Growth Hormone in Renal Transplantation—The Mode of Action, Animal Studies, and Clinical Use

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ABSTRACT

During circulation, growth hormone (GH) is bound to about 50% by the high-affinity, low-capacity GH-binding protein (BP). GHBP represents the extracellular binding domain of the GH receptor and modulates the action of GH. After binding to its receptor, GH induces the local production of insulin-like growth factor 1 (IGF-1) by autocrine and paracrine mechanisms. In uremia, the plasma GH-binding activity is low and does not get up-regulated by recombinant human GH treatment, which is in contrast to the experience in short, normal children. There is evidence that hepatic IGF-1 production is low, whereas the serum concentration of IGF-binding protein 3 (IGF-BP3) and other IGFBPs is increased because of the reduced renal clearance of the low-molecular-weight fragment of IGF-BP. This results in the reduced bioavailability of free IGF-1 and reduced IGF bioactivity. There is a strong interaction between GH and corticosteroids. Corticosteroids suppress growth by reducing the food efficiency ratio (weight gain per food intake), reduce pituitary GH secretion, and decrease the local production of and cell responsiveness for IGF-1. The growth-depressing and catabolic effects of corticosteroids can be counterbalanced dose dependently by recombinant human GH in animal experiments, and growth can be improved in corticosteroid-treated renal allograft recipients with and without normal renal function. It is not clear at this time to what extent GH may induce acute or chronic rejection crises.

Key Words: Chronic renal failure, renal transplantation, growth hormone, insulin-like growth factor, resistance to growth hormone

Although growth hormone (GH) has been identified for decades as essential for normal growth (1), relatively little is known about the mechanisms of its action on target cells. GH is secreted from the hypophyseal gland in pulses as a result of the mutual action of hypothalamic releasing and inhibiting hormones (2). As a consequence, its target cells are exposed to the hormone intermittently and would be expected to be programmed for optimal physiological response.

The cellular mechanisms involved in the processing of GH and its receptor start with the formation of a hormone receptor complex. The GH receptor status of target (liver) cells can be measured by determining somatotropic binding sites in cell membranes in vitro (3, 4). There is evidence that in vivo measurements of the GH-binding activity in the serum reflect the GH receptor status to a certain degree (5). Leung et al. demonstrated that the sequence of the rabbit GH-binding protein (GHBP) is identical to the end-terminal sequence of the GH receptor (6). Consequently, it is anticipated that the high-affinity, low-capacity GHBP represents the extracellular binding domain of the GH receptor (7, 8).

After the binding of GH to its receptor, the GH receptor complex is internalized into the cell and activation of intracellular signals occurs. At the same time, the cell membrane becomes refractory and GH binding decreases markedly until a new supply of receptors arrives from de novo synthesis or from recycling of processed receptors (8). This cycle seems to be in harmony with the secretory pattern of GH from the pituitary. Whereas the acute administration of GH induces down-regulation of the receptor, chronic exposure to GH induces up-regulation, at least in the hypopituitary state (9, 10).

For the growth cartilage, it seems that GH directly stimulates the differentiation of prechondrocytes of young differentiating cells after binding at their GH receptors (11, 12). During the process of cell differentiation, cells directly stimulated by GH become responsive to (circulating) insulin-like growth factor 1 (IGF-1). At the same time, the gene encoding for IGF-1 is expressed in the differentiating cells, which results in the local production of IGF-1. The locally produced IGF-1 subsequently interacts with receptors on the proliferating chondrocytes by autocrine or paracrine mechanisms (11). It appears that GH stimulates the growth of other tissues by identical mechanisms (13).

Body growth is not exclusively stimulated by GH. It...
seems rather that GH is the major determinant for growth only from the second year of life until puberty, whereas during the first year of life, growth is mainly determined by nutrition (14), and during puberty, sex hormones become additional important determinants (15). This may have implications for the expected therapeutical success of treatment with recombinant human (rh) GH.

RESISTANCE TO GH IN CHRONIC RENAL FAILURE

In uremia, the basal serum concentration of GH is increased (16), and the stimulated excretion of GH is exaggerated (17). This has been confirmed by our group, who analyzed stimulated GH secretion by deconvolution analysis (unpublished). When we analyzed a spontaneous nocturnal GH secretion, the mean integrated GH concentration was also significantly elevated in dialyzed children, whereas the nocturnal GH production rates of renal patients did not differ from those in healthy controls. The discrepancy between both findings is explained by the significantly higher GH half-life in the serum of dialyzed children (38.9 ± 11.2 min) versus that in the serum of controls (19.2 ± 14.4 min).

The specific binding of $^{125}$I GH on hepatic cell membranes is reduced in uremia; this was first reported by Finidori et al. in 1980 (3). Reduced GH-binding activity in the serum was reported for three patients with chronic renal failure by Baumann, et al. in 1989 (18). This observation was confirmed by our group in a larger number of children (19). According to these investigations, it seems that the GH-binding activity in the serum of dialyzed children is more reduced than that in children with chronic renal failure on conservative treatment. If one anticipates that the GHBP in the circulation reflects the GH receptor status at the cellular membrane of the liver, one might conclude that the GH receptor status is low in uremia. Although it is expected that the long-term application of GH up-regulates the GH receptor, no increase of the GH-binding capacity of serum was noted in children with chronic renal failure treated with rhGH (19).

In accordance with these findings, strong evidence exists that the hepatic production rate of IGF-1 is reduced in uremia (20). This might not be suspected, primarily if one looks to the serum concentration of IGF-1, which is measured, in our experience, in the low normal range in dialyzed children. The serum concentration of the main IGF carrier protein in IGF-BP3, however, is about four times increased because of reduced renal clearance. If one anticipates a normal production rate of IGF-1, one would expect an increased serum concentration of IGF-1 in the presence of an increased concentration of IGF-BP3. This is not the case. Consequently, a low production rate of and an increased binding activity for IGF-1 within the serum results in a decreased bioavailability and bioactivity for IGF-1 (21). The local production of IGF-1 has not been measured in the uremic organism, but it might be reflected by measurements of the hepatic (circulating) IGF-1.

It has been claimed that elevated serum concentrations for another IGF-binding protein, e.g., IGF-BP1, would be the major determinant for reduced bioavailability of IGF-1 in uremia (22). In fact, IGF-BP1 serum concentration is markedly increased in the uremic serum. The molar serum concentration of IGF-BP1, however, is much lower than that of IGF-BP3, and IGF-BP3 usually binds and transports more than 95% of circulating IGF-1. Therefore, the increased concentration of IGF-BP1 in uremia does not seem to contribute substantially to an increased IGF-binding capacity. Rather, IGF-BP1 seems to have a role quite distinct from that of IGF-BP3. Its concentration changes rapidly (circadian rhythm). It is high in the fasting state and low after a glucose load (23). This gives evidence for its role as a regulator of glucose metabolism.

POSSIBLE MECHANISMS FOR THE GROWTH-STIMULATING EFFECT OF rhGH IN UREMIA

It has been shown in animal studies that uremic resistance to GH can be overcome by rhGH in supraphysiological doses (24). One of the fascinating results was the fact that improvement of growth was accompanied by a normalization of food conversion ratio, e.g., weight gain per food intake, which was highly reduced in nontreated uremic animals (Table 1).

The mechanisms by which rhGH has these positive effects are not completely clear. The GHBP concentration is not increased by exogenous rhGH (19), which is in contrast to the experience in children with hypopituitarism (25). The IGF-1 serum concentration is markedly raised by rhGH treatment, and

<table>
<thead>
<tr>
<th>TABLE 1. Effect of rhGH in uremic rats</th>
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<tbody>
<tr>
<td>Length Gain (mm)</td>
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<tr>
<td>------------------</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Control + GH</td>
</tr>
<tr>
<td>Uremia</td>
</tr>
<tr>
<td>Uremia + GH</td>
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</tbody>
</table>

* rhGH was given twice daily in a total dose of 10 IU/kg/day for 2 wk; N = 8 animals per group. Food conversion ratio (weight gain [in grams] per food intake [in grams]) was normalized by rhGH treatment in uremic animals. The reduced weight gain of uremic animals compared with solvent-treated control animals is the result of spontaneously reduced food intake, which was not normalized by rhGH.

b $p < 0.05$; difference between GH versus solvent.
the ratio between IGF-1 and its BP is improved, resulting in normalization of somatomedin bioactivity (21). Whether this is the main mechanism and whether this mechanism also exists with respect to the local production of IGF-1 and its BP remains to be clarified. In view of this, it is important to notice that exogenous rhIGF-1 is able, like exogenous GH, to stimulate growth and to improve the food conversion ratio in uremic rats (Table 2).

## THE RATIONALE FOR rhGH TREATMENT IN CHILDREN WITH RENAL TRANSPLANTATION

Children with renal allografts often do not grow normally despite near normal GFR. This is attributed mainly to the growth-suppressing effect of corticosteroid treatment given for the prevention of rejection episodes. The effects of corticosteroids on growth appear to depend on their concentration at the site of action. In physiological concentrations, corticosteroids positively modulate the responsiveness of cells to the anabolic effects of exogenous IGF-1 (26) and regulate the basal activity and hormone responsiveness of osteoblasts (27). They also up-regulate receptors for various hormones like 1,25(OH)2D3 (28). Whether this mechanism also exists with respect to the site of action. In physiological concentrations, corticosteroids positively modulate the responsiveness of cells to the anabolic effects of exogenous IGF-1 (26) and regulate the basal activity and hormone responsiveness of osteoblasts (27). They also up-regulate receptors for various hormones like 1,25(OH)2D3 (28) and parathyroid hormone (29). Pharmacological doses of corticosteroids decrease bone formation and interfere with skeletal growth at the sites of growth cartilage (30,31). In vitro, cortisol inhibits the production of IGF-1 in liver and growth cartilage (32) cells. In vivo, decreased somatomedin bioactivity was reported in corticosteroid-treated patients (33), in children with renal allografts (34), and in corticosteroid-treated rats (35). In addition, the suppression of GH secretion during the night has been observed in children treated with corticosteroids (36). It is likely that the inhibitory action of glucocorticosteroids on GH secretion in vivo is mediated via altered hypothalamic somatostatin tone (37).

In addition to the above-mentioned effects of corticosteroids on GH secretion and skeletal growth, corticosteroids have a catabolic action, resulting in decreased muscle mass, which is usually masked in men by an increase in adipose tissue and Cushing's syndrome. In animal experiments, we have tested whether the growth-depressing and catabolic effects of corticosteroids can be compensated for by concomitant treatment with rhGH (38). The negative effects of corticosteroids on growth could be counterbalanced in a dose-dependent way by rhGH (an example is given in Table 3). Taking all reported results together, it might be that the production and responsiveness of cells for IGF-1 are a common pathway for both GH and corticosteroids, which may explain many of the antagonistic effects of both substances.

It is well known that the somatomedin (IGF) bioactivity is reduced in corticosteroid-treated children with renal allografts (34). When we measured the serum concentration of IGF-1 in transplanted children with a median GFR of 47 (range, 23 to 118) mL/min/1.73 m² and a low-dose corticosteroid treatment, this concentration was not reduced. IGF-BP3 concentration, however, was significantly increased (39). It is very likely that the high concentration of IGF-BP3 reduces the concentration of active unbound IGF-1, which results in decreased IGF bioactivity. When we treated those patients with 30 IU of rhGH/m²/wk, the IGF-1 serum concentration was raised by four SD without a significant rise in the concentration of IGF-1.

### TABLE 2. Effect of exogenous rhIGF-1 on food conversion ratio in experimental uremia

<table>
<thead>
<tr>
<th>Cumulative Length Gain (cm)</th>
<th>Cumulative Weight Gain (g)</th>
<th>Food Conversion Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1.96 ± 0.02</td>
<td>23.0 ± 0.9</td>
<td>0.14 ± 0.01</td>
</tr>
<tr>
<td>Uremia 1.54 ± 0.10</td>
<td>9.8 ± 2.3</td>
<td>0.05 ± 0.03</td>
</tr>
<tr>
<td>Uremia + IGF 2.27 ± 0.07b</td>
<td>17.8 ± 1.0b</td>
<td>0.11 ± 0.04b</td>
</tr>
</tbody>
</table>

*rhIGF-1 was given twice daily in a total dose of 300 μg/150 g/day for 2 wk; N = 8 animals per group. The food conversion ratio (weight gain [in grams] per food intake [in grams]), which was only reduced in solvent-treated uremic animals, improved significantly under treatment with rhIGF-1.

*P < 0.05; difference between IGF versus solvent in uremia.

### TABLE 3. Effect of concomitant treatment with methylprednisolone (MP) and rhGH on growth in uremic rats

<table>
<thead>
<tr>
<th>Cumulative Length Gain (mm)</th>
<th>Cumulative Weight Gain (g)</th>
<th>Weight Gain Per Food Intake (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uremia solvent</td>
<td>3.57 ± 0.53</td>
<td>29.0 ± 6.8</td>
</tr>
<tr>
<td>Uremia + MP</td>
<td>2.10 ± 0.65b</td>
<td>2.7 ± 6.9b</td>
</tr>
<tr>
<td>Uremia + MP + rhGH</td>
<td>3.07 ± 0.45</td>
<td>27.7 ± 4.6</td>
</tr>
</tbody>
</table>

*MP was administered in a dose of 6 mg/kg/day in two divided doses s.c.; rhGH was administered in a dose of 10 IU/kg/day in two divided doses s.c.; N = 10 animals per group; the duration of the experiment was 2 wk. The catabolic effects of MP, best seen from the ratio of weight gain (in grams) per food intake (in grams), were obliterated by concomitant treatment with rhGH.

*P < 0.05; difference between MP versus solvent and versus MP + rhGH.
At the same time, body growth was markedly improved, as reported below.

**GH TREATMENT OF CHILDREN WITH RENAL ALLOGRAFTS IN EUROPE**

There are three recent reports on the rhGH treatment of prepubertal and pubertal children with renal allografts (39–41). The therapeutic results were very similar in all three studies. The median height velocity, expressed as centimeters per year, more than doubled in prepubertal children. The height velocity, expressed as standard deviation score (SDS) for chronological age, was negative at baseline and became positive in nearly all patients (Table 4).

In contrast, the effect of rhGH on growth in pubertal children was rather disappointing. Height velocity expressed as centimeters per year increased, but if one looks at the data of height velocity expressed as SDS for chronological age, it becomes clear that the improvement of growth under rhGH treatment is most likely due to the pubertal growth spurt and cannot be counted as a therapeutic success. In the Heidelberg study (Figure 1), we did not observe an improvement of height SDS after a treatment period of 1 yr.

**POSSIBLE SIDE EFFECTS OF rhGH IN CHILDREN WITH RENAL ALLOGRAFTS**

**Induction of Rejection Crises**

GH exerts various actions on the immune system. In animal experiments, the removal of the pituitary gland results in the atrophy of the thymus and the secondary lymphoid tissue (42). In addition, impaired humoral and cell-mediated immune responses have been found in hypophysectomized mice and rats, suggesting a role for the pituitary gland in the maintenance of immunocompetence (43). GH treatment was able to prevent thymus involution and normalized immune responses in these animal models (44).

For the treatment of transplanted children, the

<table>
<thead>
<tr>
<th>Author (Ref. No.)</th>
<th>No. of Patients</th>
<th>Baseline 1 yr Treatment</th>
<th>Baseline 1 yr Treatment</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>cm/yr</td>
<td>(SDS chronological age)</td>
</tr>
<tr>
<td>Johansson et al. (40)</td>
<td>15 prepubertal</td>
<td>2.6 (0.9–6.1) 6.2 (3.0–10.8)</td>
<td>-2.8 (-6.6--0.7) 0.2 (2.6+5.6)</td>
</tr>
<tr>
<td></td>
<td>13 pubertal</td>
<td>3.8 (0.5–6.3) 6.7 (3.7–8.7)</td>
<td>Data not given (height SDS did not improve)</td>
</tr>
<tr>
<td>Rees et al. (41)</td>
<td>6 prepubertal</td>
<td>2.0 (0.8–4.7) 5.9 (2.7–10.9)</td>
<td>-2.0 (-3.5--0.8) 0.6 (-1.4+2.8)</td>
</tr>
<tr>
<td></td>
<td>6 pubertal</td>
<td>3.0 (0.5–6.3) 6.2 (4.5–7.0)</td>
<td>-1.0 (-2.3+1.0) 3.5 (+0.2+11.4)</td>
</tr>
<tr>
<td>Tönshoff et al. (39)</td>
<td>8 prepubertal</td>
<td>2.2 (0.5–5.8) 8.2 (4.4–9.2)</td>
<td>-1.5 (-0.2--5.2) 2.8 (+0.2+7.7)</td>
</tr>
<tr>
<td></td>
<td>4 pubertal</td>
<td>2.4 (1.7–5.5) 5.4 (0–10.6)</td>
<td>-1.5 (-0.3+2.2) 0.5 (-3.2+1.5)</td>
</tr>
</tbody>
</table>

Figure 1. Growth velocity before and during rhGH treatment in children with renal allografts. Growth velocity is expressed as SDS for chronological age. Whereas a significant response to rhGH is seen in prepubertal children, no effect was noted in pubertal children.
tion progressed more rapidly than during the year before the start of rhGH treatment. Definite answers can only be found in large, randomized, prospective, multicenter studies with a run-in period of at least 1 year and a follow-up of about 2 yr.

Induction of Malignancy

The excess of GH in acromegaly is not associated with an increased rate of malignancy, apart from polyposis of the colon in a few cases (45). A recent review deals with the incidence of acute leukemia in GH-deficient children treated with GH in relation to the general population (46). A slightly increased incidence of acute leukemia in GH deficiency treated with GH has been stated only in Japan, and no certain association with the GH treatment has been documented. Whether this increased risk is actually linked to GH treatment, to the preexisting hypopituitarism, or to other environmental factors remains unclear. Nevertheless, the Lawson Wilkins Pediatric Endocrine Society recommends particular caution for GH treatment in patients with a primary risk of malignancy such as myelodysplastic syndromes or Fanconi anemia or in patients who have received irradiation therapy or who have Down’s syndrome. The troubling question that cannot be answered today is whether GH treatment implicates a higher risk for leukemia and malignancy in renal patients who have received cytotoxic agents such as cyclophosphamide or who are under long-term immunosuppression because of renal transplantation.

REFERENCES


