic TH insufficiency (or action).

Despite early speculations that environmental chemicals may act as imperfect TH analogues (McKinney and Waller, 1994; McKinney and Waller, 1998), few studies had tested

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this hypothesis until recently. 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 thyroid hormone signaling. Perhaps the best example is that of polychlorinated biphenyls (PCBs), industrial chemicals consisting of paired phenyl rings with various degrees of chlorination (Chana and Concejero, 2002). Although the production of PCBs was banned in the mid 1970's, these contaminants are routinely detected in the environment (Breivik et al., 2002) and in human tissues (Fisher, 1999) at high concentrations. PCB body burden is associated with lower full-scale IQ, reduced visual recognition memory, attention deficits, and motor deficits (Huisman et al., 1995; Jackson et al., 1997; Osius et al., 1999; Korrick and Altshul, 1998; Ayotte et al., 2003; Walkowiak et al., 2001).

PCBs reduce circulating levels of T_4 in animals (Zoeller et al., 2000; Goldey et al., 1995; Bastomsky, 1977a,b; Bastomsky et al., 1976), and some authors propose that PCBs exert neurotoxic effects on the developing brain by causing a state of relative hypothyroidism (Crofton, 2004; Crofton et al., 2000; Brouwer et al., 1999). This concept is supported by the observations that the ototoxic effect of PCB exposure can be partially ameliorated by T_4 replacement (Goldey and Crofton, 1998), and that the cerebellum, a tissue highly sensitive to thyroid hormone insufficiency (Koibuchi and Chin, 2000; Li et al., 2004; Yousefi et al., 2005), is targeted by PCB exposure. PCB exposure alters motor behavior associated with cerebellar function (Roegge et al., 2004; Nguon et al., 2005), as well as cerebellar anatomy (Nguon et al., 2005). Interestingly, PCB exposure is associated with an increase in expression of glial fibrillary acidic protein (GFAP) (Nguon et al., 2005), which is also increased by thyroid hormone insufficiency (Granholm, 1985). Finally, in young children, the association between PCB body burden and behavioral measures of response-inhibition is stronger in those children that have a smaller corpus callosum (Stewart et al., 2003), an area of the brain affected by thyroid hormone (Traggiai and Stanhope, 2004; Schoonover et al., 2004; Berbel et al., 1994). Thus, it is possible that PCBs exert at least some neurotoxic effects on the developing cerebellum by causing a state of relative hypothyroidism.

However, PCB exposure does not produce consistent effects on animals that are indicative of thyroid hormone insufficiency, such as body weight gain during development (Zoeller et al., 2000; Gauger et al., 2004; Bansal et al., 2005) or the timing of eye opening (Goldey et al., 1995). In addition, despite the reduction in serum T_4, PCB exposure increases the expression of several thyroid hormone-responsive genes in the fetal (Gauger et al., 2004; Bansal et al., 2005) and neonatal (Zoeller et al., 2000) brain. These observations are consistent with the hypothesis that at least some individual PCB congeners, or their metabolites, can act as TR agonists in vivo. Recently, Kitamura et al. (2005) reported on their observations that nine separate hydroxylated PCB congeners can bind to the rat TR with an IC_{50} as low as 5 μM. In addition, using a human neuroprogenitor cell line, Fritsche et al. (2005) found that a specific PCB congener could mimic the ability of T_3 in increasing oligodendrocyte differentiation, and that this effect was blocked by the selective TR antagonist NH3. Finally, Arulmozhiraja and Morita (2004) have identified several PCB congeners that exhibit weak thyroid hormone activity in a yeast-two hybrid assay optimized to identify such activity.

However, not all recent reports indicate that PCBs act as agonists on the TR. Kimura-Kuroda et al. (2005) have found that two separate hydroxylated PCBs interfere with T_3-dependent neurite outgrowth in mouse cerebellar granule cell primary cultures. In addition, Bogazzi et al. (2003) 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 CAT assay and this effect required an intact TRE. However, the PCB mixture did not alter the ability of TR to bind to the ME TRE in a gel shift assay. In contrast, Iwasaki et al. (2002) found that a specific hydroxylated PCB congener inhibits TR-mediated transcriptional activation in a luciferase assay at concentrations as low as 10^{-10} M. This effect was observed in several cell lines, but was not observed using a glucocorticoid response element. Miyazaki et al. (2004) followed this report by showing that PCBs can dissociate TR:RXR heterodimers from a TRE.

It is clear that PCBs are neurotoxic in humans and animals, and that they can interact directly with the TR. However, the consequences of PCB exposure on TR action appear to be quite complex. This complexity includes acting as an agonist or antagonist and may include TR isoform selectivity in as much as most studies have been performed using the TRβ, leaving the TRα relatively unstudied in this context. In addition, considering that there are 209 different chlorine substitution patterns on the biphenyl backbone and that these can be metabolized (hydroxyl- and methylsulfonyl-metabolites (Kato et al., 1998)), it is possible that different chemical species exerts different effects. Finally, PCBs may exert different actions on TRs depending on associated heterodimer partners, promoter structure, or different co-factors. This complexity will be important to pursue because the effects of PCB exposure in humans is far better studied than for structurally related compounds such as polybrominated biphenyls (PBBs) and polybrominated diphenyl ethers (PBDEs). Thus, mechanistic studies on PCBs can be more easily and effectively coupled to specific human health outcomes.

Bisphenol-A (BPA, 4,4′ isopropylidenediphenol) is produced at a rate of over 800 million kg annually in the United States alone (Reporter, 1999), and is used primarily in the manufacture of plastics including polycarbonate plastics, epoxy resins that coat food cans, and in dental sealants (Howe et al., 1998; Lewis et al., 1999). Howe et al. (1998) estimated human consumption of BPA from expoxy-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

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