Introduction

Undernutrition and chronic inflammation is known to impair linear growth through resistance to GH [1]. Fibroblast growth factor 21 (FGF21), a member of a subfamily of FGFs (including FGF15/19 and FGF23) is considered an important regulator of the metabolic adaptation to fasting, inducing gluconeogenesis, fatty acid oxidation and ketogenesis. The activation FGF21 is highly dependent on the interaction of specific receptors (β-Klotho/FGFR1 iiIC), forming a complex with FGF21 on the cell surface [2]. Recent studies have shown that elevated expression of FGF21, secondary to prolonged undernutrition develops GH resistance and subsequent attenuation of skeletal growth and growth plate chondrogenesis in both mice and human (Fig.1) [1]. Molecular understanding of this process may open avenues for novel therapeutic intervention to enhance linear growth of children with secondary GH resistance.

Objective: To unravel the mechanistic interplay of FGF21 in GHR signaling.

Method

TRANSECTION

GENERATION OF STABLE LINES

CHONDROCYTE CELL LINES

EXPERIMENTAL DESIGN & SPECIFIC AIMS

Stable Lines

Hek-293 mGHR

Hek-293 nGHR

C2B2/12: Human costal chondrocytes

C3H 10T1/2: Mouse embryonic mesenchymal

Validation of the GHR model

Assessment of GHR signaling

Expression of FGF21 receptor complex in vitro and in vivo.

The role of FGF21 in GH resistance

Experimental analysis to examine the effect of FGF21 on JAK/STAT signaling and negative feedback regulation SOCS2.

Results

Expression of GHR in stable line model

FGF21 receptors are predominantly expressed within the proliferative and pre-hypertrophic zones

FGF21 reduces GHR half-life

Expression of the FGF21 receptor complex repertoire in stable lines

FGF21 reduces phosphorylation of STAT5

FGF21 increases SOCS2 expression

Conclusion

- Generated the tools to study GH/GHR signaling in stable cell lines and chondrocyte cell lines
- Growth hormone potentiates the activation of down-stream signaling in the JAK/STAT5 pathway
- Chronic exposure to FGF21 reduces GHR half-life and inhibits early upstream mediators (pSTAT5) in GHR signaling
- Chronic exposure to FGF21 increases SOCS2 expression

References


Disclosure Statement

I confirm that I do not have any conflict of interest in this study.

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The mechanistic role of Fibroblast growth factor 21 (FGF21) in Growth Hormone resistance secondary to chronic childhood conditions

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Growth hormone activates phosphorylation of STAT5

Cytoskeletal localization of GHR, FGF21 and β-Klotho in primary chondrocyte cultures.

C3H 10T1/2 were incubated with FGF21 (0.28ng/ml) and human recombinant GHR (10ng/ml) for 15 or 20 minutes before analysis of STAT5 and phosphorylated STAT5 by Western blot.

The proposed mechanism of FGF21 in GH resistance

- Chronic exposure to FGF21 reduces GHR half-life and inhibits early upstream mediators (pSTAT5) in GHR signaling
- Chronic exposure to FGF21 increases SOCS2 expression

Figure 1: The effect of GHR and FGF21 on GHR turnover. Hek-293 TG-FGFR (A), Hek-293 mGHR (B) and Hek-293 nGHR (C) were treated in the absence or presence of GHR (200ng/ml) or recombinant human/mouse FGF21 (5µg/ml). Hek-293 and Hek-293 mGHR were incubated overnight (16h) in GHR ligand (50ng/ml) and recombinant human/mouse FGF21 (5µg/ml) for 8 or 16 hours before analysis of SOCS2 expression by Western blot.

Figure 2: The role of FGF21 in GH resistance

- FGF21, FGF1, FGFR1 and FGFR3 are expressed in C3H 10T1/2 cells
- Expression of FGF21 receptor complex is reduced in vitro and in vivo

Figure 3: Illustration of the role of FGF21 in GH resistance

- FGF21 gene knock down
- GHR expression reduced
- GH resistance
- SOCS2 expression reduced