Insulin-like growth factor 1 (IGF-1): a growth hormone

Z Laron

Abstract
Aim—To contribute to the debate about whether growth hormone (GH) and insulin-like growth factor 1 (IGF-1) act independently on the growth process.

Methods—To describe growth in human and animal models of isolated IGF-1 deficiency (IGHD), such as in Laron syndrome (LS; primary IGF-1 deficiency and GH resistance) and IGF-1 gene or GH receptor gene knockout (KO) mice.

Results—Since the description of LS in 1966, 51 patients were followed, many since infancy. Newborns with LS are shorter (42–47 cm) than healthy babies (49–52 cm), suggesting that IGF-1 has some influence on intrauterine growth. Newborn mice with IGF-1 gene KO are 30% smaller. The postnatal growth rate of patients with LS is very slow, the distance from the lowest normal centile increasing progressively. If untreated, the final height is 100–136 cm for female and 109–138 cm for male patients. They have acromelia, organomicria including the brain, heart, gonads, genitalia, and retardation of skeletal maturation. The availability of bio-synthetic IGF-1 since 1988 has enabled it to be administered to children with LS. It accelerated linear growth rates to 8–9 cm in the first year of treatment, compared with 10–12 cm/ year during GH treatment of IGHD. The growth rate in following years was 5–6.5 cm/year.

Conclusion—IGF-1 is an important growth hormone, mediating the protein anabolic and linear growth promoting effect of pituitary GH. It has a GH independent growth stimulating effect, which with respect to cartilage cells is possibly optimised by the synergistic action with GH.

Keywords: insulin-like growth factor I; growth hormones; Laron syndrome; growth

In recent years, new technologies have enabled many advances in the so called growth hormone (GH) axis (fig 1). Thus, it has been found that GH secretion from the anterior pituitary is regulated not only by GH releasing hormone (GHRH) and somatostatin (GH secretion inhibiting hormone), but also by other hypothalamic peptides called GH secretagogues, which seem to act in synergism with GHRH by inhibiting somatostatin. One of these has been cloned and named Ghrelin. The interplay between GHRH and somatostatin induces a pulsatile GH secretion, which is highest during puberty. GH induces the generation of insulin-like growth factor 1 (IGF-1, also called somatomedin 1) in the liver and regulates the paracrine production of IGF-1 in many other tissues.

IGF-1
IGF-1 and IGF-2 were identified in 1957 by Salmon and Daughaday and designated “sulphation factor” by their ability to stimulate 35-sulphate incorporation into rat cartilage. Froesch et al described the non-suppressible insulin-like activity (NSILA) of two soluble serum components (NSILA I and II). In 1972, the labels sulphation factor and NSILA were replaced by the term “somatomedin”, denoting a substance under control and mediating the effects of GH. In 1976, Rinderknecht and Humbel isolated two active substances from human serum, which owing to their structural resemblance to proinsulin were renamed “insulin-like growth factor 1 and 2” (IGF-1 and 2). IGF-1 is the mediator of the anabolic and mitogenic activity of GH.

CHEMICAL STRUCTURE
The IGFs are members of a family of insulin related peptides that include relaxin and several peptides isolated from lower invertebrates. IGF-1 is a small peptide consisting of 70 amino acids with a molecular weight of 7649 Da. Similar to insulin, IGF-1 has an A and B chain connected by disulphide bonds. The C peptide region has 12 amino acids. The structural similarity to insulin explains the ability of IGF-1 to bind (with low affinity) to the insulin receptor.

Figure 1 The cascade of the growth hormone axis. CNS, central nervous system; GH, growth hormone; GHBP, GH binding protein; GH-S, GH secretagogues; IGF-1, insulin-like growth factor 1; IGFBP, IGF binding protein; +, stimulation; –, inhibition.
The IGF-1 gene is on the long arm of chromosome 12q23–25. The human IGF-1 gene consists of six exons, including two leader exons, and has two promoters.17

IGF binding proteins (IGFBPs)
In the plasma, 99% of IGFs are complexed to a family of binding proteins, which modulate the availability of free IGF-1 to the tissues. There are six binding proteins.18 In humans, almost 80% of circulating IGF-1 is carried by IGFBP-3, a ternary complex consisting of one molecule of IGF-1, one molecule of IGFBP-3, and one molecule of an 88 kDa protein named acid labile subunit.19 IGFBP-1 is regulated by insulin and IGF-1,20 IGFBP-3 is regulated mainly by GH but also to some degree by IGF-1.21

The IGF-1 receptor
The human IGF-1 receptor (type 1 receptor) is the product of a single copy gene spanning over 100 kb of genomic DNA at the end of the long arm of chromosome 15q25–26.22 The gene contains 21 exons (fig 2) and its organisation resembles that of the structurally related insulin receptor (fig 3). The type 1 IGF receptor gene is expressed by almost all tissues and cell types during embryogenesis.24 In the liver, the organ with the highest IGF-1 ligand expression, IGF-1 receptor mRNA is almost undetectable, possibly because of the “downregulation” of the receptor by the local production of IGF-1. The type 1 IGF receptor is a heterotrimer composed of two extracellular spanning α subunits and transmembrane β subunits. The α subunits have binding sites for IGF-1 and are linked by disulphide bonds (fig 3). The β subunit has a short extracellular domain, a transmembrane domain, and an intracellular domain. The intracellular part contains a tyrosine kinase domain, which constitutes the signal transduction mechanism. Similar to the insulin receptor, the IGF-1 receptor undergoes ligand induced autophosphorylation.25 The activated IGF-1 receptor is capable of phosphorylating other tyrosine containing substrates, such as insulin receptor substrate 1 (IRS-1), and continues a cascade of enzyme activations via phosphatidylinositol-3 kinase (P13-kinase), Grb2 (growth factor receptor bound protein 2), Syp (a phosphotyrosine phosphatase), Nck (an oncogenic protein), and She (src homology domain protein), which associated to Grb2, activates Raf, leading to a cascade of protein kinases including Raf, mitogen activated protein (MAP) kinase, 5 G kinase, and others.26

Physiology
IGF-1 is secreted by many tissues and the secretory site seems to determine its actions. Most IGF-1 is secreted by the liver and is transported to other tissues, acting as an endocrine hormone.27 IGF-1 is also secreted by other tissues,27 including cartilagenous cells, and acts locally as a paracrine hormone (fig 4).28 It is also assumed that IGF-1 can act in an autocrine manner as an oncogene.29 The role of IGF-1 in the metabolism of many tissues including growth has been reviewed recently.31 32

The following is an analysis of whether IGF-1, the anabolic effector hormone of pituitary GH, is the “real growth hormone”.

Is IGF-1 “a” or “the” growth hormone?
The discussion on the role of IGF-1 in body growth will be based on growth in states of IGF-1 deficiency and the effects of exogenous IGF-1 administration. Experiments in nature (gene deletion or gene mutations) or experimental models in animals, such as gene knockouts, help us in this endeavour. In 1966 and 1968,33 34 we described a new type of dwarfism indistinguishable from genetic isolated GH deficiency (IGHD), but characterised by high serum GH values. Subsequent studies revealed that these patients cannot generate IGF-1.35

This syndrome of GH resistance (insensitivity) was named by Elders et al as Laron dwarfism,36 a name subsequently changed to Laron syndrome (LS).37 Molecular studies revealed that the causes of GH resistance are deletions38 or mutations39 in the IGF receptor gene, resulting in the failure to generate IGF-1 and a reduction in the synthesis of several other substances, including IGFBP-3. This unique model in humans has enabled the study of the differential effects of GH and IGF-1.

Growth and development in congenital (primary) IGF-1 deficiency (LS)
Our group has studied and followed 52 patients (many since birth) throughout childhood, puberty, and into adulthood. We found...
that newborns with LS are slightly shorter at birth (42–47 cm) than healthy babies (49–52 cm), suggesting that IGF-1 has some influence on intrauterine linear growth.\textsuperscript{40} This fact is enforced by the findings that already at birth, and throughout childhood, skeletal maturation is retarded, as is organ growth.\textsuperscript{41} These growth abnormalities include a small brain (as expressed by head circumference),\textsuperscript{41} a small heart (cardiomeria),\textsuperscript{42} and acromicria (small chin, resulting from underdevelopment of the facial bones, small hands, and small feet).\textsuperscript{33, 34} IGF-1 deficiency also causes underdevelopment and weakness of the muscular system,\textsuperscript{33} and impairs and weakens hair\textsuperscript{44} and nail growth. These findings are identical to those described in IGHD.\textsuperscript{45} IGF-1 deficiency throughout childhood causes dwarfism (final height if untreated, 100–135 cm in female and 110–142 cm in male patients),\textsuperscript{40, 41} with an abnormally high upper to lower body ratio.\textsuperscript{31} One patient reported from the UK was found to have a deletion of exons 4 and 5 of the IGF-1 gene and he too was found to have severe growth retardation.\textsuperscript{46}

Impaired growth and skeletal development in the absence of IGF-1 were confirmed in mice using knockout (KO) of the IGF-1 gene or GH receptor gene.\textsuperscript{47–49} Knockout of the IGF-1 gene or the IGF-1 receptor gene reduces the size of mice by 40–45%.\textsuperscript{49} Lack of the IGF-1 receptor is lethal at birth in mice owing to respiratory failure caused by impaired development of the diaphragm and intercostal muscles.\textsuperscript{49} In another model, the mice remained alive and their postnatal growth was reduced.\textsuperscript{50}

In conclusion, findings in humans and in animals show that IGF-1 deficiencies cause pronounced growth retardation in the presence of increased GH values.

The following is a summary of the results of the growth stimulating effects of the administration of exogenous IGF-1 to children and experimental data.

**Growth promoting effects of IGF-1**

The first demonstration that exogenous IGF-1 stimulates growth was the administration of purified hormone to hypophysectomised rats.\textsuperscript{51, 52} After the biosynthesis of IGF-1 identical to the native hormone,\textsuperscript{53} trials of its use in...
Table 1  Linear growth response of children with Laron syndrome treated by means of insulin-like growth factor 1 (IGF-1)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Ref.</th>
<th>N</th>
<th>Age range (years)</th>
<th>BA SDS</th>
<th>Ht SDS</th>
<th>IGF-1 dose (µg/kg/day)</th>
<th>Growth velocity (cm/year) Year of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranke et al</td>
<td>1995</td>
<td>61</td>
<td>31</td>
<td>3.7–19</td>
<td>1.8–13.3</td>
<td>−6.5</td>
<td>40–120 b.i.d.</td>
<td>3.9 (1.8) (n = 24) 0 1st 2nd 3rd</td>
</tr>
<tr>
<td>Backeljauw et al</td>
<td>1996</td>
<td>62</td>
<td>5</td>
<td>2–11</td>
<td>0.3–6.8</td>
<td>−5.6</td>
<td>80–120 b.i.d.</td>
<td>4.0 (n = 9) 9.3 (n = 5) 6.2 6.2</td>
</tr>
<tr>
<td>Klinger and Laron</td>
<td>1995</td>
<td>63</td>
<td>9</td>
<td>0.5–14</td>
<td>0.2–11</td>
<td>−5.6</td>
<td>150–200 i.d.</td>
<td>4.7 (1.3) (n = 9) 8.2 (0.8) 6 (1.3) 4.8 (1.3)*</td>
</tr>
<tr>
<td>Guevara-Aguirre et al</td>
<td>1997</td>
<td>64</td>
<td>15</td>
<td>3.1–17</td>
<td>4.5–9.3</td>
<td>120 b.i.d.</td>
<td>3.4 (1.4) (n = 15) 8.8 (11) (n = 8) 6.4 (1.1) (n = 6)</td>
<td></td>
</tr>
<tr>
<td>Guevara-Aguirre et al</td>
<td>64</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td>80 b.i.d.</td>
<td>3.0 (1.8) 9.1 (2.2) 5.6 (2.1)</td>
<td></td>
</tr>
</tbody>
</table>

Growth velocity values are mean (SD).

*The younger children had a growth velocity of 5.5 and 6.5 cm/year.

BA, bone age; b.i.d., twice daily; CA, chronological age; i.d., once daily; Ht SDS, height standard deviation score.
IGF-1: a growth hormone

human serum and their physiologic significance. An insulin
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*Mol Path* 2001 54: 311-316
doi: 10.1136/mp.54.5.311

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