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ASAS-SSR Triennial Reproduction Symposium: Looking Back and Moving Forward—How Reproductive Physiology has Evolved: Fetal origins of impaired muscle growth and metabolic dysfunction: Lessons from the heat-stressed pregnant ewe

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ASAS-SSR Triennial Reproduction Symposium: Looking Back and Moving Forward—How Reproductive Physiology has Evolved: Fetal origins of impaired muscle growth and metabolic dysfunction: Lessons from the heat-stressed pregnant ewe¹

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ABSTRACT: Intrauterine growth restriction (IUGR) is the second leading cause of perinatal mortality and predisposes offspring to metabolic disorders at all stages of life. Muscle-centric fetal adaptations reduce growth and yield metabolic parsimony, beneficial for IUGR fetal survival but detrimental to metabolic health after birth. Epidemiological studies have reported that IUGR-born children experience greater prevalence of insulin resistance and obesity, which progresses to diabetes, hypertension, and other metabolic disorders in adulthood that reduce quality of life. Similar adaptive programming in livestock results in decreased birth weights, reduced and inefficient growth, decreased carcass merit, and substantially greater mortality rates prior to maturation. High rates of glucose consumption and metabolic

plasticity make skeletal muscle a primary target for nutrient-sparing adaptations in the IUGR fetus, but at the cost of its contribution to proper glucose homeostasis after birth. Identifying the mechanisms underlying IUGR pathophysiology is a fundamental step in developing treatments and interventions to improve outcomes in IUGR-born humans and livestock. In this review, we outline the current knowledge regarding the adaptive restriction of muscle growth and alteration of glucose metabolism that develops in response to progressively exacerbating intrauterine conditions. In addition, we discuss the evidence implicating developmental changes in β adrenergic and inflammatory systems as key mechanisms for dysregulation of these processes. Lastly, we highlight the utility and importance of sheep models in developing this knowledge.

Key words: catecholamines, cytokines, glucose oxidation, intrauterine growth restriction

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INTRODUCTION

Intrauterine growth restriction (IUGR) diminishes perinatal survival rates and encumbers long-term health in a substantial portion of the global population (Berghella, 2007; Saleem et al., 2011). It is second only to prematurity as a cause of perinatal mortality and morbidity (Alisi et al., 2011) and predisposes affected persons to metabolic dysfunction throughout life (Hales and Barker, 1992, 2001). As early as 3 yr of age, IUGR-born children exhibit greater rates of insulin resistance, high blood pressure, and obesity than their average for gestational age (AGA) counterparts

(Flanagan et al., 2000; Ong et al., 2000; Mericq et al., 2005). By adulthood, their risk for developing metabolic disorders such as type 2 diabetes, obesity, and hypertension is increased by 18-fold (Barker et al., 1993; Gatford et al., 2010). In fact, IUGR is believed to be a predisposing factor in as many as half of all clinical cases of metabolic syndrome (Vo and Hardy, 2012). Statistics confirm that IUGR is a global health issue, afflicting approximately 25% of all infants worldwide (10% of U.S. infants; Berghella, 2007; Saleem et al., 2011). The most recent perinatal data indicate that premature births in the United States have declined steadily for the last decade and the total rate of infant mortality is at a historic low (Murphy et al., 2017), yet the rate of IUGR births has remained steady since 2002; 20% greater than in the mid-1980s (Arias et al., 2003). Improved neonatal care has caused worldwide mortality rates for IUGR infants to decline considerably over the last several decades (Goldenberg and Culhane, 2007), which increases the need for a better understanding of how IUGR fetal adaptations lead to metabolic deficiencies that shorten life span and decrease quality of life.

Postnatal consequences of IUGR are not limited to humans and occur in most mammalian species. In livestock, IUGR-induced low birthweight greatly increases perinatal mortality rates due to reduced energy reserves and lack of vigor at birth (Reynolds and Caton, 2012; Dwyer et al., 2016). Consequently, the offspring are at a disadvantage during the first few months of life. The lack of available information regarding how to manage these animals costs the U.S. livestock industry ~8% of its annual product (Wu et al., 2006). This equates to a loss of about 3 million beef calves, 930,000 dairy calves, and 530,000 lambs each year. Starvation deaths of low birthweight livestock are a serious animal welfare issue for the industry and a barrier to financial sustainability for many producers. In addition, IUGR-born offspring that survive exhibit reduced efficiency and performance (Gondret et al., 2005; De Blasio et al., 2007) as demonstrated by reduced feed conversion, lighter carcasses, and reduced carcass merit (Hegarty and Allen, 1978; Powell and Aberle, 1980; Greenwood et al., 1998, 2000; Gondret et al., 2005). Greater metabolic dysfunction and perinatal mortality rates have also been documented in IUGR-born companion animals including dogs (Kliegman, 1989) and horses (Peugnet et al., 2014) and in managed wildlife species such as fallow deer (English and Mulley, 1992) and baboons (Pantham et al., 2015; Li et al., 2017).

Barker's thrifty phenotype hypothesis (Hales and Barker, 2001) states that metabolic deficits are the result of adaptive fetal programming aimed at sparing nutrients in response to placental insufficiency or other nutrient-restricting stressors. These adaptations create metabolic thrift in nonessential tissues (i.e., skeletal muscle) that is critical to in utero survival but detrimental after birth when nutrients are no longer restricted (Yates et al., 2011a, 2012b; Brown, 2014). Despite the well-established epidemiological links between IUGR and life-long metabolic dysfunction, the underlying adaptive mechanisms are not well understood. In this review, we discuss the existing knowledge regarding metabolic programming in the IUGR fetus, the essential contributions of sheep models to these discoveries, and the potential roles for adaptive changes in stress-system regulation of IUGR muscle growth and metabolism (Fig. 1).

PLACENTAL INSUFFICIENCY AND THE IUGR FETAL CONDITION

Placental Stunting

Clinical reports indicate that the majority of IUGR cases in humans are the result of placental insufficiency (Cox and Marton, 2009). Maternal conditions such as illness, stress, obesity, smoking, drug use, malnourishment, sleep disordered breathing, and even assisted reproduction technologies can stunt placental development (Carnelio et al., 2017; Woo et al., 2017). Placental insufficiency resulting from any of these maternal etiologies reduces nutrient and oxygen delivery and causes predictably poor intrauterine conditions for the fetus. Similar placental stunting can occur in pregnant livestock as the result of environmental stress (i.e., heat, cold, altitude), undernourishment, illness, and ingestion of noxious plants (Greenwood and Cafe, 2007). Stress conditions often elevate maternal body temperature, redistributing blood flow away from the uterus to peripheral tissues (Alexander et al., 1987; Wallace et al., 2005). An increase of as little as 1 °C can reduce uterine blood flow up to 30% (Dreiling et al., 1991), which if sustained will reduce placental hyperplasia (Regnault et al., 2002) and disrupt vascular endothelial growth factor-regulated vascular development (Regnault et al., 2002). The reduced number, diameter, and branching of placental arteries (Regnault et al., 2002) increases blood flow resistance 4-fold (Galan et al., 2005; Regnault et al., 2007), which in turn decreases placental O₂ permeability (Regnault et al., 2003; de Vrijer et al., 2004). Transport of glucose and amino

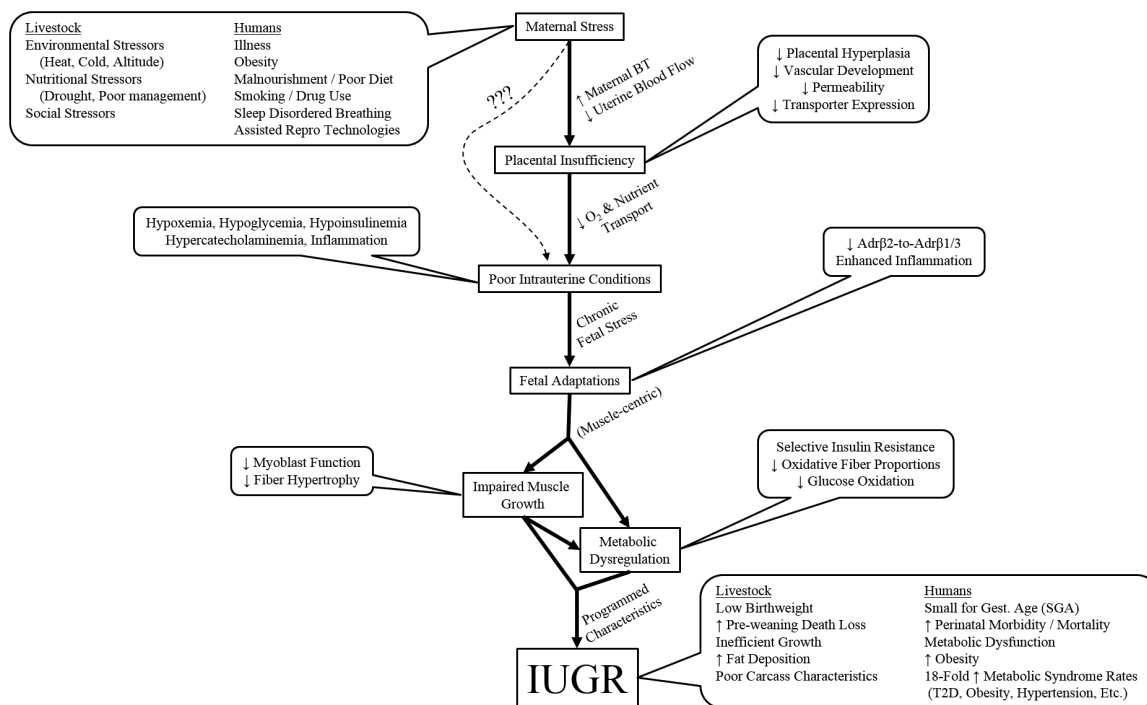


Figure 1. Working model for the mechanistic link between maternofetal stress and the postnatal consequences of intrauterine growth restriction (IUGR).

acids is also reduced by decreased placental expression of transporters for these nutrients (Malandro et al., 1996; Wallace et al., 2005; Jansson et al., 2006). Consequently, birthweight is strongly correlated with placental vascularization and mass (Pantham et al., 2015; Poudel et al., 2015).

IUGR Fetal Pathophysiology

As the fetus outgrows its stunted placenta, typically in the early third trimester, it begins to exhibit hypoglycemia and hypoxemia that progressively worsen until birth (Macko et al., 2013). Umbilical O₂ and glucose concentrations are reduced by as much as 50% near term (Limesand et al., 2007; Macko et al., 2016) despite normal concentrations in uterine blood. Placental transfer of amino acids is also markedly reduced (de Vrijer et al., 2004) by deficient active transport across the microvillous membrane (Malandro et al., 1996; Pantham et al., 2016). These deficits necessitate reductions in protein utilization by fetal tissues and in severe cases increase protein mobilization (Limesand et al., 2007; Rozance et al., 2018). To illustrate, circulating leucine concentrations are maintained in the IUGR fetus because hindlimb utilization is reduced by 32% (Rozance et al., 2018). The greatest reductions are in utilization for protein synthesis and muscle growth, as leucine oxidation rates are comparable to normal fetuses.

In concert with worsening nutrient states, the IUGR fetus exhibits progressive increases

in circulating norepinephrine and epinephrine (Macko et al., 2013; Macko et al., 2016). These catecholamines are secreted from the fetal adrenal in response to hypoxemia (Yates et al., 2012a), which inactivates O₂-sensing potassium channels on medullary chromaffin cells that normally block catecholamine exocytosis (Adams and McMillen, 2000). Chronic hypoxemia also stimulates greater circulating inflammatory cytokines (Guo et al., 2010; Kelly et al., 2017). At delivery, fetal cord blood from IUGR infants has greater concentrations of tumor necrosis factor α (TNF α), interleukin-6 (IL-6), and interleukin-18 (IL-18), as well as the chemokine C-C motif ligand 16 (CCL16) and the acute phase protein C-reactive protein (CRP) (Makikallio et al., 2012; Krajewski et al., 2014; Visentin et al., 2014). In IUGR animal models, TNF α and IL-6 are elevated in late gestation (Bertucci et al., 2011), and we recently reported that maternofetal inflammation due to maternal bacterial endotoxin injection at mid-gestation in rats results in smaller fetuses with increased circulating TNF α at term, well after maternal biomarkers of inflammation had subsided (Cadaret et al., 2017a). Reduced delivery of nutrients can also increase fetal biomarkers of inflammation late in gestation (Jones et al., 2018). The adrenergic and inflammatory systems mediate many of the physiological changes affecting growth and metabolism in the IUGR fetus, and one prominent mode of action is inhibition of growth

factors. Insulin, insulin-like growth factor (IGF)-I, IGF-II, and placental growth factor concentrations are suppressed in the IUGR fetus by the mid-third trimester (Thorn et al., 2009; Leos et al., 2010), as thoroughly reviewed by Laura Brown (2014). Catecholamines are particularly strong inhibitors of insulin secretion, as norepinephrine infusion into otherwise uncompromised fetuses substantially reduces circulating concentrations (Chen et al., 2014, 2017b), and fetal adrenal demedullation recovers glucose-stimulated insulin secretion in acutely hypoxemic fetuses (Yates et al., 2012a) and in IUGR fetuses (Macko et al., 2016). Moreover, inflammatory cytokines disrupt the ability of IGF-I to interact with its receptor (Hashimoto et al., 2010) and increase the levels of IGF-binding proteins (IGFBP) (Street et al., 2006), which impedes the activity of IGF through high-affinity binding (Hoefflich et al., 1999).

The conditions described above result in redistributed fetal blood flow. The IUGR fetus directs more blood to the brain, heart, adrenal glands, and pancreas compared to the normal fetus (Alexander et al., 1987; Poudel et al., 2015). At the same time, catecholamines mediate femoral vascular resistance, resulting in an almost 50% decrease in hindlimb blood flow (Poudel et al., 2015; Rozance et al., 2018). Redirected blood flow prioritizes nutrient and O₂ delivery to vital organs at the cost of restricted muscle growth, resulting in the hallmark asymmetric body composition of IUGR fetuses (Galan et al., 1999). Fetal growth restriction progressively worsens during the later stages of gestation in parallel with its causative conditions (Carr et al., 2012). Divergent growth starts early in the third trimester, just after characteristics of placental insufficiency begin to appear (Limesand et al., 2013; Macko et al., 2013). By midway through the third trimester, IUGR fetuses are ~28% lighter than uncompromised counterparts (Bubb et al., 2007), and by term, growth restriction can exceed 50% (Leos et al., 2010; Rozance et al., 2015; Kelly et al., 2017).

Ovine Models of IUGR

A great deal of knowledge regarding IUGR fetal and neonatal pathology has been ascertained from pregnant sheep models. The fetal sheep's tolerance of experimental conditions provides a means to characterize IUGR conditions in utero and has helped identify the nature and timing of developmental adaptations (Anthony et al., 2003; Morrison, 2008; Yates et al., 2011a, 2012b). Sheep are the ideal ruminant model for low birthweight,

as IUGR lambs share developmental characteristics with IUGR calves and other ruminant species but experience reduced rates of prenatal and perinatal death (Anthony et al., 2003). The smaller size, greater survival rates, and shorter gestation lengths allow IUGR lambs to be produced for research more consistently and at about one-tenth the expense of IUGR calves. Low birthweight due to IUGR is a particularly common problem in swine due to the natural process of runting, which results from intrauterine crowding (Foxcroft et al., 2006). It should be noted that information learned from IUGR sheep is largely applicable to IUGR swine due to similar fetal pathophysiological conditions, despite noteworthy differences in litter size, relative myogenic milestones, and perinatal mortality rates between the two species (Wu et al., 2010; Oksbjerg et al., 2013). Fetal sheep also share developmental milestones for muscle growth and metabolic responsiveness with humans (Yates et al., 2012b), making them an appropriate model for biomedical research as well. Effective methods for creating or mimicking placental insufficiency in sheep include maternal hyperthermia, uterine artery ligation, uteroplacental embolization, carunclectomy, maternal nutrient restriction, maternal overnutrition, fetal hormone infusion, and maternofetal hypoxia. Detailed comparisons among models are available (Anthony et al., 2003; Wallace et al., 2005; Vuguin, 2007; Morrison, 2008; Green et al., 2010), but maternal heat stress is perhaps the most effective method to naturally induce placental stunting and IUGR. This model originated from observations in the early 1950s of decreased birthweights and greater mortality in summer-born compared to winter-born lambs in northern Australia (Morley, 1954; Moulk, 1954). Controlled-environment studies soon confirmed that chronic exposure to high ambient temperatures was indeed the impetus for smaller, less vigorous, summer-born offspring (Yeates, 1956; Shelton and Huston, 1968). Placental insufficiency is naturally produced when timed-pregnant ewes are exposed to high ambient temperatures and humidity (typically 40 °C and 35% relative humidity) from mid-first trimester to late-second trimester, resulting in 0.7 °C to 1.5 °C increase in maternal body temperature (Yates et al., 2011a). In response, the ewe's body increases heat expulsion by rerouting blood flow from the uterus and other deep organs to body surfaces (Alexander et al., 1987; Thureen et al., 1992). The reduced blood supply stunts placental growth and development, which consistently reproduces the classic IUGR phenotype. The information obtained from almost three decades of work

in this model has helped define IUGR fetal pathophysiology and adaptive programming (Table 1).

PANCREATIC ISLET DEVELOPMENT AND β CELL FUNCTION

Pancreatic β cell dysfunction is a hallmark of IUGR-born offspring and is a product of disrupted prenatal islet development (Green et al., 2010; Boehmer et al., 2017). Human IUGR fetuses develop smaller and less vascularized islets that contain fewer β cells (Van Assche and De Prins, 1981), impairing insulin secretion during late gestation (Nicolini et al., 1990), infancy (Bazaes et al., 2003), childhood (Li et al., 2001), and adulthood (Jensen et al., 2002). Underlying islet pathologies have been characterized in detail in IUGR fetal sheep, which exhibit substantially less whole-pancreas and islet vascularity, basal insulin secretion, and glucose-stimulated insulin secretion near term (Limesand et al., 2006; Rozance et al., 2015). In addition to reduced size, IUGR islets exhibit massive reductions in insulin content and glucose oxidation, the latter of which mediates signaling-secretion

coupling (Limesand et al., 2006; Brown et al., 2016a). Interestingly, β cell development is disproportionately reduced compared to other islet endocrine cells. Islets from IUGR fetal sheep islets have less insulin content, insulin-positive (β cell) area, and β cells per islet but have normal glucagon content and α and δ cell metrics (Limesand et al., 2005; Limesand et al., 2013; Brown et al., 2016a). This is due to disruption of β cell proliferative capacity, as IUGR β cells undergo normal rates of apoptosis but exhibit substantial reductions in mitosis (Limesand et al., 2005; Limesand et al., 2013; Brown et al., 2016a). Nutrient restriction is only indirectly responsible for islet pathologies, as fetal infusion of nutrients or insulin does little to correct islet function. An exception is the partial restoration of islet size and β cell sensitivity after sustained infusion of high amount of branched-chain amino acids (Brown et al., 2016a). Rather, hypoxemia and hypercatecholaminemia appear to be the primary contributors to islet dysfunction. Elevated circulating catecholamines in fetal sheep inhibit glucose-stimulated insulin secretion during both acute (Yates et al., 2012a) and chronic

Table 1. Studies showing parallels in IUGR fetal pathology between sheep and humans

Pathology		Sheep		Human
O ₂	~28% ↓ fetal arterial O ₂ at 0.7 gestation; 30–50% ↓ fetal arterial O ₂ near term	Limesand et al., 2007; Limesand et al., 2013; Macko et al., 2013; Macko et al., 2016	~33% ↓ fetal arterial O ₂ at ~0.75 gestation; 15–40% ↓ cord blood O ₂ at delivery	Pardi et al., 1993; Roberts et al., 1999; Marconi et al., 2006
Glucose	~23% ↓ fetal arterial O ₂ at 0.7 gestation; ~40% ↓ fetal arterial O ₂ near term	Limesand et al., 2013; Macko et al., 2013; Macko et al., 2016	~33% ↓ umbilical vein glucose in 3 rd trimester; ~50% ↓ cord blood glucose at delivery	Economides et al., 1991; Roberts et al., 1999; Lee et al., 2010
Catecholamines	5 to 5.7-fold ↑ fetal arterial norepinephrine near term; ~2.7-fold ↑ fetal arterial epinephrine near term	Limesand et al., 2007; Leos et al., 2010; Macko et al., 2013; Macko et al., 2016; Rozance et al., 2018	7.4-fold ↑ fetal arterial norepinephrine near term; 3.1-fold ↑ amniotic fluid norepinephrine in third trimester	Divers et al., 1981; Greenough et al., 1990
Inflammation	5-fold ↑ fetal arterial IL-6 near term; 10-fold ↑ fetal arterial Activin A near term	Bertucci et al., 2011; Kelly et al., 2017; Jones et al., 2018	1.3 to 2.4-fold ↑ cord blood TNF α , IL-6, and IL-18 at delivery	Makikallio et al., 2012; Krajewski et al., 2014; Visentin et al., 2014
Insulin, IGF	~40% (basal) and 52% (glucose-stim.) ↓ fetal arterial insulin near term; ~33% ↓ fetal arterial IGF-I near term	Bauer et al., 2003; Leos et al., 2010; Macko et al., 2016	~50% ↓ cord blood insulin at delivery; ~38% ↓ cord blood IGF-I at delivery; ~13% ↓ cord blood insulin at delivery	Hubinont et al., 1991; Lee et al., 2010
Insulin action	1.6 to 2.4-fold ↑ perinatal insulin sensitivity; ~19% ↓ neonatal insulin sensitivity	Camacho et al., 2016a; Camacho et al., 2017; Merrick et al., 2017	3.7-fold ↑ perinatal insulin sensitivity; ~7% ↓ insulin responsive in neonatal muscle	Ozanne et al., 2005; Meral et al., 2011; Milovanovic et al., 2014
Glucose oxidation	17–30% ↓ fetal glucose oxidation near term; ~33% ↓ neonatal glucose oxidation	Limesand et al., 2007; Brown et al., 2015; Merrick et al., 2017	~23% ↓ juvenile glucose oxidation	Jornayvaz et al., 2004
Myoblast function	~13% ↓ fetal myoblast proliferation; ~46% ↓ fetal myoblast differentiation; ~12% ↓ neonatal myoblast proliferation	Yates et al., 2014; Camacho et al., 2016b; Riley et al., 2016	↓ Myonuclear content of gastrocnemius muscle	Widdowson et al., 1972

IGF, insulin-like growth factor; IL, interleukin; IUGR, intrauterine growth restriction; TNF α , tumor necrosis factor α .

exposure (Chen et al., 2014; Macko et al., 2016). Moreover, sustained infusion of norepinephrine into uncompromised fetal sheep recapitulates the IUGR phenotype for pancreatic islets, insulin concentrations, and fetal growth rates (Bassett and Hanson, 1998; Chen et al., 2014, 2017b). Surgical adrenal demedullation of IUGR fetal sheep prior to the third trimester circumvented hypercatecholaminemia and partially recovered β cell sensitivity, islet function, and fetal growth near term despite presence of fetal hypoxemia and hypoglycemia (Davis et al., 2015; Macko et al., 2016). In fact, adrenergic desensitization after chronic exposure can cause β cells to oversecrete insulin when the elevated adrenergic stimulation is reduced pharmacologically (Leos et al., 2010; Macko et al., 2013; Chen et al., 2014, 2017a) or by birth of the fetus (Camacho et al., 2017). Paradoxically, basal adrenergic stimulation appears important for islet development; adrenal demedullation reduces basal and glucose-stimulated insulin secretion in control fetuses (Yates et al., 2012a; Davis et al., 2015; Macko et al., 2016) and fails to recover β cell mitosis rates in IUGR fetuses (Davis et al., 2015). In addition, correction of fetal hypoxemia improves glucose-stimulated insulin secretion in both intact and adrenal demedullated IUGR fetal sheep, indicating catecholamine-independent as well as catecholamine-mediated effects (Macko et al., 2016).

Heightened inflammatory activity also appears to mediate β cell function and fetal growth restriction. In an unpublished preliminary study in sheep, maternal inflammation induced by serial bacterial endotoxin injection from days 100 to 113 of gestation reduced glucose-stimulated insulin secretion, semitendinosus fiber size, and fetal weights at day 125 of gestation, which is similar to rodent models of maternal inflammation (Cotechini et al., 2014; Chen et al., 2015). Incubation of normal islets with inflammatory cytokines reduces glycolysis and glucose-stimulated insulin secretion (Oleson et al., 2015), and RNA-seq data from IUGR fetal sheep islets indicate that they are desensitized to cytokine activity and binding (Kelly et al., 2017). Adrenergic and inflammatory suppression of insulin secretion helps explain the asymmetry of fetal growth restriction, as hypoinsulinemia only affects insulin-responsive tissues like skeletal muscle.

MUSCLE GROWTH CAPACITY AND METABOLIC FUNCTION

Skeletal muscle accounts for 40% of total body mass and consumes 65% of the body's total glucose

(DeFronzo et al., 1981). With metabolic rates highly responsive to endocrine regulation, muscle is a key factor in metabolic homeostasis as well as a primary target for nutrient sparing in the IUGR fetus (Brown, 2014). Consequently, reduced muscle growth capacity and altered metabolic function are key developmental adaptations that help reappportion limited nutrient and O_2 supplies during late gestation (Yates et al., 2011a, 2012b). Although critical for fetal survival, these programmed mechanisms of nutrient sparing continue to reduce nutrient utilization by muscle in offspring despite sufficient postnatal nutrient availability.

Skeletal Muscle Mass and Growth Efficiency

Throughout life, IUGR-born humans have less skeletal muscle (Kensara et al., 2005; Yliharsila et al., 2007) that strongly correlates with metabolic dysfunction due to the tissue's role in glucose homeostasis (Kim et al., 2014). Ultrasonography shows that slower muscle growth is present well before birth (Padoan et al., 2004; Larciprete et al., 2005) and continues throughout infancy and childhood (Hediger et al., 1998). Dietary nutrients that would normally be used for muscle growth are instead stored in central fat deposits that manifest in abdominal obesity in children as young as 10 yr of age (Zarrati et al., 2013). Increased body fat can lead to secondary pathologies such as systemic low-grade inflammation and hyperlipidemia (Ampem et al., 2016; Veiga-Lopez et al., 2016) that further disrupt metabolic function. Similar adaptive programming in livestock results in poor feed conversion and body composition (De Blasio et al., 2007; Madsen and Bee, 2015), as catch-up growth is driven by fat deposition rather than muscle growth (De Blasio et al., 2010; Liu et al., 2015). Consequently, carcasses of IUGR livestock have reduced merit (decreased weight, excessive 12th-rib fat thickness, and decreased subprimal weight) (Hegarty and Allen, 1978; Powell and Aberle, 1980; Greenwood et al., 1998, 2000; Gondret et al., 2005), which substantially affects profit. P.L. Greenwood has comprehensively documented the detriment of IUGR to carcass quality; longissimus dorsi muscles that comprise the loin are substantially lighter and smaller in diameter in IUGR heifers at 30 mo of age (Greenwood and Cafe, 2007). For each kilogram less that an animal weighs at birth, its HCW, LM area, and total retail yield at slaughter are reduced by an average of 2.71 kg, 0.52 cm², and 1.97 kg, respectively (Robinson et al., 2013). In fact, birth-weight differences explain up to 37% of variation in

carcass weight and yield independently of postnatal diet. Similar deficits occur in IUGR-born lambs, as carcass yield strongly correlates with birthweight and crown-rump length (De Blasio et al., 2007). Likewise, IUGR-born pigs produce carcasses with less meat and more omental and subcutaneous fat regardless of their diet (Madsen and Bee, 2015). Current USDA-AMS *Daily Beef Reports* (April 20, 2018) indicate the potential reduction in final value that an IUGR steer carcass might receive. Discounts for decreased USDA Yield Grade (reduction of ~\$10.71/45.4 kg/animal for USDA Yield Grade 4) and reduced intramuscular fat deposition (USDA Select vs. Choice) would result in a combined reduction of \$23.13/45.4 kg/animal. Per current USDA-AMS reported average dressed steer HCW (403 kg) and negotiated prices for domestic steers (\$189.78/45.4 kg), this would equate to a \$205.40 reduction in carcass value. Additionally, a reduction in HCW of 45.4 kg would equate to a loss of \$189.78/animal. The combination of reduced HCW and decreased carcass merit would equate to a loss of \$395.18/animal. Clearly, the financial implications of IUGR livestock are not trivial.

In ruminants and humans, muscle fiber hyperplasia ceases early in the third trimester (Robelin et al., 1991; Wilson et al., 1992). Subsequent muscle growth occurs by fiber hypertrophy that is facilitated by increased myonuclear content, which amplifies protein synthesis capacity (Davis and Fiorotto, 2009; Ten Broek et al., 2010). However, muscles in IUGR infants and lambs contain fewer myonuclei per fiber at birth, resulting in less DNA, RNA, and protein per fiber (Widdowson et al., 1972; Greenwood et al., 1999; Greenwood et al., 2000). Myonuclei are postmitotic and accumulation requires incorporation of muscle stem cells called myoblasts that proliferate, terminally differentiate, and then fuse with adjacent fibers, effectively donating their nuclei to the fiber (Davis and Fiorotto, 2009; Ten Broek et al., 2010). Myoblast function is rate limiting for muscle growth (Pavlath et al., 1989; Allen et al., 1999), and myoblasts isolated from IUGR fetal sheep exhibit intrinsically reduced functional capacity (Yates et al., 2014). Specifically, IUGR myoblast cultures contained fewer myogenic differentiation 1 (MyoD)-positive cells and reduced replication rates whether supplemented with fetal bovine serum, control fetal sheep serum, or IUGR fetal sheep serum. This coincided with reduced proliferating cell nuclear antigen (PCNA)-positive myoblasts in IUGR semitendinosus cross-sections near term and at 28 d of age (Yates et al., 2014; Camacho et al., 2016b). Moreover, IUGR myoblasts cultured

in differentiation media (2% fetal bovine serum) for 4 d had fewer myogenin-positive and desmin-positive cells than control fetal myoblasts (Yates, unpublished data). This explains altered myoblast populations and reduced fiber sizes in IUGR hindlimb muscles near term (Yates et al., 2014, 2016) and at 28 d of age (Camacho et al., 2016b), as postnatal muscle stem cells (satellite cells) originate from fetal myoblast precursors (Greenwood et al., 1999; Messina and Cossu, 2009). Insulin promotes proliferation and differentiation of myoblasts (Allen et al., 1985) via AKT-mediated signaling pathways (Sumitani et al., 2002), and insulin infusion into uncompromised sheep fetuses increases myoblast proliferation (Brown et al., 2016b). However, skeletal muscle AKT content is reduced in IUGR sheep fetuses (Thorn et al., 2009) and adult rats (Camm et al., 2011). Also, insulin activation of AKT is impaired in muscle from IUGR-born men (Jensen et al., 2008) and rats despite greater insulin-stimulated insulin receptor substrate 1 phosphorylation (Rueda-Clausen et al., 2011). Impaired insulin-AKT coupling is particularly noteworthy, as insulin is an important promoter of muscle growth and glucose metabolism.

Skeletal Muscle Metabolism and Glucose Homeostasis

Fetal metabolic adaptations predispose IUGR-born offspring to metabolic diseases that lower quality of life (Vickers et al., 2000; Newsome et al., 2003). Glucose intolerance and obesity rates are profoundly higher in IUGR-born individuals even at very young ages (Flanagan et al., 2000; Ong et al., 2000; Mericq et al., 2005). Poor insulin sensitivity and reduced glucose oxidation, which are hallmark characteristics of diabetics (Vind et al., 2012), are present in IUGR-born children by 12 yr of age even at normal bodyweights (Jornayvaz et al., 2004; Dulloo, 2006). A pair of pivotal studies in IUGR fetal sheep indicates that deficits in systemic glucose oxidation arise prenatally despite normal rates of whole-body glucose utilization (Limesand et al., 2007; Brown et al., 2015). Fractional reductions in glucose oxidation also coincide with greater lactate production, which indicates a metabolic shift from oxidation to anaerobic glycolysis. Interestingly, when hypoinsulinemia is corrected in IUGR fetal sheep via infusion, glucose utilization increases while O₂ consumption (an indirect measure of oxidative metabolism) does not (Thorn et al., 2013). Instead, circulating lactate concentrations further increase, indicating that the metabolic shift is not

dictated by hypoinsulinemia but rather by selectively impaired sensitivity of glucose oxidation to insulin. Impaired proximal insulin signaling in muscle from IUGR fetal sheep and adult humans (Ozanne et al., 2005; Thorn et al., 2009) may be explained in part by altered fiber type proportions.

Skeletal muscle fiber types differ in their metabolic rates, mitochondrial densities, and responsiveness to insulin and other metabolic regulators (Henriksen et al., 1990; Mackrell and Cartee, 2012). Specifically, insulin sensitivity and glucose oxidation rates are greatest in type I or slow oxidative fibers, intermediate in type IIa or fast oxidative and/or glycolytic fibers, and lowest in type IIx or fast glycolytic fibers. Semitendinosus and biceps femoris muscles from IUGR fetal sheep express proportionally fewer type I fibers and total oxidative fibers (types I and IIa) near term (Yates et al., 2016). Flexibility in fiber type composition throughout postnatal life is critical to maintaining metabolic homeostasis through changing physiological states (Costagliola et al., 2016). Our results indicate that fiber type plasticity is reduced by IUGR adaptations (Yates et al., 2016), which likely contributes to metabolic dysfunction in offspring. In fact, we report that the shift in glucose metabolism is muscle-centric and is retained in IUGR-born lambs independent of adipose-driven catch-up growth and despite normal circulating glucose, insulin, cortisol, epinephrine, and norepinephrine (Camacho et al., 2016a). In pregnant sheep, we recently observed that sustained periods of maternofetal inflammation in the early third trimester (days 100 to 115 of gestation, term = 150 d) induced by serial maternal administration of bacterial endotoxin recapitulates fetal growth restriction, deficient skeletal muscle glucose oxidation, and greater lactate production (Merrick et al., 2017). These results were consistent with altered metabolic regulation by stress components (Cadaret et al., 2017a, 2017b).

ADRENERGIC AND INFLAMMATORY ADAPTATIONS

Adrenergic and Inflammatory Regulation of Muscle Growth

Catecholamines and inflammatory cytokines are important regulators of myoblast function and muscle growth (Barnes et al., 2017; Merrick et al., 2017). Adrenergic regulation is primarily facilitated by β_2 receptors which are the most highly expressed isoform in skeletal muscle, although β_1 receptors and to a lesser extent β_3 and

α_{1D} receptors are also present (Kim et al., 1991; Shi et al., 2017). Growth studies in animals have led to the use of isoform-specific β adrenergic agonists as growth-promoting feed supplements for finishing livestock, which can increase meat yield of feedlot cattle by up to 40% (Johnson et al., 2014). In a preliminary study, proliferation of primary myoblasts from steers was increased after 48-h incubation with the β_2 agonist zilpaterol HCl but not with the β_1 agonist ractopamine HCl (Yates, unpublished data). Our preliminary findings in L6 myoblasts show that acute (4 h) incubation with epinephrine in the absence of insulin reduces proliferation rates but longer exposure (48 to 96 h) increases proliferation (Riley et al., 2016).

Myoblast regulation by inflammatory cytokines is quite complex (Kumar et al., 2012; Pilon et al., 2013). For example, TNF α and TNF-related weak inducer of apoptosis (TWEAK) stimulate proliferation in cultured myoblasts but strongly suppress differentiation and fusion (Kumar et al., 2012; Trendelenburg et al., 2012; Otis et al., 2014). Furthermore, muscle fiber size is reduced by both the knockout of and overexposure to inflammatory cytokines (Dogra et al., 2007; Kumar et al., 2012; Pilon et al., 2013). In an unpublished preliminary study with myoblasts isolated from mature cows, we observed 10% fewer differentiated (myogenin-positive) myoblasts after 4 d when media was spiked with TNF α .

Adrenergic and Inflammatory Regulation of Muscle Metabolism

Catecholamines and inflammatory cytokines also regulate muscle metabolism (Fernandes et al., 2014; Barnes et al., 2017; Cadaret et al., 2017b; Merrick et al., 2017). Acute stimulation of primary rat muscle and differentiated bovine myoblasts with the β_2 agonist zilpaterol HCl increased basal and insulin-stimulated glucose oxidation with little impact on glucose uptake (Cadaret et al., 2017b; Merrick et al., 2017). Conversely, acute stimulation with the β_1 agonist ractopamine HCl did not increase glucose oxidation and antagonized insulin-stimulated AKT phosphorylation. Zilpaterol supplementation to wethers for 21 d prior to harvest increased glucose oxidation in isolated hind-limb muscle, but ractopamine did not (Barnes et al., 2017).

Like β_2 agonists, inflammatory cytokines directly stimulate acute muscle glucose oxidation. Primary rat and fetal sheep muscle incubated with TNF α or IL-6 in the absence of insulin exhibited greater glucose oxidation rates (Cadaret et al.,

2017b; Merrick et al., 2017). However, the inflammatory cytokines impaired insulin-stimulated AKT phosphorylation, and thus insulin did not increase glucose oxidation in muscle incubated with either TNF α or IL-6. Sustained inflammation created substantial insulin resistance in ewes administered a large intravenous bolus of bacterial endotoxin; insulin-to-glucose ratios were comparable to controls after 2 h but were increased after 4 h and remained greater through 24 h (Yates et al., 2011b).

Adaptive Changes in Adrenergic and Inflammatory Regulation

We previously postulated that deficient growth and glucose metabolism in IUGR skeletal muscle are due to adaptive changes in adrenergic and inflammatory regulation. Preliminary findings indicate that differences in adrenergic regulation may be due to changes in relative proportions of β receptor isomers. Gene expression for β 2 receptors is reduced relative to that of β 1 and β 3 receptors in IUGR fetal and neonatal muscle and in fetal myoblasts (Yates et al., 2012b). Since β 2 activity stimulates growth and metabolism, the reduction in relative β 2-to- β 1/ β 3 signaling may represent the intrinsic deficit underlying impaired IUGR myoblast function and muscle hypertrophy (Yates et al., 2014, 2016). Moreover, β 2 adrenergic activity enhances insulin action, whereas β 1 and β 3 adrenergic activity disrupt insulin signaling (Jost et al., 2005; Cadaret et al., 2017b). Less relative β 2 activity is also consistent with the metabolic phenotype of IUGR muscle, as β 2 stimulation increases glucose oxidation and insulin activity (Cadaret et al., 2017b), likely via mammalian target of rapamycin complex (mTORC)-mediated pathways (Sato et al., 2014; Posont et al., 2017). Conversely, β 1 stimulation diminishes glucose oxidation and insulin signaling (Hoeks et al., 2003; Cadaret et al., 2017b). The shift in β adrenergic activity may also have indirect implications on muscle glucose metabolism, including the loss of β 2-mediated anti-inflammatory effects (Silva et al., 2014) and greater β 1-mediated disruption of IGF activity (Walker et al., 2010).

In addition to adrenergic changes, basal inflammation status is greater in IUGR-born offspring. In rats, IUGR increased circulating TNF α concentrations in 21-d-old male offspring, despite substantial catch-up growth (Riddle et al., 2014). Circulating TNF α and toll-like receptor 9 (TLR9) concentrations were also higher in IUGR-born rats at 8 wk (Oliveira et al., 2017) and 9 mo of age (Desai et al.,

2009), and hepatic TNF α and IL-6 concentrations were greater at 12 mo (Tarry-Adkins et al., 2016). In IUGR-born mice, catch-up growth had normalized body weights by 2 wk of age, yet IL-6, IL-1 β , and TNF α were all increased at 10 wk (Chisaka et al., 2016). Chronic low-grade inflammation almost certainly contributes to muscle dysregulation due to the effects of inflammatory cytokines on myoblast function (Kumar et al., 2012; Trendelenburg et al., 2012; Otis et al., 2014) and muscle hypertrophy (Dogra et al., 2007; Bhatnagar et al., 2012). Preliminary results in rats show amplified inflammatory activity prenatally, as maternal inflammation at mid-gestation increased fetal plasma TNF α by ~67% at term (Cadaret et al., 2017a). These pups also exhibited evidence of inflammatory adaptations with skeletal muscle tissues; total resident macrophages and growth-promoting M2 macrophages were reduced in hindlimb muscles. This coincided with fewer MyoD-positive and more myogenin-positive hindlimb myoblasts, indicating precocious differentiation (Cadaret et al., 2017a). Unpublished preliminary results in IUGR fetal sheep indicate enhanced cytokine stimulus-response coupling as muscle content of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B)-sequestering protein, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor (I κ B), is reduced. In addition, gene expression for TNF α and TNF receptor 1 (TNFR1) is increased in muscle of IUGR fetal sheep and white blood cells of IUGR fetal rats. The combination of greater basal inflammation and enhanced responsiveness to cytokines along with adrenergic changes likely mediate muscle dysregulation.

SUMMARY AND CONCLUSIONS

Intrauterine growth restriction is the result of fetal adaptations to poor intrauterine conditions. This adaptive programming benefits fetal survival but leads to a multitude of problems after birth. Humans and animals that experience IUGR have much greater rates of perinatal and/or neonatal morbidity and mortality, and those that survive have reduced muscle mass, increased fat deposition, and are at much greater risk for metabolic dysfunction throughout life. In livestock, IUGR-born animals exhibit low birthweight, inefficient growth, reduced carcass quality, and less lean product. In humans, IUGR is associated with reduced muscle mass and strength, greater childhood obesity, and increased risk for type-2 diabetes, hypertension, and other conditions of metabolic syndrome in adulthood.

Maternofetal stress caused by any of a number of different environmental, nutritional, and toxicity stressors diverts maternal blood flow away from the gravid uterus, thus stunting placental development. These placentas, characterized by poor vascularity and reduced permeability, fail to provide the fetus with sufficient O₂ and nutrients during the later stages of gestation. As the fetus progressively outgrows its stunted placenta, it becomes increasingly hypoxemic and hypoglycemic, resulting in sustained fetal stress responses that include hypercatecholaminemia and inflammation. As these conditions become chronic, the fetus develops two key muscle-centric adaptations to restrict nonvital use of nutrients. First, skeletal muscle growth is disproportionately reduced via impaired myoblast function, which results in the hallmark asymmetric fetal growth restriction. Second, muscle glucose metabolism is reduced via inhibition of insulin secretion and reduction of glucose oxidation. Our recent findings indicate that reduced responsiveness to β 2 adrenergic regulation and enhanced responsiveness to inflammatory regulation in IUGR skeletal muscle may be key mechanisms underlying the IUGR metabolic phenotype. Moreover, these systems may provide unique targets for interventions and treatments to improve outcomes in IUGR-born offspring.

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