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The Essential (and Targetable) Role of Inflammation in the Poor Muscle Growth and Metabolism of Heat-Stressed Livestock[1]

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[1]This manuscript includes descriptions of research that was supported by USDA NIFA Foundational Grants 2019-67015-29448 and 2020-67015-30825, NIGM Grant 1P20GM104320, Nebraska AES Hatch Act funding (1009410), and Hatch Multistate Research capacity funding (1011055 and 1009410) through USDA NIFA. The contents of this publication do not necessarily represent official views of the USDA or NIGMS.

Abstract: Heat stress is a global barrier for meat animal production. Sustained exposure of livestock to hot environmental conditions makes optimal welfare difficult to achieve and produces considerable deficits in growth and efficiency. In this review, we discuss how livestock are particularly susceptible to heat stress during the period preceding harvest (i.e., finishing), when body weights and adiposity are at their greatest. Prenatal heat stress during critical windows for fetal development also limits postnatal growth and efficiency by inducing adaptive programming in muscle and other tissues. Skeletal muscle is the epicenter of the physiological changes that occur in response to heat stress due to its substantial nutrient consumption and metabolic heat production. The high metabolic plasticity and less essential role in acute survival make muscle an effective target for nutrient reappropriation to support vital neural, cardiac, and endocrine tissues during stress. Sustained heat stress induces myoblast stem cell dysfunction, which limits the capacity for protein synthesis and, in turn, hypertrophic muscle growth. In addition, heat stress markedly reduces muscle glucose oxidation and increases lipid oxidation, glycogen deposition, and glycolytic lactate production, all of which are associated with metabolic inefficiency. Recent studies show that the effects of heat stress on muscle are facilitated in part by the induction of systemic inflammation. Cytokines like TNFα and IL-6 induce dysregulation of cellular processes for myoblast-facilitated muscle growth and intramuscular fat deposition, which is consistent with reduced carcass quality and yield observed in heat-stressed animals. Climate predictions include more frequent and extreme heat events, making practical options to manage the impact of heat stress a necessity for sustainable meat production. This review describes the associations between heat stress, systemic inflammation, and the impact on muscle growth, composition, and metabolism. It also presents recent evidence for the potential benefit of nutraceutical moderators of inflammation on heat stress outcomes.

Key words: climate change, environmental stress, fetal programming, inflammatory response
Meat and Muscle Biology 9(1): 20179, 1–16 (2025) **doi:10.22175/mmb.20179**
Submitted 30 May 2025 Accepted 13 July 2025

Introduction

Heat stress is the greatest and longest-standing natural barrier to meat animal production. A recent study found that about 80% of cattle raised worldwide experience at least 30 days of environmental heat stress conditions per year (North et al., 2023). Additionally, more than 80% of all goats and almost 60% of all sheep are raised in hot, arid climates (Marino et al., 2016; Joy et al., 2020). A survey of contemporary US cattle producers found that 75% had lost animals to heat events, yet only about 22% had developed explicit plans for heat stress mitigation (Dean et al., 2023). The jarring death loss associated with extreme heat conditions captures public attention, but moderate heat stress persisting for long durations is far more common, making it a more consistent threat to industry sustainability (Hahn, 1999; St-Pierre et al., 2003). Such chronic heat stress is less likely to be fatal, but it diminishes growth efficiency and carcass merit (Most and Yates, 2021). In pregnant animals, chronic heat stress induces adaptive fetal programming that manifests in intrauterine growth restriction (IUGR) and low birthweight (Yates et al., 2018). Offspring born with moderate IUGR (i.e., 20–35% lighter than conspecifics) typically survive but exhibit lifelong deficits in growth efficiency and body composition, regardless of postnatal environment (Greenwood and Bell, 2019; Gibbs et al., 2020; Gibbs et al., 2023). Poor growth and carcass metrics following heat stress cost the livestock industry billions of dollars in lost revenue annually (Kreikemeier et al., 1998; St-Pierre et al., 2003), which is a 10-fold greater financial impact than death losses from acute heat events (Sullivan and Mader, 2018).

Forecasted changes in global climate threaten to escalate the impact of heat stress. Experts predict that heat events will become more frequent, more severe, and less predictable over the next century (IPCC, 2022; Vargas Zeppetello et al., 2022). Adverse environmental conditions are difficult to overcome through existing management and abatement practices. Infrastructural components like water misters and shade can reduce the impact of heat in some cases (Sullivan and Mader, 2018), but they are costly and can be inconsistent (Boyd et al., 2015; Hagenmaier et al., 2016). Long-term sustainability of the livestock industry will require nutritional/pharmaceutical strategies that complement or replace infrastructural heat abatement by modifying the biological impact of heat stress on animals. Little progress has been made toward identifying biological targets for heat-stress pathologies, but recent findings in sheep and cattle indicate that systemic inflammation is one promising candidate (Barnes et al., 2019; Reith et al., 2020; Swanson et al., 2020). This review outlines the evidence that implicates heightened inflammatory tone in poor muscle growth and metabolic inefficiency of heat-stressed livestock and discusses the benefits of mitigation with anti-inflammatory dietary supplements.

The Impact of Heat Stress in The Feedlot

Hot 'n heavy: Size and adiposity increase the susceptibility of finishing livestock to heat stress

To help feed a rapidly growing world population, beef cattle are being finished at heavier weights than ever before. Feedlot steers arriving for harvest in January 2025 averaged ~24 kg heavier than in 2024 (USDA-NASS, 2025), ~114 kg heavier than in 2005 (Anderson et al., 2005), and ~240 kg heavier than in 1981 (Barber et al., 1981). At a static frame size, heavier livestock are more susceptible to heat stress due to greater metabolic heat production, less efficient heat dissipation, and a more substantive impact of reduced dietary intake (Sullivan and Mader, 2018; Shephard and Maloney, 2023). This makes heat stress particularly dangerous for feedlot livestock (Hahn, 1999; Hagenmaier et al., 2016), where confinement limits the ability to seek shade, cool water, or areas of greater air movement (Mader, 2014; Grandin, 2016). Even modestly high temperature-humidity indexes can result in negative health and productivity outcomes for fed livestock (Brown-Brandl et al., 2003; Brown-Brandl et al., 2017), leading to heat stress being recognized as a top issue for feedlot producers (Mader, 2014; Grandin, 2016).

Farewell to welfare: Heat stress devastates health and well-being in the feedlot

Heat events that are particularly intense or abrupt in nature can kill large numbers of animals in feedlots. In the last 2 decades, heat events have cost Midwestern US feedlots 5,000 or more head of cattle on at least 8 different occasions (Mader, 2014; Myers, 2022; Hammel, 2023). A single event in 2011 killed 15,000 head of cattle throughout the Midwest, and another lasting less than 48 h in 2022 cost Kansas feeders 2,300 head of cattle (Myers, 2022; Hammel, 2023). Each of these animals carried a value of more than $2,000 and represented about 365 kg of meat. In Texas, Kansas, and Nebraska, which account for 2/3rd of all US beef feedyards, heat events increase yearly death loss by an average of 51 animals per 10,000 head (Mader et al., 2002; St-Pierre et al., 2003). These deaths of confined livestock do not reflect humane production standards and are a high-visibility stigma for a closely scrutinized industry. Common factors that compound the impact of heat stress in feedlots include the dark coats of popular meat breeds, lack of acclimation opportunities, facility designs that lack shade or wind circulation, and bunching or huddling of animals together, which can occur for myriad reasons.

Even moderate heat stress increases core body temperature, triggers hyperventilation, and drives animals off feed (Mitlohner et al., 2002; Brown-Brandl et al., 2003; Brown-Brandl et al., 2017). When sustained for more than about 3 d, these conditions disrupt metabolic function, alter blood pH and electrolyte balance, and diminish rumen health (Barnes et al., 2019; Barnes et al., 2021). Heat-stressed animals exhibit aberrant responses to pathogenic toxins (Carroll et al., 2012) and frequently develop secondary pathologies such as hyperlipidemia and alkalosis (Most and Yates, 2021). Although anorexia is a hallmark response to heat stress (Brown-Brandl et al., 2003; Barnes et al., 2019), studies utilizing pair-feeding show that much of the physiological response is independent of dietary intake (Swanson et al., 2020; Grijalva et al., 2021; Reith et al., 2022). In pair-fed finishing lambs, heat stress was associated with insulin resistance, hypertension, high protein catabolism, and damage to pancreatic, liver, and muscle tissues (Swanson et al., 2020; Grijalva et al., 2021; Grijalva et al., 2023). Heat-stressed lambs also exhibited markedly increased hoof overgrowth, which is a predisposition to lameness (Barnes et al., 2019; Swanson et al., 2020).

Where's the beef? Heat stress slows muscle growth and diminishes carcass outcomes

Heat-stressed animals grow poorly, resulting in lower-yielding carcasses. A 2003 study of trends in US feedlots estimated that annual heat stress conditions reduce gain by as much as 17 kg/head in states with historically hot climates like Texas and Oklahoma, which house almost one-quarter of all cattle on feed in the US (St-Pierre et al., 2003). In Midwestern states where more than half of US beef cattle are fed, heat stress still reduces weight gain by 5 to 7 kg/head despite typically milder climates (St-Pierre et al., 2003). Recent studies using climate-controlled environmental chambers found that 4 wks of moderate heat stress (85–87 THI) reduced average daily gain by about 30% in finishing lambs compared to pair-fed thermoneutral counterparts (Swanson et al., 2020; Most et al., 2021; Grijalva, 2023). By comparison, the average daily gain of heat-stressed lambs was about 40% less when thermoneutral counterparts were not pair-fed and thus exhibited a 21% reduction in dietary intake (Barnes et al., 2019; Barnes et al., 2021). Muscle growth is disproportionately diminished compared to other tissues, which results in about 10% less meat being produced from each US beef animal (Mitlohner et al., 2002; Blaine and Nsahlai, 2011; Sullivan and Mader, 2018). Ultrasonic and bioelectrical impedance estimates indicated that 30 d of heat stress in finishing lambs reduced ribeye area by about 7% and total fat-free mass by about 5% (Gibbs et al., 2019; Most et al., 2021; Most, 2022). Necropsies performed at the conclusion of the heat-stress period showed that four-rib cutout sections contained 10–13% less muscle and up to 10% more fat (Most et al., 2021; Most, 2022). As summarized in Figure 1, heat stress consistently reduces individual muscle weights, although the magnitude of the reduction is not necessarily uniform across the various muscles (Barnes et al., 2019; Most

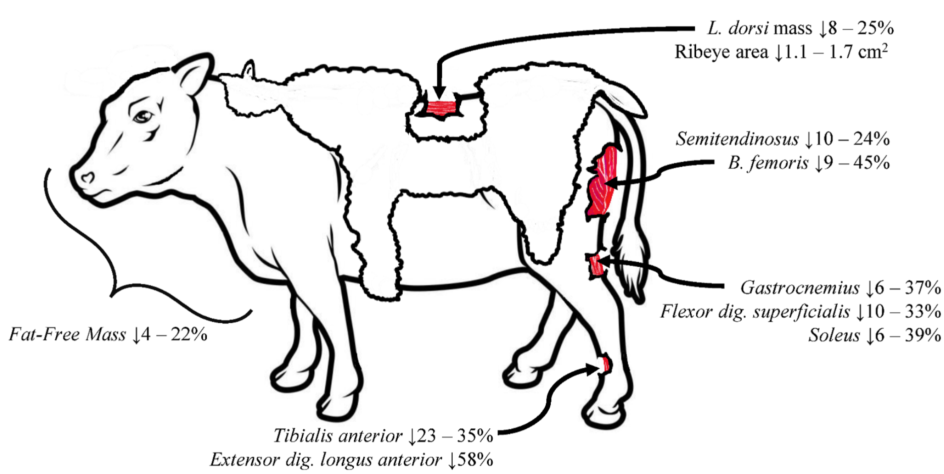

Figure 1. Heat stress reduces skeletal muscle growth whether it occurs during gestation or the finishing period. Data compiled from studies using sheep as a proxy model for beef cattle (Soto et al., 2017; Barnes et al., 2019; Chang et al., 2019; Swanson et al., 2020; Most, 2022; Gibbs et al., 2023; White et al., 2023b; Beer et al., 2024; White et al., 2025b).

et al., 2021; Most, 2022). Comparable results have been observed in commercial feedlot cattle, where heat stress caused livestock to produce smaller carcasses with diminished marbling and tenderness (Kreikemeier et al., 1998; St-Pierre et al., 2003). In feedlot heifers, for example, heat stress reduced hot carcass weight by 7 kg, lowered yield grade by 0.2, and doubled the number of dark cutters despite a modest 3% reduction in daily dry matter intake (Mitlohner et al., 2002). Heat stress also caused almost twice as many carcasses to grade USDA Select rather than USDA Choice (Mitlohner et al., 2002). In finishing steers, heat stress yielded only a 2% reduction in dry matter intake but a 4% reduction in ribeye area (Winders et al., 2023). In a recent controlled-climate study, Red Angus steers produced 5% lighter hot carcass weights and 4.5% lighter cold carcass weights following 21 d of heat stress compared to thermoneutral controls (Grijalva et al., 2022). In Brahman steers, 21-d heat stress increased carcass a^* from 26.9 to 28.4 and b^* from 12.6 to 13.5 following 7-d chilling, indicating the meat was deeper red in color but with a more yellowish tint (Rios et al., 2022). Comparable color changes occurred after 5, 7.5, and 10 d of chilling in carcasses of Dorper sheep following 2 wks of experimental heat stress (Zhang et al., 2021).

Poor cell service: Heat stress induces muscle stem cell dysfunction

Poor muscle growth during heat stress is, in large part, a product of myoblast dysfunction. Myoblasts are the skeletal muscle stem cells that facilitate postnatal muscle growth (Allen et al., 1979). In ruminants and other mammals, muscle fiber number is static after birth and thus muscle grows by incorporating additional myonuclei from myoblasts (Maier et al., 1992; Wilson et al., 1992). When activated from quiescent satellite cells, these progenitors proliferate, differentiate, and fuse with fibers, effectively donating their nuclei to expand protein synthesis capacity (Davis and Fiorotto, 2009; Ten Broek et al., 2010). Muscle growth capacity is proportional to these rate-limiting functions (Pavlath et al., 1989; Allen et al., 1999). Exposure to high temperatures in culture reduced proliferation, migration, differentiation, and fusion rates in primary sheep and pig myoblasts (Kamanga-Sollo et al., 2011; Lu et al., 2023; Lu et al., 2025). Myoblast profiles in *semitendinosus* muscle of heat-stressed lambs were likewise consistent with impaired function: at the conclusion of 30 d of heat stress, total myoblast populations (i.e., pax7$^+$ nuclei) were reduced by 21%, differentiated myoblasts (i.e., myogenin$^+$) were reduced by 20%, and average muscle fiber cross-sectional area was reduced by 9% (Most et al., 2021; Most, 2022). In addition to its function, heat stress may also reduce the survival of myoblast populations. In culture, heat stress for as little as 2 h increased mitochondrial fragmentation and reduced cellular viability in C2C12 mouse myoblasts (Yu et al., 2019). The impact of myoblast dysfunction is reflected in protein synthesis, as muscle protein content was reduced 3–5% following chronic heat stress (Zuo et al., 2015; White et al., 2025b).

Turning to alternative fuels: Heat stress disrupts glucose metabolic efficiency in muscle

Poor growth efficiency during and after heat stress is the product of metabolic changes to reduce internal heat production (Scott, 2005). A primary component of this change is skeletal muscle glucose oxidation, which *ex vivo* experiments show is reduced 18–40% in chronically heat-stressed finishing lambs (Barnes et al., 2019; Swanson et al., 2020; Grijalva et al., 2023). Reduced glucose oxidation occurs despite normal glucose uptake by heat-stressed muscle (Swanson et al., 2020; Grijalva et al., 2021; Grijalva et al., 2023), which is consistent with a greater reliance on anaerobic glycolysis that produces 91% less metabolic heat than glucose oxidation (Scott, 2012). Transcriptomic analyses of *longissimus dorsi* muscle from Red Angus steers following 21 d of heat stress showed gene expression patterns that were consistent with diminished oxidative metabolism (Reith et al., 2020; Reith et al., 2022). Inefficient glucose metabolism by muscle during heat stress helps to explain the 34% reduction in gain-to-feed ratios in heat-stressed lambs (Grijalva et al., 2021; Grijalva, 2023; Grijalva et al., 2023). Heat stress also modifies lipid metabolism. *Ex vivo* assessments showed that epinephrine-stimulated fatty acid mobilization from subcutaneous fat in steers and abdominal fat in wethers was reduced by up to 37% and coincided with reduced circulating triglycerides and high density lipoprotein (HDL)-bound cholesterol (Reith et al., 2020; Grijalva, 2023; Curry et al., 2025; White et al., 2025b). Skeletal muscle from heat-stressed lambs exhibited a 34% reduction in lipid droplet density and a 21% reduction in total lipid area (Grijalva, 2023; Curry et al., 2025). Not surprisingly, the metabolic changes coincided with greater circulating insulin and reduced glucose-to-insulin ratios (Barnes et al., 2019; Swanson et al., 2020; Grijalva et al., 2021), which are indicative of reduced insulin sensitivity.

Table 1. Heat stress during finishing alters metabolic enzymes in skeletal muscle

Enzyme	Effect of Heat Stress	Implication
Citrate synthase	No effect	No boost in glucose oxidative metabolism
Lactate dehydrogenase	↑31%	↑Potential for glycolytic lactate production
Myophosphorylase (PYGM)	↑17%	↑Utilization of stored glycogen
Fatty acid translocase (CD36)	↓53%	↓Fatty acid uptake
Long-chain fatty acid CoA ligase 1 (ACSL1)	No effect	Stable fatty acid activation capacity
PPARγ	↓33%	↓Fatty acid uptake and deposition
PPARα	↑386%	↑Fatty acid utilization for oxidative metabolism

Data compiled from studies using sheep as a proxy model for beef cattle (Curry et al., 2025; Hahn et al., 2025).

Enzyme content in the *semitendinosus* muscle of heat-stressed finishing lambs was consistent with proportionally greater utilization of glycogen for anaerobic glycolysis and with greater fatty acid utilization but less uptake (Curry et al., 2025; Hahn et al., 2025) (Table 1).

The Impact of Prenatal Heat Stress

One hot mama: Maternal heat stress impairs health and well-being of offspring

Heat stress during gestation stunts placental function, thus diminishing nutrient transfer to the growing fetus and eliciting nutrient-sparing fetal adaptations (Limesand et al., 2007; Beer et al., 2024). One such adaptation is a reduction in the formation of fat deposits and other energy reserves late in gestation, which increases neonatal morbidity and mortality (Reynolds and Caton, 2012; Dwyer et al., 2016). Statistics associated with perinatal outcomes underscore the threat of prenatal heat stress and the lack of prevention and treatment options for it. Each year, US producers lose around 4 million calves and 600,000 lambs to heat stress–induced IUGR and low birthweight (Mellor, 1983; Azzam et al., 1993; Wu et al., 2006). High early death rates are a major animal welfare issue, and the approximately $3 billion in annual losses for the beef industry alone illustrate the economic barrier of heat stress during pregnancy to sustainable animal agriculture (Wu et al., 2006; Yates et al., 2018).

Preheating the steaks: Prenatal heat stress limits postnatal muscle growth and carcass merit

Heat stress occurring during critical windows for fetal development diminishes lifelong growth capacity and metabolic efficiency (Greenwood and Cafe, 2007; White and Yates, 2023), even when IUGR and low birthweight are subtle (Wells, 2011). Poor postnatal muscle growth is a product of heat stress–induced fetal programming that slows key cellular processes for tissue hypertrophy (Yates et al., 2016; Soto et al., 2017; Posont et al., 2022) and protein synthesis (Brown et al., 2015; Rozance et al., 2018). Less muscle mass in the heat-stressed fetus produces the hallmark IUGR phenotype as a mechanism for sparing O_2 and glucose for other tissues. Muscle-centric adaptations are essential for intrauterine survival but become production liabilities after birth, as animals exposed to prenatal heat stress are devalued by poor growth efficiency and body composition (Gondret et al., 2005; De Blasio et al., 2007). Muscle mass and protein accretion deficits persist even when these animals exhibit rapid postnatal catch-up growth (Greenwood et al., 2000), which is driven by fat deposition (Madsen and Bee, 2015). The propensity for animals exposed to prenatal heat stress to produce less muscle and more fat is reflected in the carcass: meta analyses in beef cattle show that each 1.0-kg reduction in birthweight corresponds to reductions of 2.7 kg in hot carcass weight, 0.5 cm^2 in ribeye area, and 2.0 kg in total retail yield (Robinson et al., 2013). In fact, birthweight explained 37% of the variation in carcass weight and yield in these cattle (Robinson et al., 2013), and it correlated strongly with carcass yield in meat lambs (De Blasio et al., 2007). In IUGR-born heifers, loins were 8% lighter and 7% smaller in area when harvested at 30 months of age (Greenwood and Cafe, 2007). Furthermore, visceral and subcutaneous fat deposition was greater in IUGR-born cattle, but marbling was not (Robinson et al., 2013). The associated financial losses are not trivial. Based on current market prices, a reduction in beef carcass weight from 275 to below 250 kg would result in a $127 discount. An increase in fat thickness from <0.8 (Yield Grade 3) to >1.2” (Yield Grade 5) would discount the carcass by $108, and a drop from USDA Choice to USDA Select or USDA Standard would lower value by $90 and $210, respectively.

Poor muscle growth following prenatal heat stress is associated with permanent intrinsic impairment of myoblasts. Primary myoblasts from heat-stressed fetal

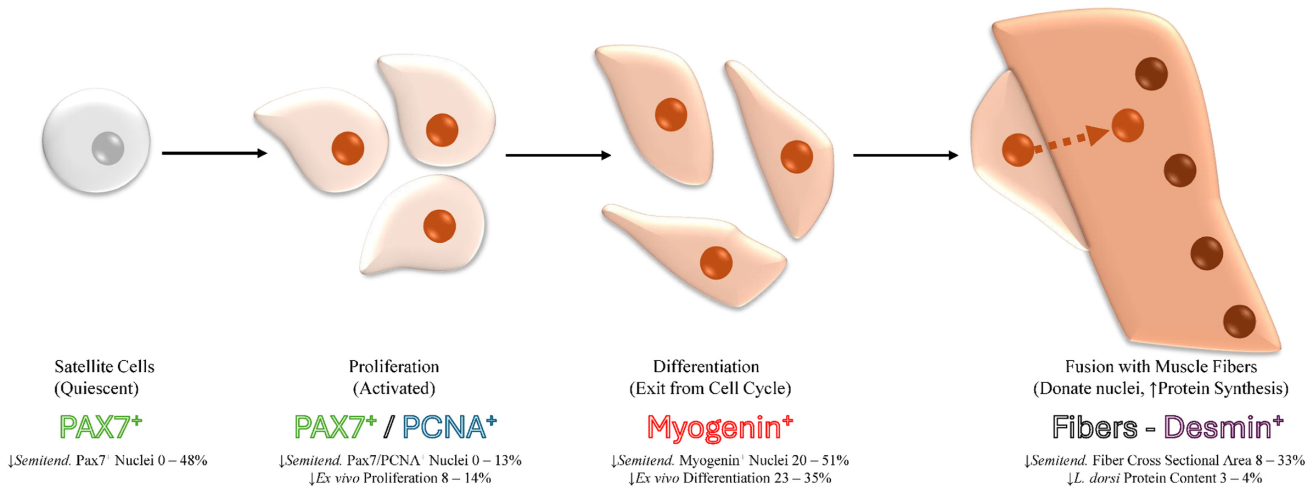

Figure 2. Heat stress during gestation or finishing impairs myoblast (muscle stem cell) function, which is rate-limiting for hypertrophic muscle growth. Data compiled from studies using a sheep model for beef cattle (Yates et al., 2014; Chang et al., 2019; Most et al., 2021; Posont et al., 2022; Gibbs et al., 2023; White et al., 2023b; Beer et al., 2024; White et al., 2025b).

sheep exhibited a poor ability to proliferate and differentiate under myriad culture conditions (Yates et al., 2014; Soto et al., 2017; Posont et al., 2022; Beer et al., 2024). This coincided with fewer total and differentiated myonuclei in the *semitendinosus* muscle near term (Beer et al., 2024). In offspring, myoblasts arise from satellite cell populations established *in utero* from fetal myoblasts and therefore are subjected to intrauterine conditions (Allen et al., 1979). Consequently, myoblast differentiation rates remained as much as 29% lower in muscles from weaning-aged lambs that had been exposed to prenatal heat stress (Gibbs et al., 2023). Myoblast dysfunction resulted in smaller muscle fibers and lighter muscles near term and after birth (Gibbs et al., 2023; White et al., 2023b; Beer et al., 2024), as illustrated in Figure 2.

A breakdown in nutrient breakdown: Prenatal heat stress permanently disrupts metabolism

Prenatal heat stress induces adaptive fetal programming that impairs the normal metabolic function of muscle, making carcasses from these animals less cost-effective to produce. Hyperinsulinemic-euglycemic clamp studies showed that the hindlimb muscle of heat-stressed fetal lambs took up glucose normally but oxidized a substantially smaller fraction (Limesand et al., 2007; Brown et al., 2015; Beer et al., 2024), as summarized in Table 2. Instead, these animals deposited more intramuscular glycogen and produced more lactate (Limesand et al., 2007; Beer et al., 2024). Diminished skeletal muscle glucose oxidation, increased glycogen content, and greater lactate production following prenatal heat stress persisted in neonates and weanlings, as did disruptions in fatty acid flux (Gibbs et al., 2024; White et al., 2025c). Although circulating lipids were slightly reduced in heat-stressed fetuses, systemic lipid dysregulation manifested in greater circulating non-esterified free fatty acids, high-density lipoprotein-bound cholesterol, and triglycerides but impaired fatty acid mobilization from abdominal fat in offspring (White, 2023; Gibbs et al., 2024; White et al., 2025c). The changes in systemic lipid flux manifested in intramuscular fat as well. Proximate analyses of *semitendinosus* muscles from neonates and juveniles exposed to prenatal heat stress revealed 20–30% more total fat than normal (White, 2023; Gibbs et al., 2024). Muscle from the juvenile lambs also had more small lipid droplets (<160 μm^2) but fewer large droplets (>240 μm^2) (Gibbs et al., 2024).

Programmed changes in several regulatory systems facilitate the shifts in glucose and lipid metabolism exhibited by fetuses and offspring following prenatal heat stress. Insulin and IGF-1 are primary drivers of glucose utilization by skeletal muscle and of lipid synthesis in fat cells. However, square-wave hyperglycemic clamps found that glucose-stimulated insulin secretion is reduced in heat-stressed sheep fetuses by up to 72% (Macko et al., 2013; Macko et al., 2016; Beer et al., 2024) and remains deficient after birth (Cadaret et al., 2022; White et al., 2023a; Gibbs et al., 2024). Circulating IGF-1 concentrations were also diminished in sheep fetuses and offspring following prenatal heat stress (Chang et al., 2019; Gibbs et al., 2023). Greater circulating glucose-to-insulin ratios, along with poor glucose oxidation and fat deposition, are consistent with peripheral insulin resistance (Beer et al., 2024; Gibbs

Table 2. Heat stress during gestation or finishing impairs muscle-centric metabolism due in part to greater inflammatory tone

	Metabolic Δ			Inflammatory Δ	
	Prenatal Heat Stress	Heat Stress During Finishing		Prenatal Heat Stress	Heat Stress During Finishing
Blood			***Blood***		
Basal insulin	No effect	↑0–45%	Total WBC	↑0–44%	↑0–19%
Glc.-stim. insulin	↓19–44%	n.a.	Monocytes	↑0–19%	↑10–32%
Glc.-to-insulin	↑40–100%	↓0–43%	Granulocytes	↑0–87%	↑19–40%
			TNFα	↑130–170%	↑170–270%
Hindlimb (in vivo)			IL-6	↑330%	↑260%
Glc. uptake	No effect	n.a.	EPA	↓23–42%	↓15–17%
Glc. oxidation	↓45–66%[1]	n.a.			
Lact. production	↑14–101%	n.a.	***Skeletal muscle***		
			TNFR1	↑0–170%	n.a.
Skeletal muscle (ex vivo)[2]			IL6R	↑45–50%	n.a.
Glc. uptake	No effect	No effect			
Glc. oxidation	↓24–46%	↓18–32%	***Myoblasts***		
			TNFR1[3]	↑30%	n.a.
			IL6R[3]	↑26%	n.a.
			p-NFκB[4]	↑120%	n.a.
			IκBα	↑46%	n.a.

[1]Insulin-stimulated glucose oxidation.

[2]*Flexor digitorum superficialis.*

[3]Gene expression.

[4]TNFα-stimulated phosphorylation of NFκB.

Data compiled from studies using sheep as a proxy model for beef cattle (Barnes et al., 2019; Swanson et al., 2020; Posont et al., 2022; Gibbs et al., 2023; Grijalva, 2023; Beer et al., 2024; Gibbs et al., 2024; White et al., 2025a; White et al., 2025c).

n.a. = not available.

et al., 2024). However, normal whole-body insulin-stimulated glucose clearance, normal glucose clearance/μg of circulating insulin, and increased muscle glycogen content indicate that insulin regulation of muscle is only selectively impaired (Cadaret et al., 2022). Selective insulin resistance could be explained by differential impacts of prenatal heat stress on the expression and activity of the insulin receptor and its downstream signaling components among muscle types, as has been observed with diabetes and other metabolic disorders (Pataky et al., 2017). Aberrant adrenergic signaling contributes to these long-term consequences, as detailed by Gibbs and Yates (2021).

The Role of Inflammation in Heat Stress Pathologies

Up in flames: Chronic heat stress induces systemic inflammation

Heat stress–induced systemic inflammation is a key component of poor muscle growth and metabolism, as both functions are highly responsive to inflammatory regulation (Liu et al., 2012; Remels et al., 2015). Finishing lambs heat-stressed for 30 d exhibited greater circulating white blood cells that coincided with elevated inflammatory cytokines (Swanson et al., 2020; Grijalva et al., 2021; Grijalva, 2023; White et al., 2025a) (Table 2). These controlled studies utilized uniform initial body weights and pair-feeding. In practice, however, feedlot animals have much greater fat mass than at other production stages, which is a compounding source of inflammation (van der Heijden et al., 2015; Krafsur et al., 2019; Reith et al., 2022). Fetuses and offspring likewise exhibit heightened inflammatory tone following prenatal heat stress, characterized by systemic inflammation as well as greater sensitivity of muscle to inflammatory mediators (Hicks and Yates, 2021; Beer et al., 2024; Gibbs et al., 2024; White et al., 2025c). Transcriptomic analysis of *semitendinosus* muscle from neonatal lambs following prenatal heat stress demonstrates the robust enhancement of canonical cytokine signaling pathways, particularly for TNFα and IL-6 (Hicks and Yates, 2021). Protein content for the respective receptors of these cytokines, TNFR1 and IL6R, was also elevated by prenatal heat stress in muscle from fetuses and offspring (Beer et al., 2024; Gibbs et al., 2024; White et al., 2025c). Importantly, experimental induction of sustained maternofetal inflammation during the same critical windows for development produces most of the hallmark characteristics of prenatal heat stress (Cadaret et al., 2019; Posont et al., 2021; Posont et al., 2022), indicating that inflammatory mechanisms are key components to lifelong pathologies associated with prenatal heat stress. Likewise, experimental induction of systemic inflammation in finishing wethers resulted in similar indicators of poor health and welfare observed during heat stress, including blood alkalosis, increased body temperatures, and hyperlactatemia (Cadaret et al., 2021).

Stifling regulatory oversight: Inflammatory cytokines dysregulate normal muscle processes

Molecular processes for muscle growth and metabolism are particularly responsive to inflammatory cytokines (Pillon et al., 2013). Although their effects are complex, sustained exposure to elevated cytokine concentrations inhibits muscle growth (Kumar et al., 2012; Pillon et al., 2013). Muscle responses to circulating cytokines are an integral component of muscle and myoblast regulation under normal conditions, but sustained overexposure to cytokines becomes problematic. In seminal rodent studies, daily TNFα, IL-1α, or lipopolysaccharide endotoxin injections in rats reduced *gastrocnemius* muscle weight and carcass protein content but increased body fat (Tracey et al., 1988; Fong et al., 1989). Similarly, weekly injections of the inflammatory cytokine TNFSF12, a member of the TNF ligand superfamily, into mice reduced *soleus* and *tibial anterior* muscle weights and fiber sizes after 4 wks by diminishing protein synthesis and increasing protein degradation (Dogra et al., 2007; Bhatnagar et al., 2012). In feedlot cattle, persistent systemic inflammation for any reason was associated with a decrease in average daily gain, hot carcass weight, and marbling (Schneider et al., 2009; Gifford et al., 2012). Poor muscle growth is partially a result of cytokine influence on myoblasts. In studies utilizing immortalized myoblast cell lines, stimulation by inflammatory cytokines impaired differentiation and fusion capacities by preventing myoblasts from exiting the cell cycle (Ji et al., 1998; Trendelenburg et al., 2012; Shirakawa et al., 2021). This was associated with reduced expression of the transcription factor myoD, which transitions myoblasts from replication to differentiation (Alvarez et al., 2020). Incubation with TNFα also suppressed protein synthesis in primary myoblasts, indicating that anabolic processes are diminished by inflammation in addition to greater protein breakdown (Frost et al., 1997; Grzelkowska-Kowalczyk and Wieteska-Skrzeczynska, 2006). Impaired differentiation capacity of fetal myoblasts and the subsequent reduction in myofiber size observed following prenatal heat stress was also observed following sustained maternofetal inflammation (Posont et al., 2022). Rapidly increased expression of the inflammatory mediator, c-Fos, is an activation step for myoblast proliferation (Almada et al., 2021). However, c-Fos also suppresses differentiation by inhibiting myoD and myogenin, and thus c-Fos concentrations within the cell must wane before myoblasts can proceed to the differentiation step (Barutcu et al., 2022). This necessary reduction in c-Fos did not occur in fetal muscle following heat stress, as concentrations remained almost 50% greater than normal (Posont et al., 2022). Myoblasts from heat-stressed fetuses were also more responsive to inhibition by cytokines than myoblasts from uncompromized fetuses (Posont et al., 2022).

Muscle-centric metabolic dysfunction is also consistent with the greater inflammatory tone associated with heat stress. Brief stimulation of muscle by cytokines can actually increase basal glucose oxidation (Cadaret et al., 2017). However, insulin signaling and insulin-stimulated glucose oxidation are substantially reduced, particularly when exposure to cytokines is chronic (Cadaret et al., 2017; Cadaret et al., 2019). Inflammatory cytokines disrupt insulin signaling by blocking its phosphorylation of Akt, which is the activation step that facilitates most downstream effects of the insulin pathway (Ji et al., 2022). Culture studies of primary muscle found that exposure to physiological concentrations of TNFα or IL-6 reduced insulin-stimulated Akt phosphorylation by over 50% in as little as 2 h and that the effect had not waned after 6 d of exposure (Grzelkowska-Kowalczyk and Wieteska-Skrzeczynska, 2006; Cadaret et al., 2017). Acute and chronic cytokine stimulation increases skeletal muscle glycogen synthesis, lactate production, and lipid oxidative metabolism by as much as 2-fold each (Al-Khalili et al., 2006). Short incubations of muscle cells with TNFα or IL-6 increased palmitate oxidation through AMPK-mediated pathways (Bruce and Dyck, 2004; Al-Khalili et al., 2006), as did brief IL-6 infusions into healthy human volunteers (van Hall et al., 2003). These IL-6 infusions also increased circulating NEFA and triglyceride concentrations (van Hall et al., 2003), which would be consistent with the phenotype of heat-stressed animals.

Fish oil ain't snake oil: Targeting heat stress–induced inflammation with ω-3 polyunsaturated fatty acids

The ω-3 polyunsaturated fatty acids (PUFA) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are naturally occurring dietary molecules with substantial anti-inflammatory properties (Caughey et al., 1996; White and Yates, 2023). These nutrients, which are plentiful in ocean fish and plant oils, mitigate inflammation by reducing cytokine synthesis and secretion as well as the expression and activity of key pathway components (e.g., TRAF6, MyD88, NFκB, IκB, JNK) (Caughey et al., 1996; Zhu et al., 2018). Moreover, bioactive metabolites of ω-3 PUFA called pro-resolving mediators increase the synthesis and secretion of anti-inflammatory cytokines like IL-10 (Gu et al., 2016; Soto et al., 2020). In the absence of inflammation-inducing stress, supplementing ω-3 PUFA to sheep during pregnancy or finishing had little effect on growth performance, metabolic efficiency, or carcass quality (Rosa-Velazquez et al., 2021). However, prenatal and postnatal heat stress not only heightened inflammation but also reduced circulating EPA concentrations (White et al., 2025a; White et al., 2025c). Despite high rates of lipid biohydrogenation in the rumen, daily supplementation of ω-3 PUFA to finishing wethers during chronic heat stress restored normal circulating EPA and resolved increases in circulating TNFα and IL-6 (Grijalva et al., 2021; Grijalva, 2023; Grijalva et al., 2023; White et al., 2025a). In turn, these supplemented wethers exhibited improved average daily gain, feed efficiency, and muscle growth. Better muscle growth was associated with recovery of heat stress–impaired myoblast differentiation, although myoblast proliferation and total myoblast numbers were not affected by ω-3 PUFA supplementation (Most, 2022). In addition to growth, heat stress–induced deficits in skeletal muscle glucose oxidation, circulating insulin, and glucose-to-insulin ratios were also improved by ω-3 PUFA supplementation (Grijalva et al., 2021; Grijalva, 2023; Grijalva et al., 2023; Curry et al., 2025). Deficits in fatty acid mobilization and circulating lipids were also recovered, but the large reductions in lipid droplet density and average size remained in supplemented wethers, indicating that ω-3 PUFA supplementation did not necessarily restore intramuscular lipid deposition. Reduced *semitendinosus* CD36 and PPARγ content and increased PPARα were recovered as well, indicating a resolution of the metabolic shift toward greater fatty acid oxidation (Curry et al., 2025; Hahn et al., 2025).

Supplementing ω-3 PUFA was also effective in mitigating the inflammation associated with prenatal heat stress. Five-day infusions of EPA into fetal sheep following chronic heat stress recovered low circulating EPA and resolved heightened TNFα, although the 50% increase in skeletal muscle IL6R remained at the end of the infusion period (Beer et al., 2024). Reduction of inflammatory tone in these fetuses improved myoblast differentiation and muscle growth. Daily supplementation of ω-3 PUFA to neonatal lambs from birth to 30 d of age following prenatal heat stress mitigated greater circulating TNFα concentrations and muscle IL6R content but did not improve heightened muscle TNFR1 content (White et al., 2025c). Although myoblast function was not assessed by the study, ω-3 PUFA-supplemented lambs exhibited improved postnatal muscle growth comparable to that observed in supplemented fetuses (White, 2023). Indicators of muscle-centric metabolic changes were likewise corrected by supplementation in fetuses and offspring, including glucose oxidation, anaerobic lactate production, and glycogen deposition (Beer et al., 2024; White et al., 2025c).

Conclusions

Systemic inflammation is a key facilitator of reduced growth efficiency, carcass quality, and welfare in chronically heat-stressed livestock. Heightened secretion of inflammatory cytokines is a transient response to postnatal heat stress, whereas greater secretion and tissue sensitivity to cytokines are permanently programmed by prenatal heat stress. In both cases, the effects of greater inflammatory tone on muscle growth are associated with myoblast dysfunction, which limits the rise in protein synthesis capacity needed for hypertrophic muscle growth. Inflammation resulting from prenatal or postnatal heat stress also partially mediates muscle-centric metabolic dysfunction, including reduced glucose oxidation coincident with greater glycogen deposits, anaerobic lactate production, and fatty acid oxidation. These changes, along with insulin resistance and aberrant lipid homeostasis, cause inefficient growth in animals facing heat stress. Recent studies implicate systemic inflammation as an effective biological target for nutrient-based therapeutic treatments to improve heat stress outcomes in livestock. Anti-inflammatory nutraceuticals improved deficits in muscle growth, metabolic efficiency, and welfare indicators when delivered in the diet of heat-stressed finishing lambs. Similar improvements were achieved in fetuses and neonates exposed to prenatal heat stress. This approach provides the opportunity to mitigate heat stress impact without manipulating dietary intake or relying on extensive infrastructural or management changes. Livestock in feedlots will particularly benefit from nutrient-driven strategies, as they are at inherently greater risk from heat stress due to their larger relative size and adiposity. Heat stress is a long-standing barrier to livestock production that will worsen with climate change. As such, targeting heat stress–induced inflammation is a promising target for mitigating the well-established outcomes of heat stress.

Conflict of Interest

The authors have no conflicts of interest to declare.

Acknowledgments

This manuscript describes research that was funded in part by the USDA National Institute of Food and Agriculture Foundational Grants 2019-67015-29448 and 2020-67015-30825, the National Institute of General Medical Sciences Grant 1P20GM104320 (J. Zempleni, Director), the Nebraska Agricultural Experiment Station with funding from the Hatch Act (accession number 1009410), and the Hatch Multistate Research capacity funding program (accession numbers 1011055 and 1009410) through the USDA National Institute of Food and Agriculture.

Author Contribution

Conceptualization, D.T.Y.; methodology, M.R.W., S.A.C., A.A.H., and D.T.Y.; curation, M.R.W., S.A.C., A.A.H., and D.T.Y.; writing—original draft preparation, M.R.W., S.A.C., A.A.H., and D.T.Y.; writing—review and editing, M.R.W., S.A.C., A.A.H., and D.T.Y.; funding acquisition, D.T.Y. All authors have read and agreed to the published version of the manuscript.

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