Growth hormone and the heart in children

Akademisk avhandling
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av

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Avhandlingen baseras på följande delarbeten:

I. **Nygren A**, Sunnegårdh J, Albertsson-Wikland K, Berggren H, Isgaard J. **Relative expression of growth hormone receptor and insulin-like growth factor-I mRNA in congenital heart disease.**
J.Endocrinol Invest 2008;31:196-200

II. **Nygren A**, Andersson B, Decker R, Nierop AF, Sunnegårdh J, Kriström B, Albertsson-Wikland K. **Cardiac structure and function in short prepubertal children. Association with spontaneous GH secretion pattern and metabolic factors.** Submitted to Clinical Endocrinology (Oxf) 2012.

III. **Nygren A**, Sunnegårdh J, Teien D, Jonzon A, Björkhem G, Lindell S, Albertsson-Wikland K, Kriström B. **Rapid cardiovascular effects of growth hormone treatment in short prepubertal children. Impact of treatment duration.** Clinical Endocrinology (Oxf) 2012, In Press. DOI: 10.1111/j.1365-2265.2012.04456.x

IV. Decker R, **Nygren A**, Kriström B, Nierop A, Gustafsson J, Albertsson-Wikland K, Dahlgren J. **Different thresholds of tissue-specific dose-responses to growth hormone in short prepubertal children.** Accepted for publication in BMC Endocrine Disorders. 2012.

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ABSTRACT

Background and Aims: The fact that growth hormone (GH) influences cardiovascular structure and function is well established through both human and animal studies. Despite being secreted in a pulsatile fashion, only the impact of peak GH concentrations on cardiac parameters has previously been reported, and the time-dependency of cardiovascular effects during GH treatment has not been detailed. The aims of this pediatric study were (i) to establish the expression of GH-receptor (GH-R) and insulin-like growth factor I (IGF-I) mRNA locally in the heart in children of different ages, (ii) to study in detail the relationship between the heart and endogenous GH secretion pattern, (iii) to study the cardiovascular effects of GH treatment and (iv) to examine organ/tissue-specific responses to GH.

Patients & Methods: Two trials were conducted. In the first, a cardiac biopsy was taken from 18 children undergoing heart surgery. GH-R and IGF-I mRNA were quantified by real-time polymerase chain reaction. In the second trial, 153 short prepubertal children were randomized to receive either a standard or an individualized GH dose. Echocardiography, blood pressure measurements and electrocardiography were performed at study start, and after 3 months, 1 year and 2 years of GH treatment.

Results: GH-R and IGF-I mRNA was found in all children studied. There was a significant relationship between their relative amounts (r=0.75, $p<0.001$), and body mass index was correlated with the relative expression of both genes (r=0.59, $p=0.01$ and r=0.50, $p=0.04$ respectively). Cardiac dimensions were not correlated with peak endogenous GH concentration but were negatively correlated with GH trough levels (r= –0.41, $p<0.001$) and positively correlated with GH secretion rate above baseline level (r=0.44, $p<0.001$). During treatment, a biphasic, time-dependent, cardiac response was seen. Initially, there was an increase in both standard deviation scores (SDS) for left ventricular (LV) diameter in diastole SDS (95% confidence interval (CI) for the increase in SDS from baseline to 3 months ($\Delta LVDd_{SDS0–3m}$): 0.05 to 0.36) and LV wall thickness, exemplified by septal thickness ($\Delta IVDd_{SDS0–3m}$: 95% CI 0.08 to 0.54). At 2 years, wall thickness returned to baseline values ($\Delta IVDd_{SDS0–24m}$: 95% CI -0.41 to 0.06) but LV diameter remained increased ($\Delta LVDd_{SDS0–24m}$: 95% CI 0.19 to 0.47). The heart was also found to be more responsive than both skeletal muscle and bone tissue to GH treatment. The dose resulting in a 50% response (ED50%) was as low as 33 µg/kg/d (90% confidence bounds: 24–38 µg/kg/d)) for LVDd compared with an ED50% of 51 (47–56) µg/kg/d for longitudinal growth and 57 (52–65) µg/kg/d for IGF-I.

Conclusion: With the presence of local GH-R and high sensitivity of the heart to GH, cardiac tissue is a primary target for GH. The GH trough levels seem to be of greater importance for cardiac dimensions than the peak GH concentrations, and the response to GH treatment is time-dependent and differs between LV wall thickness and LV diameter. This demonstrates that GH regulation of cardiovascular variables is more complex than previously demonstrated.

Keywords: Growth hormone secretion pattern, cardiovascular dimensions, Growth hormone treatment

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