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Growth hormone activates renin–aldosterone system in children with idiopathic short stature and in a pseudohypoaldosteronism patient with a mutation in epithelial sodium channel alpha subunit

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Abstract

Growth hormone (GH) treatment causes salt and water retention, and this effect has been suggested to be mediated by activation of epithelial sodium channel (ENaC). Multi-system pseudohypoaldosteronism (PHA) is a salt wasting disease resulting from mutations in ENaC subunit genes. We examined effects of GH therapy for 12–21 months on the renin–angiotensin–aldosterone system (RAAS) in 12 children with idiopathic short stature (ISS) and a PHA patient with defective ENaC function and concomitant GH deficiency. On GH therapy (0.7 U/kg/week), plasma renin activity (PRA), serum aldosterone and insulin-like growth factor-I (IGF-I) levels were periodically determined every 1–3 months in all children. The PHA patient was studied for 6 yr during which time serum, urine, and sweat electrolytes and secretion rate were also examined before, on and off GH therapy. In the PHA patient, mean plasma aldosterone concentration, 7.7 nmol/l (278 ng/dl) before therapy ($n = 9$) rose to 73 nmol/l (2650 ng/dl) 10 months after GH. PRA and IGF-I increased similarly, reaching a plateau between 8 and 12 months. Off GH, there was a decrease to pretreatment levels in 30 months. Aldosterone and PRA strongly correlated with IGF-I ($r = 0.66$ and 0.67). GH therapy also improved the growth rate, and increased both sweat secretion rate and Na^+/K^+ ratio. In children with ISS, aldosterone and IGF-I peaked 6–12 months after GH. Off GH their levels normalized in 3 months. These findings indicate that long-term GH activates the RAAS in both children with ISS and a PHA patient, and that this effect does not depend on a fully functional ENaC.

1. Introduction

Type I pseudohypoaldosteronism (PHA) is a hereditary salt wasting disease that includes two major distinct entities with different modes of inheritance [1]. The severe and rarer multi-system form of PHA is characterized by a multi-system resistance to aldosterone and is inherited as an autosomal recessive trait. We have reported that this form of PHA reflects mutations in the epithelial sodium channel (ENaC) subunits that are regulated by aldosterone [2–4].

In multi-system PHA, the mortality rate is high because of excessive loss of electrolytes from sweat, salivary glands, colonic mucosa and distal renal tubule [1]. The patients require high salt supplement in their diets in order to maintain normal electrolyte balance and to prevent recurrent life threatening salt losing episodes [1–6]. Severe salt wasting may also impair linear growth resulting in short stature [1,7]. High salt diet when started early in life accelerates the growth rate, resulting in catch-up growth especially in PHA patients with isolated renal tubular resistance [7]. In contrast, most patients with multi-system PHA exhibit poor growth even on NaCl therapy, probably because of both the severity of salt wasting and poor compliance. Other treatment modalities such as carbenoxolone and Florinef have been tried, but rarely found to be helpful [8,9].

Another alternative treatment in multi-system PHA could be growth hormone (GH). Short-term (days or weeks) GH treatment is known to result in salt and

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water retention in healthy [10–14] and GH deficient adults [13,15,16], in GH deficient animals [17], and in patients with acromegaly [18]. Thus, we initiated this study on the hypothesis that patients with multi-system PHA and poor growth may benefit from GH therapy as a supplement to dietary NaCl.

It has been suggested that the effect of GH on salt homeostasis and renin–angiotensin–aldosterone system (RAAS) is mediated by insulin-like growth factor-I (IGF-I) via ENaC in the distal tubule [19]. Investigation of the long-term effect of GH on RAAS in patients with defective ENaC activity would thus allow us to examine this hypothesis. The results presented here reveal that long-term GH therapy activates the renin–aldosterone system in GH deficient PHA patients as well as in a group of normal children with idiopathic short stature (ISS).

2. Subjects and methods

The study population included a patient with multi-system PHA and 12 children with ISS. The study protocol was approved by the E. Wolfson Hospital local ethics committee and informed consent was obtained from all the parents before the trial.

2.1. Pseudohypoaldosteronism patient

This patient presented at the age of 9 days of life with symptoms of multi-system PHA including severe salt wasting necessitating prolonged hospitalization, persistently elevated sweat saliva and urine electrolytes, extremely elevated serum aldosterone and plasma renin activity (PRA) as previously reported [1,20]. Molecular genetic analysis revealed an R508stop mutation in the α subunit of amiloride sensitive ENaCs [3].

The growth characteristics of this patient indicated poor growth (Table 1). She was dependent on high salt diet (20 g NaCl and sodium bicarbonate) [1,8]. Despite the salt treatment, catch-up growth was never observed and she remained below the third percentile. Her calculated growth rate 5 months preceding GH therapy was 1 cm/yr (Table 1). At the age of 8, GH responses to provocative tests with insulin and clonidine were low (3.4 and 3.3 mg/l, respectively). The diagnosis of GH deficiency in addition to PHA was established and GH therapy begun. She was euthyroid. Pretreatment IGF-I level was low and bone age was compatible with 4 yr (Table 1). She remained prepubertal throughout the trial.

She received s.c. recombinant GH (Biotechnology General, Rehovot) at a dose of 0.7 U/kg/week for a period of 21 months. The effects of GH on PRA, serum aldosterone and IGF-I were periodically evaluated every 1–3 months. In addition, she was extensively evaluated before, on, and after GH treatment, for a period of 6 yr during which sweat, salivary, urinary electrolytes and blood pressure were periodically examined and the effect of GH on PRA, aldosterone, and IGF-I were assessed. Her salt intake did not change during the whole study period (20 g/day) and her medical condition remained good and stable.

2.2. Children with idiopathic short stature

This group included 12 prepubertal children with a mean age of 9.1 ± 2.4 yr (range 5.8–13.4). Their height was more than 2 standard deviations below the mean for age and sex. All the children were euthyroid, and showed no underlying pathology. They underwent standard GH provocative tests with arginine or clonidine. GH concentrations after the stimulation tests were higher than 10 μg/l. Children with ISS received the same dose of recombinant GH as patients with PHA (0.7 U/kg/week) for a period of 12 months. The effects of GH on serum aldosterone, IGF-I, serum and urine electrolytes were analyzed every 3 months. The same parameters were measured 3 months after completion of GH therapy at 15 months.

Since aldosterone response to GH was found to be related to basal aldosterone concentrations, the children with ISS were divided into two subgroups according to their basal aldosterone levels: Group I, termed 'respon-

Table 1
Growth characteristics and IGF-I levels in PHA patient before during and after GH treatment[a]

	Before GH	Year 1 on GH	Year 2 on GH	After GH
Age period (years)	7.6–8.0	8.0–9.0	9.0– 9.75	9.75–10.75
Height	107.5	116.2	121.0	126.3
Height velocity (cm/years)	1.0	8.5	6.6	2.6
Height SDS*	−3.5	−2.8	−2.7	−3.1
Weight SDS	−1.8	−1.7	−0.8	−1.0
Bone age (years)	4	5	–	8
IGF-I (nmol/l)	11	54	70	38

[a] All values were determined at the end of each age period.
* SDS – standard deviation score.

ders' ($n = 8$), had basal aldosterone levels < 21 ng/ml (0.53 nmol/l), and Group 2, 'non-responders' ($n = 4$) basal aldosterone levels > 21 ng/ml.

2.3. Biochemical assays

PRA and serum aldosterone levels were determined by RIA (Rianen, DuPont, Boston, MA, and Diagnostic Products, Los Angeles, CA, respectively). GH was assayed by a solid-phase, two-site chemiluminescent immunometric assay (Immulate, Diagnostic Products) and IGF-I by an immunoradiometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA).

Sweat secretion and electrolyte concentrations were examined by pilocarpine iontophoresis. Sweating was induced on the flexor side of the forearm. Sweat was collected on a filter paper for 30 min, covered by a plastic capsule and attached with adhesive tape. Filters were weighed before and after sweat collection with a digital balance with an accuracy of 0.1 mg. Two sweat tests were performed simultaneously on both arms in every examination. The mean values of these two tests were used to determine electrolyte concentrations and sweat secretion rates (SSRs). Sweat electrolytes were analyzed by a Monarch 2000 automatic analyzer (Corometrics Medical System Inc., Wallingford, CT) with ion-selective electrodes for sodium and potassium. Blood samples were obtained in the morning when the patients became ambulatory. The patients with PHA received the morning dose of NaCl after collection of saliva. GH stimulation tests were performed in pediatric ward after overnight fast. All the aldosterone and IGF-I samples from children with ISS were run in the same assay after the completion of 15 months of study period.

Statistical evaluation: Comparisons of different treatment regimens (on and off GH) in the same children were performed by paired Student's t-test and the correlations by Pearson's correlation. Differences with $P < 0.05$ were considered significant. Unless specified otherwise, the results were expressed as mean $\pm$ S.D.

3. Results

3.1. The effect of growth hormone on growth parameters in pseudohypoaldosteronism patient

This patient has been studied over a period of 6 yr. The study period included 23 months prior to GH therapy, 21 months on GH therapy and 28 months after the cessation of GH. The linear growth before therapy was poor (Table 1). GH therapy resulted in catch-up growth and improved the growth rate significantly (Table 1). Weight standard deviation score (SDS) did not change during the first year of therapy (Table 1). GH therapy was discontinued after 21 months on the parents' request. Her height velocity decreased significantly thereafter (Table 1); GH therapy was then restarted with similar effects on height velocity and other growth parameters (data not shown). Currently she is still on GH.

3.2. The effect of growth hormone on aldosterone and plasma renin activity

3.2.1. Pseudohypoaldosteronism patient

Two years preceding GH treatment the mean aldosterone concentration was 278 ng/dl (7.7 nmol/l; range 74–500 ng/dl, 2.1–13.9 nmol/l; $n = 9$). Aldosterone concentration increased after 2 months of GH therapy, rising to 2650 ng/dl (7.4 nmol/l) after 10 months and remained high throughout the treatment period (Fig. 1). The serum electrolytes during GH therapy did not differ from the levels observed before and after the completion of GH therapy. An exceptionally high level of aldosterone at 15 months of therapy most probably resulted from an incident of hyperkalemia (7.6 mEq/l) and hyponatremia (134 mEq/l) during recovery from a lower respiratory tract infection. Discontinuation of GH therapy resulted in a significant decrease in aldosterone concentrations to near pretreatment levels within 30 months.

Before GH therapy, the mean PRA was 6.78 ± 5.1 ng/ml/h (1.9 ± 1.4 ng/(l · s)), with a range between 2.3 and 19 ng/ml/h (0.6–5.3 ng/(l · s); Fig. 1). The increase of PRA on GH therapy showed a pattern similar to that of aldosterone. The peak PRA was seen after 10 months of therapy. Similar to aldosterone, after cessation of GH therapy, PRA decreased gradually to near pretreatment levels within 30 months (Fig. 1). PRA correlated with aldosterone concentrations during the whole study period ($r = 0.78$, $P < 0.001$).

The mean systolic and diastolic blood pressures on GH therapy (91/54 mmHg, $N = 9$), were not significantly different from those before GH therapy (88/57 mmHg, $N = 9$).

3.2.2. Children with idiopathic short stature

The mean aldosterone level of the whole group ($n = 12$) was normal before GH administration, showing an increase after 3 months of treatment and remaining elevated throughout the treatment period. Peak values were reached 6–12 months after treatment, with increases over pretreatment levels ranging from nearly 2–20-fold. Three months after cessation of therapy, concentrations decreased to pretreatment levels (Fig. 2). Aldosterone levels after 12 months were significantly higher than both the pretreatment levels and the levels at 15 months ($P < 0.04$).

In the responder subgroup, aldosterone levels at 3, 6, and 12 months were significantly higher than pretreat-

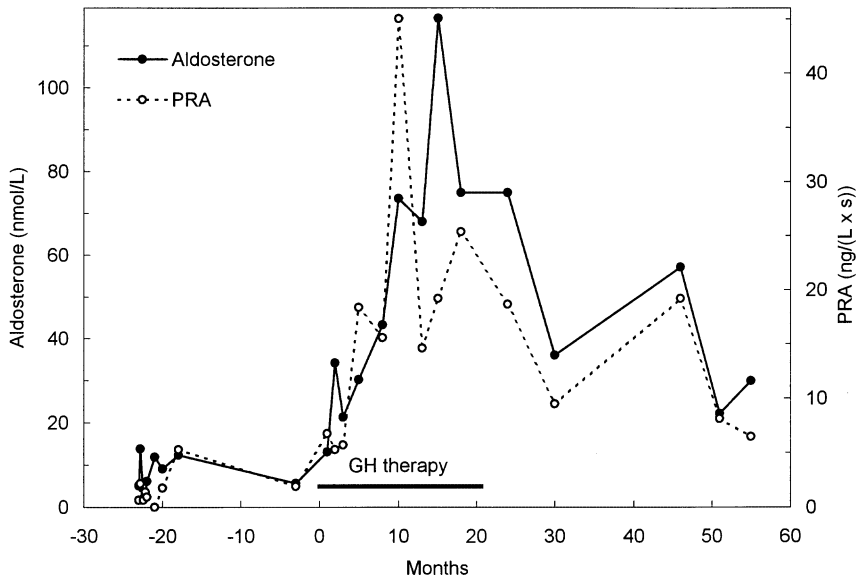

Fig. 1. The effect of GH therapy on serum aldosterone and PRA in PHA patient 1. Normal aldosterone and PRA levels are 5–20 ng/dl (139–555 pmol/l) and 0.5–3 ng/ml/h (0.14–0.80 ng/(l · s)), respectively. To convert aldosterone values to ng/dl divide by 27.74. To convert PRA to ng/ml/h divide by 0.2778.

ment levels ($P < 0.02$, 0.01 and 0.02, respectively; Fig. 2). Three months after the end of GH therapy (month 15) aldosterone levels decreased significantly to near pretreatment levels. The levels at 3 and 6 months were significantly higher than the levels observed in 15 months ($P < 0.05$ and 0.005, respectively). The non-responder subgroup had elevated baseline aldosterone levels (0.53 nmol/l, $\geqslant 21$ ng/dl) that did not change with GH therapy (data not shown).

3.3. The effect of growth hormone on insulin-like growth factor-I

3.3.1. Pseudohypoaldosteronism patient

After 1 month of GH therapy, IGF-I increased 3-fold and reached a plateau between 8 and 15 months (Fig. 3), a pattern parallel to the aldosterone response. Four months after discontinuing GH, serum IGF-I concentrations were significantly lower than levels on GH therapy (Fig. 3). Both aldosterone and PRA correlated strongly with IGF-I during the whole study ($r = 0.67$ and $r = 0.66$, respectively; $P > 0.01$).

3.3.2. Children with idiopathic short stature

On GH therapy, the mean IGF-I level of the whole group was significantly higher than the pretreatment level ($P < 0.02$, pretreatment vs. 3-month levels; $P < 0.003$, pretreatment vs. 6-, 9- and 12-month levels). After the cessation of GH treatment, IGF-I decreased to levels similar to pretreatment period. IGF-I levels peaked 6–12 months after therapy (Fig. 4). Aldosterone and IGF-I levels in the whole group were strongly correlated ($r = 0.92$, $P < 0.001$).

3.4. The effect of growth hormone on serum, sweat and urine electrolytes, sweat secretion rate and serum phosphorus

3.4.1. Pseudohypoaldosteronism patient

Since even small changes in serum K^+ can effect aldosterone levels, we examined K^+ levels before and during GH therapy. The mean K^+ level before therapy was 5.2 ± 0.7 mEq/l (range 4.4–6.3). Potassium levels did not change on GH therapy (5.4 ± 0.8; range 4.4–7.1 mEq/l). Serum aldosterone levels both before and during GH therapy were significantly correlated with K^+ levels ($r = 0.9$ and 0.8, respectively; $P < 0.01$). Similar to serum K^+ levels, mean serum Na^+ concentrations did not show a significant change before and during GH therapy (137.4 and 136.3, respectively).

Sweat electrolytes were determined periodically both before and during GH therapy. Two years preceding GH therapy, the mean Na^+ and K^+ concentrations ($n = 7$) were 162.5 ± 29 and 8.6 ± 1.2, respectively (range 141–207 and 7–10.4 mEq/l). The Na^+/K^+ ratio before the treatment was significantly higher than the ratio on GH therapy (19 ± 1.8 vs. 11.5 ± 3.5, respectively; $P < 0.006$; Fig. 5). After cessation of GH, sweat Na^+/K^+ ratio increased to levels similar to the pretreatment period (26.4 ± 5.5, $n = 5$; Fig. 5). GH therapy also affected SSR (Fig. 6). Two years preceding GH therapy, the SSR was 48.3 ± 5.4 mg/filter paper/30 min (mean $\pm$ SEM, $n = 8$). During GH therapy, the SSR rose significantly to 101.6 ± 14.5 ($P < 0.006$, $n = 8$). Consistent with this finding, the patient reported increased sweating. Two years following the cessation of GH therapy, SSR decreased to pretreatment levels

(51 ± 8, $n = 5$). During GH treatment, IGF-I levels correlated with SSR ($r = 0.64$, $P < 0.01$).

The mean urinary Na^+/K^+ ratio did not show a significant change during GH treatment. Urinary Na^+/K^+ ratios 3 months before GH therapy were 6.4 ± 0.8 (range 5.7–6.3). On GH, the Na^+/K^+ ratio measured every 1–3 months for 20 months ($n = 12$) was not significantly lower than the pretreatment period (5.2 ± 1; range 3.7–6.8). After discontinuation of GH therapy, the mean Na^+/K^+ ratio over 2 yr ($n = 12$) remained around 5.0 (4.9 ± 1.8).

The mean serum phosphorus concentrations as expected rose significantly from 4.5 ± 0.2 mg/dl ($n = 7$) before therapy to 5.75 ± 1 mg/dl on therapy ($P < 0.007$). After discontinuation of GH therapy, the mean phosphorus level decreased to 5 ± 0.26 mg/dl.

3.4.2. Children with idiopathic short stature

In children with ISS, serum Na^+, K^+ levels, and urinary Na^+, K^+ excretion and Na^+/K^+ ratio did not change on GH therapy, in comparison to pre- or post-treatment (15 months) levels. The mean serum phosphorus concentration increased significantly over the baseline value 3 months after GH therapy (4.6 mg/dl vs. 5.4 mg/dl; $P < 0.001$). In a subgroup of 8 children whose basal aldosterone levels were normal (responders), the serum phosphorus levels rose significantly at 3, 9 and 12 months over the baseline values from 4.6 to 5.4, 5.1 and 5.5 mg/dl, respectively (the respective P values were < 0.004, 0.01, 0.002).

4. Discussion

This study revealed that long-term GH therapy activates the RAAS in a group of normal children with ISS. Similar activation was also observed in a PHA patient with an alpha ENaC mutation (R508Stop), suggesting that GH effect does not depend on an intact ENaC.

4.1. The effect of growth hormone therapy on the renin–aldosterone system and electrolytes

The response of serum aldosterone to GH treatment was similar in children with different underlying conditions. Aldosterone levels increased 2–3 months after the initiation of GH therapy and reached a plateau after 6–12 months, in both the PHA patient and in children with ISS. After discontinuation of GH therapy, aldosterone decreased to pretreatment levels. Although pretreatment levels of aldosterone and PRA were very high in the PHA patient, on GH therapy their levels further increased 6–10-fold, respectively. These findings indicate that long-term GH activates the RAAS.

Despite a similar pattern of response, aldosterone levels in PHA patient were strikingly higher than those observed in children with ISS. This probably results from the hypertrophy and hyper-responsiveness of zona glomerulosa due to chronic salt loss in PHA patient [1]. As ISS patients have normal adrenal function, the mean basal and individual aldosterone responses were

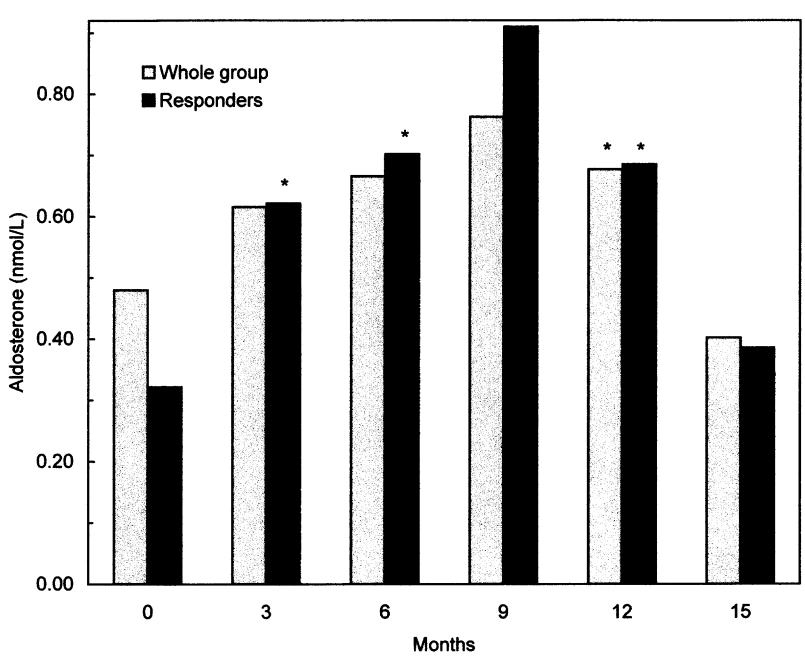

Fig. 2. Serum aldosterone levels in 12 children with ISS during and after GH therapy (GH was stopped at the end of 12 months). Responders: a subgroup of 8 children whose individual basal aldosterone levels were normal ($\leqslant 555$ pmol/l, 20 ng/dl). The mean values of columns marked with an asterisk are significantly different from the first column (month 0), before GH therapy ($P < 0.05$).

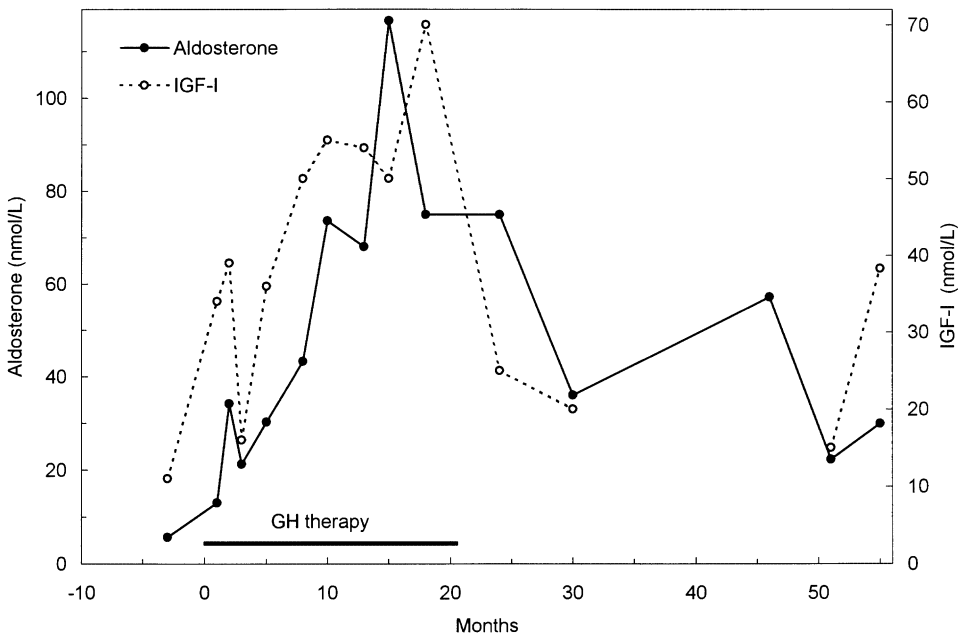

Fig. 3. The effect of GH therapy on serum IGF-I and aldosterone levels in PHA patient 1.

less pronounced, although as a group they showed up to a 20-fold increase.

In the present study, an effect of daily GH treatment on the RAAS was observed after several months and peaked after 6–12 months. In previous studies in GH deficient adults, GH treatment for 6 months did not result in any significant change in aldosterone [21,22], but one of these studies observed an increase in PRA [21]. In children with ISS, GH therapy did not increase PRA and aldosterone levels over 4 months [23]. One study reported that GH administration to 9 children with ISS, three times a week for 1 yr, did not increase aldosterone and PRA levels [24]. Thus, the negative findings of these previous studies may be due to their non-daily or short time schedules (< 6 months).

The finding of lower aldosterone levels in GH deficient subjects and animals is also consistent with a role for GH in the activation of the RAAS. In a 12 yr old girl with isolated GH deficiency, the cessation of GH therapy in two occasions, at age 16 and 21, resulted in symptomatic hyporeninemic hypoaldosteronism. The symptoms resolved and PRA and aldosterone levels normalized only after the resumption of GH therapy [25]. In GH deficient rats, aldosterone levels were significantly lower than in normal rats [17].

In our study population, the serum and urine electrolytes during GH therapy did not change over pre and posttreatment periods. Similarly, no significant changes in serum Na^+ and K^+ levels were observed in children with ISS during 5 yr of GH therapy [26]. Administration of large doses of aldosterone results in sodium retention within about 2 weeks. However, after continued administration of aldosterone, a phenomenon known as 'mineralocorticoid escape' is observed, resulting in increased urinary sodium excretion [27]. Thus, the lack of salt retention on prolonged GH therapy may be due to this phenomenon.

GH treatment may also affect SSR and composition. Our PHA patient with GH deficiency exhibited a decreased SSR that significantly improved on GH therapy. GH therapy for 21 months significantly affected the electrolyte composition of the sweat, and reduced the Na^+/K^+ ratio by more than 60%. Adult patients with GH deficiency have decreased sweating and impaired thermoregulation, thus they are at risk of developing hyperthermia during exercise or whenever core or ambient temperatures are high [28,29]. In a PHA patient who suffers from recurrent episodes of dehydration and hyponatremia, GH deficiency increases the risk of hyperthermia, and GH therapy may in turn decrease this risk.

4.2. The mechanism of growth hormone and insulin-like growth factor-I effects on renin–aldosterone system

During the course of GH treatment over 12–21 months, aldosterone and IGF-I increased in parallel and peaked about the same time, both in the PHA patient and in children with ISS. In the PHA patient, IGF-I strongly correlated with both PRA and aldosterone during the whole study period. Similarly, IGF-I and aldosterone strongly correlated in children with ISS. These correlations of IGF-I with renin and aldosterone levels suggest that GH may act via IGF-I in activating RAAS. Administration of IGF-I both in young adults [30] and elderly women [31] resulted in

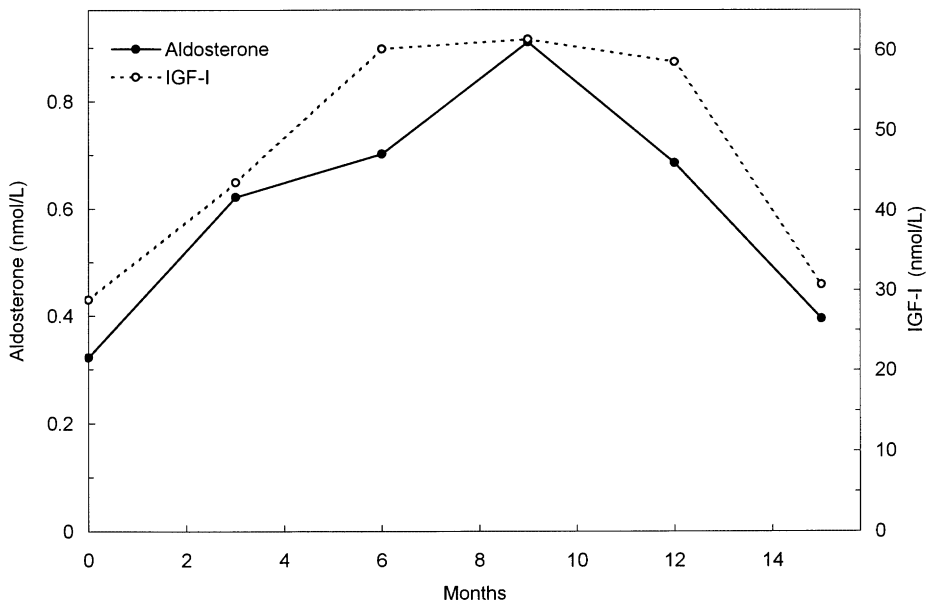

Fig. 4. The effect of GH therapy on serum IGF-I and aldosterone levels in children with ISS.

salt and water retention; neither study, however, examine the relationship between serum aldosterone and IGF-I.

The parallelism of PRA and aldosterone suggests that the GH/IGF-I effect is primarily exerted early in the RAAS, rather than on the adrenal. The mechanism of IGF-I effect on stimulation of RAAS may also include a direct effect on adrenal cortical responsiveness to angiotensin, determined by the levels of the steroidogenic enzymes [32]. In cultured adrenal cells IGF-I was shown to enhance the levels of steroidogenic enzymes and of both angiotensin II and ACTH receptors [33,34].

GH may stimulate the RAAS in additional sites. In GH deficient rats, GH therapy for 7–28 days stimulated the substrate angiotensinogen and upregulated angiotensin II receptors in kidneys and liver [16]. In healthy subjects, GH therapy for 6 days increased renin, angiotensin II and IGF-I and induced water retention. In these subjects, blockade of the RAAS by the angiotensin converting enzyme inhibitor captopril or by spironolactone prevented water retention, suggesting that blockade of the RAAS by either of the two separate mechanisms abolishes the GH effect on RAAS [14]. GH therapy may also induce hyperinsulinemia that may in turn affect RAAS. However, insulin cannot be responsible for the effects we observed, since it increases PRA while decreasing aldosterone concentration [35].

IGF-I has been suggested to increase fluid retention and renal Na^+ reabsorption through activation of amiloride sensitive Na^+ channels [19]. GH activation of RAAS in our PHA patient with a mutated ENaC (R508Stop) suggests that GH/IGF-I may exert their effects despite the lack of a fully functional ENaC. Functional expression of the same mutated ENaC subunit in Xenopus oocytes revealed significant residual activity of the channel apparently supported by the beta and gamma subunits [36]. In humans, however, this mutation is associated with severe PHA, suggesting nearly complete inactivation.

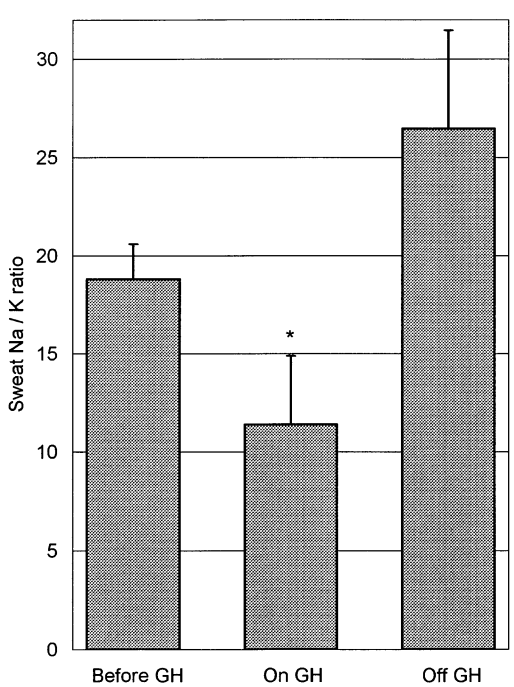

Fig. 5. The mean sweat Na^+/K^+ ratios, before, during and after GH therapy in PHA patient 1. Asterisk marks significant difference from 'before GH' mean value ($P < 0.006$).

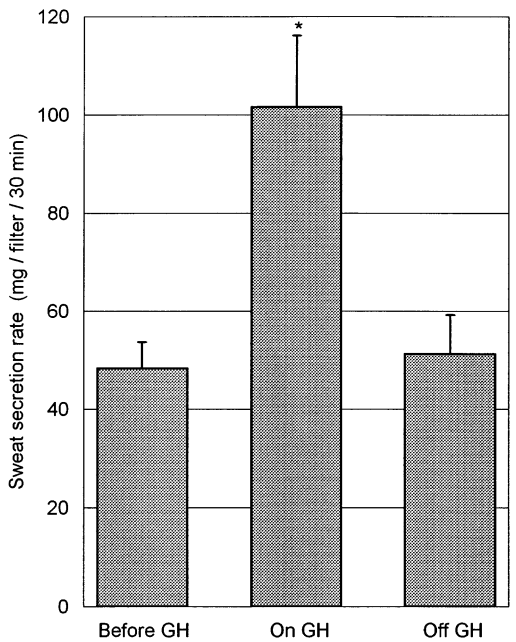

Fig. 6. SSR before, during and after GH therapy in PHA patient 1. The values are expressed as mean ± SEM. Asterisk marks significant difference from 'before GH' mean value ($P < 0.006$).

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