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Postnatal nutrient repartitioning due to adaptive developmental programming.

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Introduction

The consequences of prenatal stress on lifelong metabolic function and health was first proposed by David Barker and Nicholas Hales with the publication of their Thrifty Phenotype Hypothesis in the early 1990s.[1,2] Subsequent studies in humans and animals have further demonstrated that stress-induced adaptive fetal programming leads to tissue-specific changes in metabolic function and growth capacity.[3,4] Developmental adaptations to the intrauterine nutrient restriction that accompanies most maternofetal stressors target regulatory pathways for nutrient utilization in non-essential tissues such as skeletal muscle.[4-6] This aids intrauterine survival by re-appropriating nutrients to support neural, cardiac, and endocrine tissue function but reduces metabolic efficiency and growth capacity in offspring. Stress-induced fetal adaptations are typically characterized by intrauterine growth restriction (IUGR) during late gestation and low birthweight.[7,8] Poor postnatal growth and metabolic inefficiency associated with low birthweight can reduce value in livestock.[4,8] Experimental models of IUGR livestock show how maternofetal stress from environmental, nutritional, or health conditions lead to fetal metabolic adaptations,[5,9,10] but few studies have followed IUGR-born livestock after birth. Even less is known about how adaptive changes alter nutrient utilization in these offspring. In this review, we summarize the current literature that assesses nutrient partitioning in IUGR-born animals. In addition, we describe the key adaptive mechanisms underlying developmental changes that reduced muscle growth and impair metabolism.

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The IUGR Phenotype

IUGR is a product of developmental adaptations.

Studies in IUGR fetal sheep and other animals show that asymmetric fetal growth restriction is a consequence of nutrient-sparing developmental adaptations.[5,11] These adaptations most commonly result from placental insufficiency produced by sustained maternal stress during mid-gestation.[11,12] Placental insufficiency can result from a number of environmental challenges including heat stress, nutrient restriction, illness, but produces consistent developmental outcomes in the fetus.[12,13] Regardless of the maternal/placental insult, placental insufficiency induces changes in metabolic tissues such as skeletal muscle, pancreas, liver, and adipose tissues,[14-16] as summarized in Table 1. Together, these collective adaptive responses alter systemic nutrient repartitioning by reducing substrate utilization by non-visceral soft tissues in favor of critical brain, heart, lungs, and endocrine tissues.[13,17] Restriction of skeletal muscle growth, insulin sensitivity, and pancreatic function are chief among these fetal adaptations.[3,11,14-16]

IUGR adaptations persist in offspring.

Thrifty metabolic adaptations that develop during gestation persist after birth despite alleviation of prenatal stressors.[2,18] The first evidence that prenatal stress is associated with postnatal metabolic dysfunction arose from Barker's epidemiological studies of socioeconomic classes in the UK. In poorer industrial populations, high rates of low birthweight infants correlated with greater incidence of hypertension, obesity, type 2 diabetes, and glucose intolerance in adulthood.[1,2] Low birthweight individuals also exhibit lifelong reductions in lean mass and increased fat deposition.[19-21] These results have since been corroborated in other human populations.[22,23] Moreover, low birthweight livestock exhibit similar changes in body composition and metabolic function,[18,24,25] as illustrated in Figure 1. Recent research by our lab and others has focused on understanding the molecular mechanisms that link developmental adaptations *in utero* with lifelong changes in metabolic function, nutrient utilization, and growth capacity.

Postnatal Growth Characteristics in IUGR-born Livestock

Low birthweight animals exhibit altered body composition.

Similar to low birthweight children,[26] low birthweight animals demonstrate accelerated neonatal "catch up" growth that is driven by increased fat deposition rather than muscle growth.[18,27] In fact, persistence of poor muscle growth leads to a reduction in carcass yield, smaller high-value cuts from the loin and upper hindlimb, and increased fat thickness in both cattle and sheep.[18,28] Reduced muscle growth and increased adiposity appear to occur via independent mechanisms, and it is worth noting that fat deposits are actually reduced in the IUGR fetus due to greater mobilization.[29] Greater adiposity in offspring appears to be secondary to impaired muscle growth, as a smaller proportion of dietary nutrients are utilized for muscle growth and thus more are stored as fat.[18,30] Conversely, studies by our lab and others show that impaired skeletal muscle growth is the product of intrinsic myoblast dysfunction.[12,14,31,32]

Skeletal muscle growth is disproportionally reduced.

Reduced lean mass and muscle size in low birthweight livestock at harvest [28,33-36] is the result of impaired hypertrophic muscle growth. In IUGR fetal sheep, we observed reduced cross-sectional areas of hindlimb muscle fibers by as much as 50% but no reduction in fiber numbers.[14,31] Muscle fibers remained smaller in IUGR-born lambs at one month of age, or ~20kg BW.[28,37] Myoblast function is the rate-limiting step in hypertrophic muscle growth,[38] and impaired skeletal muscle growth in IUGR fetal and neonatal sheep coincided with intrinsic deficits in myoblast proliferative and differentiation capacities. [31,32,37,39] Skeletal muscle is the greatest utilizer of glucose in the body,[40,41] and utilization per gram of muscle is not reduced in the IUGR fetus or lamb [10,11,42]. Thus, restricting skeletal muscle mass is a key mechanism for repartitioning the limited glucose supply in the IUGR fetus from muscle to vital tissue function and development. However, persistent deficits in muscle growth capacity in IUGR-born livestock reduce their value in meat production.[4]

Skeletal muscle protein accretion is reduced.

Similar to glucose, skeletal muscle in low birthweight livestock utilize less protein during early growth.[28] Recent studies by Laura Brown's laboratory help point out several key mechanisms for adaptive changes in muscle protein utilization. As IUGR fetuses approach term, their rates of skeletal muscle protein breakdown remain comparable to uncompromised fetuses.[43] However, protein synthesis and accretion rates in IUGR skeletal muscle drop by as much as 50%, which is similar to reduction in amino acid uptake and utilization.[43] Moreover, the effects of IUGR on circulating amino acid concentrations vary widely among individual amino acids.[43,44] For example, tyrosine, arginine, and isoleucine concentrations were reduced in IUGR fetal blood; however, taurine, glycine, and alanine concentrations were increased.[43] Increasing amino acid supply via direct fetal infusion did not increase protein accretion or synthesis rates, muscle size, or fetal mass but increased amino acid oxidation rates.[44] Thus, reduced protein uptake and accretion by IUGR skeletal muscle does not appear to be the direct result of reduced fetal protein availability. Rather, it may be a product of β adrenergic adaptations due to chronic hypercatecholaminemia, as hypercatecholaminemia was not mitigated by amino acid infusion in this study. β2 adrenergic stimulation increases protein synthesis and cycling[45] but gene expression for the β2 adrenergic receptor is reduced in IUGR skeletal muscle.[4] When hypercatecholaminemia was mitigated by adrenal demedullation in IUGR fetal sheep, fetal mass was increased by 50-60%.[46,47] Diminished blood flow, reduced oxygen utilization, and hypoinsulinemia may also contribute to reduced protein accretion in IUGR muscle.[43,48]

Tissue-Specific Metabolic Changes in IUGR Livestock

Skeletal muscle glucose metabolism is altered.

In humans, skeletal muscle from IUGR-born individuals show evidence of impaired insulin responsiveness and reduced glucose oxidative metabolism.[22,23,49-51] Studies in IUGR fetal sheep show that reduced whole-body glucose oxidation rates are present near term and occur despite normal rates of glucose uptake and utilization.[10,11] We showed that reduced glucose oxidation is muscle-specific in the IUGR fetal sheep and neonatal lamb.[4,52,53] In concert with reduced glucose oxidation, IUGR skeletal muscle increases lactate production,[9,10,41]

which unlike glucose can be secreted from skeletal muscle. Lactate can then be utilized by the liver for glucose production or by cardiac tissue for energy.[11,54,55] The shift in IUGR skeletal muscle glucose metabolism coincides with a reduction in the proportion of oxidative muscle fibers relative to glycolytic fibers.[14] We are not aware of any studies measuring muscle fiber types in low birthweight offspring of ruminant livestock, but reductions in oxidative-to-glycolytic muscle fiber types have been observed in IUGR-born humans[56] and mice.[57]

Like reduced muscle growth, the metabolic shift in IUGR skeletal muscle appears to be at least partially due to changes in adrenergic activity. Studies by our lab and others have shown that skeletal muscle insulin action and glucose oxidation are stimulated by β2 adrenergic activity but reduced by β1 activity.[58-60] Fetal hypoxemia increases circulating catecholamine levels,[61] and chronic adrenergic exposure during late gestation reduces β2-to-β1 adrenergic receptor gene expression in IUGR skeletal muscle.[4] It is worth noting that slow oxidative muscle fibers express more β adrenergic receptors than fast glycolytic fibers[62,63] and thus may be affected by chronic hypercatecholaminemia to a greater extent.

Fat deposition is increased.

Adaptive changes in IUGR skeletal muscle nutrient utilization cause a greater proportion of dietary nutrients to be deposited into central fat stores.[18,26,35] In addition, IUGR fetal adipocytes undergo developmental adaptations increase their ability to proliferate and expand in size, which increases their ability to store more fat.[64] IUGR-born male rats indicate a possible adaptive mechanism is the increased activity of peroxisome proliferator-activated receptor gamma (PPARγ), which is a primary regulator of adipogenesis and lipogenesis.[16] Other studies have implicated greater expression of the lipogenic proteins, acetyl-CoA carboxylase-α, fatty acid synthase, and ATP-binding cassette transporter 1.[65,66]

Adipose tissue plays an indirect role in systemic metabolic regulation related to its effects on endocrine and immune function, and greater fat mass in IUGR-born animals disrupts these functions.[67] Immunomodulatory disruptions in IUGR-born ruminants precede obesity and are attributable to increased infiltration of macrophages into visceral and subcutaneous fat depots, creating tissue inflammation that further contributes to insulin resistance, metabolic dysfunction, and poor growth.[67,68] Hyperlipidemia also increases systemic inflammation in humans,[69] although we are not aware of any similar studies in ruminant livestock. This occurs via activation of toll-like receptor 4 (TLR4) by free fatty acids, which in turn upregulates inflammatory pathways that impair insulin signaling and induce metabolic dysfunction.[69]

Changes in hepatic function contribute to metabolic dysfunction.

Lipid homeostasis is regulated in large part by liver function, and adaptations in hepatic development contribute to metabolic dysfunction in IUGR offspring.[70-72] In sheep, IUGR liver mass is reduced in the near term fetus and in offspring.[71,73] Hepatic expression of gluconeogenic enzymes including PEPCK and G6P are increased in response to chronic hypoglycemia near term.[11,71] However, the impact on postnatal gluconeogenesis is less clear, as gluconeogenic enzymes remained elevated into adulthood in IUGR-born rats[74,75]

but are normal or even reduced in IUGR-born lambs.[76,77] Conversely, hepatic glycogen content is normal in IUGR fetal sheep[11,71] but reduced at 1 month of age.[73]

Hepatic adaptations in the IUGR fetus diminish activation of nutrient-sensing proteins including AMPK, mTOR, SIRT1.[71] This adaptation likely spares fetal hepatocytes from apoptosis but also contributes to hepatic inflammation, dyslipidemia, and reduced insulin responsiveness in offspring.[70,71,78] These pathologies are likely mediated at least in part by persistent reductions in the expression of PPARα and PPARγ.[70] Reduced lipogenesis in concert with dyslipidemia and reduced fatty acid oxidation enhance inflammatory responses in the liver and increase the synthesis of triglycerides,[70] further contributing to systemic insulin desensitization.

β-cell dysfunction impairs insulin secretion.

Insulin secretion from pancreatic β-cells is the primary regulator of glucose uptake and metabolism and contributes to anabolic processes and muscle growth.[15,79] β-cell dysfunction is a chief factor in increased risk for metabolic dysfunction IUGR offspring.[15] In low birthweight lambs, insulin stimulus-secretion coupling is enhanced at one week[42] and two months of age[81] due to residual compensation in sensitivity to glucose that develops *in utero*.[81-83] Compensatory increases are transient, however, and adaptive impairment of glucose-stimulated insulin secretion is apparent by 8 months of age,[81] as illustrated in Figure 2. The severity of β-cell dysfunction is typically proportional to the severity of placental insufficiency and is at least in part associated with impaired islet development.[15,84] IUGR fetal sheep exhibit reduced β-cell mass and intracellular insulin concentrations near term, despite minimal effects on other endocrine cell types within the islets.[15,84,85] This appears to be the product of changes in adrenergic regulation due to chronic fetal hypercatecholaminemia, which altered catecholamine-responsive genes associated with both cellular development and function[80] In addition, islets isolated from these fetuses had impaired glucose oxidation capacity,[84,85] which is a key step in secretion-stimulus coupling. Developmental adaptations in IUGR fetal islets appear to be the result of chronic adrenergic exposure, as 7-day norepinephrine infusion into otherwise uncompromised fetal sheep produced similar effects.[86,87]

Summary

Stress-induced adaptive fetal programming leads to intrauterine growth restriction and low birthweight. Low birthweight livestock are characterized by changes in nutrient partitioning, tissue-specific metabolic function, growth, and body composition. Studies in cattle and sheep show that these adaptations result in poor growth efficiency and carcass value. Skeletal muscle nutrient utilization appears to be disproportionately targeted by fetal adaptations to stress, as glucose oxidation and protein accretion are impaired. These changes coincide with reductions in slow oxidative fiber proportions, insulin responsiveness, hypertrophic growth, and β2 adrenergic stimulation. In low birthweight offspring, adaptations reduce nutrient utilization for muscle growth. Instead, a greater amount of dietary nutrients are stored as visceral fat. Adaptive changes in functional development of adipocytes, liver tissues, and pancreatic β-cells further contribute to metabolic inefficiency

and body composition changes. Poor muscle growth together with greater fat deposition leads to less efficient feed conversion, lower yields, smaller high-value cuts, and reduced value in low birthweight livestock.

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Key Points

- Fetal adaptations to nutritional stress lead to intrauterine growth restriction (IUGR) and low birthweight. This occurs in all mammalian species and is a long-standing challenge to food animal production.
- IUGR fetal adaptations repartition limited nutrients to vital neural, cardiac, and endocrine tissues by restricting skeletal muscle mass and nutrient utilization.
- Nutrient-sparing adaptations aid fetal survival of IUGR conditions but become problematic after birth when nutrient supply is not limited. IUGR-born offspring have less lean muscle and increased fat deposition, which reduces feed efficiency, carcass quality, and value.
- Developmental adaptations affect fat, liver, and pancreatic β-cells in addition to skeletal muscle. Changes include reduced tissue responsiveness to insulin, greater local inflammation, and altered β adrenergic tone.

Synopsis:

Fetal stress induces developmental adaptations that result in intrauterine growth restriction (IUGR) and low birthweight. These adaptations re-appropriate nutrients to the most essential tissues, which benefits fetal survival. The same adaptations are detrimental to growth efficiency and carcass value in livestock, however, as muscle is disproportionally targeted. IUGR adipocytes, liver tissues, and pancreatic β-cells also exhibit functional adaptations. Identifying mechanisms underlying adaptive changes is fundamental to improving outcomes and value in low birthweight livestock. In this review, we outline studies that have begun to identify stress-induced fetal adaptations affecting growth, metabolism, and differential nutrient utilization in IUGR-born animals.

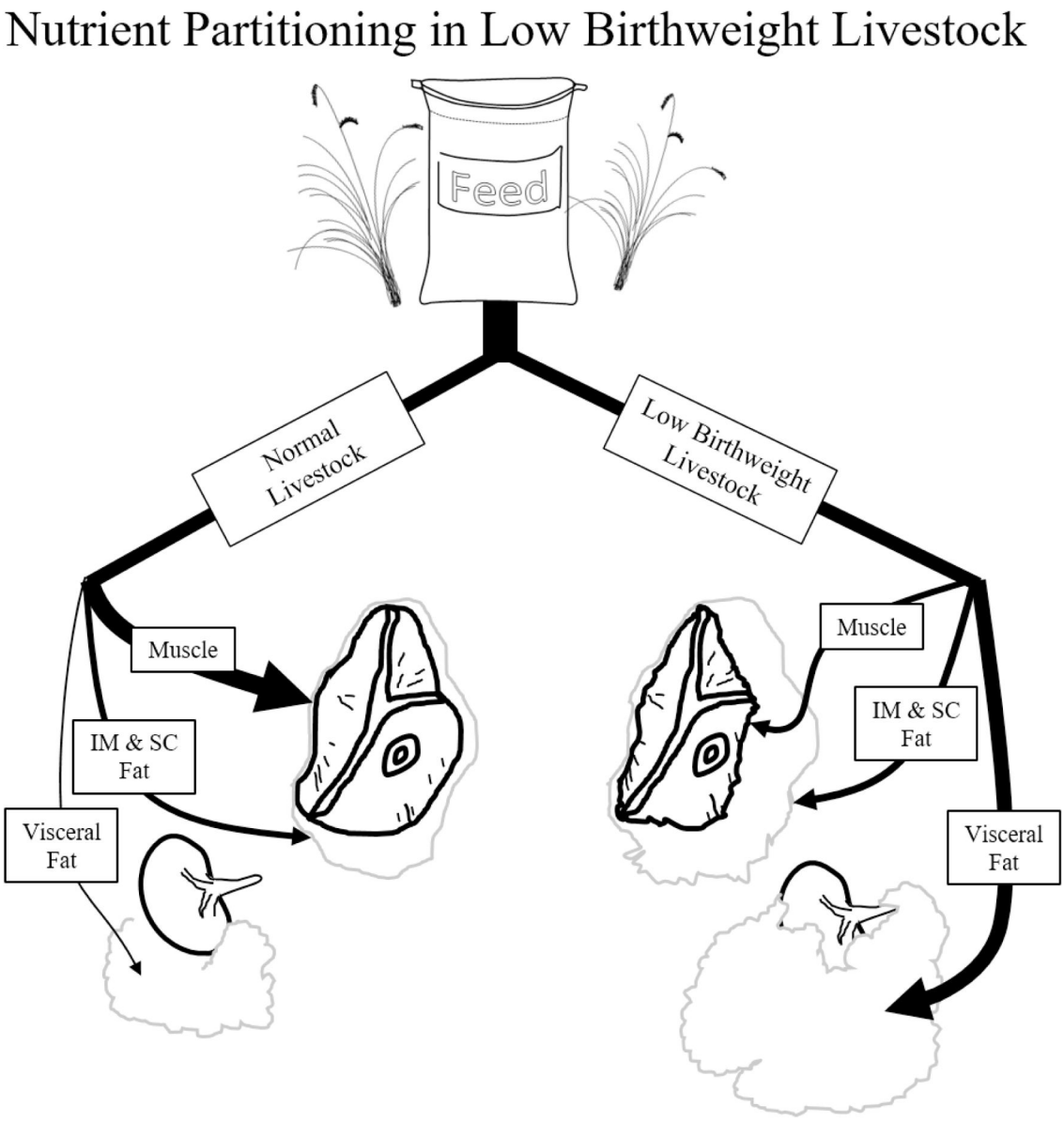

Figure 1.

Stress-induced fetal adaptations cause low birthweight livestock to re-appropriate dietary nutrients. Less nutrients are utilized for skeletal muscle growth and more are redirected to visceral fat deposits and, to a lesser extent, intramuscular and subcutaneous fat deposits.

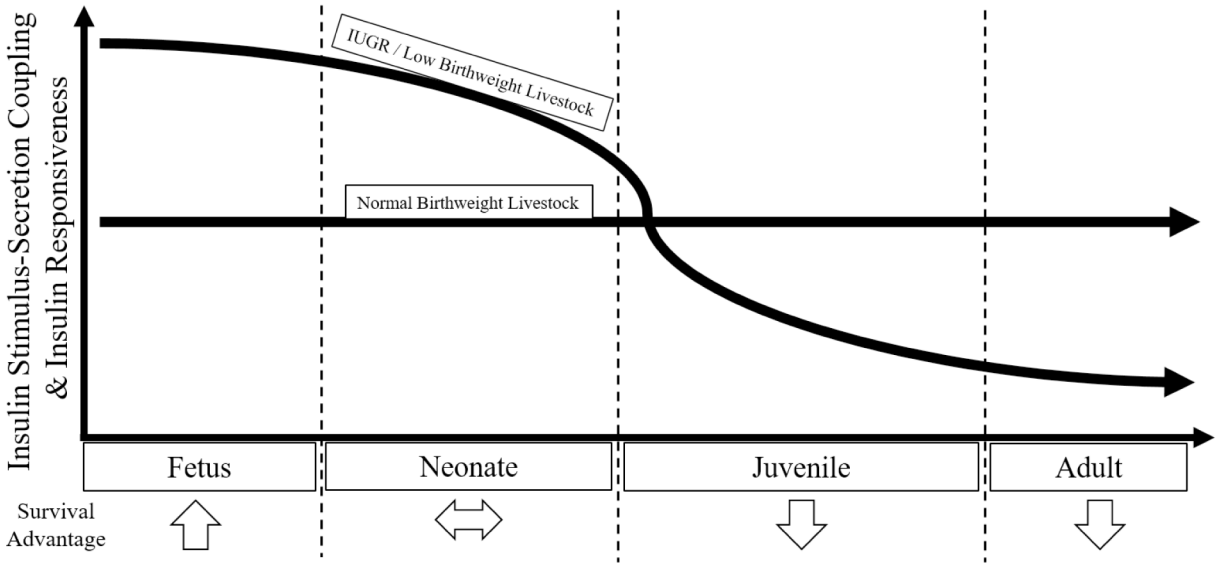

Figure 2.

Stress induced fetal adaptations impair tissue responsiveness to insulin. In prenatal and early postnatal stages, impaired insulin action is masked by transient increases in insulin sensitivity, which benefits IUGR fetal survival.

Table 1.

Low birthweight animals exhibit multi-tissue pathologies that alter nutrient partitioning and contribute to inefficient growth and metabolism.

Low Birthweight Pathology	Potential Underlying Mechanism
Skeletal Muscle	
↓ Myoblast Function	↓ β2 - to - β1 Adrenergic Activity
↓ Hypertrophic Growth	↑ Inflammatory Sensitivity / Responsiveness
↓ Glucose Oxidation	Δ Fiber Type Ratios
↓ Protein Accretion	
Adipose Tissue	
↑ Visceral Fat Deposition	↑ Macrophage Infiltration
↑ Adipocyte proliferation	↑ PPARγ
	↑ Lipogenic Proteins
	↑ Nutrient Delivery
Liver	
↓ Mass	↓ Nutrient-Sensing Proteins (AMPK, mTOR, SIRT1)
↑ Triglyceride Accumulation	↑ Hepatic Inflammation
? Gluconeogenesis	↓ Fatty Acid Oxidation
Pancreatic β-cells	
↓ Glucose-Stimulated Insulin Secretion	Δ Adrenergic Regulation
↓ Insulin Production	↓ Glucose Oxidation