supervision, frequent laboratory testing, and are extremely expensive, should only be considered if the height gain obtained is significant and if the medications are proven to be safe. As clearly stated by the authors, the costs of this form of therapy seem to overshadow the modest benefit in height gain obtained; therefore this form of therapy should not be recommended for routine use in short but otherwise healthy patients who enter into puberty at an early age.

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GH Inhibition of IGF-I in STAT5b Expression

Ligand binding of the growth hormone (GH) receptor activates, via the Jak2 tyrosine kinase, the Stat transcription factors and the MAP kinase and PI3 kinase/ Akt pathways. As is well known to the readers of GGH, GH-stimulated transcription of the insulin-like growth factor (IGF)-I gene requires the Jak2/Stat5b mechanism. However, GH signaling also leads to transcriptional repression of a cohort of genes, including the IGF binding protein (IGFBP)-1. Ono et al sought to elucidate the mechanism of this facet of GH action.

Hypophysectomized Sprague-Dawley rats were given a single systemic pulse of GH, and hepatic RNA was isolated 30, 60 or 120 minutes afterwards. By both microarray and RT-PCR methods, GH acutely increased the mRNA levels of IGF-I and Socs-2 while decreasing that of IGFBP-1. GH also acutely induced the nuclear accumulation of phosphorylated Stat5b. Adenoviral-mediated delivery of a constitutively active Stat5b construct to livers of GH-deficient rats similarly increased IGF-I and Socs-2 expression while decreasing IGFBP-1.

To further examine the transcriptional regulation of IGFBP-1, Cos-7 cells were transiently transfected with a rat IGFBP-1 promoter-luciferase reporter construct as well as an expression vector for mouse GH receptor. Cotransfection with wild-type or constitutively activated FoxO1, a transcription factor important for *IGFBP-1* expression, stimulated promoter activity. GH treatment altered neither IGFBP-1 promoter activity nor the abundance of the FoxO1 proteins. In contrast, when wild type Stat5b was also co-transfected, GH treatment led to a 35%-50% reduction of IGFBP-1 promoter activity with either type of FoxO1; GH stimulated posphorylation of the wild-type but not constitutively activated FoxO1, and abundance of the FoxO1 proteins again were not altered. Thus, GH-induced IGFBP-1 repression is mediated by Stat5b and not Akt (the constitutively activated FoxO1 is Akt resistant.)

Because IGFBP-1 expression is also repressed by insulin, which acts via Akt inhibition of FoxO1, the authors sought to further examine the interactions between Akt, Stat5b and FoxO1. A tamoxifen-inducible Akt fusion protein, iAkt, repressed IGFBP-1 promoter activity in the presence of wild type, but not a constitutively activated, FoxO1; the former form of FoxO1 was phosphorylated by Akt while the latter cannot be. In contrast, a constitutively activated Stat5b did not phosphorylate FoxO1.

Further experiments were performed to mechanistically examine Stat5b inhibition of FoxO1. Using a luciferase reporter construct driven by a minimal promoter containing 3 copies of IRSA (one of the tandem FoxO1 binding sequences found in the IGFBP-1 promoter), the FoxO1 binding site was shown sufficient for GH and Stat5b inhibition of FoxO1-stimulated gene transcription. To examine the possibility of reciprocal inhibition, a luciferase reporter construct driven by the Stat5b-dependent HS7 response element (found in the IGF-I gene) was examined. It increased activity in response to GH in the absence of FoxO1, and increased further still when wild type or constitutively activated FoxO1 were cotransfected, even though there were no FoxO1 binding sites in the HS7-promoter sequences. Thus, competition for transcriptional co-factors does not seem to be the mechanism of Stat5b's inhibition of FoxO1 activity. A dominant-negative Stat5b was shown to lose the ability to mediate GH inhibition of IGFBP-1 promoter activity, in both co-transfected Cos-7 cells in vitro and in GH-treated hypophysectomized rats in vivo. Co-transfected Cos-7 cells further showed that GH induced nuclear accumulation of Stat5b, but neither nuclear levels of FoxO1 protein nor its DNA-binding ability were reduced by activated Stat5b. Direct protein-protein interactions between FoxO1 and Stat5b from Cos-7 nuclear extracts were not detected by co-immunoprecipitation assays or avidin-biotin complex DNA binding assay.

Finally, the authors returned to their hepatic microarray results from GH-stimulated hypophysectomized rats. They compared the list of GH-repressed genes to genes repressed by adenovirally introduced constitutively activated Stat5b. Eighty-nine gene transcripts were similarly reduced by both mechanisms. *In silico* search for FoxO1 binding sites within phylogenetically conserved (rat and human) regions of these genes revealed 19 hits, or 21% of the repressed genes. Of 322 randomly selected genes not regulated by GH or Stat5b 19% were also found to contain FoxO1 binding sties. Thus, FoxO1 inhibition accounts for only a subset of transcriptional repression by GH/Stat5b.

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[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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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, Thorner 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 Thorner 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.*

Martin O. Savage, MD

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-uridyltransferase (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