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Guest Editorial

Thyroid Hormone and Brain Development: Translating Molecular Mechanisms to Population Risk

In its September 1998 issue, *Thyroid* published a review that thoroughly catalogued published work identifying a remarkable number of synthetic chemicals found in the environment that can interfere with thyroid function (1). Less than a year later, Haddow et al. (2) published work demonstrating that subtle maternal thyroid hormone insufficiency is associated with measurable neurological deficits in their offspring. As a result of these data there is growing concern that environmental chemicals can interfere with thyroid function—or more importantly, thyroid hormone action—thereby affecting neuropsychological development in human populations. But the issues confronting attempts to identify thyroid toxicants that may affect human health, or to determine whether environmental chemicals disrupting thyroid hormone signaling are affecting human health, are far more complex than might appear at first glance. The reasons for this are at least three-fold. First, the role of thyroid hormone in brain development remains poorly understood. Cao et al. (6) first reported that severe thyroid hormone insufficiency during the first trimester of fetal development, observed in a geographic area of endemic cretinism, is associated with severe neurologic abnormalities. This report in 1994 made explicit the concept that the timing of thyroid hormone action in the developing brain extends to the early fetal period, yet the report by Haddow et al. (2) 5 years later generated a great deal of concern about the relevance of Cao's observations to the clinic (7). Thus, there remain a number of important, unanswered questions about the role of thyroid hormone in neuropsychological development that impairs our ability to determine whether environmental chemicals are affecting human health via actions on thyroid hormone levels or action.

A second issue that complicates our ability to identify chemicals in the environment that may affect human health by interfering with thyroid hormone action is that the specific developmental events influenced by thyroid hormone are not well understood. Most of the experimental work has been performed in rodents, and these studies have identified the early postnatal period of the rodent as a particularly sensitive time of brain development to thyroid hormone (8). However, recent studies indicate that thyroid hormone of maternal origin can selectively regulate gene expression (9–11), and neuronal migration in the fetal cortex (12), as well as adult behavior (13). Thus, in animals as in humans, thyroid hormone plays a role in brain development over a wide development period. However, the specific developmental events affected by thyroid hormone and the mechanisms by which these events are regulated by thyroid hormone, remain incompletely understood, and the mechanisms by which thyroid hormone exerts these effects remain poorly studied.

Finally, the present approach to identify thyroid toxicants depends entirely on the ability of a chemical to reduce circulating levels of thyroid hormone (14). Clearly, there are many chemicals that have this effect (1). Moreover, these chemicals are important to identify because they may contribute to thyroid dysfunction, producing hypothyroidism or mild (subtle) thyroid hormone insufficiency and also because the long-term stimulation of the thyroid gland resulting from the action of these chemicals may lead to thyroid cancer (15–17). But this single focus will not allow detection of chemicals in the environment that interfere with thyroid hormone action without affecting circulating levels of thyroid hormone, nor will it provide information about the potential adverse consequences of these chemicals on the developing brain.

In part, the absence of experimental endpoints of thyroid hormone action in toxicologic studies is because of the lack of information in experimental studies on dose responses of thyroid hormone on these endpoints. This, in turn, reflects the different goals of experimental and toxicologic studies; in the former case, the goal is simply to determine the characteristics of thyroid hormone action on specific developmental events in the brain and in the latter case, the goal is to identify chemicals that interfere with thyroid hormone action in the brain and to determine the relative potency of their effect.

Considering the importance of thyroid hormone in brain development and the relative lack of flow of information between these three areas of thyroid research (epidemiology, basic biology, and toxicology), a conference was planned. In September 2002, the National Institutes of Environmental Health Sciences (NIEHS), Environmental Protection Agency U.S. (EPA) and the Agency for Toxic Substances and Disease Registry (ATSDR) sponsored an international conference, "Thyroid Hormone and Brain Development: Translating Molecular Mechanisms to Population Risk," held on the NIEHS campus in Research Triangle Park, North Carolina.

The goal of this conference was to bring together researchers central to these subdisciplines—both clinical and experimental—to define the state of the science, to define data gaps and areas of research required to address issues related to the role of environmental factors that impact thyroid hormone action during brain development, and to define opportunities for collaboration and future funding initiatives.

The papers collected in this special section of *Thyroid* represent a subset of the talks presented at this conference. In the first paper, Dr. Juan Bernal and his colleagues review the experimental literature on the effects of thyroid hormone and brain development. This is a seminal review because it clearly documents the range of knowledge derived from experimental studies with a focus on the large body of work published by the Bernal laboratory. Importantly, this paper places thyroid hormone action within the context of specific developmental events disturbed by hypothyroidism. For example, hypothyroidism causes a reduction in cerebellar granule cell proliferation, migration, and synaptogenesis, which has profound effects on cerebellar histogenesis and postnatal behavior. The Bernal group has contributed significantly to our understanding of the molecular events regulated by thyroid hormone that influence these developmental events. Moreover, they are using genetic mouse models to define for the first time the subtypes of thyroid hormone receptors involved in specific developmental events.

The role of thyroid hormone in retinal development provides an opportunity to study in great detail the role of thyroid hormone in development of a relatively simple neuroepithelium. Functional genomics approaches, including microarrays and serial analysis of gene expression (SAGE), are likely to be important to discover the genetic programs regulated by thyroid hormone, and how these programs help direct developmental events. Drs. Sanjiv Harpavat and Constance L. Cepko review their work in this area, which provides a clear foundation both for a genomics approach to study the action of thyroid hormone in development as well as to study a simple, but clinically important, neuroepithelium as a model to study the developmental effects of thyroid hormone.

Dr. Lars Hagmar presents a thorough review of the literature focused on the effects of developmental exposure to polychlorinated biphenyls (PCBs) on thyroid status in human populations. PCBs are ubiquitous contaminants of human samples (18); they can lower serum thyroid hormones in animals (19), have been negatively associated with serum thyroid hormone in humans (20,21), and can affect thyroid hormone-responsive gene expression both *in vivo* (22) and *in vitro* (23). Dr. Hagmar reviews 13 epidemiologic studies that fulfilled the inclusion criteria for the review. He documents the overall impression that there is a lack of consistency between studies of reported correlations between thyroid status and PCB body burden. In addition, there are no obvious interstudy dose-response associations revealed in these studies. Thus, the studies reviewed can neither fully support nor refute the hypothesis that PCB body burden is associated with thyroid dysfunction. However, it is important to be aware of the intrinsic limitations of the cross-sectional epidemiologic studies used.

Drs. Sonja Heyerdahl and Beate Oerbeck review the literature, and their work, on the neuropsychological consequences of different thyroxine treatment regimens in children diagnosed with congenital hypothyroidism. This work shows clearly that thyroid hormone insufficiency—even subtle insufficiency—produces specific neuropsychological deficits that are dependent on the timing of the insufficiency. Moreover, the work reviewed focuses in part on the question of the optimal treatment regimen for children with congenital hypothyroidism and shows this is a very complicated issue with many questions remaining to be answered.

Although PCBs reduce circulating levels of thyroid hormone, their actions in the developing brain may not be limited to this mechanism of action on thyroid signaling. In experimental systems, PCBs can exert thyroid hormone-like effects on the expression of the thyroid hormone-responsive gene, RC3/neurogranin (22), and individual PCB metabolites can bind to the human thyroid hormone receptor (24) and exert an antagonistic effect on thyroid hormone-regulated gene expression that entails a mechanism whereby the corepressor N-CoR is not released from the receptor (23). These observations indicate that recognizing the molecular mechanisms of thyroid hormone action is critical to understanding the complexity of effects of certain chemicals on thyroid hormone action. Dr. Grant Anderson and colleagues review the literature detailing the various proteins that interact with thyroid hormone receptor in regulating gene expression. Thyroid hormone action is temporally limited in a number of cases that have been well studied. Specifically, there are developmental windows of sensitivity to thyroid hormone on specific genes, which may be controlled by specific repressors of thyroid hormone receptor function, such as COUP-TF. These windows of sensitivity to thyroid hormone may provide information on windows of sensitivity to thyroid toxicants as well as provide new sites and mechanisms of their action.

The use of homologous recombination as a means of genetically deleting or modifying thyroid hormone receptors has contributed greatly to our knowledge of thyroid hormone actions in the developing brain. Dr. Douglas Forrest and colleagues review this literature. These studies show that the β form of the thyroid hormone receptor serves several key neurodevelopmental roles and its range of functions is extended by its ability to express different receptor subtypes. TRβ_2 has a unique role in photoreceptor development whereas TRβ_1 mediates actions in the brain and auditory system. The rather limited repertoire of TR isoforms, however, is unlikely to account for the full spectrum of thyroid hormone actions and future studies may reveal factors that modulate the cell- and gene-specific functions of TRs. These may include some of the many transcriptional cofactors that can interact with TRs *in vitro* (25–28). In the physiologic context, the activity of a given receptor is also subject to control through the uptake of the hormone ligand (29) and by the metabolic activation and inactivation of thyroid hormone by iodothyronine deiodinases (30,31).

An important central question is to what extent serum levels of thyroid hormone must decrease for deleterious effects to occur in the developing brain. In turn, this issue is affected by the normal variation in circulating levels of thyroid hormone, which clouds our ability to measure subtle thyroid hormone insufficiency. Dr. Stig Andersen and colleagues review their work, which demonstrates that the individual variation in circulating levels of thyroxine (T_4) is narrower

than what occurs in the population. Thus, population-based reference ranges for serum T_4 must be interpreted with some caution.

The conference also discussed recommendations for future research directions and research challenges. These include:

- More laboratory-based studies are needed to understand the relative sensitivity of various thyroid hormone-responsive end points in the developing brain to small changes in circulating levels of thyroid hormone, as well as to identify temporal windows of sensitivity to thyroid hormone.
- More information is needed to determine which environmental chemicals interact with the thyroid hormone system and to understand the site and mechanism of action of these environmental chemicals during brain development. Thus, it is critical to improve animal models of thyroid disruption as well as advance our ability to translate animal data to human risk.
- It is critical to improve our understanding of the basic biology of brain development, as well as the site and mechanism of action of environmental chemicals that target the thyroid system. To accomplish this goal it is important to increase the use of "-omics" technology (e.g., toxicogenomics, proteomics and metabonomics), develop and use new imaging technologies, develop and use genetic models of thyroid hormone receptor defects or deficiency, and increase multidisciplinary and interdisciplinary research projects.
- It is clear that thyroid deficiency during pregnancy can result in neurologic deficits in children. We also know that fetal thyroid receptors are present before the onset of fetal thyroid function, so fetal brain development is dependent on maternal thyroid hormone. Thus, one of the outcomes of the conference was a statement that it may be prudent to know maternal thyroid status before, as well as during pregnancy, to ensure that both mother and fetus are healthy. This data could result in a decrease in thyroid hormone deficiency-induced developmental and learning disabilities.
- Finally, there was consensus that conferences of this type that bring together clinicians, epidemiologists, basic biologists and toxicologists will help develop a "common language," improve understanding, and aid in the development of collaborations and coordination of research are needed to move the field forward.

A videocast of the entire conference can be found at videocast.nih.gov/PastEvents.asp?c=1&s=41 Scroll down to the specific conference.

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