The Growth Hormone and Insulin-Like Growth Factor Axis: Its Manipulation for the Benefit of Growth Disorders in Renal Failure

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Abstract. Renal failure is associated with dramatic changes in the growth hormone/insulin-like growth factor (GH/IGF) axis. In children, this results in growth retardation, which is treated with injections of recombinant human GH (rhGH). Given the many recent advances in the knowledge of the components of the GH/IGF axis, it is timely to review the role of GH in renal failure and to discuss likely new treatments for growth failure. Renal failure is not a state of GH deficiency but a state of GH and IGF resistance, making other approaches to manipulating the GH axis more logical than treatment with rhGH alone. Although in children rhGH is safe, in critically ill adults it can be lethal. As the mechanisms of these lethal actions of rhGH are unknown, caution is advised when using rhGH outside approved indications. In renal failure, an optimal balance between safety and efficacy for growth may be achieved with the use of the combination of rhGH and rhIGF-I, as animal studies have shown synergistic growth responses. However, inhibition of the GH axis, with the use of GH antagonists, is likely to be tested clinically given the beneficial effects of GH antagonists on renal function in animal models of renal disease. Manipulating IGF-I by either administering rhIGF-I or its binding proteins or increasing IGF-I bioavailability with the use of IGF displacers could prove to be a safer and more effective alternative to the use of rhGH in renal failure. In the future, both rhGH and rhIGF-I likely will be included in growth-promoting hormone cocktails tailored to correct specific growth disorders.

Normal Regulation of the GH Axis

The GH/IGF axis is a key endocrine modulator of postnatal growth and metabolism (Figure 1). The normal regulation of the axis is well understood as are some of the disruptions induced by renal failure. The axis involves the peripheral effector peptide hormones GH, IGF-I, and IGF-II and a regulatory feedback loop (reviewed in references 1–3). GH is secreted by the anterior pituitary gland in a pulsatile manner under the acute stimulatory effects of the hypothalamic peptide GH-releasing hormone (GHRH) and the inhibitory effects of somatostatin. The recent discovery of ghrelin, a naturally occurring GH-releasing peptide (GHRP) that is expressed in both the stomach and the hypothalamus and is present in the blood of rats and humans, suggests that this molecule is involved in the hormonal regulation of GH release (4). The presence of ghrelin in the stomach suggests that it may play a role in the nutritional regulation of the GH/IGF axis. However, many hormones affect GH release, including insulin, so the true functions of gut ghrelin remain to be determined.

Once GH is released from the pituitary gland, it circulates in the blood to increase IGF-I production in many tissues, leading to a rise in blood IGF-I, which provides a long-term inhibition of further pituitary GH secretion (2). Similarly, the administration of IGF-I reduces GH secretion; conversely, genetically engineered IGF-I null mutant mice show markedly increased GH secretion (5).

GH and IGF-I Physiology

In the 1970s and 1980s, the somatomedin hypothesis proposed that IGF-I (formerly termed somatomedin C) mediated all of the effects of GH (1). Liver-generated IGF-I, the major contributor to IGF-I levels in the blood, was proposed to be crucial to the growth-promoting actions of GH. However, IGF-I is produced by many tissues of both epithelial and mesenchymal origin during both fetal and adult life (6). Because GH receptors occur in many tissues and some of the effects of GH do not involve the generation of IGF-I, it was necessary to modify the somatomedin hypothesis. It was pro-
posed, therefore, that GH could act directly on many tissues, including cartilage and kidney, and produce IGF-I locally (7).

Recent studies in knockout mice have supported this modified hypothesis. As predicted by the somatomedin hypothesis, IGF-I \(^{-/-}\) knockouts are dramatically growth retarded (8). Depending on their genetic background, up to 95% of IGF-I \(^{-/-}\) dwarf mice die shortly after birth. Knockout mice that do survive show a markedly reduced growth rate compared with wild-type mice and have an adult weight of approximately 30% of normal (8). In contrast, liver-specific (Cre/lox) IGF-I knockout mice, in which only liver-generated IGF-I is reduced, have low blood levels of IGF-I but are viable and show normal growth (9).

This result was surprising given the belief that liver-generated endocrine IGF-I is important for body growth. GH supplementation in mice in which IGF-I is knocked out in all tissues does not increase growth (5). These studies suggest that although IGF-I is essential for normal postnatal body growth, liver-generated circulating IGF-I is not crucial for normal growth. In contrast, these experiments show the importance of local GH actions and/or IGF-I production, for example on bone growth (Figure 1). It is possible that liver-specific IGF-I knockout mice grow normally because the bioactivity of IGF-I in the blood is unchanged, despite that total levels of circulating IGF-I are decreased markedly. Conversely, the high GH levels in these mice argue for a reduced bioactivity of blood IGF-I.

In blood, approximately 97% of the IGF are bound to six IGF-binding proteins (IGFBP-1 to IGFBP-6), with the remaining IGF-I either in a bioactive-free fraction (approximately 1%) or in an easily dissociable form (10). Most IGF-I in the circulation is bound in a 150-kD complex of IGF-I, IGFBP-3 and a third protein, the acid-labile subunit. This ternary IGF complex is a storage form of IGF in blood and has a half-life of several hours (1). The binding of IGF-I to IGFBP limits the bioactivity of IGF-I, as bound IGF-I probably cannot activate the IGF-I receptor.

This inhibition of bioactivity, especially that by IGFBP-1 and -2, has been shown in several experiments; for example, the administration of IGFBP-1 blocks the effects of both GH and IGF-I on body growth (11), and IGFBP-1 and IGFBP-2 transgenic mice are growth retarded yet have normal total IGF-I concentrations in blood (12). Therefore, in renal failure, IGF-I bioactivity in blood is probably low as circulating concentrations of IGFBP-1 and -2 are elevated (13,14).

GH/IGF Axis and the Kidney

The GH/IGF/IGFBP system is present in the kidney and is important to kidney structure and function. GH receptors are expressed in proximal tubules and thick ascending limb, whereas IGF-I receptors are found predominantly in the glomerulus and proximal and distal tubules (15). Both GH and IGF-I increase renal plasma flow and GFR. These effects of GH are likely to be mediated by IGF-I, as IGF-I increases these parameters within minutes to hours, whereas the effects of GH are delayed until IGF-I levels rise (15).

The role of IGF-I in renal development is thought to be minor as general kidney morphology of complete IGF-I \(^{-/-}\) mice is normal (16). It is of interest to produce a kidney-specific IGF-I deletion, as it would show the relative importance of local IGF-I to kidney growth and function. Targeted gene deletion in the kidney now is feasible (17). Furthermore, in such an IGF-deleted mouse, recovery from renal injury would be of particular interest.

Although most actions of GH are mediated by IGF-I, and GH and IGF-I share several activities, there are actions of GH and IGF-I that are very different. For example, mice that are
transgenic for IGF-I develop glomerular hypertrophy, whereas mice that are transgenic for GH develop glomerular sclerosis (18). Therefore, on the kidney, GH and IGF-I can have quite different actions.

Cancer Risk

Epidemiologic studies have associated the IGF axis as a risk factor for several common cancers. Multiple prospective case-control studies have found that elevated serum IGF-I levels and low IGFBP-3 levels are associated with an increased risk of prostate, colorectal, breast, and lung cancers (19,20). It is important to note that a causal role of IGF-I in the pathogenesis of cancer has not been established and that the interpretation of these new data are the subject of much debate.

Fetal Programming, GH/IGF, and the Kidney

Large epidemiologic studies have found a strong correlation between low birth weight and the subsequent incidence of obesity, diabetes, hypertension, and renal disease during adult life (the so-called Barker hypothesis) (21). There also is evidence that intrauterine growth restriction (IUGR) results in altered programming of the GH/IGF system, altered programming of the renin-angiotensin system, and/or altered gene expression, causing abnormal renal and cardiovascular physiology (22,23). Renal abnormalities include structural changes such as a low nephron count, which eventually may underlie the development of adult hypertension (23,24).

Abnormalities in the GH/IGF axis have been associated with growth failure after IUGR and also could lead to the above-described long-term health sequelae. It remains to be established whether therapeutic interventions after IUGR aimed at deprogramming the GH/IGF axis or other regulatory systems early in life will affect the long-term outcomes of metabolic, cardiovascular, and renal disease.

Changes in GH, IGF, and IGFBP during Renal Failure

CRF is associated with several derangements in the GH/IGF/IGFBP axis (Figure 2), including in children an increased pulsatile release of GH and reduced metabolic clearance rate of GH, resulting in a rise in circulating GH concentrations (25,26). This should result in high IGF-I concentrations, but in uremia IGF-I synthesis in the liver is reduced, which results in normal concentrations of circulating IGF-I (27). However, IGF-I bioavailability probably is reduced in renal failure as a result of increased plasma levels of IGFBP-1, -2, -4, and -6 (15,28). In CRF, there are increased amounts of low molecular weight IGFBP-3 fragments, which have a reduced affinity for IGF-I and which accumulate because of reduced renal clearance (13).

The increased levels of IGFBP-1 and -2 in CRF are correlated inversely with residual GFR and with height (13). Free IGF-I levels, however, are correlated positively with renal function (14). Therefore, the high IGFBP-1 and IGFBP-2 levels probably contribute to the resistance to the metabolic and growth-promoting properties of GH and IGF-I in renal failure. There is some evidence for receptor-mediated GH and IGF resistance in CRF. In experimental CRF, there is evidence of a decreased GH receptor abundance in tibial growth plates (29) and liver (30) and a defect in IGF signaling in muscle (31). However, the weight of evidence favors a key involvement of the IGFBP in the GH and IGF resistance that can occur in renal failure. Thus, renal failure is not a state of GH or IGF-I deficiency but a state in which the regulation and bioavailability of components of the GH/IGF system are altered.
**Therapeutic Manipulation of the GH/IGF Axis in Renal Failure**

**Growth Hormone**

**Growth.** Recombinant human GH (rhGH) is approved for the treatment of growth failure in children with CRF. A daily dosage of 0.05 mg/kg body wt given by subcutaneous injection is recommended (32). Using this dose, two large multicenter clinical trials in CRF patients showed that rhGH treatment can improve statural growth (33,34). Recent studies showed that rhGH treatment is most effective when it is started at an early age and that the growth response is affected by the degree of renal impairment (35).

Although treatment with rhGH clearly stimulates body growth in children with renal failure, it is possible that rhGH may adversely affect renal function in some situations. For example, GH has been suggested to play a role in the development of glomerulosclerosis in mice (18), but there is no proof in children that rhGH has deleterious effects on renal function or, when given before renal transplantation, on graft function (36). However, rhGH treatment is not an ideal treatment for the growth disorders associated with CRF in children because a state of GH excess already exists in CRF.

RhGH therapy also has been proposed for the treatment of growth failure after renal transplantation, as catch-up growth does not occur in up to 75% of these patients (37). Guest et al. (38) showed in a prospective randomized study that rhGH therapy after renal transplantation tended to increase the number of acute biopsy-proven rejections (9 rejections in 44 rhGH-treated patients versus 4 of 46 control patients), although this was related to a previous history of rejection. RhGH treatment after renal transplantation still must be considered experimental (39).

**Anabolic and Cardiovascular Effects.** Studies have suggested a beneficial effect of rhGH treatment on left ventricular mass in patients with dilated cardiomyopathy, but this has not always been associated with an improved clinical outcome (40,41). In nine adult hemodialysis patients (median age, 48.6 yr), rhGH treatment (4 IU/m² per d for 6 mo) significantly increased lean body mass, reduced fat mass (42), and significantly increased left ventricular muscle mass but had no effect on ejection fraction, BP, or maximum exercise capacity (43). One rhGH-treated patient died as a result of severe pneumonia. Johansson et al. (44) showed that rhGH administration (66 µg/kg given three times a week for 6 mo) in 10 elderly patients (mean age, 73 yr) who were on maintenance dialysis increased serum albumin and increased muscle strength. Two patients in the rhGH group died, whereas no placebo-treated patients died during the treatment period.

The use of rhGH to treat catabolism in dialysis patients also is of doubtful value given the lack of effect on clinical outcome and the adverse side effects of rhGH in intensive care patients (45).

**Sustained-Release GH**

New formulations of rhGH, to allow more convenient administration regimens, have been tested in animals (46,47). One form, an injectable sustained-release formulation of rhGH in erodable polylactate polyglycolate microspheres, was approved recently by the FDA for use in pediatric GH-deficient patients. Two multicenter, open-label clinical studies in prepubertal GH-deficient children showed that this formulation of rhGH caused significant catch-up growth (48). Patients who were maintained on rhGH depot for 12 mo showed a mean growth rate of 7.8 ± 1.9 cm/yr, which was lower compared with the first-year growth rate of 10.0 ± 3.1 cm/yr that could be expected if the patients were given daily injections of rhGH (32).

Sustained-release rhGH has not yet been studied in patients with renal insufficiency. A potential issue in these patients is that the clearance of GH is slowed, which could lead to GH accumulation. In addition, different effects of GH can be produced by intermittent or continuous GH administration (46). For example, compared with daily GH injections, continuous GH administration in rodents produces an initial rapid response in body growth, which wanes rapidly. Long-term studies in humans comparing intermittent exposure using daily GH injections with continual exposure using the depot formulation may be needed to allay such efficacy concerns. In our opinion, the efficacy of this new formulation of rhGH needs to be established in long-term controlled studies, especially for use in pediatric CRF patients.

**Adverse Effects of GH**

RhGH treatment has been proposed as an anabolic therapy for catabolic critically ill patients (49). However, two large multicenter, double-blind, placebo-controlled Phase III clinical trials showed very clearly (P < 0.001) that rhGH (0.10 mg/kg body wt) doubled the overall mortality of critically ill patients from approximately 20 to 40% (45). The dosage of rhGH in the critically ill patients was double the recommended dosage for growth disorders in pediatric CRF.

It now is recommended that rhGH treatment not be initiated in patients with an acute critical illness. The cause of the increase in mortality is unknown; therefore, great caution needs to be exercised in the use of rhGH in adults outside the currently approved use in GH deficiency. There is no clear recommendation on the course of action to take when a patient who is already receiving rhGH treatment develops an acute illness. However, it seems reasonable to cease rhGH treatment in both children and adults if an acute illness occurs, as there are no parameters available to gauge the risk of an adverse outcome if treatment is continued. This is partly because the adverse effects of rhGH may be via either the direct or the indirect effects of GH. Initial experimental studies in animals suggest that metabolic or cytokine responses may be involved in these adverse effects (50). There has been much recent debate on the safety of manipulating the GH/IGF axis in acute critical illness (51).

Other adverse reactions to GH treatment in CRF include an increased risk of benign intracranial hypertension (52). The recent suggestion of an increased incidence of type II diabetes mellitus in children who are treated with GH also indicates that rhGH-treated patients deserve close monitoring (53).
prudent in pediatric CRF to start GH treatment with a half-dose, which should be ramped up to the therapeutic dose within 1 to 2 mo.

The use of rhIGF-I or rhIGF-I plus rhGH in catabolic states such as end-stage renal disease (ESRD), critical illness, and AIDS has not been associated with an increased mortality (54,55). These data reinforce our theme of differences between the physiology and the pharmacology of rhGH and rhIGF-I treatment.

**Insulin-Like Growth Factor-I**

Although rhIGF-I seems to be a logical treatment for growth failure in pediatric CRF, because of the increased IGFBP in this condition, clinical studies with rhIGF-I have not been performed in children outside of patients with GH insensitivity syndrome (GHS). Studies in animal models of CRF (5/6 nephrectomy) show that the growth response after rhIGF-I treatment is almost comparable to that after GH treatment (56). Besides effects on stature, rhIGF-I has direct anabolic effects and improves renal function. In normal subjects, rhIGF-I rapidly increases GFR and renal plasma flow by approximately 30% (57).

**Acute Renal Failure.** No drug has been approved as a stimulator of renal function in acute renal failure (ARF) (58). However, there is an obvious need for new treatments, as morbidity and mortality remain high after ARF. In animal models, rhIGF-I can improve both functional and histologic recovery after renal ischemia and reperfusion damage (59). These beneficial effects may be due to a variety of actions, such as increasing anabolism and hemodynamic effects in the glomerulus and the preglomerular vessels. rhIGF-I decreases both afferent and efferent arteriolar resistance in the glomerulus and increases renal blood flow by dilation of preglomerular vessels. These effects most likely are mediated by nitric oxide and vasodilatory prostaglandins (15). Recent studies also have shown that rhIGF-I can reduce the inflammatory process after renal ischemia and reperfusion by inhibiting apoptosis (60). Early timing of treatment may be crucial for these effects, although other studies have shown that rhIGF-I treatment can enhance renal repair when administered up to 24 h after injury (59).

These advantageous effects of rhIGF-I administration in animals have led to two randomized, double-blind, placebo-controlled trials (61). Franklin et al. (62) examined the effects of rhIGF-I on recovery of renal function in 58 patients who underwent vascular surgery of the renal artery or the aorta, and Hirschberg et al. (63) tested rhIGF-I in 72 intensive care unit patients with confirmed ARF from different causes. Overall, both studies failed to show clinically significant effects on renal function or outcome.

The disappointing results of these clinical studies in ARF are in contrast to the very positive results in equivalent animal models. These differences are difficult to explain. It seems unlikely that there will be additional studies to test rhIGF-I in human ARF, although the lack of other candidate drugs suggests that IGF-I does deserve additional testing in humans.

**Chronic Renal Failure.** No drug has been approved for use in patients with CRF and ESRD to stimulate renal function or to delay the need for dialysis (64). The positive effects of rhIGF-I on renal function in healthy subjects led to several studies in CRF patients. Initial studies with high doses of rhIGF-I (100 µg/kg twice a day) increased renal function for several days but caused serious side effects (65,66). Recently, studies by Vijayan et al. (67) showed in patients with ESRD that efficacy could be maintained and side effects could be reduced with the use of an intermittent treatment regimen (4 d on treatment, 3 d off treatment) for rhIGF-I (50 µg/kg per d). This approach was well tolerated and resulted in a sustained improvement in renal function, which may be related to the IGFBP’s being relatively unaffected by this mode of delivery. In other human studies, large rises in IGFBP-2 seem to be related to overdosing and the occurrence of side effects (68).

Additional rhIGF-I treatment studies, particularly in CRF in children, seem justified. However, the current limited interest by pharmaceutical companies and the lack of availability of clinical grade rhIGF-I make this unlikely.

**Combination Treatment with GH Plus IGF-I or IGF-I Plus IGFBP-3**

Studies of combinations of hormones, in animals with the use of GH plus rhIGF-I (29,56) or in humans with rhIGF-I plus IGFBP-3 (69), suggest that there may be advantages in terms of efficacy and safety for combination therapy. The combination of rhGH plus rhIGF-I has been tested in catabolic states in adults (55) but has not been tested as a growth-promoting agent in pediatric patients. Animal studies suggest that combined treatment is more effective as a growth-promoting agent in experimental uremia (29,56). In catabolic humans, an initial study of the combination of rhGH plus rhIGF-I (both given once daily) suggested a beneficial anabolic effect (55). However, a second study, in which the rhGH was given twice daily (and at half the dose), failed to show a beneficial effect in patients with AIDS-associated wasting (54). The combination of rhIGF-I plus IGFBP-3 is being tested in humans (69), but as yet no growth studies in pediatric patients have been reported, perhaps because only an intravenous formulation has been available. The combination of rhGH plus rhIGF-I remains the most attractive untested therapeutic option for treating pediatric growth disorders. In the near term, human studies with rhGH plus rhIGF-I seem unlikely, as pharmaceutical companies do not seem to be interested in exploiting this combination.

**IGF Displacers**

The concept of activating the IGF axis, or increasing endogenous IGF-I bioactivity, has been proposed as a potential treatment modality. The idea is that by displacing bound IGF-I from IGF-binding proteins, the levels of “free” IGF-I should increase and thereby activate IGF receptors (Figure 3). Two independent studies (70,71) have confirmed this hypothesis with the use of two different IGF-I analogs (Leu24,59,60,Ala31 hIGF-I and Leu24,Ala31 hIGF-I), which bind with high affinity to the IGFBP but do not activate directly the

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GH secretagogues (GHS), which also release GH, can be given orally (75).

**GH-Releasing Peptides**

GHRP or GHS are small synthetic molecules that can stimulate the release of GH from the pituitary (75). GHRP are highly specific for GH release and can be more effective at releasing GH than GHRH. However, compared with GHRH, the GHRP have little effect on GH synthesis and storage, which may limit their efficacy. The GHS receptor (GHS-R) has been cloned (76), and an endogenous ligand was discovered recently and named ghrelin (4). Ghrelin is expressed predominantly in the stomach and other tissues, including the kidney (77).

Therapeutic applications for GHRP have been studied, but no clear efficacy endpoint has been established. Potentially, GHRP could be used in situations in which rhGH is currently approved. A requirement for the use of GHRP is that the hypothalamo-pituitary function be intact (78). It has been proposed that GHRP may be preferential to rhGH treatment in some conditions, as GHRP can induce a more physiologic, pulsatile GH secretion that is self-regulating via GH and IGF-I feedback.

Small-molecule GHRP can be given orally, would be less expensive than rhGH treatment, and therefore seem attractive for treating some forms of growth failure. After the discovery of ghrelin and its receptor, it is possible that new indications for GHRP will be discovered. In renal failure, in which GH secretion is already increased, it seems unlikely that GHRP would be a preferred form of therapy.

**GH-Receptor Antagonists and Somatostatin Analogues**

Several studies that used animal models of diabetes mellitus found a relationship between elements of the GH/IGF axis and both early and late renal deterioration (79). Diabetes-associated kidney damage is reduced in genetically modified animals that either have a disrupted GH receptor gene or overexpress a GH antagonist (80,81). GH antagonists, which are GH mutant molecules that bind only to one GH receptor, prevent GH receptor dimerization and receptor activation. The administration of GH antagonists has been shown to prevent renal disease in animal models of diabetic nephropathy (82). Similar effects were seen when endogenous GH was suppressed with the use of long-acting somatostatin analogues (79).

**Conclusions**

The success of recombinant DNA technology has made GH widely available for the treatment of growth disorders. Advances in our understanding of the endocrinology of growth have produced new ways of manipulating the GH/IGF axis in renal failure. This has led to new potential treatment modalities that could affect body growth, anabolism, renal function, and even renal disease.

One reason that new treatment regimens are needed is that renal failure is not a disorder of GH deficiency but a derangement of the GH/IGF/IGFBP system, resulting in decreased effects of endogenous GH and IGF-I. The need for new treat-
mements has been highlighted recently by the questioning of the safety of rhGH treatment in critically ill adults. Two placebo-controlled, double-blind clinical trials showed that rhGH treatment in adults had lethal, acute side effects (45). The causes of the lethal effects of rhGH or the organs involved are as yet ill-defined, making it very difficult to proceed with some indications for rhGH treatment, such as congestive heart failure.

In pediatric patients, rhGH is a safe treatment. However, because we do not yet understand why rhGH treatment had lethal effects in critically ill patients, there is no way to identify patients who are at risk or markers that can be used to predict when adverse consequences will ensue from rhGH treatment.

Most of the effects of GH depend on its pattern of administration. Therefore, the lethal side effects of rhGH also may depend on its pattern of administration. Research is needed to establish the relative safety of different means of manipulating GH levels, such as depot rhGH preparation or GHS. It is possible that stimulating endogenous pulses of GH, with the use of a GH releaser, is safer than giving injections of a GH preparation.

Molecules that act as antagonists at the GH receptor show efficacy in preventing renal damage in animal models of diabetic nephropathy and are likely to be tested in humans.

An obvious alternative to the use of GH or compounds that release GH for growth promotion is the manipulation of the IGF-I axis. Unfortunately, rhIGF-I treatment has not been tested for growth promotion in pediatric CRF patients, in whom it may increase renal function and delay the need for dialysis or transplantation. Safety has been a concern for rhIGF-I treatment. An intermittent pattern of rhIGF-I administration seems to produce a sustained renal response with reduced side effects in adult CRF patients. It is likely that an optimal balance between safety and efficacy on body growth can be achieved with the use of the combination treatment of rhGH and rhIGF-I, particularly in renal failure, as animal studies have shown that in combination they cause at least additive growth responses. However, the future use of rhIGF-I in clinical studies is uncertain, given the current limited interest by pharmaceutical companies.

Binding proteins for IGF-I are targets for drug development. The administration of IGFBP-3 plus rhIGF-I is being tested in humans, but it seems unlikely that this combination will be used widely to promote growth in children. New strategies aimed at increasing endogenous levels of free, bioactive IGF-I show promise as high IGFBP levels probably mediate most of the relative IGF resistance in renal failure. A mutated form of IGF-I that binds to IGFBP but not to IGF receptors (Figure 3) caused growth promotion and affected renal structure and function in animals. Novel peptides, termed IGF displacers, which bind to IGFBP and displace IGF-I, also have been developed. It is hoped that a molecule of this type eventually will be tested in humans.

The success of rhGH as a drug has led to a large research effort and has produced a long list of new approaches to manipulating the GH/IGF axis in the laboratory and the clinic. In the future, it is likely that combinations of hormones will be used to adjust or correct the endocrine abnormalities that cause disordered growth. Children with CRF and children with isolated GH deficiency both show reduced stature. However, their GH/IGF axes are disordered in very different ways. At present, rhGH treatment is used in both cases. It seems logical that a child with CRF and a child with isolated GH deficiency should receive different and tailor-made treatments to correct their GH/IGF system. For the foreseeable future, GH will remain the cornerstone of treatment, but in the future, treatment will be tailored with other compounds, such as IGF-1, being added in a cocktail to produce an optimal growth response.

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