41

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EVIDENCE THAT POTASSIUM DEFICIENCY INDUCES GROWTH RETARDATION THROUGH REDUCED SOMATOMEDIN C PRODUCTION.

Growth retardation and impaired protein synthesis are major characteristics in potassium (K) depletion in animals and man. After K-repletion serum and muscle contents of K are normalized within few hours, while protein synthesis only reach control levels within days. In the present study we measured somatomedin C levels during K depletion (fodder containing 1 mmol/kg) and repletion in young rats (4 weeks old). Weight gain during K-depletion for 2 weeks was 3.5 ± 2.3 g (SD) and in controls 83 ± 5 g ($P < 10^{-8}$). Weight gain after K-repletion for 24 and 72 hours was 9 ± 2 g and 19 ± 9 g respectively ($p < 10^{-3}$ and $P < 10^{-2}$). Serum somatomedin C in K-depleted rats was 83 ± 50 ug/l (SD) versus 1035 ± 112 ug/l in controls ($P < 10^{-8}$). During K-repletion for 24 and 72 hours serum somatomedin C increased to 403 ± 73 ug/l and 423 ± 120 ug/l respectively ($P < 10^{-5}$ and $p < 10^{-3}$).

In conclusion K deficiency in young rats induces growth retardation and a concomitant pronounced decrease in circulating somatomedin C. These changes are promptly reversible following K-repletion within the first 24 hours. These findings demonstrate that the availability of K is essential for normal somatomedin C synthesis and growth.

42

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SERUM GROWTH HORMONE BINDING PROTEIN (GH-BP) IN PREPUBERTAL CHILDREN IS CORRELATED WITH HEIGHT.

Recently serum GH-BP has been shown to have identical N-terminal amino acid sequence as the tissue hGH receptor. Serum hGH levels and the specific binding activity of GH-BP (expressed as % of GH-BP activity of an adult reference serum = RSGH-BP) were estimated in 25 prepubertal children (19 M, 6 F, aged 6-11 yrs). When the results were related to height, 3 groups could be distinguished.

Gr.	n	A g e yrs	Height SDS	hGH ng/ml	RSGH-BP %
I	12	8.5±1.6	-1.9±0.5	4.0±6.1	53.6±11.7
II	5	9.3±1.3	+0.3±0.4	5.8±6.5	*67.0± 6.2
III	8	7.9±1.1	+2.2±0.4	2.9±4.6	**101.6±19.3
Adults	4	31±4			91.9±12.9

Mean ± SD * I vs. II $p < 0.025$; I vs. III $p \ll 0.001$

It is evident that GH-BP levels in children significantly correlated ($r=0.83$, $p \ll 0.001$) with height SDS, but not with basal hGH levels or age. It is therefore possible that GH-BP presents a simple non-invasive tool to determine growth hormone activity.

43

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Growth hormone profiles in GH-deficient children on and off twice daily sc GHRH therapy and during a sc infusion of GHRH.

We have previously shown that twice daily sc GHRH therapy promotes growth in GH-deficient children (Lancet 1987;i:5-8), however this is not an optimal method of administering GHRH and the development of a long-acting preparation would be much more satisfactory. To investigate this possibility we have studied GH profiles during twice daily GHRH treatment and the sc infusion of GHRH. 4 children who grew on twice daily sc GHRH therapy (500ug) had 24-hour GH profiles (15min sampling) whilst on treatment and in 1 before therapy and in the others one month after finishing treatment. Two children have had overnight GH profiles (20min sampling) during sc infusion of two doses of GHRH (5 and 10ug/kg/hr) and placebo. The results demonstrate that in GH-deficient

Patient and treatment	No. pulses	mean pulse amplitude mU/l	area under GH curve mU/l.min
1. No therapy(bd GHRH)	8(18)	3.0(6.0)	2355(6629)
2. No therapy(bd GHRH)	3(4)	0.3(11.0)	722(4065)
3. No therapy(bd GHRH)	7(5)	6.0(23.0)	3009(7095)
4. No therapy(bd GHRH)	5(9)	1.9(6.9)	1871(4038)
3. sc placebo infusion	4	6.9	1712
GHRH 5ug & 10ug/kg/hr	3 & 5	27.2 & 37.5	8331 & 18198
5. sc placebo infusion	4	15.4	3338
GHRH 5ug & 10ug/kg/hr	7 & 5	21.8 & 58.0	9980 & 18463

children twice daily GHRH increases pulse amplitude and AUC for GH but not always pulse frequency, a similar effect is seen during the sc infusion of GHRH. These results suggest that a depot preparation of GHRH delivering 5ug/kg/hr would promote pulsatile GH release.

44

The GH-RH European Multicenter Study Group
(To be presented by L. Tatò - Clinica Pediatrica Verona, Italy)

HEIGHT VELOCITY OF 111 PREPUBERTAL CHILDREN WITH GROWTH HORMONE (GH) DEFICIENCY TREATED WITH GROWTH HORMONE-RELEASING HORMONE (GH-RH 1-44 NH2) : A RANDOMIZED DOUBLE-BLIND DOSE RANGING STUDY.

Once daily subcutaneously synthetic GH-RH 1-44 NH2 (Sanofi Recherche France) was given in double blind fashion, for six months to 111 prepubertal children (70 boys, 41 girls, aged 2.5 to 14.3 years) with growth failure (height 2 SD below the mean for chronological age and height velocity HV < the 10th centile for bone age) due to idiopathic GH deficiency (peak GH<20mUI/L to 2 standard provocative tests). Patients were stratified in 2 classes according to body weight and randomly allocate to 1 of 7 GH-RH doses, from 30 to 300 mcg/daily dose. Mean HV, expressed in SD (+/- SEM) for bone age, increased from -2.6 (+/-0.1) during 6 months pretreatment up to -0.3 (+/-0.2) during treatment period. No relationship was found between the GH-RH dose (ranging from 1.3 to 23.1 mcg/Kg/day) and either absolute HV or the net increment in HV. During treatment HV was equal or above the mean for bone age (catch up growth criteria) in 47/111 (42%) patients. The highest height velocities HV during treatment were observed in children with less retarded growth. No clinical adverse effect was observed. Low titer antibodies to GH-RH developed in 18 patients (16%).

In summary this study documented a net increase in HV but failed to relate it to the dose of GH-RH used. Tolerance to GH-RH treatment was good. The demonstration of dose-response effect of GH-RH on HV requires to investigate a broader range of doses of GH-RH and/or different daily dosage regimen.

45

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OVERNIGHT GROWTH HORMONE (GH) RELEASE AND GH RESPONSE TO TRH IN ADOLESCENT DIABETES

GH release is abnormally regulated in insulin-dependent diabetes (IDDM). Paradoxical stimulation of GH after TRH and an association with retinopathy has been reported in young adults. However, overnight secretion of GH is also increased in IDDM, and it may be difficult to distinguish spontaneous release from that seen after TRH. To resolve this question we carried out TRH and saline control studies following overnight GH profiles in 6 adolescents with IDDM.

4 boys and 2 girls (age 11.4-14.7 y; pubertal stage 2-4: duration IDDM 2.4-6.7 y; HbA_1C 8.4-11.5%) had 2 GH profiles (15 min aliquots by continuous sampling from 20.00-08.00 hrs) 4-6 wks apart. At 08.10 hrs TRH (200 mcg) or saline (1ml 0.9%) were given IV. Samples were taken at -10, 0, 10, 20, 30, 40, 60 and 90 min for GH.

A rise in GH was seen in 4 of 6 following TRH, but with no consistent pattern, the peak occurring at any time between 10 and 90 min. A rise was also seen in 5 of 6 following saline. Mean blood glucose was identical during TRH and saline tests (9.5 ± 1.6 vs 7.5 ± 0.6 mmol/l, $\bar{x}$ ± SEM, $p = 0.35$). Peak GH levels were similar (19.3 ± 4.4 vs 25.8 ± 5.5 mU/l) after TRH and saline ($p = 0.4$), as were mean GH and areas under GH curve. The timing of the GH peak after both TRH and saline could be predicted from the overnight secretory profile.

Paradoxical GH rise following TRH is not seen in adolescents with IDDM. Previous reports of GH release after TRH may have been due to timing coincident with a normal GH pulse.

46

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CALCULATION OF PITUITARY GROWTH HORMONE (GH) SECRETION RATE IN CHILDREN.

We have assessed the half-life of endogenous GH in 8 normal adults by measuring the decline of GH concentrations in venous blood taken at 10 minute intervals following stimulation by bolus intravenous injection of GHRH followed by an infusion of somatostatin-14 (3µg/kg/min) over 120 minutes. The half-life of GH (18.24 min) was calculated from natural log transformed data, the decline being described by a simple exponential consistent with a single pool model.

GH delivery rate from the pituitary gland was calculated by deconvolution using the estimate of the endogenous half-life and 24 hr GH profiles in 16 prepubertal and 12 pubertal children. GH production was negligible at the end of each secretory cycle, an 'on-off' phenomenon. GH secretion rate was relatively constant for size during childhood but a 3-4 fold increase was demonstrated during puberty.

Knowledge of GH delivery rate from the pituitary gland should be taken into account in calculating the therapeutic regimen of GH and/or GHRH, especially during puberty.