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Developmental thyroid hormone disruption: Prevalence, environmental contaminants and neurodevelopmental consequences

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ABSTRACT

Thyroid hormones (TH) are critical for growth and development and particularly brain development. There are numerous environmental agents that lead to marginal reductions of circulating TH. Although it is clear that severe developmental hypothyroidism is profoundly detrimental to neurodevelopment, there is less information regarding the consequences of modest degrees of thyroid. The impact of low level TH disruptions induced by environmental contaminants has not been defined. This paper is a synopsis from four invited speakers who presented at the 13th International Neurotoxicology Association meeting held in Xi'an, China during the summer of 2011. An overview of the role of TH in brain development and a review of human and animal data on the neurological sequelae of disruption of the thyroid axis in the pre- and early post-natal periods were presented by Mary Gilbert and Joanne Rovet. Iodine deficiency, a common cause of TH insufficiency and mental retardation in many countries, including China, was addressed by Zupei Chen. In this presentation the current incidence of iodine deficiency and neurological outcome in China and the efficacy of recently implemented iodinization programs to eliminate this cause of mental retardation were reviewed. Joanne Rovet described the impact of TH disruption during pregnancy and under conditions of congenital hypothyroidism. Children born with normal thyroid function, but who experienced TH insufficiency in the womb, display subtle cognitive impairments and abnormalities in brain imaging. Despite early detection and treatment, deficiencies also exist in children born with thyroid disorders. Different patterns of cognitive effects result from prenatal versus postnatal TH insufficiency. Mary Gilbert reported on the effects of environmental contaminants with thyroid disrupting action on brain development in animals. Results of neurophysiological, behavioral, structural and molecular alterations that accompany modest perturbations of the thyroid axis were reviewed. Noriyuki Koibuchi described molecular targets of TH-mediated signalling accompanying exposure to persistent organic pollutants. Both polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) are prevalent environmental contaminants that disrupt TH signalling at the receptor level. This action by these chemical classes could contribute to the negative impact of these chemicals on brain function. In summary, epidemiological, preclinical and animal research has clearly identified the critical role of TH in brain development. Additional work is required to understand the impact of low level perturbations of the thyroid axis to evaluate the risk associated with environmental contaminants with thyroid action.

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1. Introduction

The hypothalamic-pituitary–thyroid (HPT) axis is responsible for regulating daily function of many biological systems in mammals and other vertebrates, and is an essential regulator of early brain development. Adequate levels of iodine are critical for normal functionality of the thyroid gland (DeLange, 1994). Thyrotropin-releasing hormone (TRH) is produced by the hypothalamus and on release stimulates the pituitary gland to increase production and release of thyroid stimulating hormone (TSH). TSH binds to receptors on the thyroid gland to stimulate synthesis and secretion of the thyroid hormones (TH), thyroxine (T4) and triiodothyronine (T3). Circulating levels of TH are maintained by regulatory feedback control mechanisms between the hypothalamus, the pituitary, and the thyroid gland (see Fig. 1, nodes 1 and 2). When levels of T4 are low, the production of TSH is increased, while

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when they are high TSH production is decreased. Regulation of individual tissue requirements are also served through a variety of local control mechanisms including peripheral and local deiodination (Fig. 1, nodes 4, 5, 8); transporter proteins that deliver the appropriate amount of hormone to the organ system or cell type as required (Fig. 1, node 7), and hepatic catabolism and clearance (Fig. 1, node 5). These regulatory and compensatory mechanisms serve to maintain serum hormones within a narrow limit on an individual level, but normal 'ranges' may be quite wide on a population level (Andersen et al., 2002).

In humans, severe deficiencies in TH during development are associated with irreversible damage to virtually all organ systems, but grave neurological impairments are of particular prominence. The primary causes of severe developmental hypothyroidism in humans include iodine deficiency and congenital hypothyroidism (Glinoer, 2001). TH is required throughout fetal life and early childhood for proper brain development. In humans, the fetal thyroid gland is not formed until the 2nd trimester of pregnancy. TH, specifically, T4, readily crosses the placenta and the developing fetus is completely reliant on this maternal source of TH during the first half of pregnancy. In rodent models, the fetal thyroid gland is not functional until the 17th day of gestation, a few days prior to birth. Brain development in the rodent in the first 2 weeks post partum is analogous to the 3rd trimester in human pregnancy.

The cellular actions of TH are mediated by nuclear receptors encoded by two genes, TRα and TRβ (Oppenheimer and Schwartz, 1997). TRα1 and TRα2 are widely expressed in similar patterns, with the highest levels found in the fetal neocortical plate. TRβ expression is more restricted, with prominent zones in the pituitary gland, cortical ventricular layer, and in sensory organs (Bradley et al., 1992; Forrest and Vennstrom, 2000). TRs can also bind to DNA in the unliganded state (i.e., the "aporeceptor") to enhance or repress gene transcription. TH transiently affects brain development by regulating the expression of many genes involved in a host of developmental processes in a temporally and spatially specific manner.

The role of THs in brain development has been extensively studied in rodent models in which hypothyroidism is induced by thyroidectomy, radioactive iodine, or administration of synthesis inhibitors such as propylthiouracil (PTU) and methimazole (MMI) throughout pregnancy and lactation. TH insufficiency during fetal and neonatal life critical phases of brain development, reduces cell number, synaptogenesis and dendritic arborization; alters cell migration patterns; and decreases axonal myelination. Abnormal development after severe TH depletion has been well documented in the cerebellum, neocortex and hippocampus, and in heavily myelinated white matter tracts such as the corpus callosum. Because structures within the brain mature at different times and different rates, the requirements for TH extend over the course of development. Different time windows of hormone deficits determine the effect TH insufficiency may have on specific brain regions.

A number of environmental contaminants with diverse structures have been shown to decrease circulating levels of TH (Brucker-Davis, 1998; Crofton and Zoeller, 2005; Howdeshell, 2002). Human exposure to some of these chemicals is associated with altered serum profiles of TH and TSH (Baccarelli et al., 2008; Blount et al., 2006; Steinmaus et al., 2010; Chevrier et al., 2007). The actions of these chemicals on TH in the fetus and neonate may

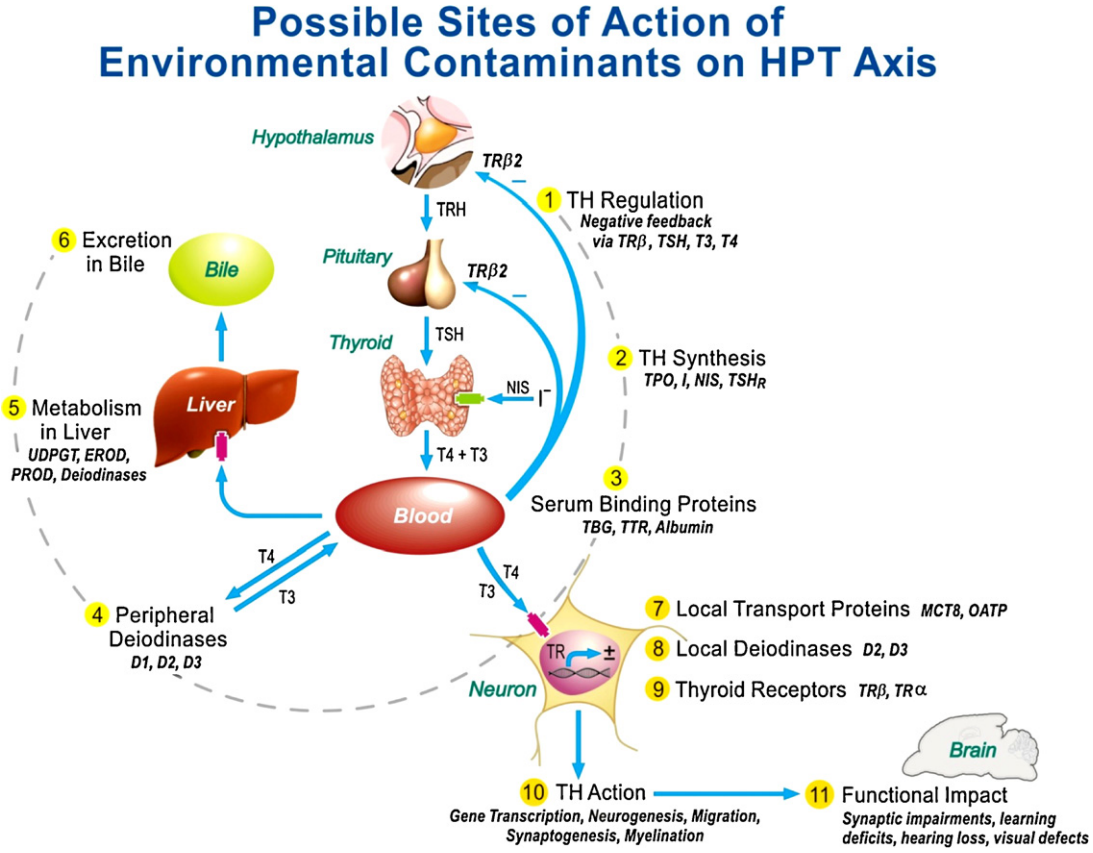

Fig. 1. The basic elements of the HPT axis showing feedback loops (center) and potential target sites where chemical interaction may alter thyroid function. Chemical sites of action are depicted in numbered circles. Text lists specific enzymes, receptors, transport proteins that may be disrupted. Environmental chemicals have the potential to disrupt several different elements of the pathway(s), alone or in combination. The impact of disrupting different elements on the function of the HPT axis, individual organs and tissues, or of the organism as a whole is dependent on the specific pathway(s) perturbed, the timing, duration and degree to which that perturbation occurs. *Source*: Adapted from Boas et al. (2006).