Hindawi Publishing Corporation
Journal of Pregnancy
Volume 2012, Article ID 631038, 10 pages
doi:10.1155/2012/631038

Review Article

Developmental Programming in Response to Intrauterine Growth Restriction Impairs Myoblast Function and Skeletal Muscle Metabolism

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Received 1 April 2012; Accepted 25 May 2012

Academic Editor: Timothy Regnault

Fetal adaptations to placental insufficiency alter postnatal metabolic homeostasis in skeletal muscle by reducing glucose oxidation rates, impairing insulin action, and lowering the proportion of oxidative fibers. In animal models of intrauterine growth restriction (IUGR), skeletal muscle fibers have less myonuclei at birth. This means that myoblasts, the sole source for myonuclei accumulation in fibers, are compromised. Fetal hypoglycemia and hypoxemia are complications that result from placental insufficiency. Hypoxemia elevates circulating catecholamines, and chronic hypercatecholaminemia has been shown to reduce fetal muscle development and growth. We have found evidence for adaptations in adrenergic receptor expression profiles in myoblasts and skeletal muscle of IUGR sheep fetuses with placental insufficiency. The relationship of β-adrenergic receptors shifts in IUGR fetuses because Adrβ2 expression levels decline and Adrβ1 expression levels are unaffected in myofibers and increased in myoblasts. This adaptive response would suppress insulin signaling, myoblast incorporation, fiber hypertrophy, and glucose oxidation. Furthermore, this β-adrenergic receptor expression profile persists for at least the first month in IUGR lambs and lowers their fatty acid mobilization. Developmental programming of skeletal muscle adrenergic receptors partially explains metabolic and endocrine differences in IUGR offspring, and the impact on metabolism may result in differential nutrient utilization.

1. Introduction

Intrauterine growth restriction (IUGR) affects 10–15% of all infants born in the USA and as many as 24% of babies born in developing countries [1, 2]. Worldwide, IUGR is the second leading cause of perinatal morbidity and mortality behind premature birth [3] and is a major predisposing factor to metabolic disorders throughout postnatal life [4, 5]. Children born SGA due to IUGR are more likely to develop insulin resistance and obesity at young ages [6–8]. As adults, these individuals face greater incidence of type 2 diabetes, hypertension, and other health issues [9–12]. In fact, IUGR offspring are 18 times more likely to develop metabolic syndrome than offspring born at an appropriate size for their gestational age (AGA) [10, 13]. Preterm infants may also be predisposed to metabolic disorders later in life. Though AGA at birth, these infants are often growth-restricted between birth and term because their oral intake of protein cannot match the levels supplied by the placenta [14]. Skeletal muscle accounts for ~40% of the body's mass and thus plays a major role in metabolic homeostasis. Growth and metabolism of skeletal muscle are influenced by a number of factors, including nutrient availability, growth factors, and endocrine signals. In this paper, we will focus on the role of the adrenergic system in fetal adaptations to intrauterine insults alter growth, development, and metabolic set-points in skeletal muscle during late gestation and throughout postnatal life.

2. IUGR Conditions: Hypoxemia, Hypoglycemia, and Hypercatecholaminemia

A frequent cause of IUGR is placental insufficiency [15], which can occur spontaneously and from undiagnosed

etiology. As the fetus grows, the stunted placenta cannot keep up with the increasing nutritional demands of the fetus, resulting in chronic fetal hypoglycemia and hypoxemia throughout late gestation. These conditions elevate circulating catecholamine concentrations [16]. Plasma norepinephrine and epinephrine concentrations are modestly elevated by fetal hypoglycemia [17–19] but greatly elevated by hypoxemia [20, 21]. Fetal adrenal chromaffin cells contain oxygen-sensitive K^+ channels that stimulate catecholamine secretion in response to low blood oxygen content, while the splanchnic nerve develops [21, 22]. In IUGR human and rat fetuses, hypoxemia increases catecholamine concentrations in plasma and amniotic fluid by as much as 5-fold [23–25]. Plasma epinephrine and norepinephrine are also elevated in IUGR fetal sheep where placental insufficiency is the known etiology [26–28]. Catecholamines act via the G-protein coupled receptors, Adrα and Adrβ [29, 30], which express multiple subtypes (α1A, α1B, α1D, α2A, α2B, α2C, β1, β2, and β3) with distinct physiological and pharmacological properties [31]. Receptor expression patterns determine how tissues respond to catecholamines, and skeletal muscle predominantly expresses Adrβ1 and Adrβ2 subtypes, but Adrβ3 and Adrα subtypes are also present. Even in healthy pregnancies, brief cord occlusions and Poseiro effects cause transient periods of fetal hypoxemia and hypoglycemia [32, 33], making it necessary for the fetus to have a protective mechanism to conserve glucose and oxygen. Skeletal muscle accounts for ~65% of fetal glucose consumption and its metabolic functions are responsive to endocrine regulation [34], making it a prime site for glucose and oxygen conservation.

3. Fetal Adaptive Response to IUGR Conditions

Both hypoxemia and hypoglycemia can impact global fetal metabolism, and the response depends upon the duration of the insult. We have shown that acute (<1 hour) fetal hypoxemia suppresses glucose-stimulated insulin secretion by increasing circulating norepinephrine and epinephrine (Yates and Limesand, unpublished), which then activate inhibitory Adrα2 receptors on pancreatic β-cells [20, 26, 35, 36]. The combination of high circulating catecholamines and low insulin concentrations contributes to hyperlactatemia, acidosis, and hypocarbia in the fetus [37] (Yates and Limesand, unpublished). We postulate that this reflects a temporary reduction in skeletal muscle glucose oxidation to spare glucose and oxygen for neural tissues. This transient coping mechanism is accompanied by increased utilization of nonglucose substrates for energy production. To illustrate, skeletal muscle enzymes associated with fatty acid oxidation are upregulated in fetal rats 24 hours after uterine artery ligation [38], and fatty acid mobilization rates in the sheep fetus increase after six hours of hypoglycemia [17]. Additionally, a greater proportion of amino acids are diverted for oxidization in these fetal sheep [39, 40]. Placental insufficiency causes a chronic state of fetal hypoxemia and hypoglycemia, and therefore hypercatecholaminemia and suppression of glucose oxidation are sustained. As a result, endocrine and metabolic adaptations develop to conserve fetal nutrients by lowering skeletal muscle energy requirements for protein synthesis and growth [41–43]. Accordingly, amino acid oxidation rates in the fetal sheep return to normal after the 8th week of hypoglycemia [41]. Similarly, the ability to mobilize fatty acids is reduced in the IUGR sheep fetus near term [44–46]. In addition to lower oxidative metabolism, the IUGR fetus induces hepatic glucose production and the Cori cycle [47], which utilizes lactate produced by anaerobic glycolysis in skeletal muscle as a substrate for glucose [47, 48]. Lactate clearance by the liver stabilizes plasma lactate concentrations in IUGR fetuses, creating only mild hyperlactatemia [47] compared to acutely hypoxemic fetuses. Thus, long durations of nutrient or oxygen deprivation produce a metabolic shift that may be explained by adaptations to catecholamine levels in fetal circulation.

Comparisons between fetal sheep made chronically hypoglycemic and those with placental insufficiency (hypoxemic and hypoglycemic) show that hypoxemia has a greater propensity than hypoglycemia for inducing metabolic adaptations, possibly due to greater adrenergic activity associated with hypoxemia. Chronic hypoglycemia increases protein breakdown and rates of amino acid oxidation, lowers plasma insulin and glucose uptake, and slows fetal growth rate, but the response is transient and euglycemic recovery normalizes these parameters within a few days [39, 49]. Conversely, in fetal sheep with placental insufficiency, euglycemic correction fails to restore glucose homeostasis or improve growth rate and in fact worsens hypoxemia and hypoinsulinemia, resulting in acidosis [50]. Therefore, the metabolic changes associated with placental insufficiency are dependent on placental oxygen supply and cannot be alleviated by removing just the nutrient deprivation.

4. Skeletal Muscle Developmental Adaptations to IUGR Conditions

The trajectory of skeletal muscle development and growth is slowed in IUGR fetuses. Ultrasonic measurements of IUGR fetuses show that muscle mass is reduced [51, 52], and animal studies show that nutrient restriction impairs fiber formation [53, 54]. Muscle fiber numbers, size, and metabolic phenotypes develop at distinct fetal stages and thus these aspects of muscle formation and growth are affected differently depending upon the timing of the fetal insult (Figure 1). Fiber numbers are determined by myogenesis (formation of new fibers), which occurs in 3 distinct phases and is completed early in the third trimester [55, 56]. Primary myotubes are generated from the fusion of progenitor cells midway through the first trimester, creating the scaffold around which smaller, secondary myotubes form near the end of the first trimester. A final wave of secondary (sometimes called tertiary) myotubes fills in the spaces not already occupied by existing fibers and completes myogenesis early in the third trimester. Nutritional insults during early or mid-gestation interfere with myotube formation and reduce fiber density in skeletal muscle. For example, maternal nutrient restriction between the mid-first and mid-second trimester in sheep lowers the number of secondary fibers

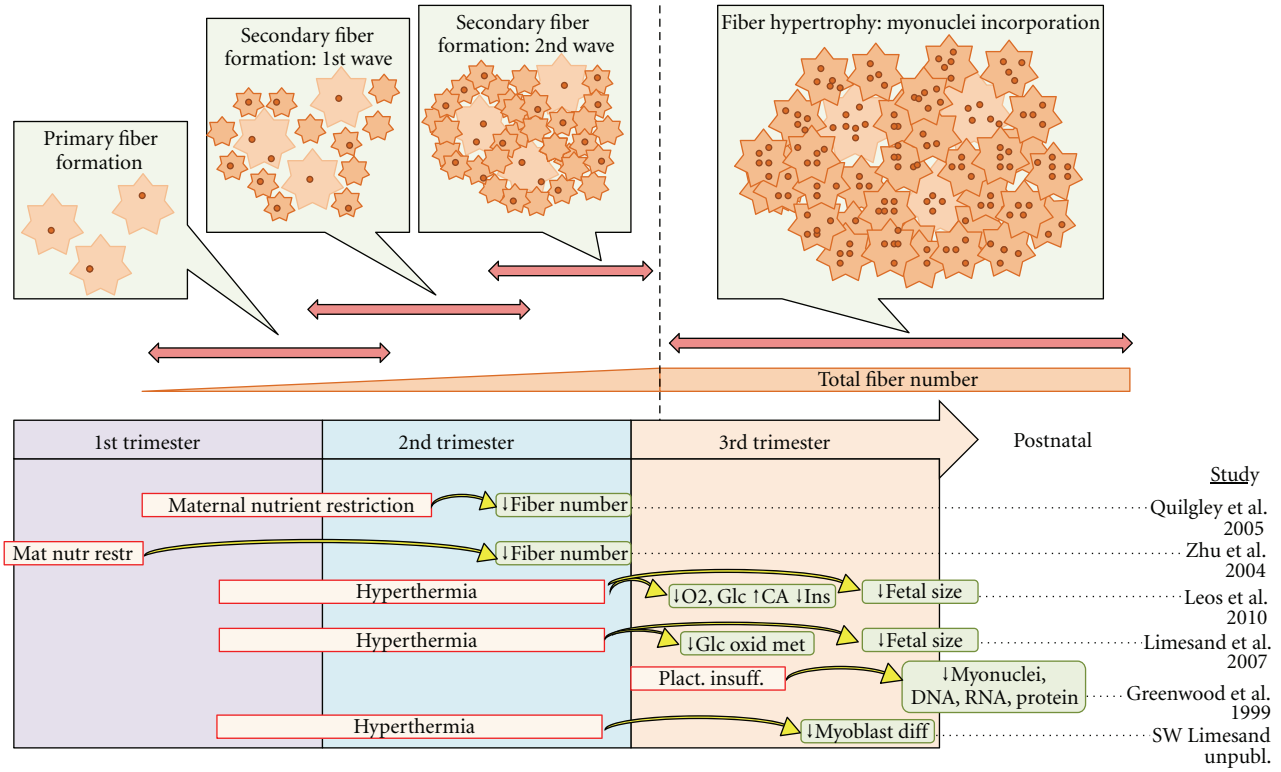

Figure 1: The stages of skeletal muscle formation relative to gestational age are depicted by the horizontal arrows and schematic diagrams (fascicular cross-sections) for the developmental process. The vertical dashed line represents the completion of myogenesis (new fiber formation) and onset of hypertrophic fiber growth. The timing, duration, and type of nutritional insult (red boxes) reported in various studies are presented below the gestational timeline, along with the fetal consequences (blue boxes).

per fasciculi in the fetal longissimus dorsi muscle [57]. In pregnant ewes recovering from malnourishment at periconception, secondary fiber density was also lower in the fetal semitendinosus muscle [58]. Although IUGR can result from maternal nutrient restriction during early gestation, placental insufficiency does not cause fetal hypoxemia and hypoglycemia until later stages of gestation, most likely after myogenesis is complete [53, 54]. As a result, placental insufficiency would reduce muscle mass by impairing fiber growth to a greater extent than total fiber number.

After myogenesis, muscle growth continues via fiber hypertrophy and requires myoblast incorporation to increase genomic DNA content [59–65]. Myonuclei incorporation precedes protein accumulation, and the size of a muscle fiber is dependent on DNA content [59–63]. Because muscle fiber myonuclei are postmitotic, DNA accumulation depends on incorporation of new nuclei from myoblasts [66]. In fact, 50–99% of total skeletal muscle DNA content accumulates postnatally [60]. In fetal sheep with placental insufficiency, skeletal muscle fibers contain fewer myonuclei than fibers from control fetuses, resulting in 33% less DNA, 40% less RNA, and 76% less protein per fiber [53, 54]. Human fetuses diagnosed as IUGR also have reduced skeletal muscle DNA content in late gestation but have normal protein-to-DNA ratios [67]. Our preliminary evidence indicates that myogenic cell populations are smaller in IUGR fetal skeletal muscle and that myoblasts isolated from IUGR fetal sheep may proliferate and differentiate at slower rates than those isolated from control fetuses (Yates, Limesand, and Rhoads, unpublished). This scenario would indicate that lower myonuclei content is a major limiting factor in IUGR skeletal muscle fiber growth and that IUGR myoblasts are impaired.

Histological measurements reveal a smaller proportion of oxidative-to-glycolytic muscle fibers in some skeletal muscles, which is another mechanism by which fetal developmental adaptations reduce muscle oxidative metabolism. In the ovine tibialis cranialis, newly forming secondary fibers express myosin-heavy chains for type II (glycolytic) fibers exclusively, but under normal conditions, ~60% of these fibers stain positive for type I (oxidative) myosin-heavy chains by the start of the third trimester [56]. The fiber-type ratio continues to shift toward oxidative fibers until a few weeks after birth [54, 68]. Together, these data reveal a multifaceted defect in IUGR skeletal muscle growth, which manifests in myoblast developmental programming that lowers myonuclei content and alters fiber phenotypes, thus preventing normal metabolic regulation.

5. Adrenergic Intervention: Catecholamines Change the Regulatory Signals

Adaptations in skeletal muscle growth and metabolism appear to be facilitated by chronic exposure to circulating

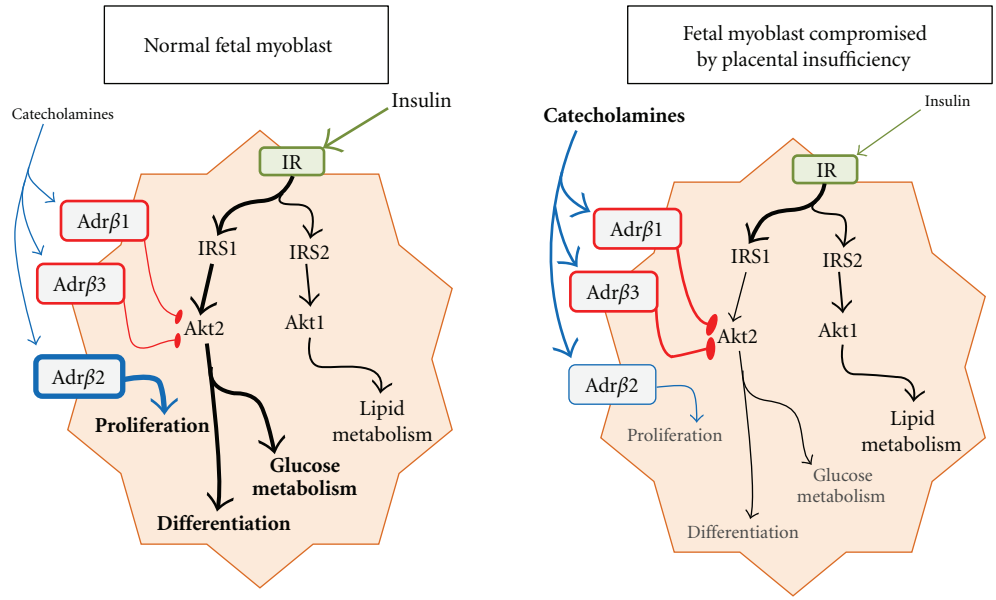

FIGURE 2: Impact of placental insufficiency on endocrine responsiveness in fetal myoblasts and myofibers. Adrenergic activity increases due to greater circulating catecholamines. Adrenergic receptor β subtype-specific desensitization results in a greater proportion of signaling through Adrβ1 and Adrβ3 because Adrβ2 expression is reduced. Insulin signaling is reduced due to adrenergic suppression of insulin secretion in pancreatic β-cells and by muscle adrenergic signaling that negatively influences the insulin-Akt2 intercellular signaling pathway. These developmental adaptations reduce rates of myoblast proliferation and differentiation as well as glucose metabolism in skeletal muscle.

catecholamines (Figure 2). In fact, intravenous infusion of norepinephrine or epinephrine for 8 days reduces plasma insulin and blood CO_2, increases plasma lactate, and slows hindlimb muscle growth rate in otherwise uncompromised fetal sheep [69]. Catecholamines affect skeletal muscle directly by selectively impairing insulin signaling and indirectly by suppressing insulin secretion from pancreatic β cells [70, 71]. Under normal conditions, insulin regulates muscle metabolism by stimulating glucose uptake, glycogenesis, glucose oxidation, and protein synthesis via the Akt2 and MAPK-Erk1,2 signaling pathways [72–74] and by stimulating lipid metabolism via Akt1 [73]. Insulin also promotes myoblast proliferation and differentiation [75–77] by activating Akt2 via IRS1 [73, 77–79], and increases protein synthesis in fetal skeletal muscle [80, 81] and in myotubes derived from isolated fetal myoblasts [82]. However, placental insufficiency in fetal sheep reduces plasma insulin by 78% [20, 26, 69, 83] and skeletal muscle Akt2 content by 40% [48]. Furthermore, in adult rats chronically infused with epinephrine, insulin administration is less effective in stimulating IRS1 tyrosine phosphorylation, IRS1 complex with PI3K and SHP2, and Akt phosphorylation in skeletal muscle [84]. In adult humans, infusion of dobutamine (Adrβ1 agonist) acutely reduces glucose oxidation rates and increases lipid oxidation rates in skeletal muscle [85]. Salbutamol (Adrβ2 agonist) has no effect on glucose oxidation rates but slightly increases lipid oxidation [85]. Furthermore, catecholamines activate hormone-sensitive lipase to release fatty acids from fat stores [86, 87], which may help replace glucose as a metabolic substrate in muscle (Akt1 expression is not altered by catecholamines [48]).

One major developmental adaptation in response to chronic catecholamine exposure is modified adrenergic signaling via alteration of Adrβ expression. Findings in other tissues show that Adrβ1, Adrβ2, and Adrβ3 have subtype-specific effects on insulin signaling. In adipocytes, Adrβ1 and Adrβ3 stimulation reduces insulin signaling by uncoupling IRS1 phosphorylation [88, 89] and Adrβ1 suppresses insulin activation of Akt in cardiac muscle [90]. Conversely, Adrβ2 amplifies insulin activation of MAPK-Erk1,2 in ovarian cells [91] and has been shown to stimulate myoblast proliferation directly in chicks and mice [92, 93]. However, we have found that expression of Adrβ2 is reduced in myoblasts isolated from IUGR sheep fetuses (Table 1; Limesand and Yates, unpublished findings), meaning that adrenergic enhancement of insulin signaling is reduced. Meanwhile, myoblast Adrβ1 and Adrβ3, which inhibit insulin-stimulated proliferation and differentiation, are expressed normally. Likewise, Adrβ2 mRNA expression is reduced in hindlimb skeletal muscle of IUGR fetal sheep and in those administered 7-day norepinephrine infusions, but Adrβ1 and Adrβ3 expression remain normal (SW Limesand and X Chen, unpublished data). The end result is a greater inhibitory effect on skeletal muscle insulin signaling which, along with reduced insulin secretion, would impair myoblast proliferation and incorporation into muscle fibers and insulin-driven glucose metabolism. Furthermore, skeletal muscle Adrβ2 continues to be reduced in placental insufficiency-compromised lambs at one month of age, showing that the adaptive Adrβ profile may be a contributing factor in postnatal metabolic disorders.

Table 1: Adrenergic receptor β (Adrβ) mRNA expression determined by quantitative PCR in placental insufficiency-induced IUGR[1] and norepinephrine-infused[2] sheep fetuses relative to control fetuses.

Treatment	Age at necropsy	Tissue	Adrβ1	Adrβ2	Adrβ3
PI-IUGR	Fetus, 134 dGA	Myoblasts[3]	↑28%	↓25%	↑800%
	Fetus, 134 dGA	Skeletal muscle[4]	NC	↓64%	NC
	Neonate, 28 days	Skeletal muscle[4]	—	↓44%	—
NE-Infused	Fetus, 140 dGA	Skeletal muscle[4]	NC	↓47%	NC

[1]Hyperthermia from 40 to 95 days of gestation (term ~145 days).
[2]Intravenous norepinephrine (NE) infusions from 130 to 137 days of gestational age.
[3]Isolated from hindlimb skeletal muscles. $n = 3$/treatment.
[4]Pooled semitendinosus and biceps femoris. $n = 6$/treatment.
NC: no change; ↑: increased relative to controls; ↓: decreased relative to controls. Constitutive control was s15 for all samples.

6. Fetal Adaptations Persist in Postnatal Life

Hypoglycemia and hypoxemia are alleviated by birth, but the thrifty metabolic adaptations persist into postnatal life [4, 5]. Children born with SGA have less skeletal muscle mass as infants and skeletal muscle mass grows at a slower rate through four years of age compared to their AGA counterparts [94–96]. Arm muscle size is reduced in infants at birth and at 3, 6, and 9 months of age [97] and upper-arm circumference and muscle area is less at 8 years of age [98]. Similarly, IUGR lambs have substantially reduced weight and protein content in the semitendinosus muscles at birth [53, 99], and daily protein accretion over the first few months of life is slowed [53]. As adults, SGA-born individuals have less lean muscle, greater fat-to-muscle ratios [100–103], and reduced muscle strength [102, 104]. Abdominal and leg muscle mass is reduced in otherwise healthy men at 19 and 22 years of age [105], and total lean muscle is lower at 50, 68, and 70 years of age [103, 106, 107]. In lambs and piglets, IUGR also impairs perinatal development of the vascular architecture [68, 108]. This may reflect an inability of myocytes to stimulate angiogenesis [109, 110] and is likely the origin of altered perfusion characteristics associated with metabolic syndrome, including vascular resistance, reduced responsiveness to adrenergic regulation, and endothelial dysfunction [111]. After birth, myoblasts form solely from the populations of quiescent satellite cells that develop along the basal lamina of muscle fibers [54, 112]. These populations, which control lifetime muscle growth and repair, accrue during fetal development and are subjected to IUGR conditions. Thus, the impairment of myoblast proliferation and differentiation responsible for slowing fetal skeletal muscle growth would also explain slower muscle growth rates in children and reduced lean mass in adults.

The thrifty metabolic phenotype that develops in utero also persists after birth. At 12 years of age, SGA-born children exhibit similar basal metabolic rates compared to AGA-born counterparts, but a smaller fraction of energy production is due to glucose oxidation and a larger fraction is from lipid oxidation [113]. Persistence of limited glucose oxidation rates in IUGR skeletal muscle can be associated with a combination of factors. First, less total lean muscle mass requires less energy. This scenario explains lower rates of systemic glucose oxidation but does not explain reduced muscle-specific glucose uptake [113, 114]. Dulloo [115, 116] postulates a second factor for reduced skeletal muscle glucose oxidation: glucose is preferentially redistributed to adipose tissues to replenish depleted fat stores. This "glucose redistribution hypothesis" has been applied to the perinatal period after IUGR as well as recovery from prolonged nutrient restriction at older ages [117]. However, SGA-born individuals continue to exhibit thrifty glucose metabolism throughout their lives, well after fat reserves are replenished, which indicates that the timing of the insult is important for persistence of the metabolic phenotype. Evidence for the permanence of developmental adaptations includes decreased oxidative-to-glycolytic fiber proportions in 8-month-old sheep exposed to fetal nutrient restriction and in mature pigs classified as runts (much smaller than littermates) at birth [45, 118]. Skeletal muscle biopsies from young-adult men born SGA reveal reduced insulin-signaling enzymes (e.g., PI3K, p85α, p110β, PKCζ, Glut4) despite normal insulin receptor content [119]. In rats, insulin signaling via Akt is reduced in offspring from dams exposed to a hypoxic or malnourished environment during pregnancy [120]. Together, these studies indicate that the sustained response is not completed after adipose stores are replenish but is rather a product of a new nutrient utilization set-point established by fetal developmental programming to IUGR conditions. This phenomenon was described by Hales and Barker [4, 5] as "metabolic dysregulation," but the connotation of a disorder may only apply because these individuals are subjected to a lifetime of diets that exceed their nutritional requirements.

7. Summary

Placental insufficiency results in conditions that restrict fetal skeletal muscle development and growth by reducing the capacity of the myofiber to maintain glucose homeostasis. Altered adrenergic receptor expression profiles in myoblasts and skeletal muscle of IUGR sheep fetuses indicate that slower growth rates and thrifty metabolism are the result of fetal adaptations to chronic catecholamine exposure in utero. As the proportion of Adrβ2 to Adrβ1 declines in IUGR skeletal muscle, adrenergic regulation promotes insulin

resistance, reduced myoblast incorporation, less fiber hypertrophy, and lower rates of glucose oxidation. Developmental programming of skeletal muscle adrenergic receptors in utero helps explain metabolic and endocrine differences in IUGR offspring as well, and the impact on metabolism may result in differential nutrient utilization and requirements.

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