Endocrine control of postnatal growth

Prenatal (trimester 2 and 3):
- Nutrients (dose response)
- Insulin
- IGF-1
- IGF-2
- Thyroid hormone?

Thyroid hormones
Growth hormone/IGF-1
Gonadal steroids

Height gain (cm/yr)

GH: Physiology and mechanism of action

Olle G P Isaksson
10-year anniversary of the "Growth House"
January 9, 2013
Body growth: Importance of GH

Dose response: 110-270 cm!

GH receptor deficiency (Laron dwarfism)

* GH treatment ineffective
* IGF-1 small effect (lack of cells with IGF-1 rec in growth plate as no GH?)
IGF-1 and IGF-1 receptor deficiency

IGF-1 gene defect

IGF-1 receptor gene defect

Chernausek S et al NEJM 2003

Woods KA et al NEJM 1996

GH receptor activation and cellular signaling
GH receptor dimerization

GH antagonist (pegvisomant, no proper dimerisation)

GH Receptor signaling: Active STAT dimer to nucleus

STAT: signal transducer and activator of transcription

SOCS2

Phosphotyrosine Binding domain
GH Regulation of Longitudinal Bone Growth: The History

A 1920-1950
Pituitary
GH
?
Bone

B 1950-1980
Pituitary
GH
Liver
IGF-I
Bone

C 1980-2000
Pituitary
GH
Liver
IGF-I
Bone
IGF-I

D 2009
Pituitary
GH
Liver
IGF-I
Bone
IGF-I

Direct effects of GH on growth plate
Local arterial femoral infusion hGH, 1 µg/day

Bone growth, µm

Control

Unilateral infusion

Local GH Infusion
Unilateral arterial versus systemic infusion of hGH, 10 μg/day

Incorporation of $^3$H-thymidine in growth plate stem cells

Control  Local treatment with GH  Local treatment with IGF-I
Liver-Derived IGF-I Regulates GH-secretion but is not Required for Postnatal Body Growth.

K Sjögren, J Liu, K Blad, S Skrtic, O Vidal, V Wallenius, D LeRoith, J Törnell, O Isaksson, J-O Jansson, C Ohlsson
Body growth in mice after depletion of liver IGF-1

Weight (g)

Days after induction

Length of Bones

Bone length (% of control)

Femur  Tibia  Spine
% of control

Age (weeks)

Control

LI-IGF-I-/-

Crown-rump length

Femur length

Tibia length

% of control

Age (weeks)

Organ Weight / Body Weight

Organ weight (% of control)

Organ

Spleen
Heart
Kidney
Liver

LI-IGF-I-/-

Control

**

**
Decreased Fat Mass in LI-IGF-I -/-

**DEXA Image**

Control  LI-IGF-I -/-

**Dissected Fat**

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<tr>
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<th>Females</th>
<th>Males</th>
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<td>LI-IGF-I -/-</td>
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<td>Control</td>
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**Retroperitoneal Fat**

**Effects of deletion of GH receptor (GHR KO), IGF-I (IGF-I KO) and the combination of GHR and IGF-I (IGF-I + GHR DKO) on body length.**

Adapted from Lupu…Efstradiates Dev Biol 2001
GH Regulation of Longitudinal Bone Growth: The History

A 1920-1950

- Pituitary
- GH
- Bone

B 1950-1980

- Pituitary
- GH
- Liver
- IGF-I
- Bone

C 1980-2000

- Pituitary
- GH
- Liver
- IGF-I
- Bone

D 2009

- Pituitary
- GH
- Liver
- Endocrine IGF-I
  - liver-derived (75%)
  - non liver-derived (25%)
  - ALS/IGFBP3

Proposed Role of Liver-Derived IGF-I

Direct Effects of Liver-Derived IGF-I
- Cortical bone
- Kidney size
- Prostate size
- Peripheral vascular resistance
- Spatial memory
- Sodium retention
- Tumour progression
- Longitudinal bone growth

Effects of Liver-Derived IGF-I via Altered GH Feedback
- Insulin sensitivity
- Liver size
- Sexually dimorphic liver functions
Acknowledgements

John-Olov Jansson

Claes Ohlsson

Johan Svensson