Pediatr Nephrol (1992) 6: 394–398

Pediatric Nephrology

Invited review

Renal effects of growth hormone. I.* Renal function and kidney growth

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Received June 6, 1991; received in revised form January 15, 1992; accepted January 16, 1992

Abstract. Growth hormone (GH) affects renal function and kidney growth. Pituitary-derived or recombinant human GH (rhGH), acting via insulin-like growth factor-1 (IGF-1), increases glomerular filtration rate (GFR) and renal plasma flow (RPF) in GH-deficient as well as in normal adults. Furthermore, GFR and RPF are low in hypopituitarism and elevated in acromegaly. These effects of GH on GFR and RPF have not been demonstrated in moderate renal insufficiency. IGF-1 is implicated in compensatory renal hypertrophy. Markedly elevated levels of serum GH accelerate glomerular sclerosis in rodents, although the significance of these findings for GH treatment in humans is uncertain. rhGH therapy offers great promise to children with short stature from various aetiologies. Preliminary reports on the use of rhGH in children with renal disease and after renal transplantation have not shown any consistent change in kidney function, although follow-up times are short. The long-term impact of rhGH therapy on kidney function in short children needs further evaluation.

Key words: Growth hormone – Insulin-like growth factor-1 – Glomerular filtration rate – Renal plasma flow – Renal hypertrophy

Introduction

Growth hormone (GH), either directly or through insulin-like growth factor-1 (IGF-1), exerts widespread physiological effects in addition to accelerating linear growth. The advent of recombinant human GH (rhGH) has led to a marked increase in the use of GH as replacement therapy, in treating children with a variety of growth disorders, and as an anabolic hormone [1–5]. Some aspects of the renal physiological effects of GH [6] and the use of rhGH in growth-retarded children with renal disease have been recently reviewed [7]. This review examines the physiological and metabolic effects of GH with emphasis on renal function and kidney growth (part 1) and on salt and water balance, calcium, phosphate and vitamin D metabolism, and body composition (part 2).

Physiology of GH

GH is a single-chain polypeptide consisting of 191 amino acids with two intramolecular disulphide bonds. GH secretion from the anterior pituitary is stimulated by hypothalamic GH-releasing hormone (GHRH) and inhibited by somatostatin. Negative feedback control of GH secretion is exercised by GH itself and by IGF-1. GH circulates in plasma bound to a protein related to the extramembranous portion of the GH receptor [8]. GH secretion is episodic and predominantly nocturnal, with 5–9 pulses/24 h in children and young adults. Secretion rises to a maximum during puberty, and declines with age [9].

GH interacts with a specific receptor on the membrane of target cells, but subsequent intracellular events are uncertain. The growth-promoting effects of GH are predominantly mediated by IGF-1 (also known as somatomedin C), but GH may directly stimulate mitogenesis [10]. The liver is the major source of circulating IGF-1; however, IGF-1 is also produced in other tissues [11]. Tissue growth through autocrine and/or paracrine mechanisms may occur by GH-induced local production of IGF-1 [12]. The relative contributions to growth of circulating and of autocrine or paracrine effects of IGF-1 are not known. The kidney is the major organ involved in the metabolic clearance of GH, and elevated serum levels of GH are therefore found in chronic renal failure (CRF) [13]. GH is extensively filtered by the glomerulus with almost complete tubular uptake and degradation [14]. Renal tubular dysfunction results in a high urinary concentration of GH [15].

* Part II of this review will be published in Pediatr Nephrol (1992) Volume 6, Number 5

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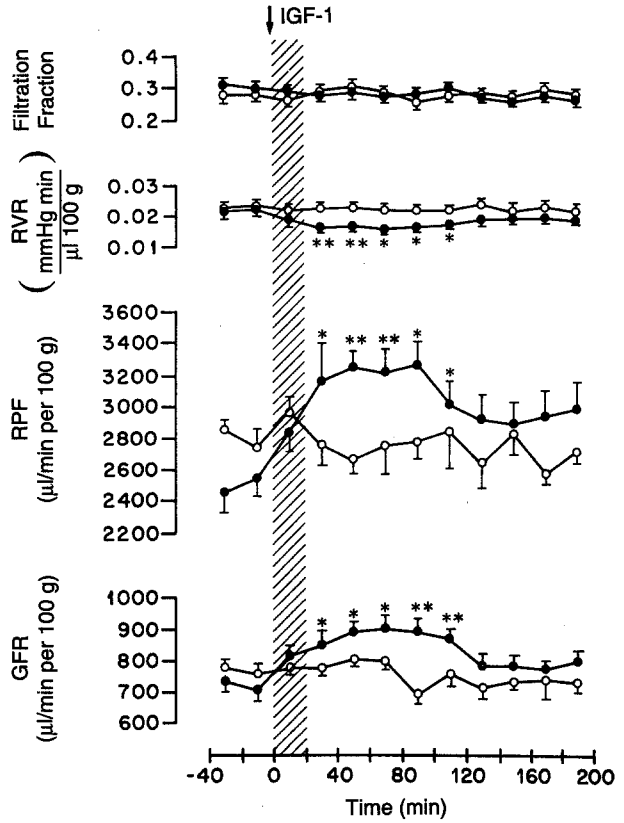

Fig. 1. Glomerular filtration rate (*GFR*), renal plasma flow (*RPF*), Renal vascular resistance (*RVR*) and filtration fraction (*FF*) before, during and after infusion of insulin-like growth factor-1 (*IGF-1*) or vehicle. ●——●, IGF-1-treated rats ($n = 8$); ○——○, controls ($n = 7$). The *shaded bar* marks the 20-min duration of the IGF-1 or vehicle infusion. Bars indicate standard error. * $P < 0.05$ compared with baseline; ** $P < 0.05$ compared with control. Reproduced with permission from J Clin Invest (1989) 83: 326–330 by copyright permission of the American Society for Clinical Investigation

Kidney function and renal growth

Effects of GH on glomerular filtration rate and renal plasma flow

As early as 1949, White et al. [16] showed that pituitary-derived GH (pdGH) increases glomerular filtration rate (GFR) and renal plasma flow (RPF) in dogs. This was confirmed in humans by Corvilain and Abramow [17] in 1962. Christiansen et al. [18] demonstrated that administration of 6 IU/day pdGH for 7 days to normal adults raised GFR (mean ± SEM) from 114±5 to 125±4 ml/min per 1.73 m^2 and RPF from 554±30 to 601±36 ml/min per 1.73 m^2. Kidney size did not change significantly. The parallel increase in GFR and RPF indicates that the rise in RPF is the main determinant of the increased GFR. Haffner et al. [19] found that rhGH elevated inulin clearance to the same extent as pdGH, proving conclusively that the changes are not due to contamination of pdGH with other pituitary substances.

Mechanism of GH action on GFR and RPF

It has become clear recently that the GH-induced rise in GFR and RPF is not due to a direct action of GH, but is mediated by the generation of IGF-1. Parving et al. [20] showed that GFR and RPF did not alter during a 2-h infusion of pdGH. Hirschberg et al. [21] employed serial para-aminohippuric acid and inulin clearances on 3 consecutive days following a single injection of pdGH (0.15 mg/kg). While serum GH peaked at 2.2 h, there was no change in IGF-1, GFR or RPF by 5.5 h. However, by day 2 IGF-1 had peaked, RPF had risen from 546 to 715 ml/min per 1.73 m^2 and GFR from 100 to 130 ml/min per 1.73 m^2. GFR and RPF remained elevated on day 3. Thus, the renal haemodynamic changes were temporally related to the rise in IGF-1 rather than GH. Hirschberg and Kopple [22] showed that infusion of IGF-1 increases RPF and GFR and reduces renal vascular resistance (RVR) in fasted rats (Fig. 1). Circulating components of the renin-angiotensin system appear unlikely to play a role in the renal haemodynamics of GH, as pre-treatment with enalapril does not block the rhGH-induced increase in GFR [19].

Under normal circumstances, paracrine or autocrine effects resulting from local production of IGF-1 may be more important for the renal effects of GH than circulating IGF-1 from GH-induced hepatic production. IGF-1 messenger RNA (mRNA) is present in the kidney [23], and IGF-1 has been localised to proximal tubules [24]. After GH injection, IGF-1 levels rise sooner and at a faster rate in the liver and kidney than in plasma [25]. Hence, circulating IGF-1 may not be a major influence on renal function under normal conditions, but merely reflect IGF-1 synthesis in these organs [21]. Glomerular mesangial cells (which express IGF-1 receptors [26]), are actively involved in the regulation of afferent and efferent arteriolar flow. IGF-1 most likely increases RPF by reducing afferent, and possibly also efferent, arteriolar resistance.

Studies in fasted and malnourished rats, in which GFR, RPF and IGF-1 are low, support this hypothesis [22, 27]. In rats starved for 60–72 h, IGF-1 administration resulted in raised GFR and RPF accompanied by a fall in RVR [22], while the filtration fraction and mean arterial blood pressure did not change. Guler et al. [28] have also shown that IGF-1 infusion in healthy human adults increases creatinine clearance by 30%.

IGF-1 may act through local synthesis of vasodilating eicosanoids. In cultured rat liver cells in the presence of tumour promoters, IGF-1 stimulates synthesis of 6-keto-prostaglandin $F_{1\alpha}$ and prostaglandin E_2 [29]. Furthermore, indomethacin blocks the renal response to IGF-1 infusion [22].

Effects of GH on renal function in hypopituitarism

The reduction in GFR and RPF reported in patients with hypopituitarism is probably multifactorial. Following hypophysectomy, GFR and RPF fall, most of the fall occurring within 2 months of surgery. Kidney size also decreases, but over a longer time period [30].

Salomon et al. [31] administered 0.49 IU/kg per week rhGH to GH-deficient adults and found that creatinine clearance rose progressively with treatment from a baseline level of 105 ml/min per 1.73 m^2 to 140 ml/min per 1.73 m^2 at 1 month and to 160 ml/min per 1.73 m^2 at

6 months. Jorgensen et al. [5] showed that 2 units/m^2 per day rhGH raised GFR and RPF from subnormal levels to those not significantly different from age-matched controls, while the filtration fraction (GFR/RPF) did not change. Urinary albumin excretion was in the low-normal range and was not affected by GH treatment.

Renal effects of excess GH

Glomerular morphology has been studied in transgenic mice chronically secreting high levels of GH, GHRH or IGF-1 [32, 33]. Doi et al. [32] found that the glomeruli were enlarged in all three strains of transgenic mice. Mesangial proliferation followed by progressive glomerulosclerosis (mimicking that seen in diabetes mellitus) was observed in the animals secreting high levels of GH and GHRH (circulating GH levels markedly elevated). In the mice with increased IGF-1 levels, the large glomeruli were otherwise morphologically normal, but IGF-1 levels were only 1.5 times normal. Kawaguchi et al. [34] observed similar findings in the glomeruli of rats with GH-secreting tumours. Both GFR and RPF are elevated in acromegaly [35–37]. However, the relative contribution of GH or the associated diabetes to the hyperfiltration is uncertain.

Short-term effects of GH on GFR in chronic renal insufficiency

Short-term administration (3 days) of 9 IU/day rhGH to uraemic adults (mean GFR 21 ml/min per 1.73 m^2) failed to increase inulin clearance [38]. In 75% nephrectomised rats (creatinine clearance 38% of control) fed a low-protein diet, exogenous GH did not increase creatinine clearance [39]. The response to an amino acid infusion (Vamin N Kabi Vitrum, Limoges, France) in CRF was similarly blunted [40]. A proposed explanation is that the rise in GFR observed in normal subjects in response to GH treatment, or with amino acid infusion, may be mediated via recruitment of "dormant cortical nephrons" together with a rise in net ultrafiltration pressure in other glomeruli, and that the CRF kidney does not have this reserve [40].

Published data in children with CRF are limited. Tonshoff et al. [41] showed no consistent effect of 4 IU/m^2 rhGH on GFR (as measured by inulin slope clearance) in CRF after 6 weeks, although GFR increased in six of ten children.

GH and diabetes mellitus

Renal enlargement and glomerular hyperfiltration occur early in diabetes [42] and may be causally related to the development of nephropathy [43]. Brenner et al. [44] have proposed that glomerular hyperfiltration results in glomerular damage which may progress to sclerosis.

The mechanism for hyperfiltration in diabetes is probably multifactorial [45]. The elevated GH levels in early juvenile diabetes [46] fall with improved metabolic control, as do GFR and RPF [47]. Conversely, following GH administration to well-controlled diabetics, GFR, RPF and kidney size increase [48], supporting a role for GH in diabetic hyperfiltration. Interestingly, exogenous GH administration does not further increase renal hypertrophy in diabetic rats [49], suggesting that maximal stimulation has already occurred. IGF-1 may contribute to the mesangial proliferation seen in diabetic nephropathy. In the mouse, IGF-1 is a potent mitogen for glomerular mesangial cells [26].

Are the renal physiological responses to protein ingestion mediated by GH?

This issue remains unresolved. Low levels of IGF-1, GFR and RPF are found in the fasting state and in chronic malnutrition [22, 27], but as the rise in GFR and RPF after a protein-rich meal or amino acid infusion occurs within 1 h, IGF-1 is unlikely to be responsible. In healthy adults, the rise in GFR and RPF following ingestion of an amino acid solution is inhibited by somatostatin and restored by combined insulin/glucagon/GH infusion (somatostatin inhibits release of all three) [50]. Involvement of one or more of these hormones was not confirmed by Bergstrom et al. [51], who found that levels of these hormones did not change after a protein-rich meal. Furthermore, the response to a protein-rich meal is obliterated in panhypopituitary patients [52], but not in those with isolated GH deficiency [53]. Thus it would appear that pituitary factors other than GH are involved.

Kidney growth and compensatory renal hypertrophy

Normal kidney growth and compensatory renal hypertrophy depend in part on the presence of an intact pituitary gland [54, 55]. In hypophysectomised rats, a purified ovine pituitary extract restored renal size to that found in intact control rats. However, GH and adrenocorticotropic hormone replacement did not normalise kidney growth, suggesting that renotropic factor(s) other than GH are present in pituitary tissue [54]. In studies of the mechanism of early renal hypertrophy in experimental diabetes in the rat, Steer et al. [56] showed that SMS 201-995 (a somatostatin analogue) inhibited renal growth and reduced the expected changes in biochemical markers associated with renal hypertrophy (increased activity of the oxidative enzymes of the pentose phosphate pathway and decreased renal phosphoribosyl pyrophosphate). These workers suggested that the data implicated involvement of GH. However, other factors inhibited by somatostatin may be responsible for the initiation of renal hypertrophy in diabetes.

The observation of compensatory hypertrophy after unilateral nephrectomy has previously been attributed to an unidentified renotropic factor. Evidence has accumulated linking compensatory renal hypertrophy (e.g. after unilateral nephrectomy) to local production of IGF-1. Fagin and Melmed [23] found elevated levels of IGF-1 and its mRNA in the remaining kidney of rats after uninephrectomy compared with sham-operated controls, whilst serum IGF-1 did not rise.

Clinical implications

In summary, GH administration, acting via IGF-1, results in hyperfiltration due to reduced RVR and increased RPF. GFR and RPF are reduced in hypopituitarism, they rise with GH treatment and are increased in acromegaly. Short-term administration of GH to normal adults increases GFR and RPF. It is not known whether this hyperfiltration occurs in children.

Animal studies show that extremely high levels of serum GH induce glomerular sclerosis. However in children, although rhGH treatment results in sustained substantially elevated serum GH levels, these levels are well below the levels reported in these animal models.

There is evidence that GH may not result in hyperfiltration in adults with reduced renal function. Apart from a few anecdotal reports, deterioration in calculated GFR attributable to rhGH treatment has not been observed in children with renal disease, although published numbers are low and follow-up times short [1, 41, 57]. There are no data on the effect of long-term rhGH treatment on the renal function of short children with normal renal function. Long-term studies are indicated to rule out potentially deleterious effects of rhGH on renal function.

Acknowledgements. Dr. G. Ogle was supported by a research grant from the Cronulla Lions Club of Sydney. We are grateful to Professor G. Antony for helpful comments on the manuscript.

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Literature abstract

Lancet (1992) 339: 280–282

Long-term follow-up of childhood Henoch-Schönlein nephritis

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A study of long-term outcome of 78 subjects who had had Henoch-Schönlein nephritis during childhood (at a mean of 23.4 years after onset) shows that severity of clinical presentation and initial findings on renal biopsy correlate well with outcome but have poor predictive value in individuals. 44% of patients who had nephritic, nephrotic, or nephritic/nephrotic syndromes at onset have hypertension or impaired renal function, whereas 82% of those who presented with haematuria (with or without proteinuria) are normal. 17 patients deteriorated clinically from an initial assessment in 1971; 7 of these had apparently completely recovered in 1976, 16 of 44 full-term pregnancies were complicated by proteinuria and/or hypertension, even in the absence of active renal disease. These findings indicate that childhood Henoch-Schönlein nephritis requires long-term follow-up, especially during pregnancy.