

The relative roles of growth hormone and IGF-1 in controlling insulin sensitivity

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Commentary

IGF-1 and growth hormone (GH) interact with insulin to modulate its control of carbohydrate metabolism. A new study (see the related article beginning on page 96) shows that blocking the effect of GH in the presence of low serum IGF-1 concentrations enhances insulin sensitivity.

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shown to contain an androgen receptor ligand (Table 1). However, the systematic study by Huang et al. reveals that a single compound found in both YZH and Yin Chin (6,7-dimethylscutellin) is sufficient to activate CAR and induce bilirubin clearance. This is a wonderful example of knowledge gained by applying the Western scientific method to an Eastern herbal remedy. It will be very exciting if a pure compound emerges from the tea leaves as a pharmacological therapy for neonatal jaundice that is complementary or alternative to the current Western practice of phototherapy (16).

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The relative roles of growth hormone and IGF-1 in controlling insulin sensitivity

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IGF-1 and growth hormone (GH) interact with insulin to modulate its control of carbohydrate metabolism. A new study (see the related article beginning on page 96) shows that blocking the effect of GH in the presence of low serum IGF-1 concentrations enhances insulin sensitivity.

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Nonstandard abbreviations used: growth hormone (GH).

Understanding the relative roles of peptide hormones in modulating responsiveness to insulin presents a major challenge because of the adaptability of the growth hormone/IGF-1/insulin system. Changes in glucose and insulin secretion result in counter-regulatory responses, and modifications in growth hormone (GH) and IGF-1 function alter insulin's ability to

maintain normal carbohydrate homeostasis. Historically, this problem has been analyzed in both human and rodent hormone-deficiency models (e.g., GH deficiency) in which the hormone of interest is replaced and the metabolic consequences are determined (1). The recent development of tissue-selective knockout animal models has brought new insights to our understanding of the relative roles of these hormones in carbohydrate homeostasis. In this issue of the *JCI*, Yakar et al. address the relative roles of GH and IGF-1 in regulating insulin sensitivity in mice (2). The authors created an animal model in which IGF-1 synthesis in the liver is eliminated and then crossed these animals with mice that overexpress a mutant form of GH that prevents GH activation of its receptor. The authors conclude that GH is a major determinant of insulin resistance in these IGF-1-deficient animals, since, in the presence of low concentrations of serum IGF-1, blocking

IGF-binding protein-3/acid-labile subunit complex in plasma, which functions to stabilize the half-life of IGF-1. In contrast to the animals with liver IGF-1 deletion, these animals showed enhanced insulin sensitivity in both adipose tissue and muscle but no change in liver. When these results are considered together with the current study (2), they suggest that the major site at which GH blocks insulin action is the liver. Although a secondary role for GH in skeletal muscle cannot be excluded, by this formulation, conditions that lead to increases in GH secretion (whether or not they are associated with lower serum IGF-1) may result in impaired hepatic insulin sensitivity, leading to decreased suppression of gluconeogenesis. Although GH no doubt has an insulin-counter-regulatory role in skeletal muscle, in that tissue the role of IGF-1 may be predominant. An additional issue is that overexpression of the GH antagonist completely eliminates GH action, and therefore this study does not definitively address the role of normal GH secretion and action in mediating insulin resistance. Thus future studies that use tissue-specific gene-deletion animal models and provide different levels of hormone-replacement therapy or that assess the effects of variable doses of the GH antagonist will be necessary to discern the relative roles of IGF-1 and GH in mediating insulin sensitivity in both normal physiologic and pathophysiologic states. Inhibiting GH action to

attain a relatively normal physiologic level rather than a GH-deficient level will be necessary to further understand the contribution of IGF-1 in maintenance of normal glucose homeostasis in these models. Nevertheless, the studies of Yakar et al. highlight the importance of GH antagonism of insulin action in the liver and provide an important step in our understanding of the relative roles of each of these three hormones in maintaining this finely balanced mechanism.

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