Role of Insulin-Like Growth Factors in Growth, Development and Feeding

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Abstract

Information about the role of insulin-like growth factors (IGFs) is mainly derived from knockout (KO) and transgenic mice, human mutations in \( IGF1 \), \( IGF1R \) and \( IGFALS \), and association studies with \( IGF1 \) SNPs. \( Igf1 \) KO mice show severely impaired pre- and postnatal growth and brain development and sensorineural hearing loss. Both local and endocrine IGF-1 are needed for normal growth. \( Igfals \) KO mice show a modest postnatal growth attenuation. Homozygous \( igf1r \) KO mice are severely growth impaired, while heterozygous mutations only show mild growth retardation. Two patients with a complete absence of biologically active IGF-1 showed severe pre- and postnatal growth, extreme microcephaly, sensorineural deafness and failure to thrive. A patient with a mutation that led to a partially functional protein had a less severe growth phenotype and no deafness, similarly to two siblings with a heterozygous \( IGF1 \) mutation. Heterozygosity for a dysfunctional \( IGF1 \) mutation leads to a mild effect on birth weight, adult height and head circumference. Patients with heterozygous mutations or deletions of \( IGF1R \) have a moderate pre- and postnatal growth failure, microcephaly and a history of feeding problems. Children with homozygous mutations of \( IGFALS \) have a low or normal birth weight, a mild growth failure, a head circumference in the lower normal range, and no failure to thrive. Association studies of \( IGF1 \) polymorphisms in large populations have shown variable results with respect to height, but a more consistent association with head circumference. In conclusion, a normal IGF-I bioactivity (normal local and endocrine IGF-1 availability, normal IGF1R function, normal signaling) is needed for a normal pre- and postnatal growth failure, microcephaly and a history of feeding problems. Children with homozygous mutations of \( IGFALS \) have a low or normal birth weight, a mild growth failure, a head circumference in the lower normal range, and no failure to thrive. Association studies of \( IGF1 \) polymorphisms in large populations have shown variable results with respect to height, but a more consistent association with head circumference. In conclusion, a normal IGF-I bioactivity (normal local and endocrine IGF-1 availability, normal IGF1R function, normal signaling) is needed for a normal pre- and postnatal longitudinal and cranial growth. IGF-1 dysfunction causes severe growth failure, while heterozygous defects of \( IGF1R \) and homozygous defects of \( IGFALS \) are associated with a milder phenotype. Feeding disturbances in infants with \( IGF1 \) and \( IGF1R \) mutations suggest a role of IGF-1 signaling in regulatory brain centers.

Information about the role of insulin-like growth factors (IGFs) in body growth and development has primarily been obtained by observations in knockout (KO) mice, human mutations of \( IGF1 \), \( IGF1 \) receptor (\( IGF1R \)) and \( IGF \) Acid Labile Subunit (\( IGFALS \)), and studies on associations of growth parameters with \( IGF1 \) polymorphisms and serum IGF-1 levels. Only limited information is available about the role of IGFs in regulation of feeding behavior. In this minireview, we shall discuss the current views on these topics.
Animal Models

The generation of mice in which the genes for IGF-1, IGF-2 and the IGF1R were knocked out by the groups of Estratiadis [1, 2] and Stewart [3] was an important breakthrough in the study of the role of IGFs on pre- and postnatal growth. *Igf1(−/−)* knockout mice had birthweights of 60% [1, 3]. Heterozygous mice were healthy and fertile, but were 10–20% smaller than wild-type littermates and had lower than normal serum levels of IGF-I [3]. *Igf1r(−/−)* mice and the double knockout mice (*Igf1(r−/−)/Igf1(−/−)) were more growth retarded at birth (45% of normal) [1]. Depending on genetic background, some of the *Igf-1(−/−)* dwarfs died shortly after birth (e.g. more than 95% of *Igf1(−/−)* pups died perinatally in one of the studies [3]), while others survived and reached adulthood [1]. *Igf1r(−/−)* knockout mice died within minutes after birth due to respiratory failure, while *Igf1r(+/−)* mice were phenotypically normal [1]. Since mice with severe growth hormone (GH) deficiency show normal intrauterine growth, these experiments suggested that in the mouse IGF-1 is the major determinant for intrauterine growth, independently of GH, and that its effects are mediated through the IGF1R.

In the first two weeks of postnatal life, growth of the Snell dwarf (*Prop1(−/−))* , the Ames dwarf (*Pit1(−/−))*, the Little (*Ghrhr(−/−))* and Laron (*Ghr(−/−))* mice was indistinguishable from their wild-type littermates [4]. At postnatal day 40, however, their size was about 50% of normal, which confirms the increasing role of GH in postnatal life. Also the size of the *Igf1* knockout mice decreased progressively from 60% of normal at birth to 30% of normal at 8 weeks [2]. The most severe growth retardation was observed in double knockout mice (*Ghr(−/−)/Igf1(−/−)).* These mice have a postnatal growth pattern of only 17% of normal [4]. The heterozygous *Igf1r(−/+)* mice were phenotypically normal, with normal expression of *igf1r* mRNA, suggesting that the intact wild-type allele is upregulated and implying that a single functional *Igf1r* allele is sufficient to assure normal growth [1]. However, later experiments inducing reduced availability of the *Igf1r* (41% less than normal) showed a growth deficit of 13% in males and of 6% in females. This implied that a partial reduction in IGF-1 signaling reduces the growth potential, at least in the male mouse [5]. These findings also demonstrated that GH-dependent IGF-1 action is the main determinant of postnatal growth, but that GH and IGF-1 have also independent effects [4].

Several studies have tried to unravel the relative effects of endocrine and local IGF-1. Opinions switched from a fully endocrine role (the original somatomedin hypothesis) to a fully local role (the ‘somatomedin hypothesis revisited’) to somewhere in the middle [6]. A study using targeted gene deletion of liver-specific IGF-1 and ALS (LID/ALSKO mouse), resulting in an 85–90% reduction of circulating IGF-1, showed a 20% lower body weight than observed in control mice. Although this is less than the 60% reduction observed in the *Igf1* knockout mice, it showed that besides the predominant effect of tissue IGF-1, also endocrine IGF-1 plays a role in postnatal growth regulation [7]. A later study showed that endocrine IGF-1 contributes approximately 30% of the adult body size and sustains postnatal development, including the
reproductive functions of both sexes [8]. An experimental model of overexpression of the rat Igf1 transgene in livers of Igf1 null mice showed that the elevated serum IGF-1 failed to overcome growth and skeletal deficiencies during neonatal and early postnatal growth, but fully compensated for the absence of locally produced IGF-1 between 4 and 16 weeks [9]. The important role of endocrine IGF-1 was also highlighted by the observations that the growth defect and bone deficiency caused by lack of growth hormone signaling (in Ghr(−/−) mice) can be effectively restored by increasing IGF-1 production (by crossing with mutant Igf1 transgenic mice) in vivo [10].

There is convincing evidence that early postnatal nutrition determines later somatotropic function in mice. A French study [11] showed that underfeeding during the early postnatal period delayed growth, whereas overfeeding accelerated it, in both cases leading to permanently altered final body size. This was associated with alterations in pituitary GH, and plasma IGF-1 and ALS, as well as in gene expression of hypothalamic GHRH. It suggested that IGF-1 plays a role in modulating hypothalamic stimulation of the developing somatotropic function. Another study from the same group [12] showed that brain IGF-1 receptors control mammalian growth and lifespan.

In the mouse, IGF-1 is not only a key player in longitudinal growth, but also in brain development. IGF-1 stimulates neurogenesis and synaptogenesis, facilitating oligodendrocyte development, promoting neuron and oligodendrocyte survival and stimulating myelination. As systemic IGF-1 is not readily transported through the blood-brain-barrier, local production of IGF-1 is considered to be responsible for these effects [13].

IGF-1 plays a special role in sensoneural hearing. Auditory brainstem response in Igf1(−/−) mice showed bilateral sensorineural hearing loss with a delayed response to acoustic stimuli along the auditory pathway, indicating that the central nervous system contributes to the hearing loss. At a cellular level a significant decrease in number and size of auditory neurons, increased apoptosis of cochlear neurons, a significant reduced volume of the cochlea and cochlear ganglion resulting in abnormal differentiation and maturation of the cochlear ganglion cells and abnormal innervation of the sensory cells in the organ of Corti was observed [14].

With respect to effects on bone, the lack of IGF-1 leads to the development of a bone structure, which, although smaller, appears more compact (for review, see [15]). IGF-1 appears to regulate peak bone mineral density by both GH-dependent and –independent mechanisms. Experiments with inducible liver IGF-I deficient (iLID) mice showed that while serum IGF-1 is essential for bone accrual during the postnatal growth phase [9], depletion of IGF-1 after peak bone acquisition is compartment-specific and does not have a detrimental effect on cortical bone mass in the older adult mouse [15, 16].

With respect to the role of IGF-1 in glucose metabolism, double-knockout studies showed that whereas GH plays a major role in inducing insulin resistance, IGF-1 may have a direct modulatory role [17]. IGF-1 has also effects on gonadal function, the immune system and longevity (for review, see [18]). We have not found information about feeding behavior in Igf1 or Igf1r knockout mice.
The significant heterogeneity in serum IGF-1 concentrations among inbred strains of mice may be explained by differences in a single sequence repeat polymorphism in the promoter region of \textit{IGF1} \cite{19}. In dogs, a single IGF1 allele is a major determinant of small size \cite{20}.

**Human Mutations**

IGF-1 defects are characterized by a very low (in case of deletion or nonsense mutation) or elevated (in case of a mutated IGF-1 molecule that is detected in the IGF-1 assay) serum IGF-1 and a normal IGFBP-3. At present, two individuals with well documented severe homozygous IGF-1 defects have been reported, and one case with a less severe phenotype. There may be a fourth case, but although the phenotype was very similar, the presumed genetic aberration at the polyadenylation site at the 3'UTR in exon 6 was later found to also occur in healthy controls. Heterozygosity for an \textit{IGF1} mutation or deletion may be associated with a mild height loss (in the order of 1 SD), that can present as more severe short stature if occurring in a genetically short family (reviewed in \cite{21}).

The clinical phenotype of the two severe cases consists of severe pre- and postnatal growth, extreme microcephaly, sensorineural deafness and failure to thrive, and in the patient described by our group there was a history of poor feeding in infancy and young childhood. A patient with a mutation that led to a partially functional protein had a less severe growth phenotype and no deafness, similarly to two siblings with a heterozygous \textit{IGF1} mutation \cite{22}. In the family with the missense \textit{IGF1} mutation, heterozygosity for a dysfunctional \textit{IGF1} mutation was associated with a mild effect on birth weight, adult height and head circumference (reviewed in \cite{21}).

Patients with heterozygous mutations or deletions of \textit{IGF1R} have a moderate pre- and postnatal growth failure, microcephaly, failure to thrive and feeding problems. Children with homozygous mutations of \textit{IGFALS} have a low or normal birth weight, a mild growth failure, a head circumference in the lower normal range, and no feeding problems \cite{21}.

**Association Studies**

In a large population study it was shown that common genetic variation in eight genes of the GH/IGF-1 axis, including \textit{IGF1}, did not contribute to adult height variation \cite{23}. A family-based association study in premenopausal women failed to show associations of \textit{IGF1} haplotypes with height, weight and BMI \cite{24}. The results of studies on associations between \textit{IGF1} polymorphisms and growth parameters in various groups of patients were recently reviewed \cite{25}. In some of these studies a statistically significant association with height was encountered, but other studies showed negative results. A more consistent association of these polymorphisms with
head circumference has been observed. For example, in preterm born children we recently reported a significant association between an IGF1 promoter polymorphism and head circumference [26]. With respect to serum IGF-1, there are several reports showing that serum IGF-1 levels are associated with pre- and postnatal growth, for example a recent study on term born children and adolescents (2–20 years) [27].

Nutrition is one of the main regulators of circulating IGF-1 (for review, see [28]). In a dietary intervention study in children, associations between serum IGF-1, IGFBP-3 and its ratio versus dietary intake were determined. In analyses adjusted for energy and time since menarche, significant correlations were found between serum IGF-1 and total protein, lactose, calcium and sodium. In multivariate analyses energy and calcium were significant predictors [29]. A study on the association between the diet as assessed by a 3-day food record and serum IGF-1 showed that cow’s milk and dairy product intakes were positively associated with IGF-1 and IGFBP-3 [30].

**Conclusion**

In conclusion, a normal IGF-1 bioactivity (normal local and endocrine IGF-1 availability, normal IGF1R function, normal postreceptor signaling) is needed for a normal pre- and postnatal longitudinal and cranial growth. IGF-1 dysfunction causes severe growth failure, while heterozygous defects of IGF1R and homozygous defects of IGFALS are associated with a milder phenotype. Feeding disturbances in infants with IGF1 and IGF1R mutations suggest a role of IGF-1 signaling in regulatory brain centers for appetite regulation.

**References**