Intrauterine Growth Restriction Alters Retinal IGF-1 Levels in Newborn Rats

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Introduction

- Infants with intrauterine growth restriction (IUGR) and poor postnatal weight gain are at risk of retinopathy of prematurity (ROP)\(^1,2\).
- Low systemic levels of insulin-like growth factor (IGF-1) are found in preterm infants with large avascular retinal zones and with later severe ROP \(^3,4\).
- Low weight pups in oxygen-induced retinopathy (OIR) models have severe retinopathy that can be rescued partly with exogenous IGF-1\(^5\).
- Male preterm infants with IUGR are affected worse than females, but the risk of ROP between males and females is similar in multicenter clinical studies\(^6,7\).

Hypothesis

- IUGR disrupts IGF-1 and VEGF expression within the retina and may have differences based on gender.

Methods

- IUGR was induced by bilateral uterine artery ligation on e19.5. Controls had anesthesia only. Term pups delivered by C-section on e21.5.
- Flat mounts labeled with lectin or ADPase to quantify vascular coverage or presence of angioblasts at postnatal day (D)0 and D7.
- D0 and D7 retinal mRNAs of IGF-1, IGF-1 receptor (IGF-1R), IGF-1 binding protein 3 (IGF-1BP3), VEGF, and VEGF-R1 by real-time PCR. Internal control GAPDH.
- D0 and D7 retinal protein for VEGF (ELISA); IGF-1, IGF-1R, VEGF-R1 and VEGF-R2 (Western blot; β Actin).
- Statistical analysis by ANOVA (*p<0.05).

Results: mRNA

- IGF-1, IGF-1BP3, IGF-1R, VEGF in IUGR and Control by Gender

Results: Protein

- IGF-1, IGF-1R, VEGFR1 and VEGFR2 in IUGR and Control by Gender

Results: Retinal Flat Mounts

- Lectin Staining in Retinal Flat Mounts at D0
- ADPase Labeled Angioblasts in D0 Retinal Flat Mounts

Results Summary

- Vascularized retina was similar in IUGR and controls at D0 (p=0.65).
- Angioblasts (ADPase labeled cells) preceded blood vessels in both groups.
- In D0 male IUGR, IGF-1, IGF-1R, and IGF1BP3 mRNAs were increased and IGF-1 protein decreased.
- In D0 female IUGR, IGF-1, IGF1R, VEGF-R1 and R2 protein were increased.
- In D7 male IUGR, IGF1R protein was reduced.

Conclusions

- IUGR does not appear to affect retinal vasculogenesis.
- IUGR alters IGF-1 and VEGF regulation.
- In D0 IUGR females, increased IGF-1, IGF1R and VEGF may support vascular development.
- In males, components of the IGF-1 signaling pathway mRNAs are increased, but protein is not and does not increase at D7.
- These results suggest a gender-specific response of IGF-1 and VEGF in growth restriction.
- Ongoing studies will determine effects of IUGR on retinal vascular development and potential risk of ROP.

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References