

Manipulating β_2 adrenergic activity in IUGR-born lambs with daily clenbuterol injections improved glucose-stimulated insulin secretion and oxidative metabolism at 60 days of age.

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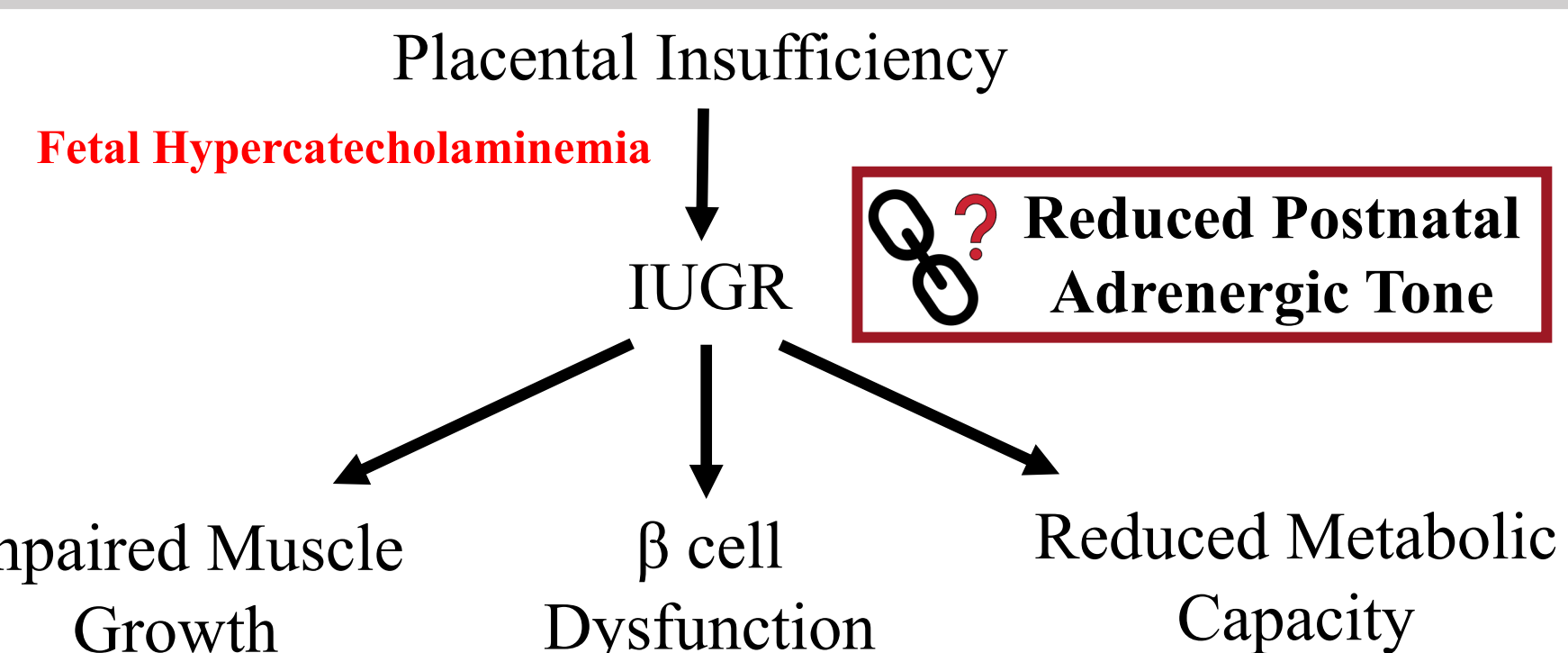


Abstract

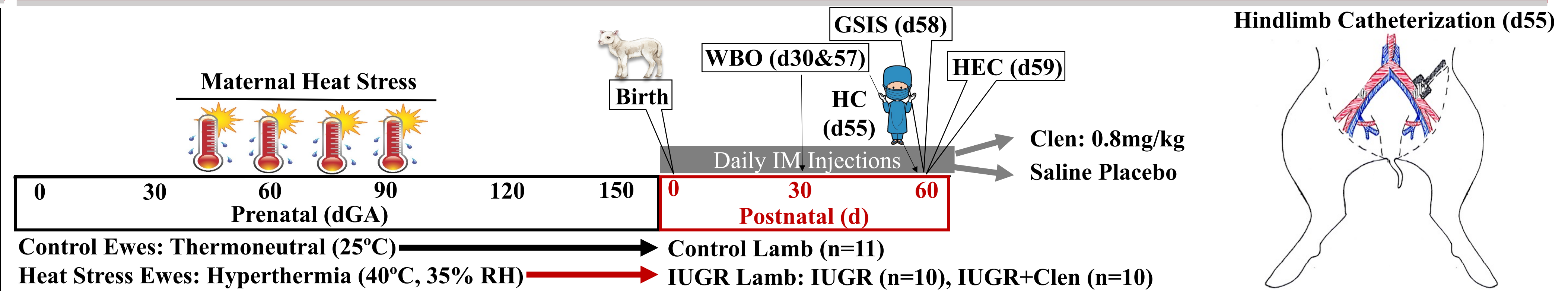
Objectives: Metabolic programming by intrauterine growth restriction (IUGR) includes reduced muscle β_2 adrenoceptors, which persists after birth. We sought to determine whether increasing β_2 adrenergic tone might improve metabolic outcomes in IUGR-born juvenile offspring.

Methods: Pregnant ewes were housed under thermoneutral or hyperthermic (40°C) conditions from d35 to 95 of gestation to produce control and IUGR-born lambs. From birth to 60d of age, IUGR lambs received IM injections of saline (IUGR; n=10) or 0.8 $\mu\text{g}/\text{kg}/\text{d}$ clenbuterol (IUGR+CLEN; n=10). Control lambs (n=11) were pair-fed and saline-injected. Lambs were catheterized on d55. Whole-body oximetry was performed on d30 and 57. Hyperglycemic and hyperinsulinemic-euglycemic clamps were performed on d58 and 59, respectively. Lambs were necropsied on d60. **Results:** Basal plasma insulin did not differ among groups. Glucose-stimulated insulin secretion was less ($P<0.05$) for IUGR lambs than controls and was intermediate ($P<0.05$) for IUGR+CLEN lambs. Basal and insulin-stimulated hindlimb glucose uptake did not differ among groups. Basal hindlimb glucose oxidation did not differ, and insulin-stimulated glucose oxidation was less ($P<0.05$) for IUGR but not IUGR+CLEN lambs compared to controls. Glucose-to-insulin ratios and high-density lipoproteins were greater ($P<0.05$) and blood urea nitrogen was less ($P<0.05$) for IUGR and IUGR+CLEN lambs than controls, regardless of period. Plasma triglycerides were not different for IUGR lambs but were greater ($P<0.05$) for IUGR+CLEN lambs than controls. Conversely, plasma non-esterified fatty acids were less ($P<0.05$) for IUGR but not IUGR+CLEN lambs compared to controls. Regardless of age, whole-body O_2 consumption was less ($P<0.05$) for IUGR and IUGR+CLEN lambs and CO_2 production was less ($P<0.05$) for IUGR but not IUGR+CLEN lambs than for controls. **Conclusions:** Deficits in metabolic substrate utilization and oxidative metabolism persisted in IUGR-born juvenile lambs but targeting underlying β_2 adrenergic dysfunction effectively improved metabolic outcomes in these offspring.

Introduction



Methodology

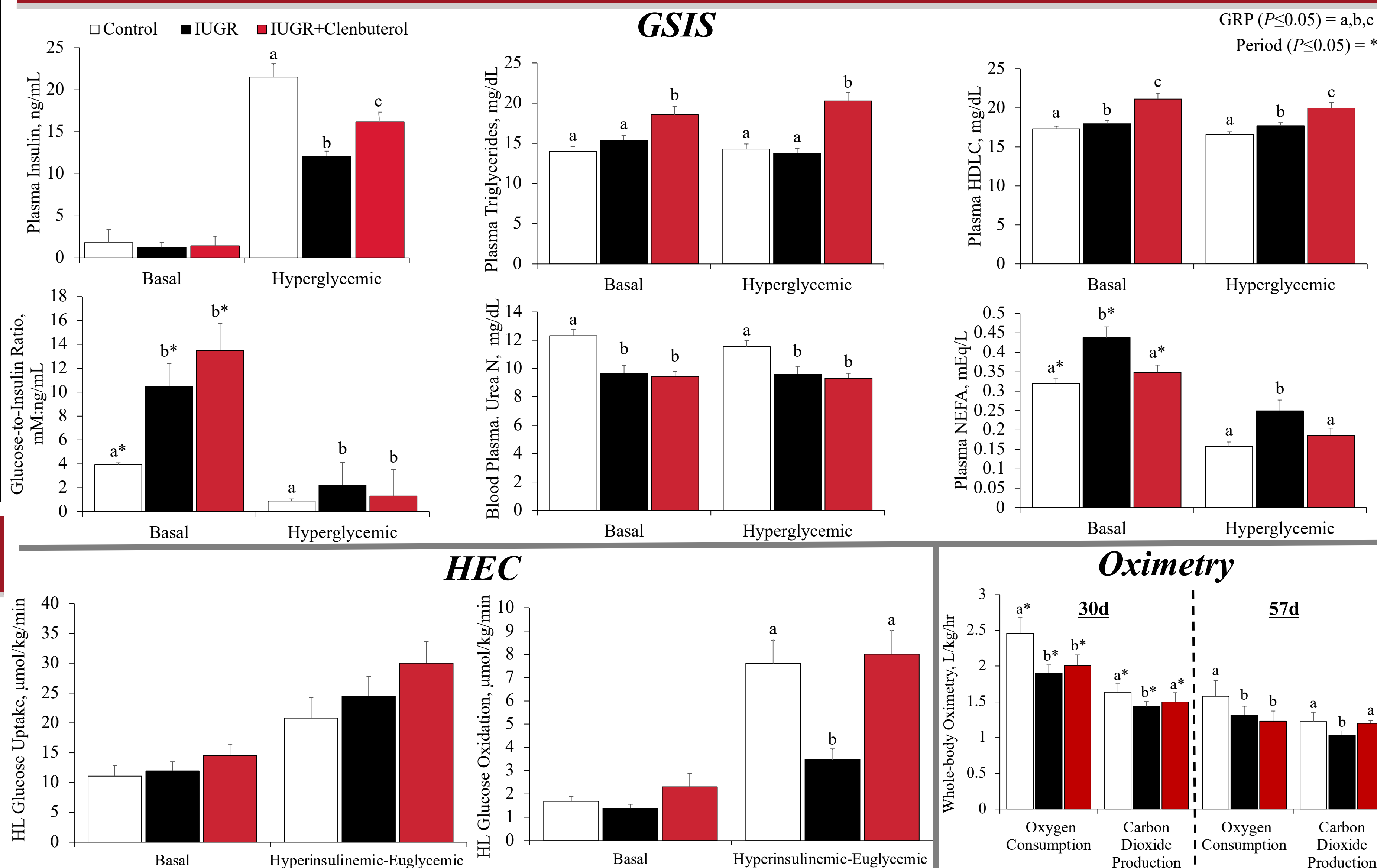


Control Ewes: Thermoneutral (25°C) → Control Lamb (n=11)
 Heat Stress Ewes: Hyperthermia (40°C, 35% RH) → IUGR Lamb: IUGR (n=10), IUGR+Clen (n=10)

Whole-Body Oximetry (d30&57)



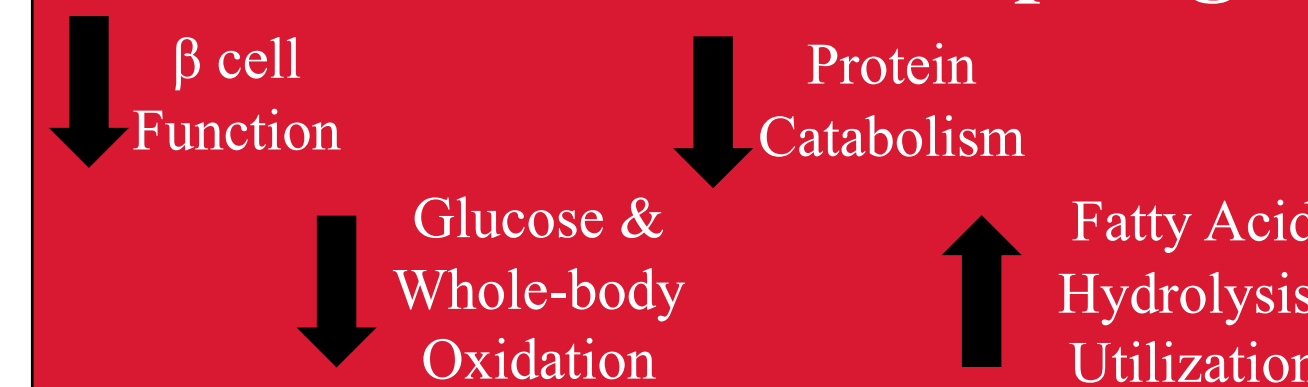
Results



Conclusions

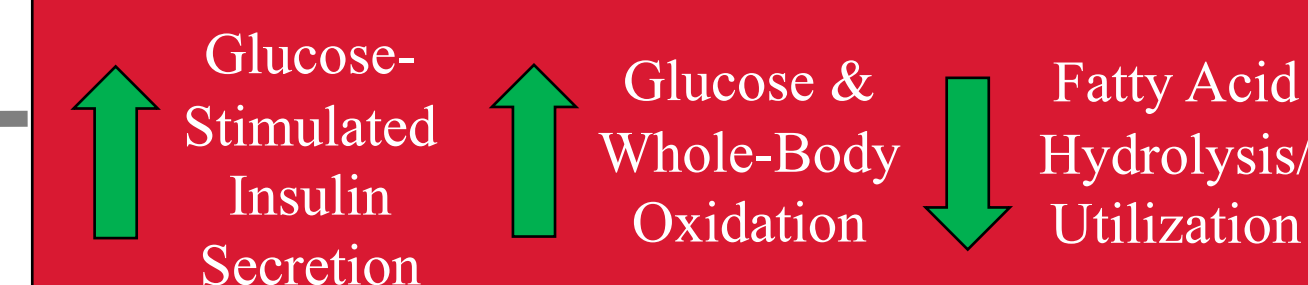
Deficits in metabolic substrate utilization and oxidative metabolism persisted in IUGR-born juvenile lambs but targeting underlying β_2 adrenergic dysfunction effectively improved metabolic outcomes in these offspring

IUGR Juvenile Offspring



But...

Clenbuterol Supplementation



Acknowledgments

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