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Invited Review

Physiological responses of growing pigs to high ambient temperature and/or inflammatory challenges

Paulo Henrique Reis Furtado Campos^{1*}, Nathalie Le Floc'h², Jean Noblet², David Renaudeau²

¹ Universidade Federal dos Vales do Jequitinhonha e Mucuri, Diamantina, Brazil.

² Institut National de la Recherche Agronomique, Agrocampus Ouest, Saint-Gilles, France.

ABSTRACT - Global warming is one of the major environmental threats facing the world in the 21st century. This fact will have a significant impact on pig production due to its direct effects on welfare, health, and performance of pigs. Besides, the effects of high temperatures will presumably become more important over the next decades due to the development of pig production in developing countries mainly located in tropical and subtropical areas, where animals are often exposed to ambient temperatures above their thermal comfort zone. Furthermore, pigs reared in tropical areas are often confronted to sanitary challenges including poor hygiene conditions, lack of respect for sanitary rules, and pathogens. This results in the stimulation of the immune system and, as a consequence, in the production of pro-inflammatory cytokines and neuroendocrine adjustments that, in turn, usually have a negative impact on growth and feed efficiency. Although the effects of high ambient temperature and disease on pig physiology and performance have been well documented in literature, little is known about the associated effects of both factors. This understanding may contribute to a better quantification and comprehension of the physiological and metabolic disturbances occurring in practical conditions of pig production in tropical areas and, more generally, in many other geographic areas that will be influenced by the perspective of global warming. Therefore, the objective of this work is to provide an overview of recent research advances on the physiological responses of growing pigs during acclimation to high ambient temperature and on the potential effects of high ambient temperature on the ability of growing pigs to resist, cope with, or recover from an inflammatory challenge.

Key Words: animal biometereology, heat stress, metabolism, physiology

Introduction

Current predictions indicate a rise in global temperature of 0.8 to 2.6 °C by 2050 and of 1.4 to 5.8 °C over the next century (IPCC, 2013). Such changes will have a significant influence on livestock production due to its direct effects on animal welfare, health, and performance. Increased global temperature will also influence pathogens and disease dissemination due to changes in the area of life of their vectors (Patz et al., 2000). In addition, the effects of high temperatures will become more important in the coming

decades due to the development of livestock production in developing countries, which are mainly located in tropical and subtropical areas (FAO, 2010). When exposed to high ambient temperatures, pigs maintain homeothermy through behavioral, physiological, and metabolic adaptations that have negative effect on growth performance (Quiniou et al., 2001; Renaudeau et al., 2011).

High ambient temperature, however, is not the only factor that negatively influences pig production. Due to intensification of animal production and the assumed lower capacity of modern genotypes to adapt to environmental challenges, pigs are often confronted to sanitary challenges. Furthermore, the association of high relative humidity and high ambient temperature, which usually occurs in tropical and subtropical areas, benefits the proliferation and dissemination of vectors and/or pathogens, resulting in a higher environmental pathogenic pressure. This results in the stimulation of the immune system and, consequently, in the production of pro-inflammatory cytokines and neuroendocrine adjustments that, in turn, usually have a negative effect on growth and feed efficiency (Johnson, 1997, 2012).

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*Corresponding author: paulo.campos@ufvjm.edu.br

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In tropical and subtropical areas, high ambient temperature and sanitary challenges may occur concomitantly and, thus, may induce responses to both challenges. However, most studies have focused on the evaluation of animal responses to high ambient temperatures or sanitary challenges alone. Therefore, the objective of this work is to provide an overview of recent research advances on the physiological responses of growing pigs during acclimation to high ambient temperature and on the potential effects of high ambient temperature on the ability of growing pigs to resist, cope with, or recover from an inflammatory challenge.

Effects of heat-stress on pig physiology and metabolism

Pigs are homeothermic animals that have the ability to maintain body core temperature within narrow limits, despite wide variations in the environmental temperature (Precht et al., 1973). Core temperature is regulated by the thermoregulatory centers in the hypothalamus that integrate thermal inputs from the blood, brain, and thermoreceptors in the spinal cord, deep tissues, and the skin surface. This information is processed and thermal deviations from a set point elicit thermoregulatory responses to increase or decrease heat production and to conserve or dissipate heat (Kurz, 2008). In growing-finishing pigs, the normal rectal temperature (i.e. a physiological indicator of core temperature) is stated as 39.2 °C, but may range from about 38 to 40 °C among animals and environmental/experimental conditions (Einer-Jensen et al., 1999). When exposed to hot conditions, the animal primary challenge is to maintain core temperature by decreasing heat production and increasing heat loss.

Voluntary feed intake and growth performance

The reduction in voluntary feed intake as ambient temperature increases is considered as one of the most effective mechanisms to reduce heat production in hot conditions (Huynh et al., 2005). Different equations have been developed to predict the relationship between ambient temperature and voluntary feed intake in pigs at different growth stages and physiological conditions, e.g., piglets, growing and finishing pigs, and lactating sows (Quiniou et al., 2000). Renaudeau et al. (2011) reported a curvilinear negative effect of temperature on feed intake, the decrease in feed intake being as important as the temperature is high. They also reported that the ambient temperature effect tends to be accentuated with the increase of pig body

weight (BW). For instance, while each degree increase in ambient temperature between 24 and 30 °C would induce a feed intake decrease of 50 g d⁻¹ in pigs of 60 kg BW, the corresponding decrease would average 80 g d⁻¹ in pigs of 90 kg BW. The principle of the reduction in feed intake as a response to reduce heat production (or reduce the thermic effect of feeding) has been consistently confirmed through calorimetry studies performed in respiration chambers either in pigs of 20-30 kg (Collin et al., 2001) or pigs of 50-60 kg BW (Renaudeau et al., 2013).

Apart from extreme situations, growth depression in growing-finishing pigs exposed to high ambient temperatures is largely explained by the reduction in feed intake. As for voluntary feed intake, Renaudeau et al. (2011) evidenced a curvilinear negative effect of ambient temperature on growth rate that tends to be accentuated as the BW is high. According to these authors, each additional degree in ambient temperature between 24 and 30 °C would induce a decrease of about 30 g d⁻¹ in weight gain, in 60-kg pigs. In more practical conditions, Saraiva et al. (2012) reported that 60 to 100-kg pigs raised during the summer season in the southeast Brazil had 15% lower growth rate (910 vs. 1010 g day⁻¹) than those raised during the winter season. Carcass composition is also likely to be altered by ambient temperature. According to Le Bellego et al. (2002), pigs of 25-65 kg BW kept at 30 °C produced fatter carcass in association with lower protein and greater lipid depositions than their pair-fed counterparts kept at 23 °C. This result demonstrates that the maximal protein deposition rate can be limited by a direct effect of elevated temperature. In this case, the higher lipid deposition is an indirect consequence of the limitation of protein deposition. These results can be interpreted as a metabolic response to reduce internal heat production in hot conditions, since the energetic efficiency for lipid deposition is greater than that for protein deposition.

Neuroendocrine adjustments

Thyroid hormones, thyroxine (T₄), and triiodothyronine (T₃) play an important role in the control of metabolic rate and thermogenesis and thus, in the ability of animals to maintain body temperature (Silva, 2006). Specifically, these hormones increase thermogenesis by stimulating energy-wasting mechanisms such as the uncoupling of oxidative phosphorylation in the mitochondria (Silvestri et al., 2005), increase in ATP intake for the maintenance of transmembrane ion gradients (Na⁺ and K⁺ gradients across the cell membrane), and acceleration of metabolite turnover to maintain the metabolite concentrations constant

(lipolysis and lipogenesis, glycolysis and gluconeogenesis cycles) (Silva, 2006). In broad terms, thyroid hormones increase metabolism and, as a result, metabolic heat production. Therefore, heat acclimation comprises reduced thyroid activity and low circulating levels of T_4 and T_3 (Bernabucci et al., 2010). Indeed, low thyroid hormone levels were observed in growing (Oliveira and Donzele, 1999) and finishing pigs (Becker et al., 1992; Becker et al., 1993).

The activation of the hypothalamic-pituitary-adrenal (HPA) axis and the consequent increase in circulating concentrations of cortisol is one of the most common response and non-specific response of an animal to stressful conditions (Silanikove, 2000). The release of cortisol stimulates physiological and metabolic responses necessary to optimize the animal capacity to overcome a stressful factor by increasing the energy availability (Sapolsky et al., 2000). Indeed, Becker et al. (1997) reported an increase in cortisol levels in finishing pigs exposed to acute heat exposure (i.e., 34 °C during 4 h). Conversely, some studies have reported a decrease in plasma concentration of cortisol in pigs exposed to hot conditions. Heo et al. (2005) observed low circulating levels of cortisol in 20-30 kg BW pigs exposed to 32 °C. In addition, Kim et al. (2009) reported that cortisol levels were 22% lower in growing pigs exposed to 40 °C when compared with pigs kept at 24 °C. From these results, it appears that, while acute heat exposure leads to HPA axis stimulation as a result of the animal non-specific response to a stressful condition, heat acclimation most likely results in a decrease of cortisol levels.

Recent studies have reported an increase in insulin levels in heat-stressed animals (O'Brien et al., 2010; Pearce et al., 2013), despite the induced reduction of feed intake. According to Pearce et al. (2013), growing pigs kept at 35 °C had greater circulating insulin concentrations than their pair-fed counterparts maintained at 20 °C. The basis and the benefits of these metabolic changes are not well known, but there is evidence that increased insulin levels may contribute to the activation and up-regulation of heat shock proteins (Li et al., 2006). In addition, other studies have suggested that the increase in insulin might result from the degradation or transitory non-binding state of insulin receptors in the adipose tissue and muscle in response to an acute heat stress that creates a transient state of insulin resistance (Zachayus et al., 1996).

Pattern of thermoregulatory responses during the process of acclimation to high ambient temperature

The processes of heat acclimation in growing pigs have not been fully investigated and only few studies have

evaluated the physiological and metabolic changes occurring during a prolonged period of heat exposure. According to Giles et al. (1991), Renaudeau et al. (2007), and Renaudeau et al. (2010), physiological responses such as skin temperature, respiratory rate, and rectal temperature have a biphasic profile of response characterized by a primary phase, in which these responses increase rapidly within the first 24-48 h after heat exposure (termed as short-term heat acclimation), and a subsequent phase, in which they gradually decrease and subsequently reach relative constant levels (termed as long-term heat acclimation). Renaudeau et al. (2010) described this biphasic profile of response for respiratory frequency and rectal temperature in growing pigs. By the use of a nonlinear function, these authors reported that an increase in ambient temperature from 24 to 32 °C at a rate of 2 °C h⁻¹ induced an increase in respiratory rate and rectal temperature during the first day (+26 breaths per minute and +0.5 °C, respectively); then, both decreased progressively during the two subsequent days (-12 breaths per minute and -0.2 °C, respectively), remaining relatively constant thereafter. In this latter study, authors also reported a biphasic response for feed intake that decreased within the first 24 h following the rise in ambient temperature; then, it gradually increased over the acclimation period.

The decline in the physiological responses during the long-term heat acclimation phase has been associated with the decrease in metabolic heat production after a medium to long-term period of heat exposure. This response presumably attenuates the pig demand for body cooling and thus the magnitude of the activation of heat dissipation mechanisms, such as panting, and the magnitude of feed intake reduction over the acclimation period (Renaudeau et al., 2007; Renaudeau et al., 2010). In agreement with this assumption, Renaudeau et al. (2013) observed that respiratory rate of growing pigs exposed to a temperature of 32 °C decreased after the first week of heat exposure in connection with a lower metabolic heat production in the same period.

Pig responses to sanitary challenges

Pigs reared in commercial conditions are often exposed to sanitary challenges (poor hygiene conditions and pathogens) (Pastorelli et al., 2012). As a consequence, the immune system interacts with physiological regulatory mechanisms to maintain animal homeostasis and body integrity.

Voluntary feed intake and growth performance

The effects of different sanitary challenges on feed intake and growth in young pigs were analyzed and

summarized by Pastorelli et al. (2012). These authors reported a reduction in feed intake of about 8% for digestive bacterial infections, 4% for poor hygiene housing conditions, 10% for lipopolysaccharide (LPS) challenges, 23% for mycotoxicoeses, 3% for parasitic infections, and 16% for respiratory diseases. Williams et al. (1997) similarly reported depressed feed intake in pigs reared in poor sanitary conditions when compared with those reared in good sanitary conditions. Infection-induced anorexia has been considered as part of the host non-specific immune response, which consists in reducing the availability of nutrients essential to development and growth of pathogens (Exton, 1997; MacDonald et al., 2011). In addition, anorexia seems to enhance function and proliferation of macrophages, contributing to recognition and elimination of pathogens (Exton, 1997).

Regarding the negative effects of inflammation on growth, some studies have reported that animals reared in clean and disinfected environments grow faster and/or are more efficient than those reared in less hygienic environments. Those studies include the experiment of Coates et al. (1963) with chickens housed in a germ-free environment and more recent studies comparing pigs reared in good or poor sanitary conditions (Le Floc'h et al., 2009; Le Floc'h et al., 2010). Such changes result essentially from the reduction in feed intake, the redistribution of nutrients from growth towards the immune system response (Johnson, 1997; Spurlock, 1997; Le Floc'h et al., 2004), and the decrease in nutrient digestibility (Le Floc'h et al., 2014). Accordingly, Daiwen et al. (2008) observed a lower weight gain and feed efficiency in pigs receiving LPS than in pair-fed control pigs administered a saline solution.

In the aforementioned study of Pastorelli et al. (2012), a reduction was observed in growth rate of about 16% for digestive bacterial infections, 10% for poor hygiene housing conditions, 12% for LPS challenges, 30% for mycotoxicoeses, 8% for parasitic infections, and 16% for respiratory diseases. These authors also evidenced that growth depression in response to LPS challenges, mycotoxicoeses, and respiratory diseases most likely results from the reduction in feed intake, whereas for digestive bacterial infections, poor housing conditions, and parasitic infections, it results mainly from increased maintenance requirements, changes in intestinal function, and changes in digestion and metabolism of nutrients.

Neuroendocrine adjustments

The activation of the HPA axis is a common response to a variety of stressors, including infectious and non-infectious

challenges and psychological disturbances (Sapolsky et al., 2000). During infectious diseases or inflammation, the pro-inflammatory cytokines initiate a cascade of reactions that ultimately results in the release of cortisol from the adrenal cortex into the blood circulation. Two major effects of cortisol during immune challenges have been identified. The first consists in an immunomodulatory function, in which cortisol inhibits the inflammatory process and pro-inflammatory cytokine release and up-regulates anti-inflammatory cytokines such as IL-4 and IL-10 (Beishuizen and Thijs, 2003). This modulatory effect contributes to restore homeostasis and protects the organism against the negative effects associated to an excessive inflammatory response (i.e., cell and tissue damage and excessive catabolism) (Beishuizen and Thijs, 2003; Karrow, 2006). The second effect of cortisol corresponds to a metabolic effect. Indeed, cortisol is a catabolic hormone, which increases energy and nutrient release due to the stimulation of adipose tissue lipolysis and skeletal muscle proteolysis (Johnson, 1997; Weibel et al., 1997). This may contribute to increase nutrient availability for the immune response. Cortisol also decreases the utilization of glucose by non-immune tissues, such as the skeletal muscle, and contributes to increase glucose availability for immune cells and the liver (Sapolsky et al., 2000; Ferris and Kahn, 2012).

A body of evidence suggests that the stimulation of the immune system also induces down-regulation of the hypothalamus-pituitary-thyroid (HPT) axis and related changes in thyroid hormone metabolism, resulting in low circulating levels of T_3 and T_4 hormones (Karadag et al., 2007; Warner and Beckett, 2010). Accordingly, Castro et al. (2013) reported that the continuous intravenous infusion of 3.5 to 5.0 μg of LPS kg^{-1} BW per hour for 48 h induced a reduction in T_3 and T_4 levels in serum and in specific tissues, including heart, liver, kidney cortex, and skeletal muscle. Theoretically, as thyroid hormones play an important role in stimulating metabolic rate, their down-regulation would contribute to reduce the energy expenditure by non-immune tissues and then spare energy to support the immune response (Fliers et al., 1997; Boelen et al., 2011).

Metabolic adjustments

When pigs are subjected to an immune challenge caused by infectious diseases, nutrients that might have been used to support growth are readily redirected to support the inflammatory response (Johnson, 1997). In addition, sick animals are often in anorexic state and have to rely on mobilization of body reserves to meet their nutritional needs. Skeletal muscle catabolism increases

free amino acids into the circulation that, in turn, can be used in the liver for the synthesis of acute phase proteins, as well as substrate for gluconeogenesis (Hasselgren and Fischer, 1999; Lerverve, 2001; Obled, 2003). Accordingly, Daiwen et al. (2008) observed lower protein retention in pigs challenged intramuscularly with LPS when compared with their pair-fed counterparts receiving a saline solution. Weibel et al. (1997) reported an increase in plasma urea nitrogen levels in association with increased circulating tumor necrosis factor (TNF) - α and IL-6 in pigs intraperitoneally challenged with LPS. It has also been suggested that protein catabolism during disease or inflammation is emphasized due to an imbalance between the supply of amino acids from endogenous proteolysis and those required for the synthesis of acute phase compounds (Reeds et al., 1994). Consequently, a greater amount of skeletal muscle protein might be degraded to provide amino acids to support the synthesis of equivalent acute phase protein (Johnson, 2012).

Potential effects of high ambient temperatures on pig health

Climatic environmental factors (e.g., ambient temperature, rain, and humidity) have the potential to influence livestock health at different levels. They may affect the intensity and frequency at which animals are exposed to sanitary challenges, as well as the immune defenses of the animal against the sanitary challenges of the environment (Johnson, 2012).

Impact on animal exposure to pathogens

There is a scientific consensus that global warming will benefit the development and dissemination of disease vectors (ticks and mosquitoes), parasites, and pathogens in the environment (Thornton et al., 2009). As a consequence, it is quite evident that pigs will become more exposed to pathogenic parasites, virus, and bacteria in the coming decades (Thornton et al., 2009; Kimaro and Chibinga, 2013). Such changes will presumably be accentuated in tropical regions where the association of high temperature and relative humidity create even more favorable conditions for the development of vectors and pathogens (Patz et al., 2000).

The rise in global temperature is also expected to affect livestock health in temperate regions (Skuce et al., 2013). In fact, a greater incidence of sanitary problems has already been observed in hot months than in cold months in temperate regions in association with better conditions (warmer temperatures) for pathogen proliferation (Skuce et al., 2013). For example, through the analysis of

fecal samples of piglets from different farms located in northwestern Germany, Meyer et al. (1999) reported that the percentage of samples infected with *Isospora suis* was greater during summer and autumn than during winter and spring seasons. According to the authors, it presumably resulted from a faster sporulation of *Isospora* oocysts during the warm to hot months leading to greater number of infectious oocytes in the environment. In addition, by the analysis of serum blood samples of growing-finishing pigs from 200 different farms, Hautekiet et al. (2008) observed higher *Salmonella* seroprevalence in pigs exposed to housing temperatures above 26 °C than in those kept at thermoneutral temperatures.

Therefore, there is a strong evidence that the actual context of global warming and livestock production intensification in hot climate areas will lead to increased exposure of animals to sanitary challenges (Thornton et al., 2009; Perry et al., 2013; Skuce et al., 2013).

Impact on animal ability to cope with a sanitary event

It has been suggested that high ambient temperature affects the immune function of livestock animals (Lacetera, 2012). Because both thermal and inflammatory challenges induce anorexia and physiological and metabolic disorders, it may be hypothetically assumed that their association results in an unsuccessful capacity of animals to adapt to or overcome such challenges. However, recent studies of Campos et al. (2014a,b) showed that acclimation to high ambient temperature might be beneficial in improving the capacity of growing pigs to limit the physiological and metabolic disturbances caused by an inflammatory challenge induced by repeated administrations of *Escherichia coli* LPS. In response to LPS and compared with pigs housed at 30 °C, pigs housed at 24 °C had higher concentrations of circulating pro-inflammatory cytokines associated with a greater magnitude of response of the HPA and HPT axes (Campos et al. 2014a). In addition, LPS induces greater reduction in feed intake and growth depression in pigs housed at 24 °C than in those at 30 °C (Campos et al., 2014a,b). Studies in literature have suggested that previous exposure to a stress factor may serve as a conditioning factor for the response to another stress in a phenomenon termed cross-tolerance (Horowitz, 2001). For instance, previous exposure of rodents to high ambient temperatures has been shown to attenuate LPS-induced lung injury (Heidemann and Glibetic, 2005) or mortality in connection with a lower production of pro-inflammatory cytokines (IL-1 and TNF- α) (Hotchkiss et al., 1993). Previous high ambient temperature exposure would result in the production of

heat shock proteins (HSP), which act preserving integrity of cells and tissues during inflammation (Heidemann and Glibetic, 2005; Hotchkiss et al., 1993). Two principal mechanisms of HSP protection have been proposed: one is by acting as molecular chaperones; the other, by attenuating the pro-inflammatory response of cytokines (Heidemann and Glibetic, 2005). Growing pigs kept at high ambient temperature have greater HSP expression than those kept at thermoneutrality (HSP70) (Pearce et al., 2013). This last mechanism might explain the lower effects of the LPS challenge when pigs were housed at 30 °C compared with those housed at 24 °C.

Conclusions

Pig acclimation to constant high ambient temperature is a biphasic process. Firstly (within the first 24-48 h after heat exposure), it is characterized by a greater internal temperature, greater body heat losses, and lower heat production associated to a reduced feed intake. Secondly (after 24-48 h of heat exposure), the magnitude of the activation of heat dissipation mechanisms is reduced in connection with a lower release of thyroid hormones and cortisol into the blood circulation to decrease metabolic heat production. It is also suggested that pig acclimation to high ambient temperature might have beneficial effects in attenuating the physiological and metabolic disturbances caused by health challenges. This knowledge provides starting points for a better understanding on the associated effects of thermal and sanitary challenges in animal production.

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