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Metabolism and endocrine alterations in growing and finishing pigs under different duration of heat stress - a review

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Pigs are less heat tolerant than other livestock species and are highly susceptible to heat stress (HS). HS is a physiological condition when an animal cannot release from its body excess heat caused by an increase in environmental temperature. Upon the pig's exposure to such conditions, their body activates several physiological and behavioral mechanisms to regulate its internal body temperature and maintain euthermia. The low thermolytic ability in pigs greatly impairs the aforementioned processes for self-regulation, having metabolic ramifications that can seriously affect the animal's productive performance and compromise its welfare. HS compromises the pigs' post-absorptive metabolism of carbohydrates, lipids, and protein by altering the use of body resources such as energy, fat, and protein. Although these consequences are evident under exposure to high environmental temperature, there is still an avenue for pigs to acclimatize, depending on the duration of exposure to such conditions. Therefore, this paper's objective is to review the influence of HS duration on the acclimatization of pigs and the metabolic consequences with emphasis on the changes in plasma biochemical compounds and hormones. A database search was used to gather information on the effect of HS duration on the plasma biochemical compounds and hormones. The collected data was then used to quantify changes in the levels of these substances as induced by HS duration. Our review showed that HS duration can influence the pigs' acclimatization to the said stressor; however, their metabolism was still compromised, as evidenced by changes in plasma biochemical compounds and hormones.

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Homoeothermic animals such as e.g. pigs have a thermo-neutral zone, where minimal energy is spent on maintaining the animals' average body temperature. However, exposure to high ambient temperature can elevate their body temperature and heat load, leading to heat stress (HS) [Bernabucci et al. 2010; Belhadj Slimen *et al*. 2016]. Growing and finishing pigs are more vulnerable to HS than young pigs due to their greater fatness, a slower rate of heat loss, and lower thermal comfort (Tab. 1). Upon exposure to HS, pigs' homeothermy is maintained through physiological, behavioral, and metabolic adaptations [Renaudeau *et al*. 2011, Campos *et al*. 2017]. This includes increased evaporative panting and reprioritization of the nutrient utilization hierarchy; as a result, productivity is deemphasized [Mayorga *et al*. 2018, Cottrell *et al*. 2020]. Pigs' thermoregulatory responses to HS have a biphasic pattern: the initial phase (short-term heat acclimation phase), which shows intense physiological strains, and the long-term acclimation phase, wherein pigs tend to develop adaptive changes that can lead to lower metabolic heat production and gradual performance improvement [Renaudeau *et al*. 2010]. Pearce *et al*. [2013a] and Pearce *et al*. [2014] observed sudden elevation of rectal temperature and respiration rate as well as poor productive performance of pigs exposed to acute HS.

Table 1. Thermal comfort of different classes of pigs

Class of pigs	Thermal comfort (°C)	Lower extreme (°C)	Upper extreme (°C)
Pre-nursery – 3 to 15 kg	26 to 32	15	35
Nursery – 15 to 35 kg	18 to 26	5	35
Growing – 35 to 70 kg	15 to 25	-5	35
Finishing – 70 to 100 kg	10 to 25	-20	35

Source – FASS [2010].

In contrast, Renaudeau *et al*. [2008] observed a significant improvement in the thermo-regulatory response and growth performance of pigs exposed to chronic HS (20 days) compared to pigs exposed to only 10 days of HS. Such an observation opens up the possibility of pigs' capacity to acclimate to high environmental temperatures and recover from the HS adverse effects. Nevertheless, HS can influence the endocrine profile and alter pigs' nutrient metabolism, which can harm their growth, welfare, body protein synthesis, and carcass quality. Even though HS is known to alter carbohydrate, lipid, and protein metabolism of growing and finishing pigs [Sanz Fernandez *et al*. 2015a], unlike broilers [Temimet *et al.* 2000, Gonzalez-Esquerra and Leeson 2005], little information is known on the HS influence at various durations on the nutrient metabolism in pigs. Understanding the changes in the endocrine profile, nutrient metabolism, and their impact on body composition under different durations of exposure to HS may aid in determining the timing of an appropriate mitigation strategy. Therefore, this paper aims to review the effect of HS duration on pigs' acclimatization, body composition, and endocrine and metabolic alteration, emphasizing changes in plasma biochemical compounds and hormones essential for metabolism.

Pig's response to heat stress

Pigs' welfare along with their productivity is compromised under HS challenge [Mayorga *et al*. 2018]. Pigs exhibit various responses to HS. One immediate behavioral response of pigs when exposed to high ambient temperature (AT), whether for a short or long term, is to reduce feed intake; this helps the animal minimize heat production to maintain body temperature within narrow limits [Collin *et al*. 2001]. The secretion of two adipokines influences this reduction of feed intake under acute or chronic HS through the pig's adipose tissue, namely leptin and adiponectin [Bernabucci *et al.* 2009, Morera *et al*. 2012]. Adiponectin and leptin levels are up-regulated when animals are exposed to HS [Aleena *et al*. 2016]. Leptin acts within the hypothalamus, which suppresses food intake [Morrison 2009], while adiponectin regulates feed intake through central and peripheral nervous mechanisms [Kubota *et al*. 2007, Hoyda *et al.* 2009]. Along with the reduction of feed intake, the nutrient intake of animals is also reduced [Baumgard and Rhoads 2013], and nutrient digestion and absorption affect insulin secretion and cortisol [Ma *et al.* 2015]. Insulin, considered a primary acute anabolic endocrine signal, plays an integral part in the metabolism of carbohydrates, lipids, and proteins [Sanz Fernandez 2015b]. In the metabolism of carbohydrates, insulin stimulates glucose transport across the cell membrane in the adipose tissue and muscles, stimulating hexokinase and 6-phosphofructokinase activity, which are essential for glycolysis. Glycogen synthesis in the muscle, adipose tissue, and liver is stimulated by insulin, and it also decreases its breakdown while inhibiting the rate of gluconeogenesis and glycogenolysis in the liver. In lipid metabolism, insulin decreases the rate of lipolysis in the adipose tissue, stimulates the synthesis of fatty acids and triacylglycerol in tissues, and lowers the plasma fatty acid level. It also influences the triglyceride uptake from the blood into the muscle and adipose tissue and decreases the fatty acid oxidation rate in the muscle and liver. Protein metabolism influences the rate of amino acid transport into tissues and facilitates protein synthesis in the muscle, adipose tissue, and liver. Moreover, the protein degradation rate in muscle and urea formation is decreased by insulin [Dimitriadis *et al.* 2011]. Maintaining homeostasis is essential; however, when pigs are exposed to high AT, it dramatically affects the said balance. Sanz Fernandez *et al*. [2015b] and Liu *et al*. [2015] reported that growing pigs under constant HS (32°C, 23% relative humidity) and cyclic HS (35°C from 09:00-17:00; 28°C overnight) for eight days showed a reduction in insulin levels, which can affect the functions of insulin. Aside from insulin, cortisol (stress hormone) secretion is also affected. Hao *et al*. [2014] observed a significant increase in plasma cortisol levels of pigs exposed to HS (30°C) for 21 days, which is similar to findings reported by Fagundes *et al*. [2008], given in Table 2. This can increase

Table 2. Serum cortisol concentration (mg/dL) of growing-finishing pigs under thermal comfort and heat stress

Days of experiment	Age (days)	Temperature range (°C)	
		Thermal comfort (15.6-26.6)	Heat stress (22.2-32.8)
7	83	4.40	5.90
11	94	3.70	4.40
17	100	3.90	4.30
24	107	6.50	5.40
31	114	2.80	5.90
38	121	5.10	7.80
45	128	9.40	11.80
52	136	2.90	4.70
59	142	6.20	11.60

Source – Fagundes *et al*. [2008].

amino acid levels in the blood, lower intracellular glucose utilization, and induce liver neoglucogenesis. Furthermore, persisting high levels of this hormone can lead to insulin resistance and dyslipidemia, which can be significantly disadvantageous for the animals' nutrition [Stachowicz and Lebiedzińska 2016].

Short-term and long-term HS impact on metabolism and body composition in pigs

As previously mentioned, pigs undergo metabolic adaptations to cope with HS, drastically affecting their performance. Regarding biological adaptation, pigs increase radiant heat loss by redistributing blood towards the skin. However, due to their thick subcutaneous adipose tissue layers and few functional sweat glands, heat loss is inefficient, forcing pigs to pant. Consequently, faster respiration takes more carbon dioxide out of the bloodstream, which is then exhaled and changes blood pH level leading to metabolic acidosis and insufficient feed intake [Mayorga *et al*. 2018]. In a short period of exposure to HS (37°C for 2-6 hours), an increase in respiration rate (RR) and a dramatic decrease in feed intake are observed [Pearce *et al*. 2014]. However, Renaudeau *et al.* [2008] observed that growing barrows under HS (36°C) for 11-20 days exhibited a reduction of RR compared to being exposed only for ten days, suggesting that prolonged exposure to heat makes evaporative heat loss per breath efficient. Animals acclimatize to certain stressors such as HS. It occurs in two phases: acute stress response (homeostatic response) and chronic stress response (homeorhetic response). The latter is responsible for the animals' conditioning to such exposure reprogramming metabolism to achieve a new physiological state. Generally, the former can lead to losses in the animals' production performance, while the latter can restore some of the losses through acclimatization to such stressors [Collier *et al.* 2018]. However, there is some evidence that pigs' exposure to HS alters their post-absorptive metabolism of carbohydrates, lipids, and protein, emphasizing changes in blood biochemical parameters and hormones [Baumgard and Rhoads 2013, Pathak *et al*. 2018].

Carbohydrate metabolism

Various studies concerning animal metabolism under constant HS showed that carbohydrate metabolism could be compromised. One of its significant effects on pigs' nutrition is the alteration of carbohydrate metabolism, supported by changes in blood glucose levels [Pearce 2011]. Researchers suggest that the duration of HS influences alterations of glucose concentration in pigs. Pigs exposed to acute HS (24 hours) demonstrated elevated levels of blood glucose [Pearce *et al*. 2013a], while long-term exposure (21 days) showed a decrease in glucose concentrations and in turn, led to a state of negative energy balance [Cui *et al.* 2019]. Glucose is an important energy source needed by all the cells and organs in the body [Mergenthaler *et al.* 2013]. High AT forces the animal to cope with its energy needs by glycogen oxidation [Sanz Fernandez *et al*. 2015b] through glycogenolysis, which increases hepatic glucose production through glycogen degeneration in skeletal muscle and the liver to maintain energy balance [Pearce 2011, Roach *et al*. 2012, Baumgard and Rhoads 2013].

Lipid metabolism

HS markedly alters lipid metabolism [Sanz Fernandez *et al.* 2015a]. Lipid metabolism is associated with carbohydrate metabolism, as acetyl-coenzyme A (CoA), a product of glucose, can be converted into lipids. As glucose level in the body decreases, triglycerides (fat) within the body (adipose tissue and the liver) will be hydrolyzed through lipolysis into acetyl-CoA molecules to generate adenosine triphosphate (ATP) [Openstax 2013]. However, HS inhibits lipolysis, leading to increased metabolic heat generation; consequently, animals reduce body fat mobilization and increase fat deposition [Gonzalez-Rivas *et al*. 2020]. Ma *et al*. [2015] described that when pigs are exposed to HS for an extended period, fatness increases and body fat shifts towards internal sites. In a study of Kouba *et al*. [2001], exposure of growing pigs to chronic HS (31°C for 21 days) enhances lipid metabolism in both the liver (very low-density lipoprotein production) and the adipose tissue (lipoprotein lipase activity). Consequently, the adipose tissue facilitates the uptake and storage of plasma triglyceride, resulting in greater carcass fatness. Pigs' exposure to HS increases the levels of triglyceride and low-density lipoprotein cholesterol (LDL-C). At the same time, lowering the concentrations of high-density lipoprotein cholesterol (HDL-C), considered good cholesterol, directly affects numerous cell types that influence metabolic health [Mineo and Shaul 2012, Wu *et al.* 2016, Fang *et al.* 2020]. Pearce *et al*. [2013b] observed an immediate increase of non-esterified fatty acid (NEFA) plasma levels in crossbreed gilts after 24 hours of exposure to HS, which continued for 7 days. In finishing pigs, constant exposure to HS (30°C) for 21 days increased plasma NEFA and very-low-density lipoprotein (VLDL), which were absorbed by the adipose tissues leading to an increased proportion of backfat and flare fat [Wu *et al.* 2016]. HS reduces the expression of lipolytic genes and increases the de novo lipogenesis in pigs with the elevation of lipogenic pathways as observed through metabolomics, hence the increase in carcass fatness [Qu *et al*. 2015, Qu and

Table 3. Plasma concentrations of insulin, glucose, lipid, and urea of growing and finishing pigs under thermal comfort (TC) and different duration of heat stress (HS)

Heat stress duration	TC (20-23℃)		HS (28-35℃)		Mean		
					TC	HS	% change
			Insulin (ng/ml)				
1[ab]	0.09	0.061	0.05	0.088	0.076	0.069	-8.61
3[ab]	0.13	0.031	0.09	0.045	0.081	0.068	-16.15
5[b]	0.124	na	0.099	na	0.12	0.10	-16.67
7[ac]	0.17	0.016	0.12	0.022	0.093	0.071	-23.66
14[c]	0.019	na	0.02	na	0.02	0.02	0.00
21[cd]	0.017	0.16	0.016	0.10	0.089	0.058	-34.46
				mean	0.080	0.064	-19.27
			Glucose (mg/dl)				
1[ab]	110.7	95.9	108.8	103.3	103.3	106.05	2.66
3[ab]	116	93.3	104.5	85.10	104.65	94.8	-9.41
5[bf]	102.5	98	83.67	97	100.25	90.335	-9.89
7[ac]	116.8	100.72	105.8	114.78	108.76	110.29	1.41
14[c]	102.7	na	110.81	na	102.7	110.81	7.90
21[cg]	104.68	148	113.51	119	126.34	116.255	-7.98
				mean	107.67	104.76	-2.70
			Triglycerides (mg/dl)				
1[a]	44	na	50.70	na	44	50.7	15.23
3[ah]	41.4	36.28	47.80	58.41	38.84	53.105	36.73
5[f]	47.5	na	39.67	na	47.5	39.67	-16.48
7[a]	37.5	na	47.3	na	37.5	47.3	26.13
21[gi]	78.7	38.94	65.5	34.51	58.82	50.005	-14.99
				mean	45.33	48.16	6.23
			HDL-C (mmol/l)				
3[h]	0.57	na	0.52	na	0.57	0.52	-8.77
21[i]	0.99	na	0.84	na	0.99	0.84	-15.15
				mean	0.78	0.68	-12.82
			LDL-C (mmol/l)				
3[h]	1.12	na	1.43	na	1.12	1.43	27.68
21[i]	1.63	na	1.71	na	1.63	1.71	4.91
				mean	1.38	1.57	14.18
			NEFA (mmol/l)				
1[a]	0.09	na	0.27	na	0.09	0.27	200.00
3[aj]	0.06	0.08	0.09	0.07	0.07	0.08	14.29
5[f]	0.09	na	0.05	na	0.09	0.05	-44.44
7[ak]	0.07	0.19	0.09	0.16	0.13	0.13	-3.85
21[gi]	0.28	0.52	0.31	0.75	0.40	0.53	32.50
				mean	0.16	0.21	35.26
			BUN (mg/dl)				
1[a]	10.2	na	13.8	na	10.2	13.8	35.29
3[al]	11.2	13.39	8.4	14.76	12.30	11.58	-5.82
5[f]	20.58	na	15.02	na	20.58	15.02	-27.02
7[al]	10	12.15	7.3	11.59	11.08	9.445	-14.72
14[l]	12.01	na	11.65	na	12.01	11.65	-3.00
21[l]	14	na	12.63	na	14.00	12.63	-9.79
				mean	13.36	12.35	-7.53

[a]Pearce *et al*. [2013a]; [b]Sanz Fernandez *et al*. [2015b]; [c]Xin *et al*. [2018]; [d]Siebert *et al*. [2018]; [e]average; [f]Kim *et al*. [2020]; [g]Kouba *et al*. [2001]; [h]Fang *et al*. [2020]; [i]Wu *et al*. [2016]; [j]Mendoza *et al*. [2017]; [k]Liu *et al*. [2018]; [l]Wen *et al*. [2019]; [na]not available; BUN – blood urea nitrogen.

Ajuwon 2018]. Changes in the concentration of plasma biochemical compounds of heat-stressed pigs are shown in Table 3.

Protein metabolism

Body protein metabolism and deposition are compromised when pigs are under HS. Protein metabolism is altered by HS, as indicated by increased skeletal muscle proteolysis leading to a decrease in lean tissue [Pearce *et al*. 2013a, Sanz Fernandez *et al.* 2015b]. Growing-finishing pigs exposed to high AT (28-35°C) for a long period develop more fat than pigs under thermal comfort [Kellner *et al.* 2016]. Several studies have shown that HS leads to increased protein degradation and reduced protein synthesis and retention [Ma *et al*. 2015]. In a proteomic study, pigs under acute HS (2 hours) showed an altered abundance of several proteins that affect metabolism and impair muscle function and growth [Cruzen *et al*. 2017]. Le Bellego *et al*. [2002] stated that pigs' prolonged exposure to HS directly negatively affects protein deposition and the partitioning of energy gain between protein and fat deposition. Those authors observed that pigs exposed to HS (30°C) (24 to 65 kg) developed fatter carcasses with lower protein levels and more lipid deposition than pigs reared under thermal comfort (23°C). This can be supported by environmental hyperthermia reducing muscle protein machinery and RNA/DNA synthesis [Streffer 1982, Baumgard and Rhoads 2013].

Furthermore, the decrease in protein accretion or synthesis can be caused by the hormonal changes during HS that influence nutrient metabolism. The said hormonal changes involve a reduction in the levels of thyroid hormones (Tab. 4): triiodothyronine (T3) and thyroxine (T4), which play a vital role in controlling metabolic rate, thermogenesis [Campos *et al*. 2017], and protein synthesis [Kenessey and Ojamaa 2006]. Besides a decrease in protein synthesis, HS also influences skeletal muscle catabolism, of which the resulting amino acids provide essential precursors for protein synthesis or as energy in the body [Baumgard and Rhoads 2013, Wolfe 2005].

Changes in plasma biochemical compounds and hormones in pigs under different duration of heat stress

To determine if heat stress duration causes changes in plasma biochemical compounds and hormone levels essential for metabolism in pigs, we searched for studies in the following databases: the ISI web of knowledge, PubMed, Google Scholar, and Science Direct. We used the following search terms: heat stress or heat stress duration or acute heat stress or long-term heat stress or nutrient metabolism or changes in nutrient metabolism or metabolic alterations or changes in plasma biochemical compounds and hormones or body composition of pigs and growing to finish pigs. Various combinations of the search terms were made, and no date or language restriction for the selection was introduced to find as many articles as possible. In our search, we found that there was no specific study on the influence of

Table 4. Levels of the thyroid hormone of pigs under thermal comfort and different duration of heat stress

Days in	Triiodothyronine (ng/ml)			Thyroxine (ng/ml)		
experiment	TC (20-22°C)	HS (31-32°C)	% change	TC (20-22°C)	HS (31-32°C)	% change
3[a]	0.0007	0.0004	-42.85	0.017	0.010	-41.17
8[b]	0.60	0.30	-50	35.00	34.00	-2.86
11[c]	0.23	0.16	-30.43	0.022	0.017	-22.73
21[d]	0.87	0.91	+4.6	72.71	70.80	-2.63
21[e]	1.07	0.75	-29.91	58.11	55.62	-4.28

[a]Le *et al*. [2020]; [b]Sanz Fernandez *et al*. [2015a]; [c]Patience *et al*. [2005]; [d]Cui and Gu [2015];[e]Kouba *et al*. [2001].

HS duration on the nutrient metabolism in pigs. However, we found fifteen articles related to our manual search interest with the relevant information we need to quantify changes in the levels of plasma biochemical compounds and hormones in pigs under HS. In these articles, the pigs' exposure to HS varied (from 1 day to 21 days); we gathered and summarized the information regarding the plasma levels of insulin, glucose, triglycerides, HDL-C, LDL-C, NEFA, BUN, and thyroid hormones (T3 and T4) and used it to quantify the changes (Tab. 3 and 4).

Based on the information we gathered from several researches, some biochemical compounds and hormones essential for pigs' metabolism differed in response to the varied duration of the animals' exposure to HS. Pigs' blood insulin concentration is negatively changed from day 1 to 21 of HS exposure. In contrast, glucose and triglyceride concentrations were inconsistent. Glucose levels increased on the 1st day and subsequently decreased on days 3 and 5. On days 7 and 14, glucose concentration increased and was negatively changed on day 21 of HS. On days 1, 3, and 7, triglyceride concentration was positively changed, but was negatively altered on the 5th and 21st days of HS exposure. Plasma concentration of HDL-C consistently decreased from days 3 and 21 of HS; in contrast, LDL-C was positively increased as observed in the same duration. NEFA concentration positively spiked on days 1 and 3 of HS, but was negatively changed on days 5 and 7. Nevertheless, prolonged exposure (21 days) led to its further increase. Blood urea nitrogen (BUN) concentration was positively affected on the 1st day of HS exposure, but was negatively changed from day 3 to 21 of exposure. The concentration of thyroid hormones (triiodothyronine and thyroxine) was negatively affected by HS, regardless of the duration of exposure.

Conclusions

The pigs' ability for thermoregulation under HS involves physiological responses, which can negatively affect the animals' performance. Nevertheless, prolonged exposure to the said stressor can influence their ability to acclimate and gradually recover from HS adverse effects. Changes in the pigs' blood biochemical compounds and hormones essential for metabolism vary. Insulin, HDL-C, LDL-C, triiodothyronine

(T3), and thyroxine (T4) showed consistent changes, while the other biochemical compounds reviewed exhibited inconsistent changes. Despite the inconsistencies, our review pointed out that the pigs' metabolism under HS is compromised, which could also affect the animals' body composition through decreased protein synthesis and increased fat deposition. Therefore, immediate intervention strategies should be applied during exposure time to alleviate the HS adverse effects and secure pigs' welfare. The variability in the plasma biochemical parameters of pigs in response to different durations of HS reviewed might also be influenced by the variation in the experimental procedure, hence a need for specified research in this area.

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