

Special Report

The 4th National Cooperative Growth Study Conference November 18-21, 1989, Palm Springs, California

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Growth, Genetics, and Hormones

Among the most important topics covered at this conference were those that pertained to growth hormone (GH), insulin-like growth factor (IGF) binding proteins, and related receptors. The GH receptor is found in large quantities in rabbit liver but also in kidney, muscle, bone, and brain (hypothalamus). Its gene is on the short arm of chromosome 5. The receptor is one of a family of a new type of receptors (prolactin and GH) that serves as a binding protein in plasma and as a receptor in tissue. These receptors do not act through tyrosine kinase and are unrelated in amino acid sequence to other known receptors. The plasma binding protein (BP) is probably the external portion of the GH receptor, which extends outside the cell membrane. This BP and the receptor have both been reported to be absent in Laron dwarfism. In order to analyze the receptor gene in patients with Laron dwarfism, nine patients with this entity were studied; two had a deletion of a large portion of the extracellular hormone-binding do-

main of the receptor gene.

The IGF receptors (IGF-1 and IGF-2) and the insulin receptor are frequently considered together, because the receptors for insulin and IGF-1 are closely related and bind IGF-1, IGF-2, and insulin in various proportions. The receptor for IGF-2, which is also the mannose phosphate receptor, is of a completely different structure and binds IGF-1 and IGF-2 but not insulin. IGF-2 promotes growth by acting through the IGF-1 receptor. IGF-2 *does not* promote growth through its interaction with the IGF-2 receptor, and what role that interaction does play remains obscure.

There are at least 3 IGF BPs. The major BP is BP-3, which comprises 98% of the circulating IGF BP and which is under GH control. IGF BP-3 increases and decreases concomitantly with GH production. This BP is produced in both breast and liver cancer as well as in intact liver. It is a large glycoprotein complex (140 kDa) that has a non-binding alpha subunit (acid labile) and a binding beta subunit (acid stable). These two BP-3 subunits, along with IGF, which is bound to the beta subunit, comprise the large BP.

The three BPs may be responsible for the true autocrine functions of IGF-1 and IGF-2. Because of its binding characteristics for IGF-1, BP-3 may protect the individual against the hypoglycemic effect of IGF-1 and increase the half-life of IGF-1. In uremia this BP-3 is increased to very high levels, possibly because the kidney clears this protein. With chronic renal disease the marked increase in BP-3 may act as the "inhibitor" described for IGF-1 in kidney disease: The excess BP-3 may bind IGF-1 so there appears to be only a small amount of IGF-1 present, which is then misinterpreted as the presence of an inhibitor.

The presenters who addressed these issues were Dr. Michael Ranke of Tübingen, FRG, Dr. Ron Rosenfeld of Stanford University, Palo Alto, CA, and Dr. William Wood of Genentech, South San Francisco, CA.

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Editor's note: *Dr. Ranke will be contributing a lead article titled "IGF BPs" in a forthcoming issue of Growth, Genetics, and Hormones. In it, Dr. Ranke will discuss how measuring IGF BP-3 may assist in diagnosing GH deficiency.*