Genome-wide analysis for native thyroid hormone targets in developing brain and mechanisms of endocrine disruption at the thyroid hormone receptor

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Abstract

Thyroid hormone (TH) plays an important role in fetal brain development. Therefore, exogenous factors that interfere with TH signaling may exert potentially important adverse effects on brain development. However the specific roles of TH in brain development are poorly understood. The goal of this research is to delineate the mechanisms of TH and potential mechanisms of endocrine disruption at the TH receptor in the developing brain. The dissertation showed that PCBs can reduce the circulating levels of TH, but simultaneously exerted TH-like effects on TH-responsive genes in fetal brain. To determine whether a specific PCB metabolite, 4-OH-PCB106, could exert a direct agonistic effect on the TRβ1, we employed chromatin immunoprecipitation (ChIP). These studies demonstrate that 4-OH-PCB106 acts as an agonist in GH3 cells, and does not alter the ability of TRβ1 to physically interact with the TRE in the growth hormone (GH) promoter, or with SRC1/NCoR. Interestingly, 4-OH-PCB106 appears to exert actions on gene expression in GH3 cells predominantly through TR, as evidenced by a focused study using differential mRNA display in GH3 cells. A significant impediment in identifying the ability of PCBs to interact with TRs *in vivo* is that few direct gene targets of TH are known. Therefore, we employed ChIP-on-chip in combination with whole transcriptome expression analysis. We identified 526 direct TH gene targets and these revealed major signaling networks regulated by maternal TH during fetal brain development, including cell-fate specification, cell migration and synaptogenesis. This combination of approaches provides a new look at the role of TH in fetal brain development. ^ In a summary, despite the great deal of research focused on the mechanism of TH action, we do not have comprehensive

understanding of the role of TH and its modulators in the brain. Therefore it is important to identify genes that may be direct targets of TH action. This is the first large *in vivo* database for native TREs in the fetal brain before the onset of fetal thyroid function. Therefore the result will provide profound impact in study of mechanisms of TH as well as endocrine disruptors at the TR in developing brain. ^

Subject Area

Biology, Molecular|Biology, Neuroscience|Anthropology, Medical and Forensic

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