

Ono M, Chia DJ, Merino-Martinez R, Flores-Morales A, Unterman TG, Rotwein P. Signal transducer and activator of transcription (stat) 5b-mediated inhibition of insulin-like growth factor binding protein-1 gene transcription: a mechanism for repression of gene expression by growth hormone. *Mol Endocrinol.* 2007;21:1443-57.

Editor's Comment: *Through a well constructed series of experiments, Ono et al clearly showed that GH inhibits IGFBP-1 expression via activated Stat5b and FoxO1. However, the exact mechanism of FoxO1 inhibition by Stat5b remains elusive; FoxO1 protein degradation, nuclear exclusion and impaired DNA binding ability were all ruled out, as was direct protein-protein interaction between Stat5b and FoxO1. Nonetheless, this paper expands our thinking along 2 lines. First, GH, via activated Stat5b, not only induces gene expression (eg. IGF-I), but also represses transcription of other genes, such*

as IGFBP-1. Thus, the genetic response to GH/Stat5b signaling is a richer compilation of coordinated alterations than previously appreciated. Second, the mechanism whereby IGFBP-1 expression is repressed by GH is clearly distinct from that of insulin (activated Akt phosphorylating FoxO1, thereby sequestering it out of the nucleus and impairing its ability to transcribe IGFBP-1'). Although we are used to thinking of GH as counter-regulatory to insulin, in certain circumstances, like IGFBP-1 expression as shown here, the two hormones can act synergistically because they effect the same molecular change through separate pathways.

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Reference

1. Guo S, Rena G, Cichy S, et al. *J Biol Chem.* 1999;274:17184-92.

GH Neurosecretory Dysfunction and Cranial Irradiation

The group of Shalet in Manchester, UK has made fundamental contributions to the understanding of the broad range of endocrinopathies which may follow cancer therapy in children. In terms of clinical practice, deficiency of growth hormone (GH) following cranial irradiation constitutes an important entity of which all pediatric endocrinologists need to be aware. Prophylactic cranial irradiation for leukemia has been largely replaced by use of intrathecal cytotoxic agents. However, targeted high-dose radiotherapy (RT) for brain tumors outside the hypothalamic pituitary region, such as medulloblastomas, remains an essential and potentially life-saving therapy.

The relationship between the dose of RT and the frequency of subsequent GH deficiency has been clearly established. This article critically considers whether patients who have normal GH responses to pharmacological testing may have a more subtle defect of physiological pulsatile GH release, ie, so-called GH neurosecretory dysfunction. The presence of this 'defect' of probably hypothalamic origin was assumed when subnormal pulsatile secretion was reported

during adolescence, particularly after low-dose RT in several studies.

Darzy KH, Pezzoli SS, Thorne M, Shalet SM. Cranial irradiation and growth hormone neurosecretory dysfunction: A critical appraisal. *J Clin Endocrinol Metab.* 2007;92:1666-72.

Editor's Comment: *The combined groups of Shalet and Thorne have performed extremely detailed assessments of physiological GH secretion (cluster analysis) in adult patients, most of whom received RT during childhood, and in normal controls. Such a study would have been impossible in pediatric subjects. The hallmarks of neurosecretory dysfunction, ie, normal GH secretion, after provocation compared with decreased spontaneous secretion were not seen. This helpful finding effectively dismisses this abnormality from potential sequelae of cranial RT in childhood. The peak GH concentration after a pharmacological provocation test can be taken as a realistic index of somatotrope secretory capacity. Performing physiological studies is unlikely to add further clinically relevant information.*

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Growth in Treated Classical Galactosemia Patients

Panis and co-workers studied height and weight growth over a period of 2 years in a group of 40 Dutch children and adolescents with classical galactosemia. These subjects (13 boys, 27 girls, median age 7.8 years, range 3 to 17 years) had the diagnosis established in the neonatal period by galactose-1-phosphate-uridylyltransferase (GALT) and enzymatic studies in erythrocytes. Of the 40 subjects, 31 were prepubertal, and 5 had reached Tanner stage 5. Urinary galactose and galactitol concentrations and GALT levels in the erythrocytes were measured during the study and all were within the

range of treated patients. Prenatal growth was evaluated by obtaining length, weight, and head circumference data from infant welfare centers or from parents. The results, corrected for gestational age, were within normal limits for the Dutch population. Yearly, for 2 successive years, postnatal growth was evaluated by z-scores and corrected for target age. Mean height growth velocity was 0.87 ± 1.2 (range -0.4 to 3.6) for boys and -0.89 ± 2.1 (range -2.5 to 3.7 , $p=0.047$) for girls. Weight growth velocity in z-scores was 0.91 ± 1.6 (range -0.8 to 4.2) for boys and -0.74 ± 1.3 (range -3.1 to 2.3 , $p=0.008$) for girls. Mean