Thyroid Hormone, Brain Development, and the Environment

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Thyroid hormone is essential for normal brain development. Therefore, it is a genuine concern that thyroid function can be altered by a very large number of chemicals routinely found in the environment and in samples of human and wildlife tissues. These chemicals range from natural to manufactured compounds. They can produce thyroid dysfunction when they are absent from the diet, as in the case of iodine, or when they are present in the diet, as in the case of thionamides. Recent clinical evidence strongly suggests that brain development is much more sensitive to thyroid hormone excess or deficit than previously believed. In addition, recent experimental research provides new insight into the developmental processes affected by thyroid hormone. Based on the authors' research focusing on the ability of polychlorinated biphenyls to alter the expression of thyroid hormone-responsive genes in the developing brain, this review provides background information supporting a new way of approaching risk analysis of thyroid disruptors. ***Key words:*** **brain development, cerebral cortex, endocrine disruption, HES-1, Notch, NSP-A, thyroid hormone.** ***Environ Health Perspect*** **110(suppl 3):355–361 (2002).**
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The importance of thyroid hormone in brain development has been extensively documented and reviewed for animals (*1–13*) and humans (*14–22*). These reviews leave no doubt that thyroid hormone deficit or excess during development can have permanent, pervasive, and profound effects on adult neurological function. Recent studies also demonstrate that relatively subtle changes in circulating levels of thyroid hormone in pregnant women can affect the neurological outcome of their children (*23–27*). Thus, it is clear that the fetus and neonate are quite sensitive to thyroid hormone. However, despite the known importance of thyroid hormone for normal brain development, and new insight into the sensitivity of neural development to maternal thyroid status, there are critical gaps in our understanding of thyroid hormone and brain development. These gaps compromise our ability to accurately determine whether environmental chemicals interact with the thyroid system and, if they do, whether the consequence of exposure is adverse. This is particularly important considering that a large number of chemicals are known to interfere with thyroid functioning and perhaps thyroid hormone action (*28–32*).

Our goal in this article is to briefly review the data that have led us to make the novel proposal that some environmental chemicals can disrupt thyroid hormone signaling without affecting circulating levels of thyroid hormone, including data from our laboratory. An important theme in this article is that measures of thyroid function such as blood levels of hormones and the processes regulating these levels are not equivalent to measures of thyroid hormone action at the receptor, such as the regulation of gene expression and the developmental processes on which they act. To provide context for this proposition, we review the literature on thyroid hormone and brain development and the effects of polychlorinated biphenyls (PCBs) on this system.

Thyroid Hormone and Brain Development in Humans

The neonatal period of development in humans is known to be sensitive to thyroid hormone, especially as revealed in the disorder known as congenital hypothyroidism (CH) (*16,18,19,21,22,33–37*). CH occurs at a rate of approximately 1 in 3,500 live births (*16*). Because CH infants do not present a specific clinical picture early, their diagnosis based solely on clinical symptoms was delayed before neonatal screening for thyroid hormone. In fact, only 10% of CH infants were diagnosed within the first month, 35% within 3 months, 70% within the first year, and 100% only after age 3 (*38,39*). The intellectual deficits as a result of this delayed diagnosis and treatment were profound. One meta-analysis found that the mean full-scale intelligence quotient (IQ) of 651 CH infants was 76 (*20*). Moreover, the percentage of CH infants with an IQ above 85 was 78% when the diagnosis was made within 3 months of birth, 19% when it was made between 3 and 6 months, and 0% when diagnosed after 7 months of age (*20,40*). Studies now reveal that the long-term consequences of CH are subtle if the diagnosis is made early and treatment is initiated within 14 days of birth (*36,37,41–43*), which can be accomplished only by mandatory screening for thyroid function at birth. This medical profile has become the principal example illustrating the importance of thyroid hormone for normal brain development.

Recent studies indicate that thyroid hormone is also important during fetal development. Thyroid hormones are detected in human coelomic and amniotic fluids as early as 8 weeks of gestation, before the onset of fetal thyroid function at 10–12 weeks (*44*). In addition, human fetal brain tissues express thyroid hormone receptors (TRs), and receptor occupancy by thyroid hormone is in the range known to produce physiological effects as early as 9 weeks of gestation (*45,46*). Finally, the mRNAs encoding the two known TR classes exhibit complex temporal patterns of expression during human gestation (*47*), and the mRNAs encoding these TR isoforms are expressed in the human oocyte (*48*). These data indicate that maternal thyroid hormone is delivered to the fetus before the onset of fetal thyroid function, and that the minimum requirements for thyroid hormone signaling are present at this time.

Two kinds of pathological situations reveal the functional consequences of deficits in thyroid hormone during fetal development. The first is that of cretinism, a condition usually associated with severe iodine insufficiency in the diet (*15*). There are two forms of cretinism based on clinical presentation: neurological cretinism and myxedematous cretinism (*15,17*). Neurological cretinism is characterized by extreme mental retardation, deaf-mutism, impaired voluntary motor activity, and hypertonia (*15*). In contrast, myxedematous cretinism is characterized by less severe mental retardation and all the major clinical symptoms of persistent hypothyroidism (*15*). Iodide administration to pregnant women in their first trimester eliminates the incidence of neurological cretinism. However, the initiation of iodine supplementation by the end of the second trimester does not prevent neurological damage (*15,49*). Several detailed studies of

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endemias occurring in different parts of the world have led to the proposal that the various symptoms of the two forms of cretinism arise from thyroid hormone deficits occurring at different developmental windows of vulnerability (*15,17,49*). Therefore, thyroid hormone appears to play an important role in fetal brain development, perhaps before the onset of fetal thyroid function.

The second type of pathological situation is that of subtle, undiagnosed maternal hypothyroxinemia. The concept and definition of maternal hypothyroxinemia were developed in a series of papers by Man et al. (*50–56*). Low thyroid hormone was initially defined empirically—those pregnant women with the lowest butanol-extractable iodine among all pregnant women (*55,57*). This work was among the first to document an association between subclinical hypothyroidism in pregnant women and neurological function of the offspring. After the development of radioimmunoassay for thyroid hormone, Pop et al. (*58*) found that the presence of antibodies to thyroid peroxidase in pregnant women, independent of thyroid hormone levels per se, is associated with significantly lower IQ in the offspring. Subsequent studies have shown that children born to women with thyroxine (T_4) levels in the lowest 10th percentile of the normal range had a higher risk of low IQ and attention deficit (*25*). Excellent recent reviews discuss these studies in detail (*24,57,59*). Taken together, these studies present strong evidence that maternal thyroid hormone plays a role in fetal brain development before the onset of fetal thyroid function, and that thyroid hormone deficits in pregnant women can produce irreversible neurological effects in their offspring (*18,19,22,37,60–62*).

Thyroid Hormone and Brain Development in Experimental Animals

Considerable research using experimental animals has provided important insight into the mechanisms and consequences of thyroid hormone action in brain development. The body of this work is far too extensive to review here but has been reviewed at critical times during the past 50 years (*4,6,11,12,18,57,63–66*). Several themes have emerged that provide a framework in which to begin to understand the role of thyroid hormone in brain development. First, the majority of biological actions of thyroid hormone appear to be mediated by TRs, which are ligand-dependent transcription factors (*67,68*). There are two genes, encoding TRα and TRβ, although these two receptors do not exhibit different binding characteristics for T_4 and for triiodothyronine (T_3). Second, based on considerable work in the cerebellum, there appear to be critical periods of thyroid hormone action during development. As originally defined (*69*), the critical period was that developmental stage where thyroid hormone replacement to CH children could improve their intellectual outcome. This definition was also applied to experimental studies to identify the developmental period during which thyroid hormone exerts a specific action. It is now generally accepted that there is no single critical period of thyroid hormone action on brain development, either in humans (*15*) or in animals (*70*). Rather, thyroid hormone acts on a specific development process during the period that the process is active. For example, thyroid hormone effects on cellular proliferation would necessarily be limited to the period of proliferation for a specific brain area. Because cells in different brain regions are produced at different times (*71*), the critical period for thyroid hormone action on cell proliferation would differ for cells produced at different times.

Maternal Thyroid Hormone and Fetal Brain Development

We recently initiated a series of studies to test the broad hypothesis that thyroid hormone of maternal origin can exert direct effects on brain development before birth. Fetal thyroid function begins in the rat at approximately embryonic day 17.5 (E17.5) (*72,73*); therefore, thyroid hormone effects exerted before this time would indicate a role for thyroid hormone of maternal origin in fetal brain development. Because thyroid hormone is known to influence many cellular and developmental processes (*11,12*), the specific genes regulated by thyroid hormone are not possible to predict *a priori*. Therefore, we used the nonbiased method of differential display (*74*) to identify putative thyroid hormone-responsive genes in the fetal cerebral cortex. Moreover, to increase the likelihood of identifying genes that are directly regulated by thyroid hormone, we used a model of acute thyroid hormone exposure (*70*).

We identified several putative thyroid hormone–responsive genes in the fetal cortex, including neuroendocrine-specific protein A (NSP-A), Oct-1, and RC3/neurogranin (*70,75,76*). Identification of these genes as thyroid hormone responsive in the fetal cortex before the onset of fetal thyroid function represents important evidence that maternal thyroid hormone can directly affect brain development. Interestingly, all of these genes are selectively expressed in the ventricular zone of the G16 cortex, where cells undergo proliferation before committing to a specific fate (*77–80*). Therefore, we tested whether thyroid hormone affects cell proliferation in the ventricular zone using bromodeoxyuridine (BrdU). This compound is incorporated into newly synthesized DNA and can be localized immunocytochemically (*81*). We found that manipulation of maternal thyroid status did not alter the number of BrdU-labeled cells in the ventricular zone (*82*); therefore, we concluded that thyroid hormone does not affect the number of cells being produced in the developing cortex.

Recently, we found that thyroid hormone enhanced contact-dependent signaling among cells in the ventricular zone of the E16 cerebral cortex. (*83*). This signaling system is mediated by the Notch receptor. Originally identified in *Drosophila*, the Notch receptor is a membrane-bound protein whose extracellular domain can bind to a ligand such as Delta or Jagged, proteins that also are membrane bound (*84*). Upon ligand binding, the Notch receptor is cleaved by a gamma-secretase activity, which liberates the Notch intracellular domain to translocate to the nucleus and regulate gene expression (*85*). An important gene regulated by Notch signaling is the basic helix-loop-helix gene HES-1 [*Hairy-Enhancer of Split* (*86*)]. Because HES expression appears to inhibit neurogenesis and favor gliogenesis (*87–90*), we are presently pursuing the working hypothesis that thyroid hormone of maternal origin is involved in controlling the balance in production of neurons and glia in the ventricular zone of the early cerebral cortex. This hypothesized role of thyroid hormone in fate specification of neural stem cells is similar to the role of thyroid hormone in the control of oligodendrocyte differentiation (*91,92*).

Taken together, our studies demonstrate that maternal thyroid status is important to the neurological outcome of the offspring, and that thyroid hormone of maternal origin can selectively affect gene expression in the fetal cortex, perhaps by modifying Notch signaling. It is also important to recognize that the actions of thyroid hormone will depend on the developmental events occurring at the time under investigation. For example, cerebellar granule cells are generated after birth in the rat, but cerebral cortical neurogenesis occurs between E13 and E17 (*71*). Therefore, it is predictable that thyroid hormone does not play a significant role in cerebellar granule cell proliferation on E16 or in cortical neurogenesis on postnatal day 5 (P5). Thus, the concept of a "critical period" of thyroid hormone action on brain development should be restricted to specific developmental events and not be viewed as a single window of brain development to which thyroid hormone action is limited.

Thyroid Hormone Action and PCBs

Considering that thyroid hormone of maternal origin is important in fetal brain development and neurological outcome of the offspring, environmental factors that affect maternal thyroid function, or thyroid hormone action directly, may affect fetal brain development and neurological outcome. Although a number of environmentally relevant compounds are known to affect thyroid status (*93*), we focus on PCBs in this review because their effects on the thyroid system illustrate several important concepts of thyroid toxicology that may not be generally appreciated.

Polychlorinated biphenyls are a class of industrial compounds consisting of paired phenyl rings with various degrees of chlorination (*94–96*). They are now ubiquitous, persistent environmental contaminants routinely found in samples of human and animal tissues. Exposure to PCBs is associated with cognitive and behavioral changes in humans (*97–100*). The effects of PCBs on brain development may be attributable, at least in part, to their ability to affect the thyroid system (*101*). This hypothesis is supported in part by the overlap in neurological deficits observed in humans associated with PCB exposure and those deficits observed in the offspring to hypothyroxinemic women (*36,41,102,103*).

PCB body burden also has been associated with measures of thyroid hormones in humans, although these data are complex. For example, Hagmar et al. (*103*) found a significant inverse association between serum levels of PCB 153 and total T_3 in fishermen's wives from the Swedish east coast. However, this association was not observed in men (*104*). Furthermore, Sala et al. (*105*) found that serum levels of both hexachlorobenzene and PCBs were inversely related to serum total T_4. Persky et al. (*106*) recently found that serum PCB levels were inversely related to serum total T_4 and free T_4 in women but only to total T_4 in men. Osius et al. (*107*) studied 7- to 10-year-old school children in three German municipalities and found a significant positive correlation between serum concentration of the mono-*ortho* congener PCB 118 and serum thyrotropin (TSH). Moreover, they found a significant negative correlation between several PCB congeners and free T_3. They found no correlation between circulating levels of PCBs and T_4. In contrast, Koopman-Esseboom et al. (*108*) measured dioxins and PCBs in human cord blood and breast milk and found that PCB exposure, estimated by toxic equivalents, was negatively correlated with circulating T_4 in infants.

It is important to recognize that the differences in circulating levels of thyroid hormones associated with PCBs are still within the normal range. Therefore, there is no formal evidence for background exposure to PCBs causing overt hypothyroidism. Because different studies reveal different associations between body burden of PCBs and various measures of thyroid hormone levels, it is possible that these associations are spurious. However, it is also possible that the environmental mixture to which different populations are exposed can produce slightly different effects.

All studies to date that focus on the relationship between PCBs and the thyroid use circulating levels of thyroid hormone as the sole indicator of an effect on the thyroid system, or focus on mechanisms by which PCBs affect thyroid hormone levels. Therefore, the prevailing view is that PCBs interfere with thyroid hormone signaling by reducing circulating levels of thyroid hormone, thereby limiting the hormone available to act on tissues (*109–111*). However, the developmental effects of PCB exposure in experimental animals are not fully consistent with a mechanism attributable to hypothyroidism. For example, PCB exposure induces hearing loss in rats (*109*) that is similar to that observed in hypothyroid rats (*112*). Moreover, this PCB-induced hearing loss can be at least partially restored in PCB-treated rats by thyroid hormone replacement (*110*). However, circulating levels of TSH were not elevated by PCB exposure as it is after exposure to the goitrogen propylthiouracil (*109,113*). Moreover, the timing of eye opening was advanced by PCB exposure, rather than delayed after exposure to the goitrogen 6-*n*-propyl-2 thiouracil (*109*). These and other observations suggest that the combination of PCB congeners present in the commercial Aroclor mixtures produces heterogeneous effects on the thyroid system (*101*).

There are 209 PCB congeners based on the number and placement of the chlorine atoms in the biphenyl backbone (*114*). Some investigators categorize PCB congeners according to their dioxinlike activity (*96*). PCBs with zero or one *ortho* chlorine, two *para* chlorines, and at least two *meta* chlorines can adopt a planar structure similar to that of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and can bind to and activate the aryl hydrocarbon receptor (AhR) (*96,115*). In contrast, some *ortho*-substituted PCBs may adopt a non-coplanar conformation that does not act through the AhR but can nevertheless produce neurotoxic effects (*115–117*).

In general, congener-specific studies demonstrate that both coplanar and non-coplanar PCB congeners can reduce circulating levels of T_4. However, the mechanism(s) by which different congeners lead to changes in circulating levels of thyroid hormones appears to differ. At least three independent, but perhaps interacting, mechanisms may account for the ability of PCBs to reduce circulating levels of thyroid hormone [see Brouwer et al. (*111*) for full discussion]. First, PCBs have been reported to alter the structure of the thyroid gland, perhaps directly affecting thyroid function (*118–120*). These observations, although not extensively investigated, are consistent with the report of Byrne et al. (*121*) that PCB exposure reduces the ability of TSH to increase serum T_4 *in vivo*. Thus, PCBs may directly interfere with the ability of the thyroid gland to respond to TSH. Second, PCBs can alter thyroid hormone metabolism. Early work demonstrated that PCB exposure increased the rate of bile flow and increased the biliary excretion of ^{125}I-T_4 (*122*). Moreover, PCB exposure induces the expression and activity of UDP-glucuronosyltransferase (*123*) and increases T_4 glucuronidation (*124*). In addition, PCB exposure selectively activates the glucuronidation of T_4 but not T_3 (*113*), suggesting that this mechanism may account in part for the failure of PCBs to alter circulating T_3. Thus, PCB exposure may facilitate T_4 clearance from serum through liver metabolism, reducing the half-life of T_4 in the blood. Finally, specific PCB congeners can bind to thyroid hormone–binding proteins in the blood and potentially can displace T_4 from the protein *in vivo* (*111,125*). These three mechanisms may combine to reduce the carrying capacity of the blood for T_4, reduce the serum half-life of T_4, and reduce the ability of the thyroid gland to respond to TSH. Although it is not clear which among these potential mechanisms are most important for mediating the effects of PCBs on circulating levels of thyroid hormone, it is likely that all are important to some extent in experimental systems.

A number of studies have focused on the structural requirements of individual PCB congeners required for binding to the T_4-binding protein transthyretin (*125–128*). These studies demonstrate that individual PCB congeners can displace T_4 from these proteins with high affinity. In addition, several investigators have speculated that certain PCB congeners may affect brain development by directly interacting with TRs (*129–132*), although the TRs are T_3-binding proteins that are structurally and evolutionarily unrelated to transthyretin. However, this concept is important to consider, because many studies have demonstrated the ability of environmental chemicals to bind directly to estrogen and

androgen receptors (*133*), and direct interaction with the TR is possible. In addition, although the two TR types bind to T_3 and to T_4 similarly, a number of analogs can differentiate between the two receptors. For example, 3,5,3′-triiodithyroacetic acid has a much higher affinity for the TRβ1 than does T_3 (*134*). In addition, the compound GC-1 is a TRβ-selective agonist (*134,135*). Moreover, the therapeutic agent desethylamiodarone is a noncompetitive inhibitor of T_3 binding to TRβ1 but a competitive inhibitor of T_3 binding to TRα1 (*136,137*). These studies demonstrate that the two classes of TRs (TRα and TRβ) can discriminate between ligands that may include compounds such as PCBs. Moreover, it is possible in principle that individual PCB congeners could produce allosteric effects on TR action, modifying their ability to interact with dimerization partners or cofactors (*131*). These interactions are not simple to fully evaluate but are important to address.

Because very few thyroid hormone–responsive end points have been evaluated to test whether PCBs act on the thyroid hormone system solely by reducing circulating levels of thyroid hormone, we tested this hypothesis in the early postnatal rat brain. During the first 3 postnatal weeks in the rat and mouse, two genes have been most extensively studied for their responsiveness to thyroid hormone: RC3/neurogranin in the forebrain and myelin basic protein (MBP) in the cerebellum (*138–141*). The expression of both of these genes is up-regulated by thyroid hormone (*139,142*). Interestingly, MBP expression in the cerebellum and RC3/neurogranin expression in the forebrain are affected by thyroid hormone during a specific period from about P7 to P25 (*64*). Therefore, we employed RC3/neurogranin and MBP gene expression during this developmental period as end points of thyroid hormone action to test the effects of PCB exposure.

For this experiment, we fed pregnant rats doses of Aroclor 1254 (A1254), from E6 to P21, as initially reported by Goldey et al. (*109*). These doses (1, 4, and 8 mg/kg) reduced circulating levels of thyroid hormones in the pups during the first 3 postnatal weeks in a dose-dependent manner. The highest dose, 8 mg/kg, reduced circulating T_4 to undetectable levels; however, RC3/neurogranin and MBP mRNA levels were both significantly increased by PCB exposure in a dose-dependent manner (*143*). Importantly, this effect of A1254 on RC3/neurogranin and MBP expression was observed on P15 but not on P5 or P30. Moreover, A1254 increased RC3/neurogranin expression only in brain areas in which it is increased by thyroid hormone (*144*). Finally, A1254 increased cellular levels of RC3/neurogranin mRNA, suggesting a transcriptional mechanism similar to that induced by thyroid hormone (*144*). These data are consistent with the interpretation that specific PCB congeners exert a thyroid hormonelike effect on the expression of these genes. These data cannot be explained by the ability of PCBs to reduce circulating levels of thyroid hormone.

We then tested whether A1254 could affect gene expression in the fetus, using genes previously identified as thyroid hormone responsive [(*70,75,76*), and reviewed here]. We found that A1254, provided to the dam from E6 to E16, increased RC3/neurogranin expression in the E16 fetal cortex (*145*). In addition, A1254 increased the expression of Oct-1 mRNA in the fetal brain but had no effect on the expression of NSP-C (*145*). NSP-C is a splicing variant of NSP-A, which we have shown is not regulated by thyroid hormone in the E16 cortex (*70,76*). Importantly, the same doses of A1254 that significantly reduced circulating levels of thyroid hormone in neonatal animals had no effect on circulating levels of thyroid hormones in the dams. Thus, the ability of PCBs to affect circulating levels of thyroid hormone is not related to their ability to affect thyroid hormone–responsive gene expression. This observation is consistent with the interpretation that PCB congeners responsible for reducing circulating levels of thyroid hormone in the rat are not the same congeners producing thyroid hormonelike effects on gene expression in the developing brain.

It will be important to determine the functional consequences of PCB effects on thyroid hormone–responsive genes in the fetal brain. For this reason, we have begun to explore the effects of PCB exposure on Notch signaling and have found that A1254 produces thyroid hormonelike effects on HES-1 expression in the E16 brain (*146*). Our working hypothesis is that PCBs increase HES-1 expression in the fetal cortex, which increases gliogenesis at the expense of neurogenesis. Clearly, the presence of an environmental contaminant that affects the balance of production of neurons and glia in the absence of effects on circulating levels of thyroid hormone is an important observation with implications for screening programs that use circulating levels of thyroid hormone as the sole index of thyroid toxicology.

The parsimonious explanation for these findings is to propose that individual PCB congeners, or classes of congeners, can directly activate the TR either as parent congeners or after metabolic activation. If true, then individual PCB congeners should be able to bind to the TR (or TRs) with high affinity. Presently, only one study has tested this hypothesis formally (*128*), and although the investigators found that individual hydroxylated PCB congeners can bind to the TRβ1 with low affinity (K_i ~ 32 mM), it is questionable that this level of binding is physiologically meaningful. Thus, this prediction remains to be fully tested.

Conclusions

Thyroid hormone is essential for brain development both before and after birth. Therefore, it is important to effectively evaluate whether environmental factors can interfere with maternal or neonatal thyroid function, or thyroid hormone action. We need to improve upon our ability to identify thyroid-disrupting environmental chemicals for several reasons. First, we know surprisingly little about the molecular and cellular mechanisms by which thyroid hormone affects brain development. Moreover, we know even less about the developmental events affected by thyroid hormone at any one time in brain development. Therefore, we have few clear and quantitative end points of thyroid hormone action in brain development that can be validated as end points of thyroid toxicity. Toxicological studies underlying risk assessment for thyroid toxicity must rely on measures of thyroid function such as hormone levels and thyroid histopathology (*147*). Therefore, environmental chemicals are tested for their ability to disrupt thyroid hormone action by measuring whether they are able to affect circulating levels of thyroid hormone. The example of PCB exposure on thyroid hormone–responsive genes described here demonstrates that thyroid hormone action may well be disrupted without changes to overt measures of thyroid function. Thus, we must develop biomarkers of thyroid hormone action in brain development that can be employed in toxicological studies for risk assessment (*147*).

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