INSULIN-LIKE GROWTH FACTORS

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THE insulin-like growth factors (IGFs) participate in the growth and function of almost every organ in the body. Because of the wide range of their biologic effects and their therapeutic potential in a variety of clinical disorders, the IGFs have become the focus of research by an increasing number of investigators. The object of this seminar is to review the clinical aspects of the IGFs, including their potential therapeutic value, and to discuss briefly their structure, synthesis, regulation, and physiologic role.

BASIC BIOCHEMISTRY AND PHYSIOLOGIC FUNCTIONS

Structure and Synthesis

The three peptide hormones, or growth factors, in the IGF family—in insulin, IGF-I, and IGF-II—have approximately 50 percent of their amino acids in common. Insulin is synthesized in the beta cells of the pancreas as proinsulin, which is cleaved to form insulin and C peptide. The IGFs, which are synthesized primarily in the liver, increase the serum concentrations of both the acid-labile subunit and IGF-binding protein 3. IGF-I appears to have the predominant role in regulating growth, whereas the physiologic role of IGF-II is unknown.

Insulin, IGF-I, and IGF-II bind specifically to two high-affinity membrane-associated receptors that are tyrosine kinases. Insulin activates the insulin receptor, and both IGFs activate the IGF-I receptor (Fig. 1). A third receptor, the IGF-II-mannose-6-phosphate receptor, binds IGF-II but has no known intracellular signaling actions. Activation of either the insulin receptor or the IGF-I receptor evokes similar initial responses within the cell. However, since insulin regulates metabolic functions and the IGFs regulate growth and differentiated functions, the final pathways these hormones activate within the cell must be separate and distinct.

Regulation and Differentiation of Function

The interaction of growth hormone with its hepatic receptor stimulates expression of the IGF-I gene and the release of the IGF-I peptide (Fig. 2, left-hand panel). Serum concentrations of IGF-I usually parallel 24-hour mean serum concentrations of growth hormone, and IGF-I inhibits the secretion of growth hormone by the pituitary. How the liver regulates the synthesis of IGF-II is unknown.

The circulating IGF-binding proteins limit the access of the IGFs to specific tissues and to the receptors for IGF-I and insulin. Of the six binding proteins, IGF-II-binding protein binds more than 95 percent of the IGF in serum. The IGF–IGF-binding protein-3 dimer forms a complex with another protein subunit, the acid-labile subunit, and in this ternary complex the IGFs have a serum half-life of many hours. Once released from the complex, the IGFs leave the circulation and enter target tissues with the aid of other IGF-binding proteins. Growth hormone increases the serum concentrations of both the acid-labile subunit and IGF-binding protein 3.

Some IGF-binding proteins bind the growth factors with greater affinity than do the IGF receptors, thereby preventing the activation of intracellular signaling pathways. The affinity of these binding proteins for the IGFs can be reduced by protease cleavage or increased phosphorylation of the binding protein or by the binding of the protein to the surface of cells rather than the extracellular matrix. The reduced affinity enhances the biologic activity of the IGFs by increasing the amount of free growth factor available to IGF-I receptors.

The mechanisms of the metabolic effects of insu-
lin and the growth effects of the IGFs differ. Liver and fat cells express only insulin receptors, whereas muscle cells express both insulin and IGF-I receptors. Insulin controls hepatic glucose production and lipolysis by signaling exclusively through insulin receptors. Similarly, insulin-stimulated uptake of glucose into cells is mediated exclusively by insulin receptors. The actions of insulin and the IGFs are also differentiated by the IGF-binding proteins, which do not bind insulin but do direct the IGFs to their specific receptors.

**Tissue IGFs**

Locally produced IGFs are important in the activity of several organ systems. Growth hormone, parathyroid hormone, and sex steroids regulate the production of IGF-I in bone, whereas sex steroids are the main regulators of local production of IGF-I in the reproductive system. The functions of circulating IGF-I are becoming clearer, but the actions of locally produced IGFs have yet to be defined.

**PATHOLOGIC CONDITIONS ASSOCIATED WITH ALTERATIONS IN THE IGF SYSTEM**

**IGF-I**

Many variables, such as age, sex, nutritional status, and growth hormone secretion, affect serum IGF-I concentrations. The concentrations are low at birth, increase substantially during childhood and puberty, and begin to decline in the third decade (Fig. 3). These changes parallel the secretion of growth hormone. In growth hormone deficiency the serum
IGF-I concentration is very low (Fig. 2, middle panel), and with excess growth hormone secretion the serum IGF-I concentration is high. Measurements of serum IGF-I are useful in the diagnosis and management of acromegaly, although the correlation between the clinical features of acromegaly and serum concentrations of IGF-I is not close.11

Growth hormone deficiency and retarded growth may result from impaired release of growth hormone from the pituitary due to diseases of the hypothalamus or pituitary gland. Alternatively, mutations in the gene for the growth-hormone receptor can cause insensitivity to growth hormone and growth retardation with low serum IGF-I concentrations (e.g., Laron dwarfism13) (Fig. 2, right-hand panel).

Nutritional status affects serum IGF-I concentrations. Fasting results in complete resistance to growth hormone, and the restriction of protein or calories (or both) causes lesser degrees of resistance to growth hormone.14 These conditions are associated with impaired signaling of the growth hormone receptor, which reduces the synthesis of IGF-I by the liver. Thus, since growth hormone and IGF-I are anabolic hormones, malnutrition leads to a state of catabolism. In other catabolic states, such as severe trauma and sepsis, the serum IGF-I concentration is low and there is resistance to growth hormone.

In both insulin-dependent and non-insulin-dependent diabetes mellitus, the growth hormone–IGF-I axis is abnormal. Many patients with insulin-dependent diabetes have some hepatic resistance to growth hormone, with elevated serum growth hormone concentrations.
concentrations and decreased serum IGF-I concentrations, probably as a result of insufficient insulin action on the liver.\(^\text{15}\) During puberty, these changes may decrease linear growth, and the increase in the secretion of growth hormone may worsen the hyperglycemia by counteracting the action of insulin in peripheral (muscle and fat) tissues. If insulin therapy is inadequate, the unopposed action of glucagon allows increased hepatic glucose production. In poorly controlled non-insulin-dependent diabetes, the hypersecretion of growth hormone may also counteract insulin in the peripheral tissues, thus allowing glucagon to act unopposed. In either type of diabetes, administration of IGF-I may improve the hyperglycemia and reduce insulin resistance by lowering serum concentrations of growth hormone and glucagon. Furthermore, in non-insulin-dependent diabetes, IGF-I can inhibit the secretion of insulin and prevent hyperinsulinemia, thereby allowing the increased expression of insulin receptors (see below).

**IGF-II**

Some tumors secrete IGF-II, which may affect the growth of tumor cells.\(^\text{16}\) Most of these tumors also overexpress IGF-I receptors and various IGF-binding proteins.\(^\text{17}\) Some mesenchymal (non–islet-cell) tumors produce and release an excessive amount of a prohormone form of IGF-II (often termed “big IGF-II”)\(^\text{18}\) (Fig. 4). The increased serum IGF-II concentration inhibits the secretion of insulin and growth hormone, and the reduction in serum growth hormone decreases the circulating levels of the ternary complex of IGF-I, IGF-binding protein 3, and the acid-labile subunit. Big IGF-II interacts poorly with the IGF-binding protein complex, and the resulting increase in unbound IGF-II causes hypoglycemia by inhibiting hepatic glucose uptake and enhancing the
disposal of glucose into muscle. Surgical removal of the tumor or radiotherapy reduces the excess IGF-II, thereby ameliorating the hypoglycemia.\textsuperscript{19-22}

**IGF-I AS A THERAPEUTIC AGENT**

Part of the allure of IGF-I as a therapeutic agent is the wide range of its biologic effects and its actions on many different tissues. IGF-I mediates many if not most of the anabolic effects of circulating growth hormone. It stimulates bone formation, protein synthesis, glucose uptake in muscle, and neuronal survival and myelin synthesis. IGF-I also reverses negative nitrogen balance during underfeeding and inhibits protein degradation in muscle. For these reasons, IGF-I has been proposed as a therapy for osteoporosis, various catabolic states, diabetes, obesity, neuromuscular disorders, growth hormone resistance, and insulin resistance. The broad spectrum of its biologic actions offers much promise for IGF-I therapy for many conditions, but it also increases the likelihood that IGF-I will have side effects or unwanted actions.

**Growth Hormone Insensitivity Syndrome**

Patients with growth hormone deficiency have reduced serum concentrations of growth hormone and IGF-I (Fig. 4). In prepubertal patients this causes short stature, a condition that responds to treatment with recombinant human growth hormone. Growth hormone deficiency in adults changes body composition (increasing fat mass and reducing lean body mass), elevates serum cholesterol levels, reduces physical performance and bone density, and diminishes quality of life. All of these conditions respond to growth hormone therapy.\textsuperscript{23} A far less common cause of short stature is insensitivity to growth hormone.\textsuperscript{13} This syndrome, originally called Laron dwarfism, consists of dwarfism, acromegria, obesity, small genitalia and gonads, and a high-pitched voice. There are low serum concentrations of IGF-I and IGF-binding protein 3 and increased serum concentrations of growth hormone. Inactivating mutations in the growth hormone receptor cause insensitivity to exogenous growth hormone.

The growth hormone insensitivity syndrome is ideal for testing the therapeutic potential of recombinant IGF-I. In the initial study by Laron et al. of five children with the syndrome, a starting dose of 150 \( \mu \)g of IGF-I per kilogram of body weight per day, given subcutaneously, increased height velocity threefold, from 3.0 cm per year to 10.8 cm per year, and decreased body fat, as reflected by decreased subcapular skin-fold thickness, without causing hypoglycemia.\textsuperscript{24} In a multicenter study of 27 patients treated with 40 to 120 \( \mu \)g of IGF-I per kilogram twice daily, height velocity increased by more than 2 cm during the first year of therapy and was maintained at 6.4 cm in the second year.\textsuperscript{25} In another study of five patients given 80 to 120 \( \mu \)g of IGF-I per kilogram twice daily for 24 months, the response was similar, with the increase in height velocity being greater during the first year of therapy.\textsuperscript{26} Less than 30 percent of patients receiving recombinant IGF-I had low titers of nonneutralizing antibodies to IGF-I.\textsuperscript{28}

These clinical studies demonstrated that the circulating endocrine form of IGF-I stimulates bone growth and alters body composition by favoring protein accretion and loss of fat mass. Growth hormone insensitivity is the first clinical syndrome for which IGF-I therapy has been approved; IGF-I is the only effective treatment for this disorder.

In some patients with growth hormone deficiency due to deletions in the growth hormone gene, antibodies to growth hormone may develop during treatment with recombinant growth hormone. When treated with IGF-I, these patients respond with increased height velocity, similar to that in the patients with growth hormone insensitivity.\textsuperscript{26}

**Insulin Resistance and Diabetes Mellitus**

**Severe Insulin Resistance**

Insulin resistance is a component of many common and several uncommon clinical syndromes. The degree of insulin resistance varies from relatively mild in obesity to more severe in the polycystic ovary syndrome or non-insulin-dependent diabetes mellitus, but it reaches dramatic proportions in several congenital and acquired syndromes.\textsuperscript{27} Patients with mutations in the insulin-receptor gene or in genes related to the signal-transduction pathways have different phenotypes, including lipoatrophy, partial lipodystrophy, the type A syndrome of insulin resistance with mutations of the insulin-receptor gene, pseudoacromegaloïdism, leprechaunism, and the Rabson–Mendenhall syndrome. In many of these patients the hyperglycemia is extremely difficult to treat, because insulin, by definition, is not effective.

IGF-I has been proposed as a therapy for severe insulin resistance because its biologic actions resemble those of insulin and it may therefore bypass the defect or defects that block the action of insulin. Intravenous administration of recombinant IGF-I was found to decrease blood glucose and serum insulin concentrations in two patients with the type A syndrome of insulin resistance\textsuperscript{28} and in one child with the Rabson–Mendenhall syndrome.\textsuperscript{29} In a study of six patients with different phenotypes of severe insulin resistance, administration of IGF-I for four weeks at a dose of 100 \( \mu \)g per kilogram twice daily decreased fasting and mean 24-hour serum insulin concentrations by 60 to 80 percent, improved glucose tolerance in patients with impaired tolerance or overt diabetes, and decreased fasting serum triglyceride concentrations.\textsuperscript{30} In another study, IGF-I reduced blood glucose and serum insulin concentra-
tions in nine patients with severe insulin resistance. How IGF-I works in insulin resistance remains uncertain, but the response to IGF-I in patients with mutations in the insulin-receptor gene or post-receptor defects supports the notion that IGF-I acts through mechanisms similar to but distinct from those of insulin itself — possibly exclusively through the IGF-I receptor.

**Insulin-Dependent Diabetes Mellitus**

Patients with poorly controlled insulin-dependent diabetes, including those entering puberty, often have high serum growth hormone and low IGF-I concentrations and some degree of insulin resistance. The increased secretion of growth hormone reflects the loss of IGF-I–mediated feedback inhibition, and because growth hormone has anti-insulin actions, it may worsen the insulin resistance. IGF-I has been proposed as an adjunct to insulin therapy in adolescents with poorly controlled diabetes because it decreases the secretion of growth hormone, increases sensitivity to insulin, and decreases insulin requirements. When administered as an overnight infusion or subcutaneous injection every evening for one month, IGF-I permitted daily insulin doses to be decreased, reduced growth hormone secretion, and lessened fluctuations in blood glucose. These beneficial effects occur at doses of IGF-I (40 µg per kilogram once daily) that produce serum IGF-I concentrations in the normal range for adolescents.

**Non-Insulin-Dependent Diabetes Mellitus**

Insulin resistance is common in patients with non-insulin-dependent diabetes. It is caused by several as yet undefined post-receptor defects in insulin action. Insulin secretion increases to overcome the defect, but this decreases the expression of insulin receptors on target tissues and worsens the insulin resistance. Hype

glycemia during IGF-I therapy is a cause for serious concern, but it can be avoided with judicious use of the hormone and careful monitoring of blood glucose concentrations. Whether long-term use of IGF-I can cause features of acromegaly or hypertrophy of tissues such as the arterial walls or the uterine endometrium, or even potentiate the proliferation of tumor cells, remains to be determined.

**Side Effects of Short-Term IGF-I Administration**

A single intravenous dose of IGF-I can cause dramatic cardiovascular responses, including asystole and hypotension. Some of these effects may be due to acute hypophosphatemia induced by IGF-I, because they were prevented by the simultaneous administration of phosphate. Given the seriousness of these responses, however, the Food and Drug Administration has limited the dose and rate of infusion of intravenous IGF-I but continues to allow subcutaneous injections of up to 120 µg per kilogram twice a day.

**Side Effects of Multiple Subcutaneous Doses of IGF-I**

High-dose IGF-I given subcutaneously for more than 10 days can cause temporomandibular discomfort, facial and hand edema, weight gain, and dyspnea. It also causes sinus tachycardia, thought to be due to reflex sympathetic activation in response to lowered peripheral vascular resistance. Increased intracranial pressure, gynecomastia, acromegaloïd features, and avascular necrosis of the head of the femur have occurred, as has Bell’s palsy; all diminish after therapy ends. The fact that IGF-I is an endothelial-cell growth factor necessitates careful surveillance of microvessels in patients treated with IGF-I. Hypoglycemia during IGF-I therapy is a cause for serious concern, but it can be avoided with judicious use of the hormone and careful monitoring of blood glucose concentrations. Whether long-term use of IGF-I can cause features of acromegaly or hypertrophy of tissues such as the arterial walls or the uterine endometrium, or even potentiate the proliferation of tumor cells, remains to be determined.
CONCLUSIONS

The broad range of the biologic actions of IGF-I makes it an attractive therapy for several diseases. However, our understanding of the IGF–IGF-binding protein system in normal physiology remains incomplete. The availability of recombinant human IGF-I may clarify this system and provide a useful tool to probe the pathophysiology of several diseases in the quest for new or better therapies.

DISCUSSION

DR. GEORGE KING: Can you comment on the fact that according to some reports, patients with acromegaly, who produce a lot of IGF-I, have a higher incidence of tumors?

DR. DEREK LE ROIITH: It is not absolutely clear that these patients have a higher incidence of tumors, and because they also overproduce growth hormone, which may have its own effects in addition to those of IGF-I, it may be hard to attribute any higher tumor incidence solely to IGF-I.

DR. JEFFREY S. FLIER: Can you expand on the possible role of IGFs in enhancing mitogenesis, especially of vascular smooth-muscle cells?

DR. LE ROIITH: IGFs have been implicated with other mitogens as causative agents in vascular complications of some disorders, such as diabetes. The evidence that IGFs may be directly involved is far from convincing, and what data are available suggest they have more of a potentiating role.

DR. FLIER: Since IGF-I has many actions, can you expand on the other possible conditions that may respond beneficially to recombinant human IGF-I?

DR. LE ROIITH: Patients with one of several conditions are presently being studied, including those with neuromuscular conditions such as amyotrophic lateral sclerosis, myotonic dystrophy, and multiple sclerosis. In addition, IGF-I therapy is being evaluated in patients with acute catabolic states, osteoporosis, healing wounds, and renal failure. In some cases, the preliminary results are promising.

REFERENCES