Growth hormone, insulin-like growth factor and the kidney

Structure and biochemistry

Human growth hormone is a protein encoded by a gene cluster composed of five loci found in a 50 kb portion of chromosome 17 [1]. One locus encodes the two main circulating variants of human growth hormone protein, the most abundant form of human growth hormone being a single polypeptide of 191 amino acids with two disulfide bridges and molecular weight of 22,000 daltons or 22 kD. Alternative mRNA splicing gives rise to a 176 amino acid peptide, the 20 kD human growth hormone variant, which accounts for 5 to 10% of total pituitary growth hormone [2]. Another locus of the growth hormone gene cluster encodes an additional growth hormone variant, different by 13 amino acids from the main 22 kD growth hormone peptide. This growth hormone peptide is produced by the placenta and represents the predominant circulating form of growth hormone in late pregnancy [3]. The other three loci correspond to chorionic somatomamtomotropin genes.

Up to 50% of circulating serum growth hormone is bound to proteins [4, 5]. The 22 kD growth hormone peptide is vehiculated by a high-affinity binding protein which is a single chain glycoprotein whose structure corresponds to the extracellular domain of the growth hormone receptor [6]. This growth hormone binding protein may be originated from proteolytic cleavage of the membrane growth hormone receptor and/or be directly synthesized from an alternatively spliced messenger RNA (mRNA) produced from the same gene as the receptor [7, 8]. Truncated forms of growth hormone receptor mRNA have been identified in animal species having analogous high affinity growth hormone binding protein such as rat [9], mouse [10, 11], and rabbit [12]. The great majority of circulating 20 kD variant of growth hormone is vehiculated by a low-affinity growth hormone binding protein which is not related to the growth hormone receptor [13, 14].

The mature human growth hormone receptor consists of 620 amino acids with an extracellular domain of 246 amino acids and the transmembrane and intracellular domains containing 24 and 350 amino acids, respectively [15]. It has been found widely distributed in a variety of tissues from different species of animals, the liver being the tissue containing the highest growth hormone receptor concentrations [16, 17]. There seems to be only one growth hormone receptor gene [18–20] and it has been cloned from hepatic tissue.

Previously known as somatomedin C, insulin-like growth factor I (IGF-I) is a single chain peptide of 70 amino acids and molecular weight of 7.5 kD [21, 22]. Its structure is almost identical in different mammalian species and is closely related to that of insulin and insulin-like growth factor II (IGF-II) [23]. IGF-I is encoded from one single gene located on chromosome 12 [24, 25]. Human and rat IGF-I genes contain at least five exons, separated by four introns ranging in size from 1.9 to 50 kb [26]. Several different IGF-I mRNAs result from alternative processing of the primary gene transcript [27]. In rat liver, at least 12 different IGF-I mRNAs have been identified [28]. In humans, the IGF-I gene is transcribed and processed into two types of mRNA, which are translated in two different IGF-I precursor peptides of 153 and 195 amino acids [21]. Little is known on the synthesis of the IGF-I peptide from these precursors.

Circulating IGF-I is vehiculated by carriers called binding proteins (IGFBP) in such a way that virtually no free IGF-I is measurable in serum and less than 1% of IGF-I activity in serum is unbound [20, 29]. Six classes of IGFBP have been identified in humans [30–32]. IGFBP-3 was first isolated from human serum and comprises two glycosylated binding proteins migrating at 41.5 and 38.5 kD and, in association with IGF-I or IGF-II and an acid-labile non-IGF binding subunit of approximately 85 kD, forms a high molecular weight ternary complex of 150 kD. The other three types of IGFBP, IGFBP-1, -2 and -4, are proteins with a molecular weight of approximately 30 kD, 34 kD, and 24 kD, respectively, that associate with IGFs to form binary complexes of about 40 kD.

The IGF-I receptor is a tetrameric glycoprotein, structurally similar to the insulin receptor, located on the plasma membranes of target cells. It is composed of two alpha-subunits containing the binding domain and two beta-subunits containing tyrosine kinase domains. Phosphorylation of the beta-subunit, which occurs as a result of coupling of IGF-I to the alpha-subunit, is likely related to the transmission of the IGF-I signal across the plasma membrane, although the intracellular signaling mechanisms are not clearly determined [33, 34].

Neuroendocrine control of growth hormone secretion

The pulsatile nature of growth hormone secretion is one of the most notable and important characteristics of growth hormone physiology. A typical pattern of growth hormone concentrations in the blood is one of conspicuous pulses superimposed upon a background of relatively low tonic secretory concentrations. In laboratory animals, there is a clear sexual dimorphism of growth hormone secretion [35]. Male animals show extremely low background concentrations with high amplitude pulses occurring at regular intervals of approximately three hours. Female animals show a significantly higher background concentration with moderate-sized pulses occurring at random intervals. The mechanisms which translate these differences in pulsatile growth hormone secretion to sexual differences in body growth remain to be determined.

The ultimate source of control of the pulsatile growth hormone rhythm is the brain, by means of neurohormones. The final common pathway of neuronal connections is located in the
hypothalamus. Specific regulatory nuclei include the ventromedial and arcuate nuclei for growth hormone releasing hormone, and the periventricular nucleus for the inhibitory neurohormone, somatostatin [36, 37]. Axons of the neurosecretory neurons converge on the median eminence. The neurohormones are secreted into perivascular spaces around the primary capillary plexus of the hypophyseal portal system. Blood borne neurohormones are carried by the portal veins to the secondary capillary plexus in the anterior pituitary gland where they cause the synthesis and release of growth hormone, or the inhibition of its secretion (Fig. 1).

Growth hormone releasing hormone (GHRH) is a peptide presenting in both 40 and 44 amino acid forms. The initial purifications were from ectopic GHRH produced by tumors of the pancreas [38, 39]. These forms were later found to be nearly identical to human hypothalamic GHRH [40]. Rat hypothalamic GHRH shows 67% homology with the 44 amino acid human GHRH [41]. The peptides act via receptors on the membranes of the growth hormone-producing cells. These “somatotropes” make up slightly more than 35% of the total number of anterior pituitary cells [42]. Cyclic AMP is thought to be the primary second messenger for the stimulation of growth hormone release, although calcium-dependent mechanisms are also known to be involved [43]. Besides release of growth hormone, GHRH also stimulates growth hormone synthesis by means of increased gene transcription [44].

The low concentrations of growth hormone between pulses is most likely the result of tonic somatostatin output from the hypothalamus. This neurohormone was initially purified as a tetradecapeptide [45], but may be more active as a 28 amino acid form [46]. The mechanism of action is thought to be by means of inhibition of the cAMP system, but might also involve a decrease in membrane permeability to calcium [47].

Once secreted by the pituitary gland, growth hormone (Fig. 1) causes its growth promoting effects indirectly by the production of insulin-like growth factor-I (IGF-I). Although IGF-I is produced in large quantities by the liver in response to growth hormone, there is a strong probability that growth hormone effects are mediated by the local production of IGF-I at the target tissues [48]. IGF-I would then act by a local paracrine or autocrine effect on the tissues themselves. IGF-I is also known to have a potent negative feedback effect on growth hormone secretion both by an action on the hypothalamic control mechanisms and a direct negative effect on pituitary gland secretion of growth hormone [49].

Recent studies have shown that infusion of heterologous growth hormone causes a synchronization of endogenous growth hormone pulsatile release [50]. The negative feedback of growth hormone on its own secretion is thought to occur via its influence on the output of GHRH and somatostatin from the hypothalamus [51, 52]. From these studies, and others, it can be hypothesized that the rhythm of growth hormone secretion involves a tonic secretion of somatostatin to produce the low background concentration of growth hormone, with occasional bursts of GHRH secretion producing the growth hormone pulses. The GHRH bursts may or may not be accompanied by a coordinated decrease in the output of somatostatin. The potential for the neural integration of these signals by means of interactions of blood-borne growth hormone and IGF-I, as well as the neurohormones themselves by means of synaptic contacts certainly exists, but remains to be clearly defined.

Adrenergic mechanisms within the hypothalamus are known to modulate growth hormone secretion. Alpha-2 receptors are thought to be involved in the stimulation of growth hormone secretion by either the stimulation of GHRH output [53] or inhibition of somatostatin release [54]. Beta-adrenergic systems are involved with growth hormone control both within the hypothalamus and directly at the level of the pituitary gland. By means of cyclic AMP (cAMP) production, stimulation of the beta-adrenergic system, like that of GHRH itself, results in growth
hormone release. This effect is relatively small, however, in comparison to beta-adrenergic inhibition of growth hormone release [55]. This latter effect is probably the result of somatostatin secretion from the hypothalamus [56]. The inhibition of growth hormone release by the beta-adrenergic system is the basis for the augmentation of growth hormone release by beta-blockers, such as propranolol and atenolol [57].

Steroid hormones are also known to be important modulators of growth and growth hormone secretion. With respect to sex steroids, it is commonly accepted that gonadectomy of the male leads to decreased growth, while gonadectomy of the female is likely to facilitate growth [35]. The mechanisms underlying these effects, however, are anything but clear. Concerning growth hormone secretion, removal of the testes decreases GHRH responsiveness of dispersed pituitary cells in vitro [58]. This can be at least partially reversed by treatment with testosterone. Estrogen treatment of gonadectomized males leads to a decreased GHRH responsiveness of the pituitary cells in vitro. On the other hand, low dose estrogen administration has the capability to increase the growth hormone response to pharmacological stimuli in humans [59]. This effect might be related to previous findings of increased numbers of somatotropes in pituitary glands of estrogen-treated animals [60], as well as to increased growth hormone mRNA expression [61] and growth hormone synthesis [62]. Androgens, on the other hand, might augment growth hormone secretion by increasing mRNA for GHRH in the hypothalamus [63]. The growth hormone content of pituitary glands from male animals is also known to be significantly larger than that of females. In general, it might be concluded that the effects of male sex steroids are facilitatory to growth hormone secretion and growth, secondary to the hypothalamic secretion of GHRH as well as by augmentation of growth hormone content of the pituitary gland. Estrogenic effects are less straightforward. Whereas ovariectomy leads to the potential for increased growth, and estrogen treatment can decrease GHRH responsiveness of pituitary cells in vitro, estrogen in low doses augments the growth hormone response to pharmacological stimuli.

Adrenal steroids also have significant effects on growth and growth hormone secretion. Chronic glucocorticoid treatment is desirable for its immunosuppressive effects, but is also well known to significantly retard body growth [64]. A consensus is now being reached that growth hormone responsiveness to releasing stimuli is most commonly inhibited in vivo [65]. This is probably due to glucocorticoid stimulation of somatostatin secretion from the hypothalamus. An interesting paradox is that pituitary cells from glucocorticoid-treated animals are clearly facilitated in their response to GHRH [66, 67]. Another interesting phenomenon is that acute treatment with glucocorticoids leads to a spontaneous release of growth hormone within a fairly brief period of time [68]. The long-term effect, however, remains one of inhibition. In this respect, glucocorticoids probably inhibit growth by a long-term inhibition of growth hormone secretion by means of increased somatostatin secretion from the hypothalamus. But acute stimulation of growth hormone release and facilitation of pituitary gland growth hormone secretory mechanisms is also an expected paradoxical effect of these steroids. The possibility that glucocorticoids might influence GH target tissue by changing levels of GH receptors or its mRNA [69] and/or by changing IGF-I production should not be overlooked.

The relationship of growth hormone secretion to nutrition is also an important aspect of the neuroendocrine control of this hormone. Because the anorexia of uremia gives rise to malnutrition, the effects of nutrition on growth hormone secretion deserves consideration here. Fasting in humans is well known to result in increased growth hormone secretion [70]. This fasting-induced increase also occurs in rabbits [71], pigs [72], gonadectomized sheep [73], and steers [74]. The increased growth hormone output is most likely to be due to a decrease in somatostatin secretion by the hypothalamus [73].

Complete clarification of the mechanisms underlying the relationship of nutrition to growth hormone secretion, however, has not yet been achieved. This is particularly true with respect to understanding the actual growth retardation resulting from fasting and undernutrition. The rat, the model in which many of the relevant studies have been performed, shows a unique response to fasting, that is, a decrease in growth hormone secretion. This condition may actually be highly pertinent to the overall growth retarding effects of undernutrition. Hypothetically, this decrease in growth hormone secretion may be due either to an increase in somatostatin or a decrease in GHRH. Previous studies have shown that neither the content of somatostatin itself [75] nor its mRNA [76] in the hypothalamus is increased by fasting in the rat. Concentrations of somatostatin in the peripheral circulation are known to be increased during fasting, however, and may be due to an increase in gastrointestinal and pancreatic production of the hormone itself [75] as well as its mRNA [77]. Besides these changes in somatostatin in the peripheral circulation, hypothalamic concentrations of GHRH mRNA have been found to be profoundly decreased after fasting [76]. The content of GHRH itself, however, was found to be unchanged. These data indicate that the decrease in growth hormone observed in the rat after fasting might be due to an increase in somatostatin in the peripheral circulation related to changes in the gastrointestinal system, and potentially to alterations in hypothalamic GHRH mRNA.

Other factors might also be involved in growth hormone secretion during fasting. Thyroid hormone is known to be important to the production of growth hormone by pituitary cells [78], and a decrease in triiodothyronine during fasting might be related to the decrease in growth hormone mRNA in the pituitary gland under these conditions [79]. Retinoic acid is also known to act with thyroid hormone to facilitate growth hormone production in pituitary cells [80], and, in this respect, the growth impairment associated with vitamin A deficiency might be related to a decrease in growth hormone production. Disruption of growth hormone secretion may also be related to the growth impairment and decreased IGF-I concentrations observed in deficiencies of lysine [81], potassium [82], and zinc [83], as well as in an excess of selenium [84].

In summary, the pulsatile nature of growth hormone secretion is important to its physiological effects. The brain, more specifically the hypothalamus, controls growth hormone release by a pattern of neurosecretion of GHRH and somatostatin. These hypothalamic mechanisms are profoundly influenced by a number of factors, some of which include growth hormone itself, IGF-I, adrenergic mechanisms, sex and adrenal steroids, and food intake. Along with direct effects of these and other substances on the pituitary gland, the end result is a growth hormone secretory pattern which is significantly related to the course of normal body growth and metabolism.
Table 1. Actions of growth hormone on carbohydrate and lipid metabolism

<table>
<thead>
<tr>
<th>Type</th>
<th>In vitro effects</th>
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</thead>
<tbody>
<tr>
<td>Insulin-like actions (most rapidly)</td>
<td>1. Increased glucose uptake, glucose oxidation, and glucose conversion to fatty acids in adipose tissue, adipocytes and muscle.</td>
</tr>
<tr>
<td></td>
<td>2. Inhibition of adrenaline-stimulated lipolysis in adipose tissue.</td>
</tr>
<tr>
<td>Anti-insulin-like actions (mostly slowly)</td>
<td>1. Transient hypoglycemia in hypophysectomized dog and rat and growth hormone-deficient children.</td>
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<tr>
<td></td>
<td>2. Transient fall in free fatty acids.</td>
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</table>

In vivo effects

1. Decreased glucose oxidation and conversion to fatty acids in adipose tissue from dwarf mice (after 4 hr) and in 3T3 adipocytes (after 24–48 hr).
2. Refractoriness to the insulin-like actions of growth hormone.
3. Increased lipolysis in adipose tissue (after 1 hr).

A. In vitro effects

1. Decreased glucose oxidation and conversion to fatty acids in adipose tissue from dwarf mice (after 4 hr) and in 3T3 adipocytes (after 24–48 hr).
2. Refractoriness to the insulin-like actions of growth hormone.
3. Increased lipolysis in adipose tissue (after 1 hr).

B. In vivo effects

1. Hyperglycemia, especially in dogs.
2. Impaired glucose tolerance.
3. Lipolysis.
4. Resistance to the actions of insulin.

Physiology of growth hormone

Growth hormone is the main regulatory hormone of body's growth and it is also involved in carbohydrate, lipid, and protein metabolism. It is generally accepted that its longitudinal growth stimulating effect is mostly mediated by IGF-I whereas its actions on carbohydrate and fat utilization result from a direct hormonal effect (Table 1) [85].

In vitro studies have shown a different ability of tissues to metabolize free growth hormone. Thus, at neutral pH, human growth hormone is proteolytically degraded by rat skeletal muscle and thyroid gland preparations whereas it is stable in liver and kidney homogenates [86]. In vivo, renal catabolism accounts for about 70% of the plasma turnover of growth hormone in rats [87]. Growth hormone is extensively filtered by the glomeruli but only about 70% of the plasma turnover of growth hormone in rats [87].

Growth hormone is internalized in the intracellular compartment. Twenty-four-hour urinary excretion of growth hormone has been shown to correlate well with serum growth hormone levels in normal prepubertal children but not in those in mid to late puberty [88].

The physiologic role of growth hormone binding proteins (GHBP) is uncertain. The majority of studies have focused on the high affinity growth hormone binding protein because it mediates the major form of circulating growth hormone, the 22 kD peptide. Serum concentrations of GHBP are growth hormone dependent in such a way that they show a pulsatile pattern which parallels that of endogenous serum growth hormone, the great majority of growth hormone pulses being followed by GHBP pulses within 30 minutes in normally growing children [89]. On the other hand, prolonged administration of exogenous growth hormone to growth hormone-deficient children has been shown to induce a sustained elevation of serum growth hormone binding protein concentrations [90]. Mean values of serum growth hormone binding protein are also influenced by an individual's age, the serum concentrations increasing progressively in childhood and reaching adult values after 20 years of age [17]. During puberty, no modification or slight decline of growth hormone binding protein concentrations is observed, probably as a result of the negative effect of sex steroids such as testosterone and estrogens [91, 92]. The function of growth hormone binding protein is likely related to its ability to diminish the amount of free circulating growth hormone and, accordingly, prolong the hormone half-life. Studies in rats [93, 94] have demonstrated that exogenous growth hormone binding protein decreases the degradation rate and extravascular availability of growth hormone. In vivo experiments [4, 95, 96] have also shown that growth hormone binding protein competes with the growth hormone for the occupancy of growth hormone receptor, and the presence of increasing serum concentration of growth hormone binding protein is associated with a decreased ability of growth hormone to bind to growth hormone receptors. In addition, GHBP has also been found in the cytosol and nucleus [97, 98], suggesting a potential modulating effect of the carrier protein on the growth hormone action at the target tissue. It has also been suggested that circulating values of growth hormone binding protein could reflect the status of tissue growth hormone receptor. This might be true for liver but not for other peripheral tissues whose contribution to the total serum concentration of growth hormone binding protein is minimal, if any [6].

Growth hormone receptor is present in most rat tissues, a close correlation having been found between growth hormone binding and the concentrations of growth hormone receptor mRNA [16, 99]. Control of growth hormone receptor gene expression is complex and dependent on tissue-specific, developmental, hormonal, and nutritional factors [15]. Binding of growth hormone induces phosphorylation of the receptor [100, 101]. The further changes occurring in the cell at the molecular level are mostly unknown. It is known that following binding to its receptor, growth hormone is internalized in the intracellular compartment. It was previously thought that intracellular growth hormone was directed toward lysosomal degradation. Recent investigations detecting growth hormone binding protein in the nucleus [98] suggest that nuclear growth hormone receptors may mediate the transcriptional effects of growth hormone, while the membrane growth hormone receptors are responsible for the short-term metabolic actions [102].

Physiology of growth hormone administration

Growth hormone administration transiently increases glucose oxidation by adipocytes [3]. Because this short-term insulin-like effect is physiologically unimportant [103], growth hormone has traditionally been considered as a "diabetogenic" hormone because, in contrast to IGF-1 [104, 105], prolonged administration of growth hormone causes hyperglycemia and lipolysis in the presence of elevated insulin concentrations [102]. In addition, growth hormone-deficient children characteristically tend to be mildly obese and their adipocytes, although reduced in number, contain a higher than normal amount of fat. These anomalies are reversed with growth hormone supplementation. As shown by Salomon et al [106] in adults with growth hormone deficiency and by Rudman et al [107] in men over 60 years old, treatment with human growth
hormone induces changes in body composition such as increased lean body mass and decreased fat mass. Hypercholesterolemia is not an usually observed complication in humans treated with growth hormone [106, 107]. However, elevated serum cholesterol concentrations have been shown in rats having very high growth hormone circulating concentrations as a result of tumor-secreted growth hormone [108]. On the other hand, recent investigations have demonstrated that growth hormone stimulates hepatic synthesis of apolipoprotein-B mRNA, the essential apolipoprotein of chylomicrons, intermediate-, low-, and very low-density lipoproteins, suggesting a role of growth hormone in the regulation of lipid and lipoprotein metabolism.

Growth hormone administration has been shown to stimulate synthesis of IGF-I mRNA in most rodent tissues [21, 109]. Peak concentrations of IGF-I mRNA are achieved three to nine hours after a single growth hormone injection, although the degree of stimulation depends on the tissue and the subclass of mRNA. Nutrition and hormonal factors also influence IGF-I production. In rats, fasting gives rise to reduced number of hepatic growth hormone receptors, and decreased concentrations of both growth hormone receptor mRNA and IGF-I mRNA [110]. The effect of fasting on IGF-I mRNA, IGF-I receptor mRNA, and IGF-I receptor binding is not uniform, differing in kidney, muscle, gastrointestinal tract, testis, and brain [111]. Protein malnutrition reduces hepatic IGF-I mRNA, but by a different mechanism because growth hormone binding to liver is not depressed, suggesting that protein restriction may induce a postreceptor resistance to the growth hormone action [112]. Whatever the underlying mechanism, fasting and malnutrition result in low serum concentrations of IGF-I and a subnormal increment of serum IGF-I concentrations in response to growth hormone administration [112, 113].

Physiology of insulin-like growth factor-1

IGF-I exerts its action at the cellular level by binding to its receptor which undergoes a conformational change that results in activation of tyrosine kinase activity and phosphorylation of specific proteins [33]. IGF-I, IGF-II, and insulin overlap in their receptor specificity. Insulin can bind IGF receptors with approximately 1% the affinity of IGF-I and, in turn, IGF-I and IGF-II can cross react with insulin receptor by approximately 2%. Affinity of IGF-II for the IGF-I receptor is about one third that of IGF-I [23]. In vitro the three peptides stimulate glucose and amino acid uptake, protein synthesis, thymidine incorporation into DNA, and cell proliferation [29]. In vivo, the biological potency of IGFs and insulin differs depending on the type of receptor present on the cell surface. For instance, IGF-I is not a potent stimulator of lipogenesis because adipocytes do not contain IGF-I receptors [23]. Likewise, circulating IGF-I exerts no influence on its hepatic production because normal liver is devoid of IGF-I receptors. On the contrary, hepatic IGF-I receptors have been found in fetus and liver in a state of regeneration, suggesting that, in these conditions, liver growth is influenced by IGF-I action [114, 115]. On the other hand, the stage of development markedly influences the expression of the IGF-I receptor gene because a dramatic decrease of IGF-I receptor mRNA concentrations has been found in rat tissues during postnatal life [116].

The effects of IGF-I on target tissues can be carried out by circulating IGF-I, functioning as an endocrine factor, and by locally produced IGF-I, acting as an autocrine/paracrine factor.

<table>
<thead>
<tr>
<th>Table 2. Potential functions of insulin-like growth factor-I binding proteins (IGFBP)</th>
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</thead>
<tbody>
<tr>
<td>1. Reservoir of active hormone</td>
</tr>
<tr>
<td>2. Maintenance of a constant concentration of hormone</td>
</tr>
<tr>
<td>3. Targeting to specific tissues</td>
</tr>
<tr>
<td>4. Modulation of biological action</td>
</tr>
<tr>
<td>a) Inhibition</td>
</tr>
<tr>
<td>b) Potentiation</td>
</tr>
<tr>
<td>5. Metabolism of the hormone</td>
</tr>
<tr>
<td>a) Protection from degradation</td>
</tr>
<tr>
<td>b) Removal of hormone from tissues</td>
</tr>
</tbody>
</table>

From: HINTZ RL: Role of growth hormone and insulin-like growth factor-binding proteins. *Horm Res* 33:105-110, 1990 (used with permission).

The relative importance of both forms of action varies from tissue to tissue and with the stage of development. Autocrine and paracrine actions are probably more important in tissues with IGF-I receptors and high IGF-I concentrations such as lung, kidney, and ovarian granulosa cells, and where anatomical barriers limit entry of IGF-I from the circulation as in testis and the central nervous system. In these organs, local production of IGF-I appears to be mainly related to processes of tissue hypertrophy and repair [21].

The function of the IGFBP in the metabolism of IGF-I is not well understood (Table 2) [117]. Most of serum IGF-I forms part of the 150 kD complex, whereas a minor fraction is vehiculated into the 40 kD complex, and almost undetectable amounts circulate as free IGF-I. The half-life in serum of these three fractions of IGF-I is different: 12 to 15 hours for the 150 kD material, 20 to 30 minutes for the 40 kD complex, and 10 to 12 minutes for the free IGF-I [31]. These differences suggest varying bioavailability of IGF-I for the different serum fractions. Likewise, only free IGF-I and the 40 kD IGF-I complex enter glomerular ultrafiltrate and are catabolized in the proximal tubule cells [118]. Only 30% of urinary IGF-I is found in the free form [21]. The 150 kD IGFBP and total IGF-I are parallel throughout life with low concentrations of both at birth, rising during childhood and puberty, and declining as age increases [119]. This pattern is the inverse to that found for the 40 kD IGFBP complex which has high concentration early in life, with a decline during childhood, lowest value during puberty and a slight elevation with increasing postpubertal age [120, 121]. Whereas 150 kD IGFBP concentrations are growth hormone dependent, there is an inverse relation between growth hormone production and serum concentrations of the 40 kD complex [122]. Recent reports [105, 123] have shown elevation of serum IGFBP-1 concentrations following recombinant human IGF-I administration in healthy humans, suggesting that this effect is likely mediated by IGF-I induced suppression of insulin concentrations. Insulin may also play a still underdetermined role in the regulation of IGFBP-2 [123].

IGF-I bound to IGFBP-3 in the 150 kD material cannot cross the capillary barrier [31]. Therefore, the 150 kD complex likely serves as a circulating reservoir of IGF-I and controls its bioavailability [32] in such a way that it compensates for the fact that, unlike most peptide hormones, IGF-I is not stored in secretory granules for secretion by exocytosis but is released as it is synthesized. Binding of IGF-I to IGFBP-3 depends on a serum protease whose activity varies acutely in different conditions [120]. The physiological role of the 40 kD IGFBP complex is not clear.
impairment in weight gain in Sprague-Dawley rats made acidic with ammonium chloride ingestion is correlated with inhibition of hepatic IGF-I expression. The data in the pair-fed animals support the possibility that protein/calorie malnutrition may play an important role in this inhibition in pituitary growth hormone secretion and reduced IGF-I expression. However, acidosis inhibits growth hormone in a specific fashion because acidosis does not affect the half-life or the number of pulses of growth hormone [126]. In addition, despite the suppression of hepatic IGF-I mRNA in both acidic and pair-fed animals (Table 3), the hepatic growth hormone receptor mRNA is depressed only in the acidic rats [127].

**Growth hormone/IGF-I axis and the kidney**

The major site of renal synthesis of IGF-I is located at the collecting duct [128–130] where growth hormone enhances IGF-I gene expression [131]. Collecting ducts do not have receptors for IGF-I [131]. Therefore, IGF-I action must be exerted at other sites where IGF-I receptors are present, such as mesangial cells [132–134], and proximal tubular cells [135, 136]. Receptors for growth hormone have also been found in the basolateral membrane of proximal tubule cells [137], suggesting a direct action of circulating growth hormone at this kidney location.

The current availability of biosynthetic human growth hormone has raised enormous interest on the therapeutic benefits of promoting catch-up growth in uremic children, but the potential of growth hormone-induced deterioration of renal function is a concern. This apprehension on the renal effects of growth hormone is in part supported by the fact that growth hormone transgenic mice have a shortened life expectancy, renal failure being the primary cause of death [138, 139]. In growth hormone transgenic mice [140–142], renal lesions characterized by large kidneys with tubular atrophy, enlarged glomeruli and glomerulosclerosis are found. These lesions are absent, or they are much milder, in IGF-I transgenic mice [140, 141, 143]. Increased kidney size and glomerulosclerosis have also been demonstrated in rats with pituitary tumor transplants [103] and humans with acromegaly [144], and in both situations the circulating concentrations of growth hormone are markedly elevated. In aging rats, the severity

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Table 3. Effects of metabolic acidosis on insulin-like growth factors (IGFs), IGF-binding protein-3 (IGFBP), mRNA of IGF-I and growth hormone (growth hormone) receptor

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (N = 5)</th>
<th>Pair-fed (N = 5)</th>
<th>Acidotic (N = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum IGF-I ng/ml</td>
<td>818.0 ± 130.9a</td>
<td>233.6 ± 45.6b</td>
<td>411.8 ± 57.3c</td>
</tr>
<tr>
<td>Serum IGF-II ng/ml</td>
<td>18.6 ± 1.8ab</td>
<td>10.4 ± 1.4a</td>
<td>11.8 ± 1.5cd</td>
</tr>
<tr>
<td>IGFBP-3 ng/ml</td>
<td>11.5 ± 9.0</td>
<td>10.1 ± 2.6</td>
<td>11.9 ± 6.2</td>
</tr>
<tr>
<td>Hepatic IGF-I mRNA (ADU)</td>
<td>1.4 ± 0.3a</td>
<td>0.6 ± 0.2b</td>
<td>0.9 ± 0.3c</td>
</tr>
<tr>
<td>Hepatic growth hormone receptor mRNA (ADU)</td>
<td>2.9 ± 1.6a</td>
<td>1.7 ± 0.4</td>
<td>1.4 ± 0.9d</td>
</tr>
</tbody>
</table>


In each row values with the same superscript are not significantly different. Different superscripts indicate different concentrations of statistical significance: a vs. b, P < 0.005; b vs. c, P < 0.01; a vs. d, P < 0.025; b vs. d, P < 0.05.

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**Growth hormone secretion and IGF-I expression in acidosis**

Using multiple parameter deconvolution analysis, growth hormone secretion was found to be inhibited in rats during metabolic acidosis (Fig. 2). This inhibition of growth hormone secretion may be a proximal cause of the growth failure with renal tubular acidosis. The growth hormone secretory pulse areas for both acidic and pair-fed animals are reduced [126].

Another recent study [127] demonstrated that the marked

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Fig. 2. Data from deconvolution analysis of pulsatile growth hormone (growth hormone) secretion in the control (N = 9), acidic (N = 9), pair-fed-1, given food in the morning (N = 8), and pair-fed-2, given food in the evening (N = 6) groups. Values for mean growth hormone secretory pulse amplitude (height), pulse area (mass), pulse number, and total growth hormone secreted as pulses (total growth hormone secretion) are shown. Data are expressed as means ± SEM. In each panel, values without common letters ("a", "b", or "c") are significantly different (P = 0.05 or lower). (From Challa A, Krieg RJ Jr, Thabet MA, Veldhuis JD, Chan JC: Metabolic acidosis inhibits growth hormone secretion in the rat. Mechanisms of growth retardation. *Am J Physiol* 265:E547–E553, 1993; used with permission of the American Society of Physiology).
of nephrosclerosis was correlated with the plasma concentrations of growth hormone [145]. In the renal ablation uremia model, proteinuria, hypertension and severe renal scarring were observed 120 days after subtotal nephrectomy. In contrast, growth hormone-deficient rats appear to be partly protected against glomerular sclerosis and tubulointerstitial scarring found in control rats 120 days after subtotal nephrectomy [146]. Transgenic mice carrying different portions of bovine growth hormone demonstrated different body growth and glomerulosclerosis [147].

In addition, a considerable body of evidence points to a significant role of locally produced IGF-I in the regeneration of the proximal tubule following ischemic injury in the rat [148] as well as in the compensatory growth of remaining renal tissue after unilateral nephrectomy [149]. Increased rat kidney IGF-I content have been found, three to five days following partial nephrectomy [146, 149, 150]. Conversely, data on IGF-I mRNA in the remaining kidney tissue are not uniform, high [149] and unchanged [151] concentrations having been reported. From a different point of view, IGF-I acting through an autocrine mechanism might be an important pathogenic factor in certain proliferative glomerulonephritis [134]. Growth hormone-independent synthesis and release of IGF-I has been demonstrated in cultures of mesangial cells [134, 152] with an increased amount of mesangial cell mitosis occurring in response to the locally produced IGF-I.

It has been well established in animals [153] and humans [154, 155] that growth hormone increases glomerular filtration rate and renal plasma flow in a parallel manner. This effect is mediated by IGF-I [156-158] which likely enhances renal plasma flow resulting from reduced vascular resistance of afferent and efferent glomerular arterioles [159]. The hemodynamic action of IGF-I on renal vascular resistance is not dependent on intrarenal angiotensin because it is not blocked by angiotensin-converting enzyme inhibitors [160]. By contrast, it is blocked by indomethacin administration, which suggests a mediator role of vasodilatory eicosanoids [161]. Hirschberg et al [162] investigated the effects of recombinant human IGF-I administration on renal hemodynamics in rats, showing that the increased glomerular filtration rate was due not only to increased single nephron plasma flow rate, but also to a marked increment in the glomerular ultrafiltration coefficient to twice the control values. More recently, Hirschberg et al [163] demonstrated that in human subjects, recombinant human IGF-I administration stimulated renal plasma flow and the glomerular filtration rate, increased microproteinuria and tubular phosphate reabsorption, but caused no change in calcium reabsorption.

Both growth hormone and IGF-I stimulate proximal tubular gluconeogenesis [20]. Sodium and water retention has long been shown to occur in humans receiving growth hormone [164]. This effect persists in the absence of adrenal glands [165]. It is completely suppressed by prior administration of actinomycin D [166], and may be, at least in part, due to direct stimulation of tubular Na-K-ATPase activity [167]. IGF-I has been shown to enhance sodium transport in the toad bladder [168].

**Growth hormone secretion and expression in chronic renal insufficiency**

Studies on growth hormone secretion in chronic renal insufficiency have been inconclusive and have often led to contradictory results [169, 170], possibly due to the pulsatile nature of growth hormone secretion, increased retention and catabolism in uremia, variable activities of the binding proteins and the effects of stress, undernutrition and other influences not being carefully examined or controlled. Single sample techniques, or even short term samplings, may be inappropriate to characterize the state of the growth hormone secretory system in uremia. Comparison of uremics to controls of equivalent nutritional status (pair-fed) is necessary for accurate assessment, because underfeeding profoundly affects growth hormone secretion [171, 172].

Using highly specific assays, Haffner et al [173] demonstrated an inverse hyperbolic correlation between plasma growth hormone concentrations and the metabolic clearance rate. Recent data by Santos et al [174] indicated that pituitary cells of uremic rats responded normally to growth hormone releasing hormone. Krieg et al [175] also showed that the half-life of growth hormone in the circulation of uremic rats was significantly greater than either untreated controls or pair-fed controls using deconvolution analysis of pulsatile growth hormone secretion in stable uremic rats. There was no apparent difference between uremic and control animals in the intervals between growth hormone secretory pulses, but the mass of growth hormone secretion by pair-fed animals was significantly less than that of the untreated controls [175]. In uremic animals, the growth hormone mass was not different from that of pair-fed controls. These new data suggest that growth hormone secretory episodes might be significantly different in uremia compared to pair-fed controls with respect to half-life and the numbers of pulses.

Preliminary data have also shown that pituitary growth hormone mRNA expression is reduced in the uremic animals and that pituitary IGF-I receptor mRNA expression is enhanced [176]. These studies utilized pituitary tissues collected and homogenized in guanidine isothionate in the uremic rat model. Furthermore, reductions in pituitary growth hormone receptor and IGF-I receptor gene expression [177] have been demonstrated at a food restriction to 60% of control intakes, which is a comparable food intake as in uremic animals [178] and humans [174].

**Growth hormone resistance in chronic renal insufficiency**

Growth hormone resistance is presumed to be present in uremia. No study has found subnormal serum growth hormone concentrations in uremic animals [179] or humans [180]. In addition, insulin-like growth factors have also been shown to be normal in uremic children [181]. However, the uncertain reductions in renal excretion associated with varying degrees of chronic renal insufficiency and the variable rates of catabolism render the interpretation of serum growth hormone and IGF-I concentrations less reliable in the uremic condition. A significant reduction in liver IGF-I mRNA was recently demonstrated in uremic animals compared to pair-fed and control animals [182]. After growth hormone administration, the expected increase in liver IGF mRNA in both controls and pair-fed animals did not materialize in the uremic animals. This first direct evidence of tissue resistance to growth hormone in uremia by Chan, Valerie and Chan [182], and later confirmed by others [183], provided a powerful rationale for the use of recombinant human growth hormone in uremic children.

It is possible that in uremia, the growth promoting effect of exogenously administered recombinant human growth hormone results from changes of IGF-I mRNA and/or IGF-I in tissues other than liver, such as kidney, bone and muscle, where the paracrine/autocrine action of IGF-I is of critical importance in
growth promotion [184]. In addition, the growth hormone receptor was markedly reduced in livers of uremic animals but not in control or pair-fed animals [182, 183]. This relationship persisted after growth hormone administration. It is also possible that the effect of exogenous recombinant human growth hormone is exerted on the IGF-I binding proteins [185, 186], which was likely to exert profound effects on the availability and function of IGF-I. Recent findings [187, 188] suggest that, in the serum of patients with chronic renal failure, there is a disequilibrium between the concentrations of IGF-I binding protein-3 (IGFBP-3) and IGF-I, in such a way that there is an excess of unsaturated low-molecular weight forms (19 and 14 kD) of IGFBP-3 not seen in normal serum. Accordingly, there is less circulating bioactive IGF-I. It has also been proposed [181, 189] that accumulation of IGFBPs in chronic renal failure impedes normal longitudinal growth either by inhibiting IGF-I actions by a paracrine mechanism or in other yet unidentified IGF inhibitors.

Reduced growth hormone binding in uremic rats demonstrated by Finidori, Postel-Vinay and Kleinnecht [190] and in uremic children demonstrated by Postel-Vinay et al. [191], together with the documentation of tissue resistance to growth hormone demonstrated by Chan et al. [182] and Tonshoff at al. [183] led to the suggestion that in uremia, the defect in growth hormone receptor binding is extended to the transcriptional level. Liver growth hormone receptor mRNA was unaffected in hypophysectomized rats, even in the face of 50% reduction in growth hormone binding compared to intact animals [192]. Such data suggested that in hypophysectomized rats, the growth hormone receptor function was controlled by its translation rather than by its transcription [193].

Fasting or the lack of insulin caused a reduction in the abundance of liver growth hormone receptor for mRNA, unaffected by low protein intake [194]. Because defective growth hormone receptor can lead to growth hormone insensitivity as manifested in Laron syndrome [195], it has been suggested that decreased growth hormone receptor function may contribute to the growth hormone resistance in uremia.

**Growth hormone/IGF-I, vitamin D and bone interactions**

Growth hormone and IGF-I synergistically act at the growth plate of long bones to stimulate longitudinal growth in humans and animals. Direct action of growth hormone on cartilage is suggested by the presence of growth hormone receptors in growth plate chondrocytes [196] and expression of growth hormone receptor mRNA in response to growth hormone in monolayer cultures of epiphyseal chondrocytes [197]. Growth hormone induces local production of IGF-I as demonstrated by increased concentrations of IGF-I [198] and IGF-I mRNA [199, 200] in the rat’s growth plate in response to growth hormone administration, chondrocyte IGF-I mRNA being more effectively stimulated by pulsatile than constant growth hormone concentrations [201]. In addition, the growth stimulating effect of growth hormone on rat bones has been shown to occur after a time lag longer than two days and be abolished by administration of a monoclonal antibody to IGF-I [202]. Circulating IGF-I also appears to play a major role as stimulus of longitudinal growth because the increase in tibial bone growth and cartilage plate width obtained by local administration of growth hormone is significantly less than that observed in response to systemic growth hormone [21]. According to the hypothesis proposed by Green, Morikawa and Nixon [203] and supported by other investigators [204–206], growth hormone and IGF-I act on different cells in the growth plate. It is postulated that growth hormone induces differentiation of precursor cells toward chondrocytes enabling the expression of IGF-I mRNA, locally produced IGF-I acts through autocrine and paracrine mechanisms to stimulate clonal proliferation of adjacent differentiated chondrocytes. This “dual effector” hypothesis has been challenged by Hunziker, Wagner and Zapf [207], who have recently presented evidence that IGF-I is also capable of stimulating stem cells of growth plate cartilage in hypophysectomized rats, although IGF-I is not as effective as growth hormone.

The action of growth hormone and IGF-I on bone is not exclusively restricted to cartilage cells. IGF-I receptors have been found in osteoblast-enriched cultures from fetal rat parietal bone [208] and in vitro studies have shown stimulation of bone, collagen and non-collagen protein synthesis in response to IGF-I [209]. In addition, growth hormone has been found to increase IGFBP-2 and IGFBP-4 concentrations in rat osteoblast-like cell cultures without inducing changes in IGF-I synthesis [210]. This supports a role for growth hormone in bone metabolism by modulating the biological functions of IGF-I through its binding proteins. There is an undefined influence of the parathyroid hormone and 1,25 dihydroxyvitamin D axis on bone IGF-I metabolism because parathyroid hormone enhances the transcription and release of IGF-I in bone cell cultures [211, 212] and 1,25 dihydroxyvitamin D increases IGF-I receptors in clonal osteoblastic cells [213].

There is also evidence linking growth hormone and IGF-I to metabolism of calcium and phosphate in the kidney. Treatment with growth hormone increases urinary calcium excretion in humans [164] and stimulates proximal tubular reabsorption of phosphate in both humans and experimental animals [154, 164, 214]. In addition, high circulating concentrations of 1,25 dihydroxyvitamin D have been reported in acromegalic individuals [215] and elderly people receiving growth hormone administration [216]. This effect is likely mediated by IGF-I because, in hypophysectomized rats, IGF-I infusion has been shown to increase 1,25 dihydroxyvitamin D concentrations [217] and restore, in part, the responsiveness of serum 1,25 dihydroxyvitamin D to phosphate deprivation which is abolished in untreated hypophysectomized rats [218]. These findings are consistent with a IGF-I stimulated activity of tubular 1 alpha-hydroxylase enzyme. Finally, IGF-I stimulates vitamin D receptor expression of cultured growth plate chondrocytes [219].

The activation of renal 1,25-dihydroxyvitamin D synthesis by low dietary phosphate is blocked in hypophysectomized animals [201]. This effect is restored by growth hormone treatment as well as by IGF-1 administration [220]. The effectiveness of IGF-I in restoring the increased renal synthesis of 1,25-dihydroxyvitamin D induced by dietary phosphate restriction indicates that, in this respect, the IGF-1 again mediates the action of growth hormone [220]. In addition, several lines of evidence point to the synergistic effect of IGF-1 and 1,25-dihydroxyvitamin D₃ and bone cell proliferation and differentiation—steps necessary for bone growth [221]. In osteoblast cells, growth hormone treatment increases intracellular IGF-1, which leads to increased cell proliferation, and DNA and protein synthesis in cultured rat calvaria [220]. 1,25-dihydroxyvitamin D receptor gene expression is stimulated by growth factors, including IGF-1. 1,25-dihydroxyvitamin D also increases IGF-1 receptor. In addition, in the osteoblast cells, 1,25-dihydroxyvitamin D is shown to regulate the production of
IGF-I and IGF-I binding protein, effectively controlling proliferation and enhancing differentiation [221].

Another major effect of growth hormone relevant to chronic uremia is that growth hormone administration in uremia induced a shift in the target cells from proliferative to hypertrophic zone [222]. It was found that growth hormone administration stimulates the more mature hypertrophic chondrocyte instead of the immature proliferating chondrocytes [222]. Growth hormone and IGF-I can both stimulate all phases of chondrocyte differentiation [207], although IGF-I is not as effective as growth hormone [207]. Growth hormone stimulates renal 1α-hydroxylase activity, resulting in increased synthesis of 1,25-dihydroxyvitamin D [223]. Recent studies have provided convincing evidence for a role of 1,25-dihydroxyvitamin D in restoring the production of transforming growth factor beta (TGF-β) which leads to osteoinduction [224], in contrast to the lack of osteoinduction in vitamin D deficiency. In other words, 1,25-dihydroxyvitamin D is required for the synthesis of transforming growth factor, TGF-β. Thus TGF-β is required in the osteoinduction process. These all point to the intricate interrelationship of the growth factors enumerated here on bone growth.

In chronic uremia, the destruction of renal tissue gives rise to impaired synthesis of 1,25-dihydroxyvitamin D, resulting in a decrease in its serum concentration. This usually occurs when the glomerular filtration rate is less than 50% of normal for age. How this diminished 1,25-dihydroxyvitamin D affects TGF-β synthesis is just beginning to be explored. Finally, it has been observed that in anephric patients, who were on dialysis, recombinant human growth hormone might have a diminished effectiveness in promoting growth, possibly due to decreased 1,25-dihydroxyvitamin D production.

Exogenously administered growth hormone has been shown to promote growth in uremic children [225-228]. However, only pharmacological dosages of recombinant human growth hormone were found to be effective. As indicated earlier, it has recently been suggested that the depressed TGF-β in vitamin D deficiency increased 100% with 1,25-dihydroxyvitamin D administration [224]. It is possible that without adequate 1,25-dihydroxyvitamin D, as often occurs in chronic renal failure, growth hormone might fail to exert its full effect in the bone.

Recent animal experiments by Santos et al [174] in early chronic renal insufficiency, showed growth failure was secondary to caloric insufficiency and the growth response to recombinant growth hormone was less dramatic, whereas in advanced uremia, growth hormone treatment enhanced food efficiency and promoted significant growth. In addition, steroid-induced growth retardation was reversible with exogenous human recombinant growth hormone [229].

Conjoint use of growth hormone and 1,25-dihydroxyvitamin D in uremic rats has been shown to be associated with increased hypercalcuria [230], even when the 1,25-dihydroxyvitamin D and recombinant human growth hormone were used at therapeutic dosages.

**Clinical use of recombinant growth hormone in chronic renal insufficiency**

Fine [231], Tonshoff et al [226], and Hokken-Koelega et al [228] demonstrated significant growth acceleration in uremic children treated with recombinant human growth hormone therapy. The recommended dosage of recombinant human growth hormone was 0.3 to 0.4 mg/kg body wt/week in three equal divided dosages. Intraperitoneal administration of 0.05 mg/kg body wt/day also improved the short stature in a small number of children [232] and adults [233] on chronic peritoneal dialysis. In children after renal transplantation, growth hormone therapy at 0.3 to 0.4 mg/kg body wt/week was recommended, together with continuation of all immunosuppressive therapy [180, 231, 234]. The serum IGF-binding protein-3, which was already elevated in chronic renal failure, rose to even higher concentrations after growth hormone administration. In chronic renal failure, IGFBP-6 was notably elevated, and this decreased after renal transplantation [235]. Because excess IGFBPs likely interferes with attainment of renal growth [189], the decrease of excess IGFBP-6 after renal transplant [235] may be causally associated with better growth potential. Growth hormone-binding activity is low in uremic children [191]. This does not change with growth hormone therapy, although enhanced growth velocity and serum insulin-like growth factor concentration increased significantly with growth hormone administration [191].

In relation with the effect of growth hormone administration on thyroid function, Moller et al [236] demonstrated that growth hormone administered for 14 days to normal adults elevates energy expenditure, and suggest that this effect may be mediated by an increase in peripheral T₄ and T₃ conversion. Administration of IGF-I and insulin to healthy young adults has been shown to increase glucose uptake and oxidation and suppress glucose production, free fatty acid concentrations and fat oxidation rates in a similar manner [237]. On the other hand, rhIGF-I administered as an intravenous bolus to healthy humans produces a hypoglycemic response [238] and decreases plasma insulin levels [239]. Nevertheless, the hypoglycemic effect of IGF-I is likely due to supraphysiologic concentrations of free circulating IGF-I, an unlikely situation in patients with chronic renal failure, in whom serum IGFBP concentrations are in relative excess to IGF-I.

Recombinant human insulin-like growth factor-I (rhIGF-I) has been used in patients with end-stage renal failure [240, 241], resulting in enhanced insulin and PAH clearance but declining IGF binding protein-3. Complications include tachycardia, Bell's palsy, papilledema, and hypoglycemia. These side effects were dose-dependent and may be avoided by dose reduction [240]. In uremic rats, the joint use of IGF-I and growth hormone significantly increased body growth while reducing serum concentrations of insulin and cholesterol [242].

In patients on maintenance peritoneal [243] or hemodialysis [244], the use of rhIGF-I promotes positive protein balance and may be efficacious in the treatment of malnutrition in these patients [245]. Despite these reports on the positive responses of patients with chronic renal failure, the deleterious effect on renal structure and function in rat studies [246, 247] suggest that caution is warranted in the use of growth hormone in patients with severe glomerular diseases. High circulating concentrations of growth hormone by itself may not cause renal damage, as end-stage renal disease is not seen in higher frequency in acromegolic subjects, but this may not apply in patients with pre-existing renal diseases as suggested by the results of experimental uremic studies [248, 249]. In summary, the growth failure in chronic renal insufficiency, despite elevated serum growth hormone concentration, is supportive of growth hormone resistance in uremic humans [173] and in rats [182], and provides the
rationale for using recombinant human growth hormone in uremia. However, insulin-like growth factor is likely the better therapeutic agent to achieve the desirable growth promotion [249], without the potential of growth hormone-induced glomerulosclerosis [249], seen in mice transgenic to growth hormone and not to insulin-like growth factor.

**Human recombinant IGF-I administration in acute renal failure**

Because acute renal failure is associated with increased protein breakdown, recombinant human IGF-I has been used as an anti-catabolic agent in rats with ischemic acute renal failure [250–254]. A slower rate of rise in creatinine plus increased renal plasma flow and enhanced glomerular filtration rate suggest a potential for this growth factor in the treatment of acute renal failure. Finally, intraventricular IGF-1 administration given within two hours of hypoxic-ischemic brain injury reduced neuronal death, with IGF-1 acting to block apoptosis [188].

**Human recombinant growth hormone or IGF-I in nephrotic syndrome**

Children with nephrotic syndrome suffer from increased urinary losses of IGF carrying protein [255]. The depressed serum concentrations of IGF-I and IGF-II demonstrated by Garin, Grant and Silverstein [255] may result partly from the loss of IGF carrying protein in the massive proteinuria. In experimental nephrotic syndrome, Thabet et al [256] demonstrated significant depression of growth hormone receptor mRNA and IGF-receptor mRNA in addition to reduced serum IGF-1, IGF-II, IGFBP-3 and IGFBP-4. These results suggest that the growth retardation of nephrosis may be due to the significant reduction in these growth factors and IGF-receptor mRNA [256]. The growth retardation of children with nephrotic syndrome, even before steroid treatment, may be related to this lack of growth factors [255]; to reverse the growth retardation by administration of growth hormone or IGF-I in nephrotic syndrome required a close examination of the risk/benefit ratio. In puromycin aminonucleoside nephrosis in rats, Trachtman et al [246] demonstrated that administration of growth hormone binding protein complex: A major constituent of plasma growth hormone in man. Endocrinology 122:976–984, 1988


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