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Heat stress: influence on the physiology, productive and reproductive performance of the pig

Estrés por calor: influencia sobre la fisiología, comportamiento productivo y reproductivo del cerdo

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ABSTRACT

Heat stress (HS) compromises reproductive and growth parameters. Pigs subjected to heat stress reduce voluntary intake and modify their energy metabolism causing a reduction in daily weight gain and an increase in subcutaneous fat accumulation, which negatively affects the carcass quality of fattening pigs. In the sow it causes a negative energy balance affecting reproductive performance by increasing the post-weaning estrus interval, decreasing gestation rate, farrowing rate and litter size and weight at birth and weaning. Many of the negative consequences of HS appear to be mediated by hyperpermeability of the intestinal barrier, causing physiological changes such as nutrient partitioning to an activated immune system and adverse effects on the ovaries through elevated endotoxin and insulin signaling, resulting in failure of the sow's reproductive function.

Keywords: pig, heat stress, reproductive performance, productive performance.

RESUMEN

El estrés por calor (EC) compromete parámetros reproductivos y de crecimiento. Los cerdos sometidos a estrés por calor reducen el consumo voluntario y modifican su metabolismo energético provocando la reducción en la ganancia diaria de peso y un incremento en la acumulación de grasa subcutánea, que afecta de manera negativa la calidad de la canal de los cerdos de engorda. En la cerda provoca un balance energético negativo afectando su desempeño reproductivo al incrementar el intervalo celo posdestete, disminuir la tasa de gestación, tasa de partos y tamaño y peso de la camada al nacimiento y al destete. Muchas de las consecuencias negativas del EC parecen estar mediadas por la hiperpermeabilidad de la barrera intestinal, provocando cambios fisiológicos como el reparto de nutrientes hacia un sistema inmunológico activado y efectos adversos en los ovarios a través de la señalización elevada de endotoxinas e insulina, que resultan en fallas en la función reproductiva de la cerda.

Palabras clave: cerdo, estrés por calor, desempeño reproductivo, desempeño productivo.

INTRODUCTION

Stress is the biological response to an event that the individual perceives as a threat to their homeostasis, it is commonly related to increased activity of the hypothalamic-pituitary-adrenal (HPA) axis and activation of the Adreno-Medullary Sympathetic System (Joseph & Whirledge, 2017). Activation of the HPA axis results in the release of a variety of peptides, primarily corticotropin-releasing hormone (CRH) and vasopressin from the hypothalamus; CRH secretion stimulates the release of adrenocorticotropic hormone (ACTH) and beta-endorphins. ACTH induces corticosteroid secretion from the adrenal cortex, also triggering the release of progesterone, possibly prostaglandin $F_{2\alpha}$ and even inhibin α (Herman *et al*., 2016). Glucocorticoids stimulate lipolysis and gluconeogenesis, leading to increased metabolism that promotes the ability to cope with stress; activation of the Sympathetic Nervous System (SNS) and adrenal medulla cause the release of catecholamines (adrenaline and noradrenaline) into the bloodstream, which causes an increase in glucose supply by accelerating the breakdown of hepatic glycogen (Webster & Glaser, 2008).

Prolonged or chronic stress usually results in inhibition of reproduction, whereas the effects of transient or acute stress in certain cases are stimulatory (e.g. anestrus). The effect of stress on reproduction will depend on the duration of the stressful event, genetic predisposition and the type of stress the pig is subjected to (Joseph & Whirledge, 2017).

Heat stress (HS) is one of the major impediments to efficient animal production. In the U.S. livestock industry alone, annual economic losses associated with CE are estimated to approach USD 1.5 billion for dairy and USD 1 billion for swine (Key *et al.*, 2014). HS will become an increasing complication for animal production if climate change continues, as predicted by most models (Ganesan *et al*., 2017); moreover, almost all economically important traits (lean tissue accumulation rates, fecundity, etc.) are subject to intense genetic selection that are accompanied by increased basal heat production (Baumgard & Rhoads, 2013; Ross *et al*., 2015). The objective of the present work was to review the influence of heat stress on physiology, productive and reproductive behavior of swine.

Impact of heat stress on animal health and production

Heat stress results from the inability to maintain a balance between heat production and heat loss and is highly dependent on environmental conditions (Volodina *et al*., 2017). Prolonged exposure to elevated environmental temperatures causes heat stress in humans and animals, which negatively affects human health, animal welfare and livestock production (Cui *et al*., 2016), this can lead to clinical manifestations that can range from exacerbation of cardiovascular risk factors such as hypertension (Fonseca *et al*., 2015) or disruption of the intestinal barrier (Xu *et al*., 2015).

HS contributes to increased morbidity and mortality in humans and animals, and is an agricultural economic challenge because it reduces livestock productivity Volodina *et al*., 2017). In addition to the detrimental effects on human health, heat stress results in agricultural losses of approximately $2.4 billion annually, due to production losses (Key *et al*., 2014) and costs associated with medical care and maintaining animal welfare (Ross *et al*., 2015). It is estimated that the U.S. swine industry loses more than $900 million annually, primarily due to decreased meat production (Baumgard & Rhoads, 2013) and reduced fertility (Nteeba *et al*., 2015). In pigs, HS decreases feed intake, body weight gain, meat quality and fertility, which may explain the large economic losses (Cruzen *et al*., 2015).

Pigs experience HS when the ambient temperature exceeds their neutral thermal zone (16-22 °C and 50-75 % RH; Botto *et al*., 2014). Compared to other animals, pigs are more sensitive to HS due to their high metabolic heat production, rapid fat deposition, and lack of sweat glands (Baumgard & Rhoads, 2013).

Physiological and behavioral effects of heat stress in swine

Behavioral effects of heat stress in swine. Pigs subjected to large ambient temperature challenges tend to reduce nutrition and caloric intake (Cui *et al*., 2016); this, is a highly conserved response among species under heat stress (Pearce *et al*., 2014). Animals have been observed to reduce feed intake to lower metabolic heat production (Renaudeau *et al*., 2013). Cui & Gu (2015), demonstrated that chronic mild heat stress (30°C for three weeks) reduces feed intake and daily body weight gain in finishing pigs by 16 and 25 %, respectively; in parallel, it increases rectal temperature, respiration rate and plasma cortisol, decreases plasma free triiodothyronine and growth hormone; these parameters are commonly considered indicators of the consequences of heat on animal physiology (Morera *et al*., 2012). Unlike acute stress (40-42 °C, less than 24 h), chronic stress (33-35 °C, more than 24 h), poses a different challenge for animals (Cui & Gu, 2015). Cui *et al*. (2016) and Ganesan *et al*. (2017) indicated that exposure to HS for more than 12 h causes oxidative stress in pigs. Compared to hyperthermia and even death caused by acute stress, chronic stress can be tolerated for a longer period of time (weeks); however, physiological changes in response to chronic stress in various species, including finishing pigs, suggests that mild chronic stress alters animal performance and physiology (Hao *et al*., 2014). In this regard, it has been observed that when animals are exposed to a warm environment, various physiological mechanisms in the thermoregulatory system are adjusted (Cui *et al*., 2016).

Hormonal changes in animals under heat stress. To survive in a high temperature environment, animals have evolved specific responses to hyperthermia by regulating endocrine systems; in this regard, Cui & Gu (2015) observed that chronic heat stress reduces triiodothyronine and growth hormone in stressed pigs, having a synergistic effect to reduce heat production.

One response to acute stressors is activation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in elevated levels of corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH) and other peptides. Elevated ACTH stimulates the release of glucocorticoids from the adrenal cortex into the blood of stressed farm animals. Activation of the HPA axis and the consequent increase in circulating cortisol concentrations is one of the most common and nonspecific responses of an animal under stress conditions (Becker *et al*., 2020). Cortisol release stimulates the physiological and metabolic responses necessary to optimize the body's ability to overcome a stressor by increasing energy availability (Preiser *et al.*, 2014).

Effect of heat stress on gastrointestinal integrity. The gastrointestinal tract plays the critical role of selectively absorbing nutrients and water (Pearce *et al*., 2014), acting as a defensive barrier against endogenous and dietary pathogens as well as toxic compounds. Changes in gastrointestinal functions and integrity could be detrimental to mammalian health, performance and welfare (Cui & Gu, 2015). HS causes a detour of blood flow from the splanchnic bed to the periphery in a thermoregulatory effort to increase radiant heat loss, reducing blood flow and nutrient delivery to the gastrointestinal tract, leading to local hypoxia, free radical production, and altered intestinal architecture (Yu *et al*., 2013; Pearce *et al*., 2014; Cui & Gu, 2015; Ogden *et al*., 2020). In addition, reduced intake in pigs subjected to HS has detrimental effects on intestinal integrity (Pearce *et al*., 2013a).

Acute caloric stress has also been observed to cause hypoxia and inflammation of the intestinal epithelium (Qi *et al*., 2011), negatively affecting the function of tight junction (TJ) proteins of the intestinal epithelium, including myosin light chains (MLC), occludin, claudin, and MLC kinase (MLCK) (Pearce *et al*., 2013b), which are responsible for maintaining intestinal function and integrity; leading to increased intestinal permeability (Pearce *et al*., 2013b; Sanz-Fernández *et al*., 2014; Gabler *et al*., 2018). The dysfunctional intestinal barrier allows translocation of dietary and microbial antigens triggering local and systemic inflammatory responses (Ogden *et al*., 2020); proinflammatory cytokines (TNFα, interleukins: 1α, IL-1β, IL-6) increase; presumably related to an increase in circulating lipopolysaccharide (LPS) (Johnson *et al*., 2016; Alhenaky *et al*., 2017). An activated immune system requires a substantial amount of energy. Nutrients (specifically glucose and amino acids) are diverted to support the immune response (Iseri & Klasing, 2013; Kvidera *et al*., 2017), affecting the productive performance of the pig.

When intestinal barrier permeability is increased, LPS entry at the systemic level alters the hypothalamic-pituitary-ovarian (HPO) axis by reducing gonadotropin-releasing hormone (GnRH) secretion. Consequently, LPS reduces 17β-estradiol during the follicular phase of the estrous cycle, attenuating the subsequent release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which can later lead to delayed ovulation Bidne *et al*., 2018. During the luteal phase, LPS alters progesterone production, compromising *corpus luteum* (CL) formation and causing early luteolysis by inducing prostaglandin $F_{2\alpha}$ production; also, LPS alters uterine expression of progesterone and estradiol receptors, a response likely mediated by reduced levels of circulating progesterone and estradiol; any deregulation in the expression of these receptors, due to LPS may negatively influence embryo survival and result in miscarriage or premature delivery (Agrawal *et al*., 2013).

HS also affects the expression of key enzymes involved in intestinal glucose and energy metabolism, including phosphoglucomutase 2 (PGM2), Malate dehydrogenase (MDH2), NADH dehydrogenase 1 alpha subcomplex subunit 10 (NDUFA10), NADH-coenzyme Q reductase (NDUFS3), NADH-ubiquinone oxidoreductase (NDUFS), mitochondrial ATP synthase alpha subunit (ATP5A1) and mitochondrial ATP synthase beta subunit (ATP5B); PGM2 and MDH2 are involved in glycolysis and the citric acid cycle, respectively; both are decreased in animals subjected to heat stress (Cui & Gu, 2015), suggesting that heat stress slows energy metabolism.

Effect of heat stress on muscle and productive behavior in swine. Studies in various species have indicated that muscle growth is affected by HS+-related alterations in muscle physiology (Locke & Celotti, 2014). HS effects on skeletal muscle satellite cell proliferation, growth and apoptosis could play a crucial role in determining its impact on muscle physiology (Gao *et al*., 2015). In this regard, it is known that cell number depends on the balance between cell proliferation and cell death, while cell size depends on cell growth (Tumaneng *et al*., 2012). It has been observed that HS can induce cell division arrest, and exposure of cells to acute or chronic stress induces cell death by apoptosis, necrosis or autophagy (Zhang *et al*., 2012). Growing pigs are highly susceptible to heat stress, decreasing their productive performance (Pearce *et al*., 2013a), as well as nitrogen intake and retention (Renaudeau *et al*., 2013). In addition, metabolic responses are altered in stressed pigs, decreasing heat production and feeding behavior compared to pigs raised under thermo-neutral conditions.

Effect of heat stress on immune response. HS is considered one of the main factors that impose negative impacts on production and reproduction in farm animals, as they alter the animal's immune functions making them susceptible to infectious diseases (Inbaraj *et al*., 2016).

The adaptive response, via HPA axis, is known to be ACTH-induced glucocorticoid elevation, which produces gluconeogenic, antiphlogistic and immunosuppressive effects. The immunosuppressive effects of glucocorticoids include suppression of lymphocyte proliferation, IL-2 production, and neutrophil function; in addition, they inhibit proinflammatory cytokines, namely TNF-α, IL-6, IL-8, which are required to initiate an innate immune response by inhibiting the p38 MAPK pathway that helps maintain their stability (Abraham *et al*., 2006; Jankord *et al*., 2010): also, it inhibits the release of IL-12 and IFNγ which are the main cytokines involved in Th1-based cell-mediated immunity. The expression of IL-12 receptors on NK cells and Th1 cells is negatively regulated by glucocorticoids and, therefore, immune function is shifted from Th1 to Th2, so it is considered that HS acts to shift adaptive immune function from cell-mediated humoral immunity and, therefore, weakens the immune function of the animal (Inbaraj *et al*., 2016). In addition, HS, reduce in the intestine innate immune components, such as mucosal barrier, Toll-like receptors (TLR), secretory IgA, intestinal intraepithelial lymphocyte production (Deng *et al*., 2012), expression of cytokines responsible for humoral and cell-mediated immune response. Reduced intestinal immune function allows bacterial translocation to the mesenteric lymph node (Liu *et al*., 2012).

Effect of heat stress on energy metabolism: its impact on carcass quality and reproductive physiology. The animal response to stress involves energy expenditure to eliminate or reduce its impact, which increases its energy requirements for maintenance to the detriment of energy for production; however, stress does not uniformly affect the energy balance. Depending on the stress, phage drive may increase (gestation, lactation, cold) or decrease (heat, social, immune, farrowing); likewise, in some cases energy expenditure is increased (gestation, lactation, cold, immune stress) or decreased (fasting and heat) by stressors (Collier *et al*., 2017). Pigs stressed by caloric load generally have a depressed activity level, their behavioral behavior is to lie down and, therefore, have significantly fewer periods of feeding and physical activity (Cross *et al*., 2020), so they decrease feed intake to reduce metabolic heat production and maintain homeothermia, resulting in slower growth. Pigs raised under HS conditions have reduced muscle mass and increased adipose tissue (Qu *et al*., 2016), as elevated ambient temperature promotes lipid deposition in back and visceral fat. According to Baumgard & Rhoads (2013), heat stress decreases protein deposition to reduce metabolic heat production; therefore, more energy is available for fat deposition, resulting in increased carcass fat content. It has been suggested that the effect of HS on feed intake and growth of pigs is

more pronounced in recent years, supporting the hypothesis that genetic selection for growth and lean carcass traits increases pig thermal sensitivity, (Renaudeau *et al.*, 2011). HS has been observed to increase insulin levels (Sanz-Fernández *et al*., 2015), hepatic glucose production (glycogenolysis and gluconeogenesis), lipid deposition and reduce protein deposition (Johnson *et al*., 2015b); likewise, when intestinal permeability is increased, LPS passage reduces protein synthesis and stimulates skeletal muscle catabolism during immune challenges (Gordon *et al*., 2013).

HS-induced hyperinsulinemia alters ovarian biology, affecting oocyte development through activation of the phosphatidylinositol-3-kinase (PI3K) pathway. PI3K plays a key role in different ovarian cellular processes, including oocyte recruitment, corpus luteum survival, and oocyte maturation; therefore, dysregulation in this pathway can directly influence ovarian function and contribute to infertility (Makker *et al*., 2014). HS not only increases circulating insulin, but also enhances the ability of the ovary to respond to insulin by increasing insulin receptors and downstream signaling pathways, which regulate gamete quality and steroidogenesis, a scenario that contributes to reproductive dysfunction (Nteeba *et al*., 2015; Dickson *et al*., 2018).

Regarding lipid metabolism, it is known that fatty acids used to synthesize triglycerides (TG) are mainly derived from a novel synthesis in adipose tissues of pigs (Xin *et al*., 2016), however HS depresses malic enzyme (ME) and glucose-6-phosphate dehydrogenase (G6PDH) activities in backfat and visceral fat of pigs (Rinaldo & Le Dividich, 1991); even, at a similar level of feed intake, acetyl-CoA-carboxylase (ACC) activity is lower in heat-stressed pigs (Xin *et al*., 2016); these findings indicate that new fatty acid synthesis is inhibited in backfat and visceral fat of pigs in HS. Another source of fatty acids used to synthesize triglycerides are plasma triglyceride-rich lipoproteins (e.g. intestinal chylomicrons and hepatic very low density lipoprotein); this, by action of lipoprotein lipase (O'Hea & Leveille 1969). This enzyme tends to increase its concentration in visceral fat of pigs under caloric stress (Sanders *et al*., 2009), indicating that adipose tissue of hyperthermic animals has an increased capacity to absorb and store intestinal and liver-derived triglycerides (Baumgard & Rhoads, 2013); therefore, chronic exposure of growing pigs to high environmental temperature enhances lipid metabolism in liver (hepatic very low density lipoprotein production) and adipose tissue (lipoprotein lipase activity), and as a consequence plasma triglyceride absorption and storage is facilitated in adipose tissue, resulting in increased fat deposition (Sanz-Fernandez *et al*., 2015).

Effect of heat stress on feed intake and productive behavior of swine. The thermal environment affects all animals and, therefore, represents the largest stress factor in animal production (Collier *et al*., 2017). Different animal species have a thermo-neutral zone where they are able to manifest their productive potential; it is defined as the ambient temperature zone with minimum heat production at constant body temperature; above this zone, the core temperature rises and pigs become heat stressed (Gourdine *et al*., 2021).

Compared to other farm animal species, pigs are more sensitive to high environmental temperatures because they cannot sweat and do not pant very well, responding to heat stress through a complex of physiological, behavioral and anatomical mechanisms, aimed at facilitating heat loss or minimizing heat gain from the environment, so the swine industry is particularly affected, as pigs are not physiologically adapted to dissipate all heat through sweating or respiration (Renaudeau *et al*., 2011), which has a detrimental effect on the productive performance of pigs.

When environmental conditions exceed the pig's thermoneutral zone, nutrients are diverted from product synthesis (meat, fetus, milk), towards maintenance of body temperature, which compromises productive efficiency (Ross *et al*., 2015).
The main consequence of HS is decreased feed intake (Cervantes *et al*., 2018), negatively affecting the performance of the finishing pig, producing less muscle and increased fat deposition (Zhao *et al*., 2018), which decreases carcass value. In general, as the pig gets older, its optimal environmental temperature decreases; therefore, the effects of heat stress are of more concern in finishing pigs (> 50 kg). Finishing pigs begin to feel the negative effects of HS at ambient temperatures of 20 °C (> 50 kg), manifesting in lower feed intake, resulting in reduced daily weight gain (Myer & Bucklin, 2012). At temperatures above 30 °C feed conversion is also negatively affected in growing pigs (25 to 50 kg); at this stage the negative effects of heat stress are not as noticeable as in heavier pigs, but temperatures above 30 °C can reduce performance (+0.2 kg/kg between 30 to 36 °C) (Renaudeau *et al*., 2011). Myer & Bucklin (2012) observed that pigs raised during the summer grew 11 % slower and required 5 % more feed per unit of weight gain compared to pigs raised during the fall, when ambient temperatures were mostly within the pig's thermo-neutral zone (comfort zone).

Effects of heat stress on sow reproductive performance. Sows respond to HS with an increase in rectal temperature, respiratory rate and skin temperature, and tend to reduce their activity, which can change their body composition, increasing the adipose-to-muscle ratio (Lucy & Safranski, 2017). Sows under HS reduce their feed intake (Renaudeau *et al*., 2012), which results in a negative energy balance, loss of body condition and reproductive problems associated with inadequate ovarian function, manifested in anestrus, weak or irregular expression of estrus, irregular estrous cycles, delayed puberty, prolonged wean-to-estrus interval, higher abortion rates, low farrowing rate and small litter size at birth and weaning; as well as, a decrease in milk production, which can negatively affect piglet growth during lactation and weaning weight. In early gestation, heat stress increases embryonic mortality, increases the number of stillborn piglets and reduces piglet birth weight (Wegner *et al*., 2016; Lucy & Safranski, 2017).

In addition, maternal exposure to HS has negative consequences on offspring (Johnson *et al.,* 2013; Boddicker *et al*., 2014; Johnson *et al*., 2015a). Porcine fetuses exposed to HS during the first half of gestation increase backfat and circulating insulin early in the finishing phase (Boddicker *et al*., 2014). Maternal exposure to HS appears to have long-lasting consequences on the future performance of the offspring, which can negatively influence animal productivity and profitability (Mayorga *et al*., 2020); during gestation, HS, can cause developmental damage to the offspring, which will manifest in the following productive stages of the pig (Lucy & Safranski, 2017).

In lactating sows, temperatures above 25 °C have been observed to reduce feed intake (6.1 vs. 4.2 kg/d with temperatures of 25 and 30 °C, respectively), causing a decrease in milk production and an increase in sow weight loss (-7.9 vs. -24.2 kg/lactation with temperatures of 25 and 30 °C, respectively); therefore, pigs are weaned smaller (6. 9 vs. 6.4 kg with temperatures of 25 and 30 °C, respectively), and the sow's ability to return to production after weaning is compromised, due to her large weight loss (Myer & Bucklin, 2012); it has also been observed that high environmental temperature delays or prevents the onset of estrus, reduce conception rate, and increase early embryonic death (Plush *et al*., 2019; Bunz *et al*., 2019; Liu *et al*., 2019, 2022); in addition, HS in the last weeks of gestation, prior to parturition, may result in a higher number of dead piglets at birth. Unfortunately, genetic selection for increased litter size and leaner phenotypes decreases pigs' tolerance to heat, as fetal development and protein synthesis increase basal heat production (Ross *et al*., 2015). Although HS is currently a major impediment to pig production performance, it will likely become a production constraint in the future if genetic selection for increased lean tissue synthesis and reproductive capacity (piglets born and weaned) continues to be emphasized, as these traits are accompanied by increased basal heat production (Merks *et al*., 2012). When analyzing a sow's production cycle, which includes animal growth, HS has a substantial economic impact on the swine industry worldwide (Liu *et al*., 2022), as it compromises farrowing rates and is believed to delay the onset of puberty, decrease fertility in multiparous sows and gilts, which typically manifests as seasonal infertility (Lucy & Safransk, 2017; De Rensis *et al*., 2017). While the mechanisms through which stress alters endocrine signaling are not entirely clear, evidence suggests that the hypothalamic-pituitary-gonadal and hypothalamic-pituitary-adrenal axes are particularly sensitive to stress, including heat stress. When stress is perceived, the hypothalamic-pituitary-adrenal axis is activated, resulting in increased glucocorticoid levels. Glucocorticoid production is critical in the "fight or flight" response and in the reallocation of biological resources to resume homeostasis. Ultimately, this response suppresses reproductive function (Joseph & Whirledge, 2017) by exerting a negative feedback stimulus on the hypothalamus, preventing the production of GnRH, which affects the release and action of gonadotropins.

CONCLUSIONS

Heat stress in sows causes prolonged intervals between weaning and service, embryonic death and resorption (first third of gestation), a greater number of regular and irregular returns to estrus, spontaneous abortions (last third of gestation), reduced gestation and farrowing rates, reduced litter size and weight, and reduced milk production. In fattening pigs, heat stress manifests itself mainly in a reduction in daily weight gain and carcass quality.

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Errata Erratum
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