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Thyroid Hormone Action in Fetal Brain Development and Potential for Disruption by Environmental Chemicals

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Abstract: *Thyroid hormone is well-known to play essential roles in brain development. Therefore, environmental factors that interfere with thyroid function or thyroid hormone action may produce deleterious effects on brain development by interfering with thyroid hormone action in the developing brain. Therefore, the purpose of this review is to identify in broad terms the gaps in our knowledge of thyroid hormone action in brain development, to relate these gaps to present information on thyroid disruption, and to review briefly our recent research that is germane to these issues. The endocrinology of the thyroid system is first reviewed briefly with an emphasis on the neuroendocrine and extrathyroidal mechanisms controlling circulating levels of thyroid hormones. The second section reviews the evidence that thyroid hormone is important for fetal, as well as neonatal, brain development. We review the mechanism of thyroid hormone action in the third section and briefly relate this information to information about the mechanism of thyroid hormone action on brain development. In the final section, we review the endocrinology of thyroid disruption with an emphasis on disruption of thyroid hormone action.* © *2000 Intox Press, Inc.*

Key Words: Thyroid Hormone, Endocrine Disruptors, Brain Development

INTRODUCTION

There is increasing public concern that incidental exposure to environmental chemicals can disrupt hormone signaling during development, thereby causing permanent effects on brain development in humans and wildlife. These concerns are especially grave for disruption of thyroid hormone action because this hormone is an essential factor in normal brain development (Dussault and Ruel, 1987; Escobar *et al*., 1997; Myant, 1971; Porterfield and Hendrich, 1993; Timiras and Nzekwe, 1989). A growing scientific literature documents the association between concentrations of circulating thyroid hormone and exposure to specific environmental chemicals or chemical mixtures to which we are exposed in our environment. However, there are critical gaps in our understanding of thyroid hormone action on fetal brain development that severely limit our ability to attribute experimental or epidemiological observations to disruption of thyroid hormone action. Therefore, the purpose of this review is to identify in broad terms the gaps in our knowledge of thyroid hormone action in brain development, to relate these gaps to present information on thyroid disruption, and to review briefly our recent research that is germane to these issues.

THYROID ENDOCRINOLOGY

The iodothyronines are formed in the thyroid gland from two iodinated tyrosyl residues on the large hormone "precursor", thyroglobulin (TG) (Taurog, 1996). The most important iodothyronines are 3,5,3′,5′-tetraiodothyronine (thyroxine, T_4), 3,5,3′-triiodothyronine (T_3), and 3,3′,5′-triiodothyronine (reverse T_3). Circulating triiodothyronines are formed largely from peripheral deiodination of T_4, which is the major product released from the thyroid gland (Leonard and Koehrle, 1996). The pituitary glycoprotein

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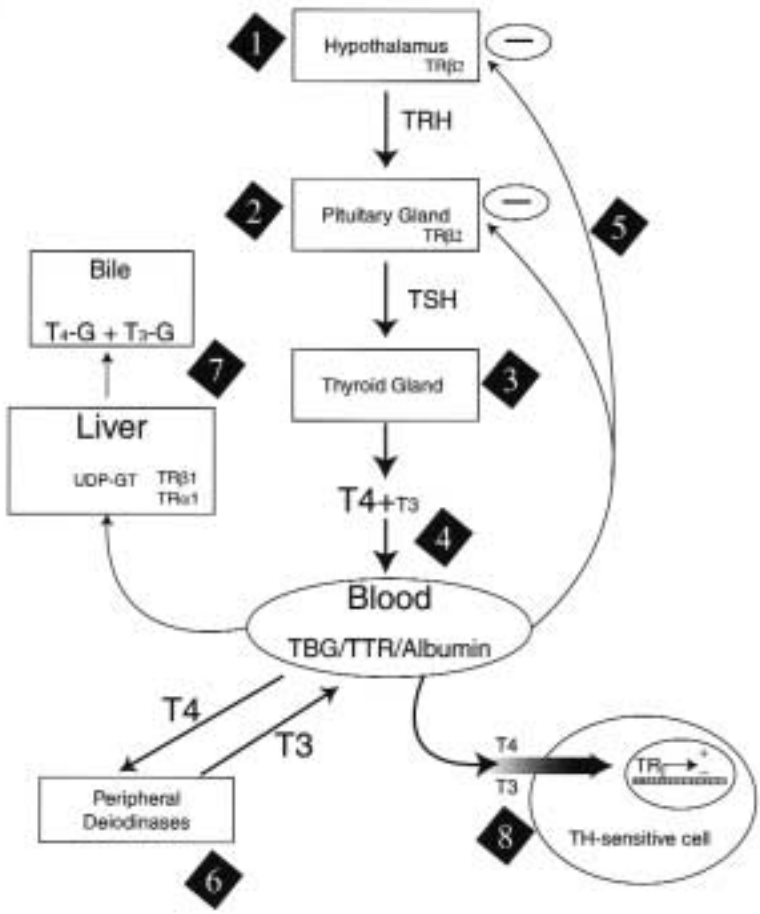

FIG. 1. Basic elements of thyroid endocrinology. Numbers in filled diamonds refer to the legend below that provides descriptions of the specific level of the thyroid system.

1. Neurons whose cell bodies reside in the hypothalamic paraventricular nucleus (PVN) synthesize the tripeptide Thyrotropin-Releasing Hormone (TRH) (Segersen et al., 1987a; Segersen et al., 1987b). Although TRH-containing neurons are widely distributed throughout the brain (Jackson et al., 1985; Lechan et al., 1986), TRH neurons in the PVN project uniformly to the median eminence (Ishikawa et al., 1988; Merchenthaler and Liposits, 1994), a neurohemal organ connected to the anterior pituitary gland by the hypothalamic-pituitary-portal vessels (Martin and Reichlin, 1987), and are the only TRH neurons to regulate the pituitary-thyroid axis (Aizawa and Greer, 1981). **2.** TRH is delivered by the pituitary-portal vasculature to the anterior pituitary gland to stimulate the synthesis and release of Thyroid Stimulating Hormone (TSH) or "Thyrotropin" (Haisenleder et al., 1992). TSH is one of three glycoprotein hormones of the pituitary gland and is composed of an alpha and a beta subunit (Wondisford et al., 1996a). All three pituitary glycoproteins (Luteinizing Hormone, LH; Follicle Stimulating Hormone, FSH; and TSH) all share the same alpha subunit (Hadley, 2000). TRH selectively stimulates the synthesis of the TSH beta subunit (Haisenleder et al., 1992). However, TRH also affects the post-translational glycosylation of TSH which affects its biological activity (Harel et al., 1993; Lippman et al., 1986; Magner et al., 1992; Taylor et al., 1986; Taylor and Weintraub, 1985; Weintraub et al., 1989). **3.** Pituitary TSH binds to receptors on the surface of thyroid follicle cells and stimulates their activity (Taurog, 1996; Wondisford et al., 1996b). This activity includes uptake of iodide, iodide organification, synthesis and oxidation of thyroglobulin (TG), TG uptake from thyroid colloid and production of the iodothyronines T4 and T3. T4 is by far the major product released from the thyroid gland (Taurog, 1996). **4.** Thyroid hormones are carried in the blood by specific proteins. In humans, about 75% of T4 is bound to thyroxine-binding globulin (TBG), 15% is bound to transthyretin (TTR) and the remainder is bound to albumin (Schussler, 2000). TBG, the least abundant but most avid T4 binder, is a member of a class of proteins that includes Cortisol Binding Protein and is cleaved by serine proteases in serum (Fink et al., 1986). These enzymes are secreted into blood during inflammatory responses and, in the case of CBP, can induce the release of cortisol at the site of inflammation. The physiological significance of this observation is presently unclear for TBG (Schussler, 2000), but it raises the possibility that TBG may selectively release of T4 under specific circumstances. **5.** Thyroid hormones (T4 and T3) exert a negative feedback effect on the release of pituitary TSH (Chopra, 1996; Scanlon and Toft, 1996; Stockigt, 1996) and on the activity of hypothalamic TRH neurons (Koller et al., 1987; Rondeel et al., 1989; Segersen et al., 1987b). Because circulating levels of T4 and of T3 fluctuate considerably within an individual, and because the radioimmunoassays for T4 and for T3 are associated with a fairly high intra-assay coefficient of variation, TSH measurements are considered to be diagnostic of thyroid dysfunction (Chopra, 1996; Roti et al., 1993; Stockigt, 1996). **6.** T4 and T3 are actively transported into target tissues (Docter et al., 1997; Everts et al., 1994a; Everts et al., 1994b; Everts et al., 1995; Friesema et al., 1999; Kragie, 1996a; Kragie, 1996b; Moreau et al., 1999; Oppenheimer, 1983). T4 can be converted to T3 by the action of outer-ring deiodinases (ORD, Type I and Type II) (Germain and Galton, 1997). Peripheral conversion of T4 to T3 by these ORDs accounts for nearly 80% of the T3 found in the circulation (Chopra, 1996). **7.** Thyroid hormones are cleared from the blood in the liver following glucuronidation by UDP-glucuronosyl transferase (Hood and Klaassen, 2000). These modified thyroid hormones are then eliminated through the bile. **8.** T4 and/or T3 are actively concentrated in target cells about 10-fold over that of the circulation. The receptors for T3 (TRs) are nuclear proteins that bind to DNA and regulate transcription (Lazar, 1993; Lazar, 1994; Mangelsdorf and Evans, 1995; Oppenheimer and Schwartz, 1997; Oppenheimer et al., 1994). There are two genes that encode the TRs, c-erbA-alpha (TRa) and c-erbA-beta (TRb). Each of these genes is differentially spliced, forming 3 separate TRs, TRa1, TRb1, and TRb2. The effects of thyroid hormone are quite tissue-, cell-, and developmental stage-specific and it is believed that the relative abundance of the different TRs in a specific cell may contribute to this selective action.

hormone, thyrotropin (TSH) (Wondisford *et al*., 1996b), regulates the synthesis and secretion of thyroid hormones by activating guanylate cyclase in thyroid follicular cells (Rapoport and Spaulding, 1986). However, there are a number of important extrathyroidal processes that maintain circulating thyroid hormones within a relatively narrow concentration range (Leonard and Koehrle, 1996). Normal variation in circulating concentrations of T_4 reflects short-term pulsatile and diurnal variation (Stockigt, 1996). T_4 and/or T_3 exert a negative feedback effect on pituitary secretion of TSH (Morley, 1981; Scanlon and Toft, 1996), and on the hypothalamic secretion of the releasing factor, thyrotropin-releasing hormone (TRH) (Koller *et al*., 1987; Rondeel *et al*., 1988; Segersen *et al*., 1987b), which controls the amount of TSH in the blood. Finally, TRH from the hypothalamus stimulates the pituitary gland to release TSH (Jackson and Lechan, 1983), and modulates the sensitivity of the pituitary gland to negative feedback by thyroid hormone (Greer *et al*., 1993; Taylor *et al*., 1990). Thus, circulating levels of thyroid hormones, and the balance between different forms of these hormones, are controlled by a number of processes (Figure 1).

THYROID HORMONE AND FETAL BRAIN DEVELOPMENT

Despite early work suggesting that the human placenta is impermeable to maternal thyroid hormones (Fisher *et al*., 1977), it is now well accepted that iodothyronines of maternal origin reach the fetal compartment (Porterfield, 1994; Porterfield and Hendrich, 1993; Porterfield and Stein, 1994). Several recent observations account for this change in perception. First, thyroid hormones have been 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 (Contempre *et al*., 1993). Moreover, neonates born with an autosomal disorder resulting in the complete inability to synthesize T_4, are euthyroid at birth, but become severely hypothyroid as the hormone is metabolically cleared (Vulsma *et al*., 1989). The maternal thyroid gland was the only source of thyroid hormone in these neonates. In addition, human fetal brain tissues express receptors for thyroid hormone, and receptor occupancy by thyroid hormone is in the range known to produce physiological effects as early as 9 weeks of gestation (Bernal and Pekonen, 1984; Ferreiro *et al*., 1988). There is also a 3-fold gradient of cytosolic free T_3 to nuclear T_3 in cells of the human fetal brain (Ferreiro *et al*., 1988), suggesting that compartmentalization of T_3 in brain cells may favor hormone action. These data all suggest 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.

Functional studies indicate that thyroid hormone is essential for normal fetal brain development. For example, iodine administration to pregnant women in their first trimester eliminates the incidence of cretinism in geographic areas that are iodine insufficient. However, by the end of the second trimester, iodine supplementation does not prevent neurological damage (Cao *et al*., 1994; DeLong *et al*., 1994), indicating that thyroid hormone plays an important role in brain development perhaps before the onset of fetal thyroid function. In addition, children born to pregnant women with untreated hypothyroidism during the second trimester exhibit measurable neurological deficits despite normal circulating thyroid hormone at birth (Haddow *et al*., 1999; Pop *et al*., 1999). Extensive reviews on this issue have been recently published (Delange, 1996; Escobar *et al*., 1997; Porterfield, 1994; Porterfield and Hendrich, 1993; Porterfield and Stein, 1994). It is clear that the fetus is equipped with a variety of mechanisms to obtain and maintain exposure to maternal thyroid hormones even before the onset of fetal thyroid function, including increased uptake and conversion of T_4 to T_3 (Calvo *et al*., 1992; Escobar *et al*., 1997). These data present strong evidence that maternal thyroid hormone play a role in fetal brain development prior to the onset of fetal thyroid function, and that the consequences of thyroid hormone deficits or disruption during pregnancy are neurological and irreversible (Dussault and Walker, 1983; Foley, 1996; Gupta *et al*., 1995; Klett, 1997; Miculan *et al*., 1993; Vanderschueren-Lodeweyckx *et al*., 1983; Vliet, 1999). However, this view is not uniformly held (Fisher, 1999; Schwartz *et al*., 1997).

MECHANISM OF THYROID HORMONE ACTION

It is generally held that the majority of biological actions of thyroid hormone are mediated by nuclear receptors for T_3 (Lazar, 1993; Lazar, 1994). T_3 receptors (TRs) are members of the steroid/thyroid superfamily of ligand-dependent transcription factors (Lazar, 1993; Lazar, 1994; Mangelsdorf and Evans, 1995), indicating that effects on gene expression mediate the majority of biological actions of thyroid hormone. TRs are encoded by two genes, designated α and β c-*erb*A (Sap *et al*., 1986; Weinberger *et al*., 1986). These two genes produce three functional TRs: TRα1, TRβ1, and TRβ2 (Hodin *et al*., 1989; Izumo and Mahdavi, 1988; Koenig *et al*., 1988; Murray *et al*., 1988; Thompson *et al*., 1987). Although there are several TRs expressed, the binding affinity for T_3 and for T_4 are not different among the various forms (Oppenheimer, 1983; Oppenheimer *et al*., 1994; Schwartz *et al*., 1992). These studies demonstrate that TRs exhibit a 10-fold greater affinity for T_3 than for T_4 and that T_3 is the physiologically important regulator of TR action.

However, TRα1 and TRβ1 exhibit different profiles of binding to the thyroid hormone analogue desethylamioderone (Bakker *et al*., 1994; Beeren *et al*., 1995). Therefore, it is possible that other exogenous compounds, specifically environmental chemicals, may bind differentially to these two TRs.

Despite the observation in rats that TRs are expressed in fetal brain (Bradley *et al*., 1992; Bradley *et al*., 1989; Falcone *et al*., 1994; Perez-Castillo *et al*., 1985; Strait *et al*., 1990), and that maternal T_4 can cross the placenta and be converted to T_3 (Calvo *et al*., 1990; Contempre *et al*., 1993; Escobar *et al*., 1990; Escobar *et al*., 1997; Vulsma *et al*., 1989), few thyroid hormone-responsive genes have been identified in the fetus. In truth, remarkably few studies have even examined thyroid hormone responsiveness of the fetal brain (Bonet and Herrera, 1988; Escobar *et al*., 1997; Escobar *et al*., 1988; Geel and Timiras, 1967; Hadjzadeh *et al*., 1989; Porterfield, 1994; Porterfield and Hendrich, 1993). The lack of information concerning molecular mechanism(s) of thyroid hormone action on brain development has two important consequences. First, we have little appreciation for the molecular events or developmental processes by which thyroid hormone produces the effects observed in humans and animals briefly discussed above. Second, we have no direct measures of thyroid hormone action in fetal brain. Therefore, we cannot directly test the hypothesis that specific chemicals can interfere with thyroid hormone action because the only measures available are indirect such as thyroid hormone concentration in serum or in specific tissues.

To address this weakness, we recently initiated a study to test the hypothesis that maternal thyroid hormone can influence gene expression in the fetal rat brain (Dowling *et al*., 2000). Our strategy was to identify genes in the fetal cortex that are responsive to acute manipulation of maternal thyroid status. We focused on the embryonic day 16 (E16) fetus because fetal thyroid function does not begin until E17 (Fisher *et al*., 1977); thus, these genes would be regulated solely by *maternal* thyroid hormone. In addition, E16 is the time when most of the neurons of the cerebral cortex are generated and begin to differentiate (Bayer and Altman, 1995). Our paradigm for thyroid hormone manipulation was also novel among studies designed to identify thyroid hormone-responsive genes. For example, we surgically thyroidectomized female rats two weeks before they were mated to allow thyroid hormones to decline before pregnancy. Next, on G15, we administered two half-doses of T_4 (12.5 μg/kg each) so that the concentration of thyroid hormone in the dam's blood would not be supraphysiological. We reasoned that this combination of a physiological dose of T_4 and an acute injection paradigm would allow us to identify genes directly responsive to thyroid hormone and would be physiologically relevant.

We identified a number of genes expressed in the fetal brain that appear to be responsive to maternal thyroid hormone. Two of these genes, encoding neuroendocrine-specific protein (NSP) (Velde *et al*., 1994a; Velde *et al*., 1994b) and Oct-1 (Dominov and Miller, 1996; Kambe *et al*., 1993; Suzuki *et al*., 1993), exhibited complementary patterns of expression in the fetal brain and responses to thyroid hormone. Oct-1 mRNA is elevated by T_4 injection and is expressed selectively in the periventricular zone where neuroblasts continue to proliferate. In contrast, NSP mRNA is suppressed by thyroid hormone and was selectively expressed in the intermediate zone where neurons are beginning to differentiate. Oct-1 is a member of the POU-domain family of transcription factors (Dominov and Miller, 1996) that is implicated in the control of neuronal proliferation. NSP is a neural-specific protein associated with endoplasmic reticulum that may be involved in the acquisition of neuronal polarization and differentiation (Senden *et al*., 1996; Velde *et al*., 1994b). These experiments demonstrate first that thyroid hormone of maternal origin can affect gene expression in the fetus and provide "biomarkers" of thyroid hormone action in the fetal brain. Second, these data provide circumstantial evidence supporting the view that maternal thyroid hormone may affect proliferation and differentiation of cortical neurons. In addition, because we found that NSP and Oct-1 retain their sensitivity to thyroid hormone in adulthood, our results suggest that the concept of "critical windows" of thyroid hormone action apply to specific developmental events, but probably not to thyroid hormone sensitivity *per se*.

From this perspective, it is easy to imagine that thyroid hormone plays an important role in developmental processes such as neuronal proliferation that occur in different brain areas at different times (Bayer and Altman, 1995). Therefore, the temporal "window" of thyroid hormone sensitivity will depend on the developmental period over which a particular process occurs, and this will differ for different brain areas. For example, in humans, acute disruption of thyroid hormone action selectively during the first trimester might affect proliferation of cortical neurons, but would not affect proliferation of cerebellar granule cells that undergo proliferation in the third trimester. Considering that many endocrine disruptors, such as polychlorinated biphenyls, are lipophilic and accumulate in the body, it is difficult to imagine that there would be selective exposure windows during development. However, it is possible that the congener profile or dose of exposure might be different for fetal versus lactational exposure. Moreover, we are not certain of the roles thyroid hormone plays in different elements of brain development. For example, we know that thyroid hormone affects proliferation of cerebellar granule cells (Eayrs and Taylor, 1951; Nicholson and Altman, 1972), but we still do not know if this is true for cortical neurons. Therefore, lipophilic chemicals may exert temporally specific effects on brain development through the thyroid hormone signaling system because

this system exerts temporally specific effects. In addition, the various TRs may play different roles in brain development (Bradley *et al*., 1992; Bradley *et al*., 1994; Forrest *et al*., 1990), and if different PCB congeners act preferentially on different TRs, the ultimate consequences of this action may represent only a subset of thyroid hormone dependent phenotypes.

ENDOCRINOLOGY OF THYROID DISRUPTION

The general definition of an endocrine disruptor is "any exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes" (Kavlock *et al*., 1996). Each process in the pathway from hormone production to hormone action is itself composed of several biochemical or physiological steps. Because each of these steps may be an independent site of disruption, it is reasonable to predict that different classes of synthetic or natural environmental chemicals may interfere with a specific hormonal signaling pathway at different steps from hormone production to hormone action. Clearly, this is true for the thyroid system. Environmental agents producing goitrogenic and/or antithyroid effects have been categorized according to chemical class (Gaitan and Cooksey, 1989). These classes range from complex anions such as perchlorate or lithium which block iodide uptake into the thyroid gland (Green, 1996), to halogenated biphenyls, which appear to have a variety of effects on thyroid hormone transport, metabolism, and perhaps hormone binding (Brouwer *et al*., 1998; Brucker-Davis, 1998; Cheek *et al*., 1999). However, despite the variety of mechanisms by which goitrogenic or antithyroid agents have been shown to act on the thyroid system, all ultimately affect circulating thyroid hormone concentrations (Brucker-Davis, 1998; Gaitan, 1989; Green, 1996). In fact, it was the effect on circulating thyroid hormone that identified these agents as goitrogens or antithyroid agents initially.

In general, the ability of a chemical to influence circulating levels of thyroid hormone does not necessarily provide a clear indication of its effects on thyroid hormone action, though it is often assumed. For example, PCB exposure does not always produce a compensatory increase in circulating TSH, despite profound reductions in circulating levels of thyroid hormone (reviewed in (Brouwer *et al*., 1998; Kolaja and Klaassen, 1998)), suggesting that unidentified individual PCB congeners may suppress TSH (Brouwer *et al*., 1998; Kolaja and Klaassen, 1998). In addition, developmental exposure to PCBs advances the onset of eye opening in rats (Goldey *et al*., 1995), an event associated with hyperthyroidism. Children exposed to high levels of PCBs can exhibit hyperactivity (Guo *et al*., 1994), a symptom that also may be associated with subclinical hyperthyroidism (Suresh *et al*., 1999). Finally, we have recently shown that developmental exposure to PCBs can increase the expression of two thyroid hormone-responsive genes in the developing brain; namely, RC3/Neurogranin, and myelin basic protein (Zoeller *et al*., 2000). Thus, in the case of PCBs, their ability to reduce circulating levels of thyroid hormone is not uniformly associated with effects consistent with hypothyroidism.

Although PCBs do not exert effects fully consistent with hypothyroidism, they do produce specific effects that appear to be mediated by reduced thyroid hormone concentrations. For example, PCB exposure reduces circulating levels of thyroid hormone and produces hearing loss in rats (Goldey *et al*., 1995) that can be partially ameliorated by T_4 administration (Goldey and Crofton, 1998). In addition, T_4 can normalize the PCB-induced suppression of choline acetyltransferase activity in the forebrain of neonatal rats (Ku *et al*., 1994). Finally, postnatal PCB exposure can increase testis size of the adult rat (Cooke *et al*., 1996), an effect that is identical to that of perinatal treatment with goitrogens (Cooke *et al*., 1993). Taken together, these data suggest that PCBs can produce effects consistent with an antithyroid action as well as effects consistent with a thyroid hormone-like action.

PCBs are a class of industrial compounds consisting of paired biphenyl rings with various degrees of chlorination (Tilson and Kodavanti, 1997). The pattern of chlorine substitution on the biphenyl rings can produce a structure that appears to be similar to that of thyroxine (Chauhan *et al*., 1999). Several studies have shown that individual PCB congeners can bind to thyroxine-binding proteins with high affinity (Brouwer *et al*., 1998). Specifically, individual PCB congeners can bind to transthyretin (Chauhan *et al*., 1999), intracellular T_4-binding sites (Brundl and Buff, 1993) and nuclear T_4-binding sites (McKinney *et al*., 1987). However, the evidence that PCBs can bind to the classic thyroid hormone receptor is weak. Cheek *et al.* (1999) have recently shown that some individual PCB congeners can bind to the human TRβ1 with a very low affinity (K_i = 30μM). It seems unlikely that this would be of physiological significance. However, there are a large number of PCB congeners present in common mixtures, and there are a large number of possible metabolic modifications (Seegal, 1996; Tilson *et al*., 1998). Perhaps some individual congeners do bind to the TR, or alter their ability to respond to thyroid hormone.

An alternate, or additional, mechanism by which PCB exposure may produce a thyroid hormone-like effect on the developing brain is by enhancing thyroid hormone uptake into tissues and increasing the conversion of T_4 to T_3. Specifically, PCB-induced hypothyroxinemia may increase cellular uptake of T_4 or T_3 and increase the expression of deiodinases responsible for intracellular conversion of T_4 to T_3. Tissue uptake of T_3 or T_4 is elevated by reduced levels of

thyroxine (Everts *et al*., 1994b; Friesema *et al*., 1999; Moreau *et al*., 1999) which also increases the expression of type II deiodinase in brain (Burmeister *et al*., 1997; Germain and Galton, 1997). However, these processes are affected by hypothyroxinemia caused by goitrogens or PCBs, yet the two kinds of chemicals produce very different effects on thyroid hormone-responsive measures. Therefore, the differences in effects of these two treatments may not arise from the induction of compensatory mechanisms alone. Clearly, further work is required to understand the role of T_4 transport and deiodination in the regulation of thyroid hormone action during periods of hypothyroxinemia caused by different agents.

CONCLUSIONS

Clinical studies show that maternal thyroid hormone reaches the fetus and that fetal hypothyroidism can produce neurological deficits. Experimental work is beginning to confirm that thyroid hormone of maternal origin can reach the fetus and affect gene expression in the fetal brain. Therefore, factors that affect thyroid hormone action in the fetal brain, either directly or indirectly by disrupting maternal thyroid economy, have the potential to affect brain development. However, the developmental processes affected by thyroid hormone during fetal life, the molecular mechanisms mediating these thyroid hormone effects, the developmental periods during which thyroid hormone is important for a particular event, and the ultimate consequences to brain function in the adult, are poorly understood. Until these issues are better understood, it will be difficult to determine the full extent of thyroid disruption and to link thyroid disruption to specific measures of intellectual performance.

The extremely pleiotropic nature of thyroid hormone action will also present a challenge to those working in the field of thyroid disruption. For example, thyroid hormone induces a negative transcriptional effect on the gene encoding TRH (Hollenberg *et al*., 1995), but this only occurs in TRH neurons located in the hypothalamic paraventricular nucleus (Koller *et al*., 1987; Segersen *et al*., 1987b; Zoeller *et al*., 1993), despite the widespread distribution of TRH in TR-containing neurons throughout the brain (Bradley *et al*., 1992; Segersen *et al*., 1987a). Another example is that Oct-1 expression is enhanced by thyroid hormone before birth, but suppressed by thyroid hormone after birth, in the same tissue (Dowling *et al*., 1998). Therefore, evaluating the effect of thyroid disruptors on thyroid hormone action will require an appreciation for this plasticity.

The molecular mechanism(s) believed to be responsible for the variable effects of thyroid hormone action reveal the possibility that thyroid action can be disrupted without affecting hormone delivery to the cell. Thyroid hormone receptors are believed to require the formation of heterodimers with other transcription factors, including receptors for retinoids or vitamin D, to affect the expression of some genes (Lazar, 1993; Lazar, 1994; Mangelsdorf and Evans, 1995). Therefore, disruption of retinoic acid signaling may disrupt thyroid hormone action without affecting circulating concentrations of thyroid hormones or TSH. This same logic applies to the many types of proteins that have been shown to interact with TRs, including corepressors and coactivators (Koenig, 1998). Although speculative, it would explain why PCB exposure produces effects in animals which simultaneously appear to be anti-thyroid and thyroid hormone-like.

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