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Maternal thyroid hormone regulates gene expression in the fetal rat brain

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Abstract

Recent clinical evidence indicates that thyroid hormone plays an essential role in fetal brain development. However, the mechanism by which thyroid hormone affects development has been largely unexplored. Because thyroid hormone receptors (TRs) are ligand-activated transcription factors, the TR-mediated effects of thyroid hormone in the fetal brain will necessarily be manifested first by changes in gene expression. Therefore, I used differential display to identify genes expressed in the fetal brain that are affected by acute thyroxine administration to the dam before the onset of fetal thyroid function. ^ I identified 11 putative thyroid hormone-regulated genes using differential display. Eight of these genes are selectively expressed in areas of the gestational day (G) 16 brain that contain TRs, indicating that these genes may be directly regulated by maternal thyroid hormone. Next, the distributions of three of these genes, neuroendocrine-specific protein (NSP), Oct-1, and a known thyroid hormone-regulated gene, RC3/neurogranin, were characterized. All mRNAs are expressed from at least G14 until adulthood in brain areas that contain TRs and their regulation by maternal thyroid hormone was confirmed using *in situ* hybridization in the G16 cortex. Additionally, I examined the effects of thyroid hormone on NSP and Oct-1 in the adult brain. I demonstrated that NSP and Oct-1 are expressed in the adult brain and are regulated by thyroid hormone. ^ These studies provide the first evidence that maternal thyroid hormone directly affects fetal brain development by regulating the expression of specific genes *in vivo*. These data support the concept that maternal thyroid hormone exerts a direct action on the expression of genes that are important for normal neurological development of the fetus. Collectively, these data have clinical importance because thyroid hormone affects NSP, Oct-1, and RC3/neurogranin expression in brain regions affected in cretinism and

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congenital hypothyroidism. These three genes are regulated by thyroid hormone from at least G14 to adulthood and are expressed in brain areas known to be affected by hypothyroidism. These areas include the cortex, hippocampus, and cerebellum. The data presented in this dissertation provide experimental evidence that NSP, Oct-1, and RC3/neurogranin may be partially responsible for the detrimental effects of hypothyroidism in developing brain and support several recent clinical studies indicating that untreated fetomaternal hypothyroidism adversely affects fetal brain development. ^

Subject Area

Biology, Molecular|Biology, Neuroscience

Recommended Citation

Amy Louise Skinner Dowling, "Maternal thyroid hormone regulates gene expression in the fetal rat brain" (January 1, 2000). *Doctoral Dissertations Available from Proquest*. Paper AAI9978490.

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