3993

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 VEGFR1 by real-time PCR. Internal control GAPDH.
- D0 and D7 retinal protein for VEGF (ELISA); IGF-1, IGF-1R, VEGFR1 and VEGFR2 (Western blot; β Actin)
- Statistical analysis by ANOVA (*-p<0.05).

References

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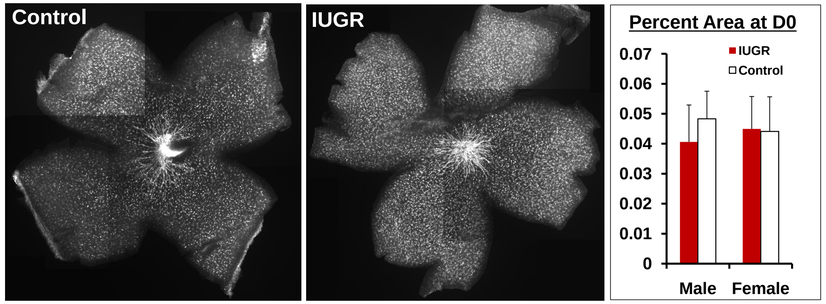
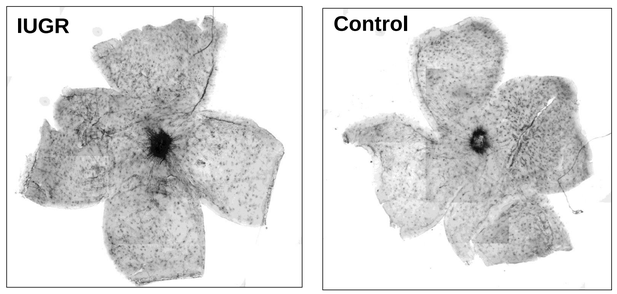
Results: Retinal Flat Mounts

Lectin Staining in Retinal Flat Mounts at D0

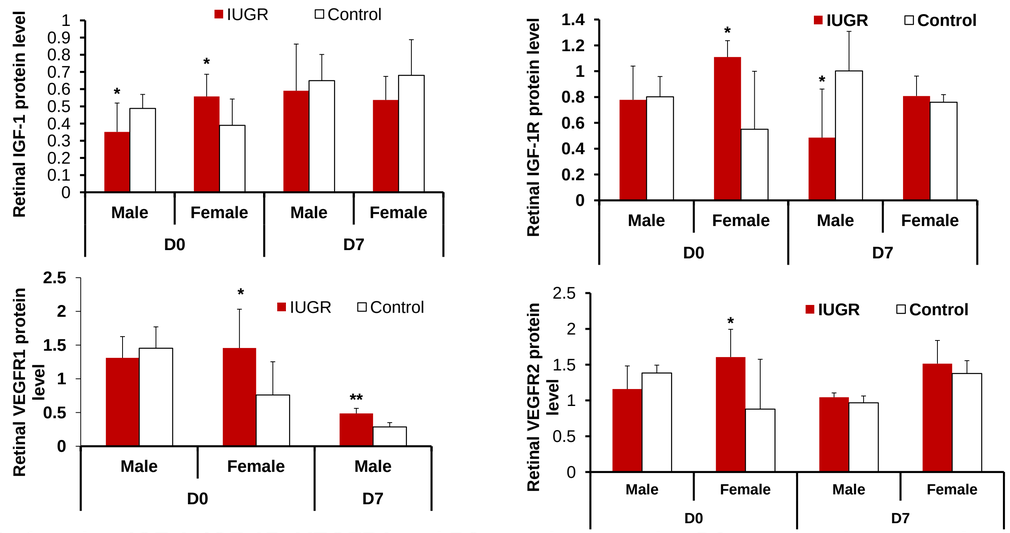


ADPase Labeled Angioblasts in D0 Retinal Flat Mounts



Results: Protein

IGF-1, IGF-1R, VEGFRs in IUGR and Control by Gender



- **In females, IGF-1, IGF-1R, VEGFR1 and R2 were increased at D0 compared to control**
- **In males, IGF-1R was reduced at D7.**

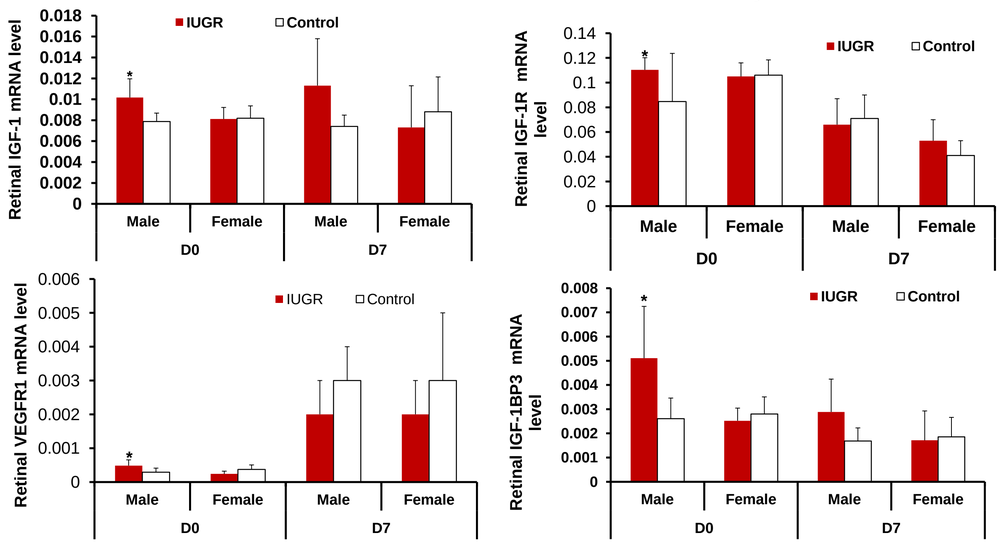
Total VEGF Protein Levels (pg/mL) in IUGR and Controls

Age	Gender	IUGR	Control
D0	Female	193 ± 34	243 ± 13
	Male	160 ± 5	154 ± 35
D7	Female	176 ± 44	127 ± 22
	Male	188 ± 37	209 ± 79

- **There were no differences in VEGF (pg/mL) by ELISA.**

Results: mRNA

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



- **In males only, IGF-1, IGF-1BP3, VEGFR1 and IGF-1R mRNAs were increased in IUGR at D0 compared to control.**

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, IGF1R, and IGF-1BP3 mRNAs were increased and IGF-1 protein decreased.
- In D0 female IUGR, IGF-1, IGF1R, VEGFR1 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, IGF-1R and VEGFR 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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