

Adaptive Responses in Uteroplacental Metabolism and Fetoplacental Nutrient Shuttling and Sensing During Placental Insufficiency

Hannah M. Kyлло¹, Dong Wang¹, Ramón A. Lorca², Colleen G. Julian³, Lorna G. Moore², Randall B. Wilkening¹, Paul J. Rozance¹, Laura D. Brown¹, Stephanie R. Wesolowski¹

¹ Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO

² Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Aurora, CO

³ Department of Biomedical Informatics, University of Colorado School of Medicine, Aurora, CO

Glucose, lactate, and amino acids are major fetal nutrients. During placental insufficiency-induced intrauterine growth restriction (PI-IUGR), uteroplacental weight-specific oxygen consumption rates are maintained, yet fetal glucose and amino acid supply is decreased, and fetal lactate concentrations are increased. We hypothesized that uteroplacental metabolism adapts to PI-IUGR by altering nutrient allocation to maintain oxidative metabolism. Here, we measured nutrient flux rates, with a focus on nutrients shuttled between the placenta and fetus (lactate-pyruvate, glutamine-glutamate, and glycine-serine) in a sheep model of PI-IUGR. PI-IUGR fetuses weighed 40% less and had decreased oxygen, glucose, and amino acid concentrations and increased lactate and pyruvate versus control (CON) fetuses. Uteroplacental weight-specific rates of oxygen, glucose, lactate, and pyruvate uptake were similar. In PI-IUGR, fetal glucose uptake was decreased and pyruvate output was increased. In PI-IUGR placental tissue, pyruvate dehydrogenase (PDH) phosphorylation was decreased and PDH activity was increased. Uteroplacental glutamine output to the fetus and expression of genes regulating glutamine-glutamate metabolism were lower in PI-IUGR. Fetal glycine uptake was lower in PI-IUGR, with no differences in uteroplacental glycine or serine flux. These results suggest increased placental utilization of pyruvate from the fetus, without higher maternal glucose utilization, and lower fetoplacental amino acid shuttling during PI-IUGR. Mechanistically, AMP-activated protein kinase (AMPK) activation was higher and associated with thiobarbituric acid-reactive substances (TBARS) content, a marker of oxidative stress, and PDH activity in the PI-IUGR placenta, supporting a potential link between oxidative stress, AMPK, and pyruvate utilization. These differences in fetoplacental nutrient sensing and shuttling may represent adaptive strategies enabling the placenta to maintain oxidative metabolism.