Introduction

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Insulin and insulin-like growth factors (IGFs) are a family of peptides, each of which interacts with a distinct, specific, high-affinity cell surface receptor. In addition the IGFs, but not insulin, circulate in complexes with specific binding proteins (IGFBPs), which have been shown to modulate the biologic actions of the IGFs.

Although insulin has been used in the treatment of diabetes for more than 70 years, IGF-I has only recently become available for testing in humans due to the advent of recombinant DNA technology. This technology has also increased our capabilities of synthesizing modifications of these peptides that could potentially improve patient care. In addition, molecular biology has increased our ability to explore basic mechanisms involved in hormone action, as has been the case with regard to insulin and IGF-I action, by studying their receptors and post-receptor mechanisms. Growth hormone (GH), administered to children with growth retardation, was originally obtained from tissue extracts, but is now derived by recombinant DNA technology.

The symposium entitled Insulin, IGFs and Growth Hormone from Basic Research to Novel Clinical Applications was planned in an attempt to describe the numerous advances in the field pertaining to insulin, IGF-I and GH. Mutation of the insulin molecule through recombinant DNA technology has produced 'monomeric' insulin, which does not form hexamers and is therefore more readily absorbed following subcutaneous injection. The pharmacokinetics and biological actions are thus altered, and as described by Dr. DiMarchi have enormous potential in the therapy of patients with diabetes. The IGF-I molecule has similarly been altered, and a number of ana-

logs have been studied by Dr. Cascieri and colleagues. Many of the analogs have been designed not to bind to the IGFBPs, but to retain binding capabilities to the IGF-I receptor. These analogs generally have increased biologic activity and a shorter duration of action, demonstrating the inhibitory role of the IGFBPs in IGF-I action.

The insulin and IGF-I receptors are very similar, both containing tyrosine kinase activity which is essential to their function. The activated insulin receptor phosphorylates insulin receptor substrate 1, which acts as a docking protein by interacting with multiple substrates that are responsible for the commonly recognized actions of insulin, including glucose uptake (Professor Roth). Isoforms of the insulin receptor have been identified in different tissues, and these isoforms seem to be expressed differentially in patients with non-insulin-dependent diabetes mellitus (Professor Häring). As their function is altered, this may be an important aspect of the alteration in insulin action in these patients. The physiologic role of protein

kinase C in insulin action remains controversial, but in vitro studies suggest a possible function in feedback inhibition of activated insulin receptor.

The IGF-I receptor, though similar in structure, does have some structural and functional differences from the insulin receptor. These differences, described by Professor LeRoith, may in part explain the major role of IGF-I and the IGF-I receptor in growth, development and differentiation, in contrast to the major metabolic function of insulin and its receptor. In addition to the normal insulin and IGF-I receptors, hybrid and atypical receptors are also expressed by different tissues. The hybrid receptors comprise half of the insulin receptor and half of the IGF-I

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receptor and add an important aspect to the normal biological actions of insulin and IGFs (Professor Siddle). The IGF-II receptor is identical to the mannose-6-phosphate receptor, the latter being important for shuttling lysosomal enzymes from the Golgi apparatus to the lysosomal compartment. When on the surface of the cell, the IGF-II receptor is involved in internalizing IGF-II and extracellular lysosomes. By internalizing IGF-II, it can control the extracellular concentration of this hormone, thereby altering its biologic potential (Dr. Kiess). On the other hand, in contrast to the IGF-I receptor, there is no convincing evidence to date of the role of this receptor in signal transduction.

Because the IGF-I and insulin receptors are similar, investigators have postulated that IGF-I may also affect glucose metabolism, and perhaps this therapeutic modality may be useful in patients with insulin resistance.

Dr. Sherwin described how he and his colleagues have shown, using recombinant human IGF-I, that in humans IGF-I enhances whole body glucose disposal, confirming the hypothesis that IGF-I may be useful for short-term therapy to overcome states of insulin resistance. The exact mechanism of this effect needs to be elucidated. As long-term IGF-I therapy may result in adverse effects, short-term therapy seems more appropriate.

In addition to its effect on longitudinal growth, GH has other effects (Dr. Strasburger).

Modifications of the GH molecule by site-directed mutagenesis has enabled investigators to evaluate the specific regions that are important for interactions with the GH receptor (Professor Gertler). These and similar studies are essential for our understanding of these interactions and provide the foundation on which more selective hormones might be developed.