

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 hypertension (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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endemics 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 TR α and TR β , 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 T₃ 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 T₄. Persky et al. (106) recently found that serum PCB levels were inversely related to serum total T₄ and free T₄ in women but only to total T₄ 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 T₃. They found no correlation between circulating levels of PCBs and T₄. 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 T₄ 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 T₄. 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 T₄ *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 ¹²⁵I-T₄ (122). Moreover, PCB exposure induces the expression and activity of UDP-glucuronosyltransferase (123) and increases T₄ glucuronidation (124). In addition, PCB exposure selectively activates the glucuronidation of T₄ but not T₃ (113), suggesting that this mechanism may account in part for the failure of PCBs to alter circulating T₃. Thus, PCB exposure may facilitate T₄ clearance from serum through liver metabolism, reducing the half-life of T₄ in the blood. Finally, specific PCB congeners can bind to thyroid hormone-binding proteins in the blood and potentially can displace T₄ from the protein *in vivo* (111,125). These three mechanisms may combine to reduce the carrying capacity of the blood for T₄, reduce the serum half-life of T₄, 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 T₄-binding protein transthyretin (125–128). These studies demonstrate that individual PCB congeners can displace T₄ 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 T₃-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 T₃ and to T₄ similarly, a number of analogs can differentiate between the two receptors. For example, 3,5,3'-triiodothyroacetic acid has a much higher affinity for the TRβ1 than does T₃ (134). In addition, the compound GC-1 is a TRβ-selective agonist (134,135). Moreover, the therapeutic agent desethylamiodarone is a noncompetitive inhibitor of T₃ binding to TRβ1 but a competitive inhibitor of T₃ 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 T₄ 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 toxicity.

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_d ~ 32 nM), 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).

REFERENCES AND NOTES

1. Brown DD, Wang Z, Kanamori A, Eliceiri B, Furlow JD, Schwartzman R. Amphibian metamorphosis: a complex program of gene expression changes controlled by the thyroid hormone. *Recent Prog Horm Res* 50:309–315 (1995).
2. Brown DD, Wang Z, Furlow JD, Kanamori A, Schwartzman RA, Remo BF, Pinder A. The thyroid hormone-induced tail resorption program during *Xenopus laevis* metamorphosis. *Proc Natl Acad Sci U S A* 93:1924–1929 (1996).
3. Chan S, Kilby MD. Thyroid hormone and central nervous system development. *J Endocrinol* 165:1–8 (2000).
4. Dussault JH, Ruel J. Thyroid hormones and brain development. *Annu Rev Physiol* 49:321–334 (1987).
5. Morelle de Escobar GM, Obregon MJ, Calvo R, Pedraza P, Escobar del Rey F. Iodine deficiency, the hidden scourge: the rat model of human neurological cretinism.

- In: *Recent Research Developments in Neuroendocrinology—Thyroid Hormone and Brain Maturation* (Hendrich CE, ed). Trivandrum, India: Research Signpost, 1997;55–70.
6. Koibuchi N, Chin WW. Thyroid hormone action and brain development. *Trends Endocrinol Metab* 11:123–128 (2000).
 7. Porterfield SP, Hendrich CE. The role of thyroid hormones in prenatal neonatal neurological development—current perspectives. *Endocr Rev* 14:94–106 (1993).
 8. Porterfield SP, Stein SA. Thyroid hormones and neurological development: update 1994. *Endocr Rev* 3:357–363 (1994).
 9. Puymirat J. Functions of thyroid hormone receptors in prenatal rat brain development. *Recent Res Dev Neuroendocrinol* 1997:103–111 (1997).
 10. Schwartz HL. Effect of thyroid hormone on growth and development. In: *Molecular Basis of Thyroid Hormone Action* (Oppenheimer JH, Samuels HH, eds). New York: Academic Press, 1983;413–444.
 11. Thompson C. Molecular mechanisms of thyroid hormone action in neural development. *Dev Neuropsychol* 16:365–367 (1999).
 12. Thompson CC, Potter GB. Thyroid hormone action in neural development. *Cereb Cortex* 10:939–945 (2000).
 13. Timiras PS, Nzekwe EU. Thyroid hormones and nervous system development. *Biol Neonate* 55:376–385 (1989).
 14. Boyages SC, Halpern JP. Endemic cretinism: toward a unifying hypothesis. *Thyroid* 3:59–69 (1993).
 15. Delange FM. Endemic cretinism. In: *Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text*, 8th ed. (Braverman LE, Utiger RD, eds). Philadelphia: Lippincott Williams and Wilkins, 2000;743–754.
 16. Delange F. Neonatal screening for congenital hypothyroidism: results and perspectives. *Horm Res* 48:51–61 (1997).
 17. DeLong GR, Ma T, Cao XY, Jiang XM, Dou ZH, Murdon AR, Zhang ML, Heinz ER. The neuromotor deficit in endemic cretinism. In: *The Damaged Brain of Iodine Deficiency* (Stanbury JB, ed). New York: Cognizant Communications, 1994;9–17.
 18. Dussault JH, Walker P. Congenital Hypothyroidism. New York: Marcel Dekker, 1983.
 19. Foley TP. Congenital hypothyroidism. In: *Werner and Ingbar's The Thyroid*, 7th ed. (Braverman LE, Utiger RD, eds). Philadelphia: Lippincott-Raven, 1996;988–994.
 20. Klein R. History of congenital hypothyroidism. In: *Neonatal Thyroid Screening* (Burrow GN, Dussault JH, eds). New York: Raven Press, 1980;51–59.
 21. Krude H, Biebermann H, Krohn HP, Gruters A. Congenital hyperthyroidism. *Exp Clin Endocrinol Diabetes* 105:6–11 (1977).
 22. Miculan J, Turner S, Paes BA. Congenital hypothyroidism: diagnosis and management. *Neonatal Netw* 12:25–34 (1993).
 23. Glinoe D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocr Rev* 18:404–433 (1997).
 24. Glinoe D, Delange F. The potential repercussions of maternal, fetal, and neonatal hypothyroxinemia on the progeny. *Thyroid* 10:871–887 (2000).
 25. Haddow JE, Palomaki GE, Allen WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 341:549–555 (1999).
 26. Klein RZ, Haddow JE, Faix JD, Brown RS, Hermos RJ, Pulkkinen A, Mitchell ML. Prevalence of thyroid deficiency in pregnant women. *Clin Endocrinol* 35:41–46 (1991).
 27. Pop VJ, Kuijpers JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga WM, Drexhage HA, Vader HL. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. *Clin Endocrinol* 50:149–155 (1999).
 28. Brucker-Davis F. Effects of environmental synthetic chemicals on thyroid function. *Thyroid* 8:827–856 (1998).
 29. Delange F. Cassava and the thyroid. In: *Environmental Goitrogenesis* (Gaitan E, ed). Boca Raton, FL: CRC Press, 1989;173–194.
 30. Gaitan E. Epidemiological aspects of environmental goitrogenesis. In: *Environmental Goitrogenesis* (Gaitan E, ed). Boca Raton, FL: CRC Press, 1989;161–169.
 31. Gaitan E, Cooksey RC. General concepts of environmental goitrogenesis. In: *Environmental Goitrogenesis* (Gaitan E, ed). Boca Raton, FL: CRC Press, 1989;3–14.
 32. Gaitan E, Lindsay RH, Cooksey RC. Goiter endemias attributed to chemical and bacterial pollution of water supplies. In: *Environmental Goitrogenesis* (Gaitan E, ed). Boca Raton, FL: CRC Press, 1989;207–232.
 33. Calvo R, Obregon MJ, Ruiz de Ona C, Escobar del Rey F, Morealle de Escobar G. Congenital hypothyroidism, as studied in rats. *J Clin Invest* 86:889–899 (1990).
 34. Fisher DA, Dussault JH, Foley TP, Klein AH, LaFranchi S, Larsen PR, Mitchell ML, Murphey WH, Walfish PG. Screening for congenital hypothyroidism: results of screening one million North American infants. *J Pediatr* 94:700–705 (1979).
 35. Koistra L, Laane C, Vulsma T, Schellekens JMH, van der Meere JJ, Kalverboer AF. Motor and cognitive development in children with congenital hypothyroidism. *J Pediatr* 124:903–909 (1994).
 36. Rovet JF. Neurobehavioral consequences of congenital hypothyroidism identified by newborn screening. In: *Therapeutic Outcome of Endocrine Disorders* (Stabler B, Bercu BB, eds). New York: Springer-Verlag, 2000;235–254.
 37. van Vliet G. Neonatal hypothyroidism: treatment and outcome. *Thyroid* 9:79–84 (1999).
 38. Alm J, Hagenfeldt L, Larsson A, Lundberg K. Incidence of congenital hypothyroidism: retrospective study of neonatal laboratory screening versus clinical symptoms as indicators leading to diagnosis. *Br Med J* 289:1171–1175 (1984).
 39. Jacobsen BB, Brandt NJ. Congenital hypothyroidism in Denmark: incidence, types of thyroid disorders and age at onset of therapy in children: 1970–1975. *Arch Dis Child* 56:134–136 (1981).
 40. Klein RZ, Mitchell ML. Neonatal screening for hypothyroidism. In: *Werner and Ingbar's The Thyroid*, 7th ed. (Braverman LE, Utiger RD, eds). Philadelphia: Lippincott-Raven, 1996;984–988.
 41. Mirabella G, Feig D, Astzalos E, Perlman K, Rovet JF. The effect of abnormal intrauterine thyroid hormone economies on infant cognitive abilities. *J Pediatr Endocrinol Metab* 13:191–194 (2000).
 42. Hanukoglu A, Perlman K, Shamis I, Brnjac L, Rovet J, Daneman D. Relationship of etiology to treatment in congenital hypothyroidism. *J Clin Endocrinol Metab* 86:186–191 (2001).
 43. Leneman M, Buchanan L, Rovet J. Where and what visuospatial processing in adolescents with congenital hypothyroidism. *J Int Neuropsychol Soc* 7:556–562 (2001).
 44. Contempre B, Jauniaux E, Calvo R, Jurkovic D, Campbell S, de Escobar GM. Detection of thyroid hormones in human embryonic cavities during the first trimester of pregnancy. *J Clin Endocrinol Metab* 77:1719–1722 (1993).
 45. Bernal J, Pekonen F. Ontogenesis of the nuclear 3,5,3'-triiodothyronine receptor in the human fetal brain. *Endocrinol* 114:677–679 (1984).
 46. Ferreiro B, Bernal J, Goodyer CG, Branchard CL. Estimation of nuclear thyroid hormone receptor saturation in human fetal brain and lung during early gestation. *J Clin Endocrinol Metab* 67:853–856 (1988).
 47. Iskaros J, Pickard M, Evans I, Sinha A, Hardiman P, Ekins R. Thyroid hormone receptor gene expression in first trimester human fetal brain. *J Clin Endocrinol Metab* 85:2620–2623 (2000).
 48. Zhang SS, Carrillo AJ, Darling DS. Expression of multiple thyroid hormone receptor mRNAs in human oocytes, cumulus cells, and granulosa cells. *Mol Hum Reprod* 3:555–562 (1997).
 49. Cao XY, Jiang XM, Dou ZH, Murdon AR, Zhang ML, O'Donnell K, Ma T, Kareem A, DeLong N, DeLong GR. Timing of vulnerability of the brain to iodine deficiency in endemic cretinism. *N Engl J Med* 331:1739–1744 (1994).
 50. Man EB, Jones WS. Thyroid function in human pregnancy. Part V. *Am J Obstet Gynecol* 104:898–908 (1969).
 51. Man EB, Jones WS. Thyroid function in human pregnancy. V. Incidence of maternal serum low butanol-extractable iodines and of normal gestational TBG and TBPA capacities; retardation of 8-month-old infants. *Am J Obstet Gynecol* 104:898–908 (1969).
 52. Man EB, Reid WA, Hellegers AE, Jones WS. Thyroid function in human pregnancy. II: Serum butanol-extractable iodine values of pregnant women 14 through 44 years. *Am J Obstet Gynecol* 103:328–337 (1969).
 53. Man EB, Holden RH, Jones WS. Thyroid function in human pregnancy. VII: Development and retardation of 4-year-old progeny of euthyroid and of hypothyroxinemic women. *Am J Obstet Gynecol* 109:12–19 (1971).
 54. Man EB, Jones WS, Holden RH, Mellits ED. Thyroid function in human pregnancy. VIII: Retardation of progeny aged 7 years, relationships to maternal age and maternal thyroid function. *Am J Obstet Gynecol* 111:905–916 (1971).
 55. Man EB, Serunian SA. Thyroid function in human pregnancy. IX: Development or retardation of 7-year-old progeny of hypothyroxinemic women. *Am J Obstet Gynecol* 125:949 (1976).
 56. Man EB, Brown JF, Serunian SA. Maternal hypothyroxinemia: psychoneurological deficits of progeny. *Ann Clin Lab Sci* 21:227–239 (1991).
 57. de Escobar GM, Obregon MJ, Escobar del Rey F. Is neuropsychological development related to maternal hypothyroidism or to maternal hypothyroxinemia? *J Clin Endocrinol Metab* 85:3975–3987 (2000).
 58. Pop VJ, de Vries E, van Baar AL, Waalkens JJ, de Rooy HA, Horsten M, Donkers MM, Komprou IH, van Son MM, Vander HL. Maternal thyroid peroxidase antibodies during pregnancy: a marker of impaired child development? *J Clin Endocrinol Metab* 80:3560–3566 (1995).
 59. Klein RZ, Mitchell ML. Maternal hypothyroidism and child development. *Horm Res* 52:55–59 (1999).
 60. Gupta RK, Bhatia V, Poptani H, Gujral RB. Brain metabolite changes on *in vivo* proton magnetic resonance spectroscopy in children with congenital hypothyroidism. *J Pediatr* 126:389–392 (1995).
 61. Klett M. Epidemiology of congenital hypothyroidism. *Exp Clin Endocrinol Diabetes* 105 (suppl 4):19–23 (1997).
 62. Vanderschueren-Lodeweyckx M, Debryne F, Doms L, Eggermont E, Eeckels R. Sensorineural hearing loss in sporadic congenital hypothyroidism. *Arch Dis Child* 58:419–422 (1983).
 63. Balazs R, Cocks WA, Eayrs JT, Kovacs S. Biochemical effects of thyroid hormones on the developing brain. In: *Hormones in Development* (Hamburg M, Barrington EJW, eds). New York: Appleton-Century-Crofts, 1971;357–379.
 64. Oppenheimer JH, Schwartz HL, Strait KA. Thyroid hormone action 1994: the plot thickens. *Eur J Endocrinol* 130:15–24 (1994).
 65. Oppenheimer JH, Schwartz HL. Molecular basis of thyroid hormone-dependent brain development. *Endocr Rev* 18:462–475 (1997).
 66. Pickard MR, Evans IM, Bandopadhyay R, Leonard AJ, Sinha AK, Ekins RP. Thyroid hormone action in rat brain from fetal to adult life. In: *Recent Research Developments in Neuroendocrinology—Thyroid Hormone and Brain Maturation* (Hendrich CE, ed). Research SignPost, 1997;15–29.
 67. Lazar MA. Thyroid hormone receptors: multiple forms, multiple possibilities. *Endocr Rev* 14:184–193 (1993).
 68. Mangelsdorf DJ, Evans RM. The RXR heterodimers and orphan receptors. *Cell* 83:841–850 (1995).
 69. Brown AW, Bronstein IP, Kraines R. Hypothyroidism and cretinism in childhood. VI. Influence of thyroid therapy on mental growth. *Am J Dis Child* 57:517–523 (1939).
 70. Dowling ALS, Martz GU, Leonard JL, Zoeller RT. Acute changes in maternal thyroid hormone induce rapid and transient changes in specific gene expression in fetal rat brain. *J Neurosci* 20:2255–2265 (2000).
 71. Bayer SA, Altman J. Neurogenesis and neuronal migration. In: *The Rat Nervous System*, 2nd ed. (Paxinos G, ed). San Diego, CA: Academic Press, 1995;1079–1098.
 72. Fisher D, Dussault J, Sack J, Chopra I. Ontogenesis of hypothalamic-pituitary-thyroid function and metabolism in man, sheep, rat. *Rec Progr Horm Res* 33:59–107 (1977).
 73. Bernal J, Nunez J. Thyroid hormones and brain development. *Eur J Endocrinol* 133:390–398 (1995).
 74. Liang P, Pardee AB. Differential display of eukaryotic messenger RNA by means of the polymerase chain reaction. *Science* 257:967–971 (1992).
 75. Dowling ALS, Zoeller RT. Thyroid hormone of maternal origin regulates the expression of RC3/neurogranin mRNA in the fetal rat brain. *Brain Res* 82:126–132 (2000).
 76. Dowling ALS, Iannacone EA, Zoeller RT. Maternal hypothyroidism selectively affects the expression of neuroendocrine-specific protein A messenger ribonucleic acid in the proliferative zone of the fetal rat brain cortex. *Endocrinology* 142:390–399 (2001).

77. Takahashi T, Nowakowski RS, Caviness VS. The leaving or Q fraction of the murine cerebral proliferative epithelium: a general model of neocortical neurogenesis. *J Neurosci* 16:6183–6196 (1996).
78. Takahashi T, Nowakowski RS, Caviness VS. Cell cycle parameters and patterns of nuclear movement in the neocortical proliferative zone of the fetal mouse. *J Neurosci* 13:820–833 (1993).
79. Takahashi T, Nowakowski RS, Caviness VS. *BudR* as an S-phase marker for quantitative studies of cytokinetic behaviour in the murine cerebral ventricular zone. *J Neurocytol* 21:185–197 (1992).
80. Chenn A, Braisted JE, McConnell SK, O'Leary DM. Development of the cerebral cortex: mechanisms controlling cell fate, laminar and areal patterning, and axonal connectivity. In: *Molecular and Cellular Approaches to Neural Development* (Cowan WM, Jessell TM, Zipursky SL, eds). New York:Oxford University Press, 1997:440–473.
81. Mione MC, Cavanagh JFR, Harris B, Parnavelas JG. Cell fate specification and symmetrical/asymmetrical divisions in the developing cerebral cortex. *J Neurosci* 2018–2029 (1997).
82. Iannacone EA, Zoeller RT. Unpublished data, 2000.
83. Herzig CTA, Iannacone EA, Dowling ALS, Zoeller RT. Notch signaling is reduced in fetal rat brain by maternal hypothyroidism [Abstract]. *Neurotoxicology* 22:152 (2001).
84. Artavanis-Tsakonas S, Rand MD, Lake RJ. Notch signaling: cell fate control and signal integration in development. *Science* 284:770–776 (1999).
85. Fortini M. Notch and presenilin: a proteolytic mechanism emerges. *Curr Opin Cell Biol* 13:627–634 (2001).
86. Jarrault S, Le Bail O, Hirsinger E, Pourquie O, Legat F, Strong CF, Brou C, Seidah NG, Isra IA. Delta-1 activation of Notch-1 signaling results in HES-1 transactivation. *Mol Cell Biol* 18:7423–7431 (1998).
87. Morrison SJ, Perez SE, Qiao Z, Verdi JM, Hicks C, Weinmaster G, Anderson DJ. Transient Notch activation initiates an irreversible switch from neurogenesis to gliogenesis by neural crest stem cells. *Cell* 101:499–510 (2000).
88. Lowell S. Notch signaling: you make me feel so glial. *Curr Biol* 10:R595–R597 (2000).
89. Wang S, Barres BA. Up a notch: instructing gliogenesis. *Neuron* 27:197–200 (2000).
90. Gaiano N, Nye JS, Fishell G. Radial glial identity is promoted by notch1 signaling in the murine forebrain. *Neuron* 26:395–404 (2000).
91. Barres BA, Lazar MA, Raff MC. A novel role for thyroid hormone, glucocorticoids and retinoic acid in timing oligodendrocyte. *Development* 120:1097–1108 (1994).
92. Dubois-Dalq M, Armstrong RC. The oligodendrocyte lineage during myelination and remyelination. In: *Myelin Biology and Chemistry* (Martenson RE, ed). Boca Raton, FL:CRC Press, 1992:81–122.
93. Gaitan E. *Environmental Goitrogenesis*. Boca Raton, FL: CRC Press, 1989:250 pp.
94. Erickson CK. Ethanol clearance in nine inbred rat strains. *Alcohol Clin Exp Res* 8:421–494 (1984).
95. Safe S. Polychlorinated biphenyls (PCBs): environmental impact, biochemical and toxic responses, and implications for risk assessment. *CRC Crit Rev Toxicol* 24:87–149 (1994).
96. Safe S. PCBs as aryl hydrocarbon receptor agonists: implications for risk assessment. In: *PCBs: Recent Advances in Environmental Toxicology and Health Effects* (Robertson LW, Hansen LG, eds). Lexington, KY:University of Kentucky Press, 2001:171–177.
97. Jacobson JL, Jacobson SW, Humphrey HEB. Effects of exposure to PCBs and related compounds on growth and activity in children. *Neurotoxicol Teratol* 12:319–326 (1990).
98. Schantz SL. Developmental neurotoxicity of PCBs in humans: what do we know and where do we go from here? *Neurotoxicol Teratol* 18:217–227; 229–276 (1996).
99. Stewart P, Darvill T, Lonky E, Reihman J, Pagano J, Bush B. Assessment of prenatal exposure to PCBs from maternal consumption of Great Lakes fish: an analysis of PCB pattern and concentration. *Environ Res* 80:S87–S96 (1999).
100. Stewart P, Reihman J, Lonky E, Darvill T, Pegano J. Prenatal PCB exposure and neonatal behavioral assessment scale (NBAS) performance. *Neurotoxicol Teratol* 22:21–29 (2000).
101. Zoeller RT. Polychlorinated biphenyls as disruptors of thyroid hormone action. In: *PCBs: Recent Advances in the Environmental Toxicology and Health Effects of PCBs* (Fisher LJ, Hansen L, eds). Lexington, KY:University of Kentucky Press, 2001:265–272.
102. Rice DC. Neurotoxicity produced by developmental exposure to PCBs. *Ment Retard Dev Disab* 1997:223–229 (1997).
103. Hagmar L, Rylander L, Dyremark E, Klasson-Wehler E, Erfurth EM. Plasma concentrations of persistent organochlorines in relation to thyrotropin and thyroid hormone levels in women. *Int Arch Occup Environ Health* 74:184–188 (2001).
104. Hagmar L, Bjork J, Sjodin A, Bergman A, Erfurth EM. Plasma levels of persistent organohalogen and hormone levels in adult male humans. *Arch Environ Health* 56:138–143 (2001).
105. Sala M, Sunyer J, Herrero C, To-Figuera J, Grimalt J. Association between serum concentrations of hexachlorobenzene and polychlorobiphenyls with thyroid hormone and liver enzymes in a sample of the general population. *Occup Environ Med* 58:172–177 (2001).
106. Persky V, Turyk M, Anderson HA, Hanrahan LP, Falk C, Steenport DN, Chatterton R Jr, Freels S. The effects of PCB exposure and fish consumption on endogenous hormones. *Environ Health Perspect* 109:1275–1283 (2001).
107. Osius N, Karmaus W, Kruse H, Witten J. Exposure to polychlorinated biphenyls and levels of thyroid hormones in children. *Environ Health Perspect* 107:843–849 (1999).
108. Koopman-Esseboom C, Morse DC, Weisglas-Kuperus N, Lutkeschiphout IJ, van der Paauw CB, Tuinstra LGMT, Brouwer A, Sauer PJJ. Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. *Pediatr Res* 36:468–473 (1994).
109. Goldey ES, Kehn LS, Lau C, Rehnberg GL, Crofton KM. Developmental exposure to polychlorinated biphenyls (Aroclor 1254) reduces circulating thyroid hormone concentrations and causes hearing deficits in rats. *Toxicol Appl Pharmacol* 135:77–88 (1995).
110. Goldey ES, Crofton KM. Thyroxine replacement attenuates hypothyroxinemia, hearing loss, and motor deficits following developmental exposure to Aroclor 1254 in rats. *Toxicol Sci* 45:94–105 (1998).
111. Brouwer A, Morse DC, Lans MC, Schuur AG, Murk AJ, Klasson-Wehler E, Bergman A, Visser TJ. Interactions of persistent environmental organohalides with the thyroid hormone system: mechanisms and possible consequences for animal and human health. *Toxicol Ind Health* 14:59–84 (1998).
112. Goldey ES, Kehn LS, Rehnberg GL, Crofton KM. Effects of developmental hypothyroidism on auditory and motor function in the rat. *Toxicol Appl Pharmacol* 135:67–76 (1995).
113. Hood A, Klaassen CD. Differential effects of microsomal enzyme induces on *in vitro* thyroxine (T_4) and triiodothyronine (T_3) glucuronidation. *Toxicol Sci* 55:78–84 (2000).
114. Tilson HA, Kodavanti PR, Mundy WR, Bushnell PJ. Neurotoxicity of environmental chemicals and their mechanism of action. *Toxicol Lett* 28:631–635 (1998).
115. Tilson HA, Kodavanti PRS. Neurochemical effects of polychlorinated biphenyls: an overview and identification of research needs. *Neurotoxicology* 13:727–744 (1997).
116. Ness DK, Schantz SL, Moshtaghian J, Hansen LG. Effects of perinatal exposure to specific PCB congeners on thyroid hormone concentrations and thyroid histology in the rat. *Toxicol Lett* 68:311–323 (1993).
117. Shain W, Bush B, Seegal R. Neurotoxicity of polychlorinated biphenyls: structure-activity relationship of individual congeners. *Toxicol Appl Pharmacol* 111(1):33–42 (1991).
118. Collins WT, Capen CC, Kasza L, Carter C, Dailey RE. Effect of polychlorinated biphenyl (PCB) on the thyroid gland of rats. Ultrastructural and biochemical investigations. *Am J Pathol* 89:119–130 (1977).
119. Kasza L, Collins WT, Capen CC, Garthoff LH, Friedman L. Comparative toxicity of polychlorinated biphenyl and polybrominated biphenyl in the rat thyroid gland: light and electron microscopic alterations after subacute dietary exposure. *J Environ Pathol Toxicol* 1:587–599 (1978).
120. Collins WT, Capen CC. Fine structural lesions and hormone alterations in thyroid glands of perinatal rats exposed *in utero* and by the milk to polychlorinated biphenyls. *Am J Pathol* 99:125–142 (1980).
121. Byrne JJ, Carbone JP, Hanson EA. Hypothyroidism and abnormalities in the kinetics of thyroid hormone metabolism in rats treated chronically with polychlorinated biphenyl and polybrominated biphenyl. *Endocrinology* 121:520–527 (1987).
122. Bastomsky CH, Murthy PVN, Banovac K. Alterations in thyroxine metabolism produced by cutaneous application of microscope immersion oil: effects due to polychlorinated biphenyls. *Endocrinology* 98:1309–1314 (1976).
123. Kolaja KL, Klaassen CD. Dose-response examination of UDP-glucuronosyltransferase inducers and their ability to increase both TGF-beta expression and thyroid follicular cell apoptosis. *Toxicol Sci* 46:31–37 (1998).
124. Visser TJ, Kaptein E, van Toor H, van Raay JAGM, van den Berg KJ, Joe CJT, van Engelen JGM, Brouwer A. Glucuronidation of thyroid hormone in rat liver: effects of *in vivo* treatment with microsomal enzyme inducers and *in vitro* assay conditions. *Endocrinology* 133:2177–2186 (1993).
125. Chauhan KR, Kodavanti PR, McKinney JD. Assessing the role of *ortho*-substitution on polychlorinated biphenyl binding to transthyretin, a thyroxine transport protein. *Toxicol Appl Pharmacol* 162:10–21 (2000).
126. Lans MC, Spiertz C, Brouwer A, Koeman JH. Different competition of thyroxine binding to transthyretin and thyroxine-binding globulin by hydroxy-PCBs, PCDDs and PCDFs. *Eur J Pharmacol* 270:129–136 (1994).
127. Darnerud PO, Morse D, Klasson-Wehler E, Brouwer A. Binding of a 3,3',4,4'-tetrachlorobiphenyl (CB-77) metabolite to fetal transthyretin and effects on fetal thyroid hormone levels in mice. *Toxicology* 106:105–114 (1996).
128. Cheek AO, Kow K, Chen J, McLachlan JA. Potential mechanisms of thyroid disruption in humans: interaction of organochlorine compounds with thyroid receptor, transthyretin, and thyroid-binding globulin. *Environ Health Perspect* 107:273–278 (1999).
129. McKinney J, Fannin R, Jordan S, Chae K, Rickenbacher U, Pedersen L. Polychlorinated biphenyls and related compound interactions with specific binding sites for thyroxine in rat liver nuclear extracts. *J Med Chem* 30:79–86 (1987).
130. McKinney JD. Multifunctional receptor model for dioxin and related compound toxic action: possible thyroid hormone-responsive effector-linked site. *Environ Health Perspect* 82:323–336 (1989).
131. McKinney JD, Waller CL. Molecular determinants of hormone mimicry: halogenated aromatic hydrocarbon environmental agents. *J Toxicol Environ Health* 1:27–58 (1998).
132. Porterfield SP, Hendry LB. Impact of PCBs on thyroid hormone directed brain development. *Toxicol Ind Health* 14:103–120 (1998).
133. McLachlan JA. Environmental signaling: what embryos and evolution teach us about endocrine disrupting chemicals. *Endocr Rev* 22:319–341 (2001).
134. Baxter JD, Dillmann WH, West BL, Huber R, Furlow JD, Fletterick RJ, Webb P, Apriletti JW, Scanlan TS. Selective modulation of thyroid hormone receptor action. *J Steroid Biochem Mol Biol* 76:31–42 (2001).
135. Wagner RL, Huber BR, Shiau AK, Kelly A, Cunha Lima ST, Scanlan TS, Apriletti JW, Baxter JD, West BL, Fletterick RJ. Hormone selectivity in thyroid hormone receptors. *Mol Endocrinol* 15:398–410 (2001).
136. Bakker O, van Beeren HC, Wiersinga WM. Desethylamiodarone is a noncompetitive inhibitor of the binding of thyroid hormone to the thyroid hormone beta-1 receptor protein. *Endocrinology* 134:1665–1670 (1994).
137. van Beeren HC, Bakker O, Wiersinga WM. Desethylamiodarone is a competitive inhibitor of the binding of thyroid hormone to the alpha-1 receptor protein. *Mol Cell Endocrinol* 112:15–19 (1995).
138. Rodriguez-Pena A, Ibarrola N, Iniguez MA, Munoz A, Bernal J. Neonatal hypothyroidism affects the timely expression of myelin-associated glycoprotein in the rat brain. *J Clin Invest* 91:812–818 (1993).
139. Iniguez M, Rodriguez-Pena A, Ibarrola N, Aguilera M, Escobar GMD, Bernal J. Thyroid hormone regulation of RC3, a brain-specific gene encoding a protein kinase-C substrate. *Endocrinology* 133:467–473 (1993).
140. Iniguez MA, DeLecea L, Guadano-Ferraz A, Morte B, Gerendasy D, Sutcliffe JG, Bernal J. Cell-specific effects of thyroid hormone on RC3/neurogranin expression in rat brain. *Endocrinology* 137:1032–1041 (1996).

141. Marta CB, Adamo AM, Soto EF, Pasquini JM. Sustained neonatal hyperthyroidism in the rat affects myelination in the central nervous system. *J Neurosci Res* 53:251–259 (1998).
142. Farsetti A, Mitsuhashi T, Desvergne B, Robbins J, Nikodem VM. Molecular basis of thyroid hormone regulation of myelin basic protein gene expression in rodent brain. *J Biol Chem* 266:23226–23232 (1991).
143. Zoeller RT, Dowling AL, Vas AA. Developmental exposure to polychlorinated biphenyls exerts thyroid hormone-like effects on the expression of RC3/neurogranin and myelin basic protein messenger ribonucleic acids in the developing rat brain. *Endocrinology* 141:181–189 (2000).
144. Guadano-Ferraz A, Escamez MJ, Morte B, Vargiu P, Bernal J. Transcriptional induction of RC3/neurogranin by thyroid hormone: differential neuronal sensitivity is not correlated with thyroid hormone receptor distribution in the brain. *Mol Brain Res* 49:37–44 (1997).
145. Gauger KJ, Herzig CAT, Bansal R, Zoeller RT. Developmental exposure to polychlorinated biphenyls exerts thyroid-like effects on the expression of thyroid hormone-responsive genes in the fetal rat brain [Abstract]. 41st Annual Meeting of the Society of Toxicology, 17–21 March 2002, Nashville, Tennessee. Abstract 1650.
146. Herzig CAT, Zoeller RT. Maternal exposure to a mixture of polychlorinated biphenyls (Aroclor 1254) exerts thyroid hormone-like effects on Notch signaling in the fetal cortex [Abstract]. 41st Annual Meeting of the Society of Toxicology, 17–21 March 2002, Nashville, Tennessee. Abstract 126.
147. Zoeller RT. Interpreting thyroid toxicity for risk assessment [Abstract]. 41st Annual Meeting of the Society of Toxicology, 17–21 March 2002, Nashville, Tennessee. Abstract 1357.