Thyroid Hormone Response Gene and Brain Development

➤ Thyroid hormone (TH) deficiency during fetal life and up to 6 months of age causes irreversible mental retardation; the hormone is key to many brain developmental processes, including neuronal maturation, neurite outgrowth, synapse formation, cell proliferation, and timing of cell differentiation and myelination.

Research has identified *Krüppel-like factor 9 (Klf9)* as a direct TH response gene. The gene promotes differentiation of mammalian and amphibian neuronal cells, mediating TH actions on neurite extension and branching. To further clarify the molecular basis for TH action in brain development, Robert J. Denver, Ph.D., and Keith E. Williamson, B.S., both at the University of Michigan, Ann Arbor, investigated the regulation of *Klf9* by TH in the mouse brain.

They analyzed the mouse *Klf9* gene and its 5' flanking region for the presence of putative TH response elements. *Klf9* mRNA is strongly induced in the mouse hippocampus and cerebellum in a developmental stage- and TH-dependent manner.

The scientists, who report their findings in an upcoming issue of ***Endocrinology,**** identified a functional TH response element called DR-4 3.8 kb upstream from the transcription start site of the mouse *Klf9* gene, explaining its regulation by TH during early postnatal life. The team showed that this TH response element might be evolutionarily conserved among mammals. They suggest that TH receptors are recruited to chromatin upon ligand binding, and they note that further studies could analyze dynamic changes in TR recruitment, corepressor/coactivator exchange, and histone modifications at the mouse *Klf9* gene and other TH-responsive genes in vivo. ■

* Denver RJ, Williamson KE. Identification of a thyroid hormone response element in the mouse *Krüppel-like factor 9* gene to explain its postnatal expression in the brain. *Endocrinology*, in press.

STATS

Globally, excess fat causes

17%

of cancers of the breast, bowel, esophagus, kidney, pancreas, endometrium, and gall bladder.

Source: World Cancer Research Fund report. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective, May 11, 2009.*

Estradiol/Kisspeptin's Effect on Puberty

➤ Researchers are zeroing in on the molecular mechanisms of puberty. Although activation of gonadotropin-releasing hormone (GnRH) neurons is critical for normal puberty onset in mammals, the exact mechanisms responsible for their activation are unresolved. One key suspect is kisspeptin, yet its precise function in the brain is a mystery.

In a series of mouse studies, Allan E. Herbison, M.B.Ch.B., Ph.D., at the University of Otago School of Medical Sciences in New Zealand, and his colleagues, found that kisspeptin is expressed in neurons of the periventricular region of female mice beginning around postnatal day 15 (P15) and rapidly increasing to achieve adult-like levels at P30, the time of mouse puberty onset. Furthermore, female pups ovariectomized at P15 had a 70%–90% reduction in kisspeptin in that region by P30 and P60. When these pups received 17-β-estradiol (E_2) from P15 to P30 or P22 to P30, kisspeptin expression in the periventricular region was completely restored.

The team further investigated the link between estrogen and kisspeptin by examining aromatase knockout mice. Kisspeptin in these mice appeared in the arcuate nucleus, but was completely absent from the periventricular region of the adult females.

The team concludes in their upcoming article in ***Endocrinology**** that an E_2–kisspeptin positive-feedback mechanism exists to facilitate puberty, whereby E_2 stimulates kisspeptin, which in turn activates GnRH neurons to secrete gonadotropins that further yield E_2. This E_2-dependent amplification of GnRH neuronal activity by kisspeptin seems not only to be used at puberty, but also to generate the preovulatory luteinizing hormone surge in each adult female cycle. ■

* Clarkson J, Boon WC, Simpson ER, Herbison AE. Postnatal development of an estradiol-kisspeptin positive feedback mechanism implicated in puberty onset. *Endocrinology*, in press.