

# Environmental neuroendocrine and thyroid disruption: relevance for reproductive medicine?

R. Thomas Zoeller, Ph.D.

Biology Department, University of Massachusetts Amherst, Morrill Science Center, Amherst, Massachusetts

The thyroid hormone is well known to be essential for development of many tissues, including the brain and heart. Less is understood concerning the potential role of the thyroid hormone in the development of reproductive tissues that might impact fertility. However, important new information is appearing concerning the association between thyroid hormone levels and fertility in humans, as well as animal studies focused on its role in testis development. (Fertil Steril® 2008;89:e99–100. ©2008 by American Society for Reproductive Medicine.)

The thyroid hormone is well known to be essential for development of many tissues, including the brain (1) and heart (2). Less is understood concerning the potential role of the thyroid hormone in the development of reproductive tissues that might impact fertility. However, important new information is appearing concerning the association between thyroid hormone levels and fertility in humans, as well as animal studies focused on its role in testis development. This may be an important mechanism by which environmental chemicals could interfere with fertility. A large number of contaminants commonly found in human tissues are considered to be thyroid toxicants (3). These toxicants have been identified by their ability to alter serum concentrations of the thyroid hormone. However, recent evidence also indicates that some chemicals—polyhalogenated aryl hydrocarbons—can interfere directly with thyroid hormone receptors (TRs), and perhaps in a TR isoform-specific manner (4, 5). These kinds of chemicals may affect sterility either by changing the course of testicular development or by interfering with testicular function in the adult.

The thyroid hormone may be best known for its role in brain development, but recent studies indicate that it is important in pregnancy outcome as well. For example, Casey et al. (6) found that pregnancies in women with subclinical hypothyroidism were three times more likely to be complicated by placental abruption and twice as likely to end in a preterm birth. In contrast, subclinical hyperthyroidism was not associated with adverse pregnancy outcome (7). Overt hypothyroidism occurs in about 0.5%–0.7% of women of reproductive age (8). Hypothyroidism may alter estrogen metabolism, accounting for the development of impaired ovulation (9). Hypothyroidism is less common in men, and has less predictable effects on reproduction (10). Thyroid hormone receptors are selectively expressed in Sertoli cells (11). The thyroid hormone may play an important role in Sertoli cell proliferation early in development, in part by regulating the expression of connexin 43 (12, 13).

Environmental chemicals that act solely on circulating levels of thyroid hormones may have predictable effects on reproductive outcome, based on our working knowledge of the effects of thyroid hormone insufficiency or excess. However, environmental chemicals that directly interfere with the TR may produce quite unpredicted effects on fertility or reproductive outcome, especially if they act in ways that are not fully explored. For example, a specific hydroxylated polychlorinated biphenyl (4-OH-PCB106) has been found to cause the TR to dissociate from a canonical response element *in vitro* (14). This may be important because it would abrogate the ability of the thyroid hormone to regulate a gene associated with that regulatory element. However, much is unknown about this type of mechanism. For example, the DNA sequence of the thyroid hormone response element is quite variable and not well understood (15). Thus, it is possible that 4-OH-PCB106, or chemicals that act similarly, may interfere with TR binding to a specific DNA motif. This would present a very challenging kind of situation to identify symptomatically, or even to recognize it as a thyroid disruptor. Likewise, considering that there are two classes of TRs (TR $\alpha$  and TR $\beta$ ), if such a chemical interacts selectively with a TR isoform, it would be even more difficult to predict consequences.

One such chemical that may act in a TR isoform-specific manner is bisphenol A (BPA) (16). This chemical is widely distributed in the environment, and is a common contaminant in human tissues (17). This chemical binds to the TR with almost the same affinity as it binds to the estrogen receptor. In developing rats, BPA exposure increased serum T<sub>4</sub> without a concomitant increase in serum TSH—a pattern that is consistent with its antagonist action on the TR *in vitro* (16). However, measures of thyroid hormone action on the TR $\alpha$  suggested that BPA might act selectively on the TR $\beta$ . Although speculative, these data suggest two important issues. First, there may well be common environmental contaminants that act selectively to interfere with thyroid hormone signaling through its receptors. Second, there may well be common environmental contaminants that act simultaneously as estrogens and as thyroid hormone antagonists/agonists. The consequences of exposure to these

Reprint requests: R. Thomas Zoeller, Biology Department, University of Massachusetts Amherst, Morrill Science Center, 611 N. Pleasant Street, Amherst, Massachusetts 01003.

chemicals during development—as well as in adulthood—will be an important challenge to identify.

New approaches to study the actions of nuclear proteins on fertility may be important applications in future studies. Specifically, chromatin immunoprecipitation will allow investigators to identify DNA elements to which nuclear receptors—such as receptors for thyroid hormone and sex steroids—are bound at any time during development and in any tissue. These kinds of studies, coupled with focused investigations on important environmental contaminants, may yield new insights into the ability of environmental contaminants to interfere with fertility by disrupting thyroid hormone signaling.

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