Regulation and modulation of growth : insights from human and animal studies

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Chapter 8

Summary

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Postnatal growth in humans is programmed by a person's individual genetic blueprint and fine-tuned by hormonal, environmental, psychosocial and nutritional factors. For decades, scientists have been determined to identify regulatory mechanisms associated with growth and to unravel the pathophysiological processes underlying growth disorders. Increased insight into those mechanisms and processes is fundamental for the development of novel treatment strategies for enhancing growth in children with idiopathic short stature. This thesis consists of three parts, in which several aspects of growth modulation and regulation are investigated.

Part A describes the long-term results of two randomized controlled clinical trials in which novel treatment modalities for children with ISS were analyzed. At the time these clinical trials were initiated, there were several unresolved issues with respect to the optimal growth hormone treatment strategy for children with ISS:

(1) What is the effect of a high GH dosage on growth velocity, bone maturation, puberty and adult height?
(2) What is the relative contribution of GH treatment before and during puberty?
(3) Which factors can predict the individual growth response to GH treatment?
(4) Can height gain be optimized by co-treatment with a GnRH agonist?

Chapter 2 describes that high dose GH treatment restricted to the prepubertal period, and administered to young children, increased height gain during treatment, but simultaneously accelerated bone maturation and ultimately did not lead to an increased adult height. Moreover, there were indications that high dose GH treatment may have led to an advanced pubertal onset. Our results are in contrast with data from other groups that have reported a positive effect of high dose GH treatment on adult height in older children. We speculate that the discrepancy between our and other trials may rely on an increased sensitivity of the epiphyseal growth plates of younger children in comparison with those of older children to high doses of GH (and/or IGF-I). The finding of a similar predicted adult height in treated and untreated groups at the time of discontinuation of treatment (at pubertal onset) makes it unlikely that prolonged GH treatment during pubertal development would have led to better adult height results. Age at onset of treatment was found to show a positive correlation with height outcome, which is in contrast with data from other trials that have identified a negative correlation between age at onset and adult height. Again, an explanation for this difference

may reside in the considerably younger age at onset of treatment in our trial. Apart from age at onset, our study did not identify other predictive factors for growth response to GH therapy. We concluded that a regimen of high dose GH started at an early age in children with ISS, and restricted to the prepubertal phase, was not effective and therefore not to be advised.

Chapter 3 demonstrates that the addition of a GnRHa to GH treatment in children with ISS and a relatively early onset of puberty increased adult height, especially in girls. However, postponing pubertal development may have a negative impact on psychosocial development in young children, and there were also indications of a lower bone mineral density of the lumbar spine in treated boys. These aspects require additional investigation. In the meantime, combined GH and GnRHa treatment should not be routinely prescribed for growth stimulation in children with ISS, but it may be considered in strictly selected individual cases, especially in girls with an extremely low predicted adult height, an early onset of puberty, and considerable psychosocial problems associated with being short.

Part B assesses the effect on growth and the potential side effects of estrogen depletion by treatment with an aromatase inhibitor (exemestane) on growth in an experimental animal model. Aromatase inhibition resulted in a sexual dimorphic response in young rats. In female rats, exemestane treatment resulted in augmented length and weight gain, longer femurs and an increased growth plate width, as illustrated in ***Chapter 4***. However, adverse effects on genital development were found, including uterus atrophy and polycystic ovaries. The observed effects on growth and genital development are consistent with the phenotype of female aromatase-deficient patients. As long as it is uncertain whether the genital abnormalities are reversible or whether long term effects on fertility and reproduction are to be expected, aromatase inhibitors should not be considered in the treatment of girls with ISS.

In male rats, a decreased weight gain was found, without effects on axial and appendicular growth and genital development (***Chapter 5***). In contrast, the growth phenotype of male estrogen-deficient or estrogen-resistant patients is characterized by the absence of a pubertal growth spurt and ongoing growth into adulthood resulting in a tall stature. Also, clinical trials with aromatase inhibitors in boys with ISS or short stature due to constitutional delay of growth and puberty have demonstrated a positive effect of estrogen depletion on adult height. The difference between these data and our results may rely on species differences. It suggests that the rat, at least the male rat, is not a suitable animal model for studying the effect of aromatase inhibition on growth.

In both male and female rats, we found evidence of osteopenic changes of the bone due to aromatase inhibitor treatment, which may precede the development of osteoporosis. In aromatase-deficient patients, osteoporosis has also been described. Recently, MRI-analysis of

the spine in boys treated with an aromatase inhibitor revealed the occurrence of vertebral body deformities. These collective data urge for a reluctant attitude towards the application of aromatase inhibitors in growth-enhancing treatment strategies in children with ISS. Additional research is necessary to identify the pathological mechanisms underlying the observed changes in bone quality.

In **part C** the role of mesenchymal stem cells differentiating towards the chondrogenic lineage as a potential new *in vitro* model for growth plate physiology is evaluated. Development of alternative model systems is required, as the available animal models for growth studies are all hampered in the sense that they do not fully represent the human growth pattern, and species differences sometimes hamper the interpretation of results from animal experiments. In ***Chapter 6*** it is shown that human fetal MSCs can indeed differentiate into chondrocytes, and that the gene expression profile bears more resemblance to the profile of epiphyseal than to that of articular chondrocytes. This model is suitable to further study the role of the numerous genes that are associated with growth plate maturation and fusion. This may aid in the identification of new angles for the development of novel treatment strategies as alternatives to regular GH therapy for enhancing growth in children with ISS.

In ***Chapter 7*** the major findings of this thesis are summarized and critically reviewed in the perspective of current literature. It is discussed that high dose GH or combined GH and GnRHa treatment are no routine alternatives to standard GH treatment schedules. Results from rat studies also do not support the use of aromatase inhibitors in growth enhancement strategies. Future studies may need to ameliorate the tools to assess psychosocial consequences of short stature and to develop better methods for counselling short children who suffer from being short.
Finally, the limited role of animal models for the analysis of human growth regulation and modulation has urged the development of an alternative human model system. Using a model of human fetal mesenchymal stem cells differentiating towards the chondrogenic lineage may render new insights into human growth regulation and may aid the development of new methods for growth modulation.