Korean Journal Of Agricultural Science

pISSN : 2466-2402
eISSN : 2466-2410

ANIMAL

Supplementation of δ-aminolevulinic acid to sows' diet from day 100 of gestation to lactation improves the feed intake and red blood cells of sows and improves the birth weight of offspring

Qianqian Zhang, Yanjiao Li, In Ho Kim*

Department of Animal Resource and Science, Dankook University, Cheonan 31187, Korea

*Corresponding author: inhokim@dankook.ac.kr

Abstract

This experiment was conducted to evaluate the effects of δ-aminolevulinic acid (ALA) when added to sows' diet on their reproductive performance and growth performance and on the hematology parameters of the sows and their piglets. Sixteen multiparous sows (Yorkshire × Landrace) were allotted into two treatment groups and fed basal diets (CON, piglets were injected with iron dextran) or the basal diet containing 0.1% ALA (ALA, piglets were not injected with iron dextran) from day 100 of gestation to day 28 of lactation. Supplementation of ALA had no effect on the body weight (BW), backfat thickness (BFT), or litter sizes of sows in the present experiment. However, the average daily feed intake (ADFI) of the sows was significantly improved ($p < 0.05$) in the ALA group. Supplementation of ALA had no effect on the growth performance or survival of suckling piglets but had a significant effect on the birth weight ($p < 0.05$). With regard to the blood profiles, serum concentrations of iron were unaffected in sows and piglets as compared to the control group. Red blood cell (RBC) counts were significantly improved ($p < 0.05$) in sows during late gestation to the time before farrowing period and in piglets at weaning. In summary, these results suggest that dietary supplementation of ALA can have positive effects by improving growth performance and blood RBC in sows and suckling piglets.

Key words: iron status, performance, piglet, sow, δ-aminolevulinic acid

Citation: Zhang Q, Li Y, Kim IH. Supplementation of δ-aminolevulinic acid to sows' diet from day 100 of gestation to lactation improves the feed intake and red blood cells of sows and improves the birth weight of offspring. Korean Journal of Agricultural Science 49:297-306. https://doi.org/10.7744/kjoas.20220028

Received: April 15, 2022

Revised: April 14, 2022

Accepted: May 10, 2022

Introduction

Iron (Fe) is a vital micronutrient and associated with many metabolic processes in the body, such as binding oxygen, as a cofactor in many enzymes, energy metabolism, and gene synthesis (Frazer and Anderson, 2005; Youdim et al., 2009; Antonides et al., 2015). For the gestating mammal, Fe deficiency can cause some adverse impacts on their reproductive performance, such as reduced fertility, increased risk of premature birth and stillbirth (Buffler et al., 2017; Wan et al., 2018). Similarly, iron deficiency also affects young animals, leading to anemia, reduced activity of the iron enzyme, reduction in defense capabilities, and growth retardation (Haas and Brownlie, 2001; Tang et

al., 2015). Moreover, several studies have identified the probability of early Fe deficiency in nursery piglets was higher than in other growth stages (Mateo et al., 2006; Chen et al., 2008a). Supplementation additives have been suggested for improving the health status of sows or nursery piglets (Val-Laillet et al., 2018; Palade et al., 2019).

The δ-aminolevulinic acid (ALA) is a non-protein amino acid, which plays a role in regulating heme biosynthesis and metabolism (Kang et al., 2012). The heme is the prosthetic group of hemoglobin (Hb), myoglobin, and other substances, and affects physiological functions in the animal body (Ogun and Valentine, 2019). ALA has been reported to improve animal health and production performance (Kommera et al., 2006; Sonhom et al., 2012; Phour et al., 2018). Min et al. (2004) reported that dietary supplementation of ALA improved the concentration of Fe, Hb, and the total Fe binding capacity in weaned pigs. Chen et al. (2008a) observed that Fe and Hb levels were increased with supplementation of ALA while that of plasma tumor necrosis factor-α was reduced under the inflammatory challenge. Similarly, Mateo et al. (2006) reported that sow diets containing 0.05% ALA increased the RBC counts in nursery pigs. Wang and Kim (2012) also indicated that first-party sows that fed ALA during the gestation and lactation period not only increased the concentration of Fe in the plasma and milk but also increased the birth weight and weaning weight of piglets. Moreover, ALA supplementation in the diet improved Fe concentration and immune function in broilers and egg quality in laying hens as reported by Wang et al. (2011) and Yan et al. (2010).

The findings from the above-mentioned studies indicated that dietary supplementation of ALA can affect the health condition and the production performance of swine and poultry. We hypothesized that the supplementation of ALA to sows might reduce the probability of Fe-deficiency anemia in piglets by improving Fe status in sows and promoting the reproductive performance and growth performance in sows and piglets, respectively. However, in previous studies, ALA was generally added to the diet in combination with other additives. Therefore, the objective of this study was to investigate the effect of dietary ALA on sows on the performance and Fe status in sows and suckling piglets.

Materials and Methods

The experiment was conducted at the swine experimental unit of Dankook University. The protocols used in the current experiment were approved by the Animal Care and Use Committee of Dankook University, South Korea.

Experimental design and diet

A total of 16 multiparous sows (average 2.6 parities; Yorkshire × Landrace) were allocated to two treatments based on parity, body weight (BW), and backfat thickness (BFT). The experimental treatments were the basal diet group (CON; piglets were injected with iron dextran (50 mg·pig^{-1}) subcutaneously within 24 h postpartum) and the basal diet containing 0.1% ALA group (piglets were not injected with iron dextran). The ALA was supplemented in the diet from day 100 of gestation until day 28 of lactation and was produced by recombinant *Escherichia coli* which contains the *Rhodobacter capsulatus* hemA gene (Easy Bio System Inc., Seoul, Korea). The experimental diets were formulated to meet and exceed the nutritional requirement recommended by NRC (2012). Sows were fed a gestation diet and were restricted to feed (approximately 2.5 kg·day^{-1}) during late gestation and then allowed *ad libitum* access to the lactation diet after 4 days of farrowing (Table 1). On day 107 of gestation, all sows were moved into farrowing crates (2.50 × 1.80 m^2) with space on both sides of the crates (2.5 × 0.5 m^2) for the neonatal pigs, also it can provide free access to drinking water for sows and piglets in the overall period. The temperature in the farrowing house was maintained at a minimum of 20°C and supplemental heat was provided for nursing piglets using heat lamps.

Table 1. Composition of experimental diets (as-fed basis).

Item	Gestation diet	Lactation diet
Ingredient (%)		
Corn	57.1	51.12
Soybean meal, 46% CP	10.65	24.61
Wheat bran	12	4
Rapeseed meal	3.7	2.5
Rice bran	6	5
Tallow	3.59	6.05
Molasses	3.6	3.5
Dicalcium phosphate	1.52	1.64
Limestone	0.99	0.76
Salt	0.6	0.5
Lysine, 98%	0.05	0.12
Vitamin premix[y]	0.1	0.1
Mineral premix[z]	0.1	0.1
Calculated composition		
Metabolizable energy ($MJ \cdot kg^{-1}$)	3.19	3.44
Crude protein (%)	13.1	17.1
Crude fat (%)	6.89	9.1
Lysine (%)	0.65	1
Calcium (%)	0.87	0.85
Phosphorus (%)	0.76	0.73

[y] Provided per kilogram of complete diet: Vitamin A, 10,000 IU; vitamin D3, 2,000 IU; vitamin E, 48 IU; vitamin K3, 1.5 mg; riboflavin, 6 mg; niacin, 40 mg; D-pantothenic, 17 mg; biotin, 0.2 mg; folic acid, 2 mg; choline, 166 mg; vitamin B6, 2 mg; and vitamin B12, 28 μg.
[z] Provided per kilogram of complete diet: Fe (as $FeSO_4 \cdot 7H_2O$), 90 mg; Cu (as $CuSO_4 \cdot 5H_2O$), 15 mg; Zn (as $ZnSO_4$), 50 mg; Mn (as MnO_2), 54 mg; I (as KI), 0.99 mg; and Se (as $Na_2SeO_3 \cdot 5H_2O$), 0.25 mg.

Performance measurement

The BW and BFT of sows were measured on day 100 of gestation, farrowing (24 h postpartum), and on day 28 of lactation (weaning day). The BFT was measured at the P2 position (both sides of the last rib and 65 mm from the backbone) using Ultrasound (Piglog105, Frontmatec, Kolding, Demark) referring to the method of Hoque et al. (2021). According to dietary treatments, the piglets were cross-fostered to balance the number of suckling piglets within 3 days. However, we just collected the growth performance data of cross-fostered pigs and did not collect blood parameters. The individual weight of piglet was measured at birth (within 24 h postpartum) and on day 14 and day 28 of lactation. During the lactation period, the daily feed intake of sows was recorded.

Sample collection and chemical analyses

At farrowing and on day 14 and 28 of lactation, blood samples were collected from 8 sows in each treatment (5 mL) and 30 suckling piglets of each treatment (2 piglets each litter) *via* anterior vena cava (2 mL) into a 5 mL tube (with K_3EDTA as an anticoagulant). Each anticoagulant blood sample was divided into 2 portions. The first portion was used to determine red blood cells (RBC) using an automatic blood analyzer (Nihon Kohden, Celltac Alpha, Tokyo, Japan). The second portion was centrifuged at 3,000 × g for 15 min at 4℃ (Eppendorf centrifuge 5810R, Hamburg, Germany) to obtain plasma. Fe concentration was determined using the colorimetric method with the commercial kit (Olympus Diagnostics, Hamburg, Germany).

Statistical analysis

All data were analyzed by t-test procedure of SAS (SAS Inst. Inc., Cary, NC, USA) with each sow being the experimental unit. Data variability was expressed as the standard error of means (SEM). The p-value of ≤ 0.05 was considered significant, and p ≤ 0.1 was considered a trend.

Results

Reproductive performance of sows

The effects of supplementation of ALA in the sow's diet on the reproductive performance of sows are shown in Table 2. During the lactation period, supplementation of ALA significantly increased the average daily feed intake (ADFI) ($p < 0.05$) of sows during lactation, whereas there was no difference ($p > 0.05$) in BW, BFT gain and loss, or litter size of sows between the control and ALA groups.

Table 2. Effect of δ-ALA supplementation on reproduction performance in sows[x].

Item	CON	ALA	SEM	p-value
Body weight (kg)				
Initial		221.8	4.58	0.46
Before farrowing	234.3	234.2	3.51	0.25
After farrowing 24 h	215.4	215.6	3.60	0.43
Weaning	198.3	199.0	3.63	0.24
Gainy	12.4	12.4	1.54	0.81
Loss 1[y]	-18.9	-18.6	1.95	0.28
Loss 2[y]	-17.2	-16.7	0.78	0.70
ADFI (kg)				
Lactation	6.80b	6.97a	0.03	0.01
Backfat thickness, mm				
Initial	19.4	19.4	0.38	0.50
Before farrowing	19.9	19.9	0.27	0.45
After farrowing 24 h	18.4	18.4	0.32	0.41
Weaning	17.0	16.9	0.30	0.52
Gainz	0.6	0.5	0.15	0.98
Loss 1[z]	-1.5	-1.4	0.17	0.73
Loss 2[z]	-1.4	-1.5	0.05	0.35
Litter size (head)				
Total birth	13.0	12.5	0.51	0.56
Total alive	11.9	11.6	0.38	0.35
Stillbirth	0.7	0.6	0.24	0.29
Mummification	0.4	0.3	0.25	0.68
Survival (%)	91.2	93.2	2.41	0.43

SEM, standard error of means; ADFI, average daily feed intake.

[x] CON, basal diet; ALA, CON + 0.10% δ-aminolevulinic acid, n = 8.

[y] Body weight difference: Gain, initial to before farrowing; Loss 1, before farrowing to after farrowing; Loss 2, after farrowing to weaning.

[z] Back fat difference: Gain, initial to before farrowing; Loss 1, before farrowing to after farrowing; Loss 2, after farrowing to weaning.

a, b: Means in a row with different letters are significantly different ($p < 0.05$).

Growth performance of piglets

The birth weight of piglets was increased ($p < 0.05$) by supplementation of ALA in the sows' diet (Table 3). No differences were observed in BW, average daily gain (ADG), or survival of piglets during the lactation period ($p > 0.05$).

Table 3. Effect of δ-ALA supplementation on growth performance in suckling piglets[y].

Item	CON	ALA	SEM	p-value
Initial[z] (head)	11.00	11.00	-	-
Finish (head)	10.10	10.20	0.18	0.60
Survival (%)	91.82	92.73	1.76	0.63
Body weight (kg)				
0 d (birth)	1.23b	1.27a	0.01	0.02
14 d	3.17	3.20	0.04	0.17
28 d (wean)	7.41	7.72	0.18	0.11
Average daily gain (g)				
0 - 14 d	138	137	3.51	0.63
0 - 28 d	238	248	4.22	0.14

SEM, standard error of means.

[y] CON, basal diet; ALA, CON + 0.10% δ-aminolevulinic acid, n = 8.

[z] Initial: Piglets were cross-fostered to balance the number of suckling piglets within 3 days, however, the cross-fostered pigs were only collected growth performance data, not blood parameters.

a, b: Means in a row with different letters are significantly different ($p < 0.05$).

Blood profiles of sows and piglets

Before farrowing, RBC counts were increased ($p < 0.05$) in sows, when ALA was supplemented in the diet, however, the concentration of Fe was not affected during the experiment ($p > 0.05$) (Table 4). Additionally, the number of RBC on day 28 were observed in weaning piglets born to sows that received 0.1% ALA in the lactation diet ($p < 0.05$) (Table 5). Although Fe concentration in the piglets showed a trend in increment on day 28 ($p = 0.09$). However, from day 0 to day 14, differences were not observed in treatment groups.

Table 4. Effect of δ-ALA supplementation on blood profile in sows[z].

Item	CON	ALA	SEM	p-value
RBC ($10^{12} \cdot L^{-1}$)				
Gestation d 100	6.57	6.60	0.25	0.38
Before farrowing	6.40b	7.33a	0.17	0.04
Lactation d 1	6.59	6.68	0.32	0.99
Lactation d 28	6.44	6.70	0.20	0.21
Iron ($\mu g \cdot dL^{-1}$)				
Gestation d 100	201.0	200.8	10.5	0.93
Before farrowing	195.1	206.5	8.87	0.44
Lactation d 1	200.4	206.3	6.12	0.23
Lactation d 28	201.2	210.3	7.14	0.07

SEM, standard error of means.

[z] CON, basal diet; ALA, CON + 0.10% δ-aminolevulinic acid; RBC, red blood cell. n = 8.

a, b: Means in a row with different letters are significantly different ($p < 0.05$).

Table 5. Effect of δ-ALA supplementation on blood profile in piglets[z].

Item	CON	ALA	SEM	p-value
RBC (10^{12}·L^{-1})				
0 d	3.75	4.02	0.19	0.26
14 d	5.40	5.61	0.34	0.82
28 d	6.74b	7.28a	0.24	0.02
Iron (μg·dL^{-1})				
0 d	27.01	28.66	8.44	0.11
14 d	68.42	71.69	2.13	0.62
28 d	143.56	148.03	5.89	0.09

SEM, standard error of means.

[z] CON, basal diet; ALA, CON + 0.10% δ-aminolevulinic acid; RBC, red blood cell. n = 8.

a, b: Means in a row with different letters are significantly different ($p < 0.05$).

Discussion

Growth performance of sows and piglets

Recently, ALA is widely used as a feed additive in animal feed, because of its beneficial effects on growth performance, nutrient digestibility, immunity, and blood Fe status (Sato et al., 2012; Pedrosa-Gerasmio et al., 2019; Chen et al., 2020). In the present study, dietary supplementation with ALA improved the ADFI of sows during lactation, the result was consistent with the previous study, which observed that the ADFI and BFT loss was improved by feeding ALA to lactation sows (Wang et al., 2009). Moreover, some previous studies also indicated that the ALA had positive effects on improving the growth performance of sows (Cho and Kim, 2011; Wang and Kim, 2012). Because ALA is closely associated with the synthesis of heme which is the main stable structure of the hemoglobin molecule, subsequently it plays the same role in oxygen and carbon dioxide transport. Supplementation of ALA was effective to enhance the blood oxygen contents, activate cell functions, and accelerate intracellular redox reactions (Fujii et al., 2017; Chernova and Smith, 2020). In the present study, supplementation of ALA to lactating sows was conducive to the recovery of self-metabolism of postpartum sows as it improved feed intake of sows. However, Wang and Kim (2012) demonstrated that the sows fed diets containing 90 mg·kg^{-1} ALA had no effect on feed intake during the lactation period of sows. Similarly, Yan and Kim (2011) and Chen et al. (2008a) reported that supplementation of ALA with different levels (3 mg·kg^{-1} and 0, 5, 10, and 15 mg·kg^{-1}, respectively) in weaning pig diets had no effects on feed intake. The discrepancies in results might be due to different growth phases, additive doses, and environmental conditions during the experiment.

Blood profiles of sows and suckling piglets

Additionally, the birth weight of suckling piglets was higher when sows fed with ALA, which indicated dietary supplementation with ALA had a positive effect on the growth performance of their offspring. Similarly, Lee et al. (2016) reported that supplementation with different levels of ALA in lactation sows' diets significantly improved BW and ADG of suckling pigs. In line with our findings, Wang and Kim (2012) also reported that supplementation of 90 mg·kg^{-1} ALA to sows' diet increased the BW of suckling piglets on day 7 and 21 of postpartum and enhanced the ADG of suckling piglets during

0 to 7 days. Hossain et al. (2016) demonstrated that when post-weaning piglets fed with 0.5 or 1 $g \cdot kg^{-1}$ ALA increased their growth performance (BW, ADG, and body weight gain/feed intake) as compared to the piglets fed on the control diet. In addition, Chen et al. (2008a) reported that diet supplemented with ALA (15 $mg \cdot kg^{-1}$) improved the ADG of weaned piglets challenged by *Escherichia coli lipopolysaccharide*. On the contrary, no significant differences were observed in response to the supplementation of ALA in weaning pigs (Mateo et al., 2006) and broilers (Chen et al., 2008b). The inconsistent results of the above studies might be due to the different ages of animals, the feeding form of additive, and different species.

Some studies indicated that ALA as a vital precursor for biosynthesis tetrapyrrole played an important role in controlling heme synthesis (Xiong et al., 2018). Also, heme has a unique property, namely a Fe molecule can be combined within a tetrapyrrole (Battersby, 2000; Terry and Smith, 2013), which allows heme to exert activity both as an electron carrier and a catalyst for redox reactions (Ajioka et al., 2006). Hence, heme was the major functional form of Fe (iron-heme) (Smith and Wilks, 2012). Adding ALA to the diet may increase the concentrations of heme and iron-heme, thereby improving the utilization of Fe (Anderson, 2001). In the current study, the addition of ALA in sows' diet increased the RBC counts in sows before farrowing and maintained the counts of RBC in sows' blood closer to initial values. This was similar to the findings of Wang et al. (2009) and Mateo et al. (2006). Moreover, the RBC concentration of piglets also increased in response to the treatment effect of ALA on day 28, which agreed with Hossain et al. (2016) who reported that supplementation of ALA in weaning piglets' diet improved plasma RBC concentration of weaning pigs. Similarly, Yan and Kim (2011) demonstrated that dietary ALA supplementation increased RBC counts in weaning pigs. It has been revealed that feeding ALA to animals had positive effects on the synthesis of blood cells and RBC (Chen et al., 2008a; Hossain et al., 2016).

Besides, the RBC count is an important indicator for assessing Fe concentration in the blood (Tang et al., 2015). With regards to serum concentrations of Fe, no significant effect was observed in this study. Nevertheless, the concentration of Fe in suckling piglets showed trends in increment until weaning, which is in line with the previous report from Lee et al. (2016), who reported that dietary supplementation with ALA to lactation sows increased Fe concentration in the blood of suckling pigs. The finding of the present study corroborated with previous studies which demonstrated that the Fe concentration was increased when weaning pigs were fed diet containing ALA (Chen et al., 2008a; Wang et al., 2009). Wang and Kim (2012) reported similar results that dietary treatments with ALA enhanced the plasma Fe concentrations of piglets. Although in the present study, the Fe concentration was not improved significantly between the two treatment groups, however, the increasing trend of Fe status may reduce the incidence rate of Fe-deficiency anemia and improve the growth performance of piglets.

Conclusion

The results of this study revealed that the supplementation of ALA in sows' diet from day 100 of gestation to lactation improved the ADFI during the lactation and improved the RBC counts of sows. Meanwhile, the supplementation of ALA to the sows' diet had positive effects on suckling piglets on birth weight and blood RBC levels. However, the iron status of piglets in the two treatment groups was similar.

Conflict of Interests

No potential conflict of interest relevant to this article was reported.

Authors Information

Qianqian Zhang, https://orcid.org/0000-0003-3442-4461

Yanjiao Li, https://orcid.org/0000-0002-7145-9578

In Ho Kim, https://orcid.org/0000-0001-6652-2504

References

Ajioka RS, Phillips JD, Kushner JP. 2006. Biosynthesis of heme in mammals. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research 1763:723-736.

Anderson KE, Sassa S, Bishop DF, Desnick RJ. 2001. Disorders of heme biosynthesis: X-linked sideroblastic anemias and the porphyrias. pp. 2991-3062. In Metabolic and Molecular Bases of Inherited Disease edited by Scriver C, Beaudet A, Sly W, Valle D. McGraw-Hill, New York, USA.

Antonides A, Schoonderwoerd AC, Scholz G, Berg BM, Nordquist RE, van der Staay FJ. 2015. Pre-weaning dietary Fe deficiency impairs spatial learning and memory in the cognitive holeboard task in piglets. Frontiers in Behavioral Neuroscience 9:291.

Battersby AR. 2000. Tetrapyrroles: The pigments of life. Natural Product Reports 17:507-526.

Buffler M, Becker C, Windisch WM. 2017. Effects of different iron supply to pregnant sows (*Sus scrofa domestica* L.) on reproductive performance as well as iron status of new-born piglets. Archives of Animal Nutrition 71:219-230.

Chen J, Wang Y, Guo X, Rao D, Zhou W, Zheng P, Ma Y. 2020. Efficient bioproduction of 5-aminolevulinic acid, a promising biostimulant and nutrient, from renewable bioresources by engineered Corynebacterium glutamicum. Biotechnology for Biofuels 13:41.

Chen YJ, Kim IH, Cho JH, Min BJ, Yoo JS, Wang Q. 2008a. Effect of δ-aminolevulinic acid on growth performance, nutrient digestibility, blood parameters and the immune response of weanling pigs challenged with Escherichia coli lipopolysaccharide. Livestock Science 114:108-116.

Chen YJ, Kim IH, Cho JH, Yoo JS, Kim HJ, Shin SO. 2008b. Utilization of delta-aminolevulinic acid for livestock: Blood characteristics and immune organ weight in broilers. Journal of Animal and Feed Science 17:215-223.

Chernova T, Smith AG. 2020. HEME IN BRAIN FUNCTIONS: POSITIVE AND NEGATIVE ROLES. In HEME BIOLOGY: Heme Acts as a Versatile Signaling Molecule Regulating Diverse Biological Processes 2020:113-161.

Cho JH, Kim IH. 2011. δ-Aminolevulinic acid (ALA) as a potential feed additive in pig: A review. Journal of Animal and Veterinary Advances 10:1627-1631.

Frazer DM, Anderson GJ. 2005. Iron imports. I. Intestinal iron absorption and its regulation. American Journal of Physiology-Gastrointestinal and Liver Physiology 289:G631-G635.

Fujii C, Miyashita K, Mitsuishi M, Sato M, Fujii K, Inoue H, Nakajima M. 2017. Treatment of sarcopenia and glucose intolerance through mitochondrial activation by 5-aminolevulinic acid. Scientific Reports 7:4013.

Haas JD, Brownlie IVT. 2001. Iron deficiency and reduced work capacity: A critical review of the research to determine a causal relationship. The Journal of Nutrition 131:676S-690S.

Hoque MR, Ahn JM. 2021. Effects of flaxseed oil supplementation on lactating sows and their offspring. Korean Journal of Agricultural Science 48:11-19. [in Korean]

Hossain MM, Park JW, Kim IH. 2016. δ-Aminolevulinic acid, and lactulose supplements in weaned piglets diet: Effects on performance, fecal microbiota, and *in-vitro* noxious gas emissions. Livestock Science 183:84-91.

Kang Z, Zhang J, Zhou J, Qi Q, Du G, Chen J. 2012. Recent advances in microbial production of δ-aminolevulinic acid and vitamin B12. Biotechnology Advances 30:1533-1542.

Kommera SK, Mateo RD, Neher FJ, Kim SW. 2006. Phytobiotics and organic acids as potential alternatives to the use of antibiotics in nursery pig diets. Asian-Australasian Journal of Animal Science 19:1784-1789.

Lee SI, Li TS, Kim IH. 2016. Dietary supplementation of delta-aminolevulinic acid to lactating sows improves growth performance and concentration of iron and hemoglobin of suckling piglets. Indian Journal of Animal Science 86:781-785.

Mateo RD, Morrow JL, Dailey JW, Ji F, Kim SW. 2006. Use of δ-aminolevulinic acid in swine diet: Effect on growth performance, behavioral characteristics and hematological/immune status in nursery pigs. Asian-Australasian Journal of Animal Science 19:97-101.

Min BJ, Hong JW, Kwon OS, Kang DK, Kim IH. 2004. Influence of dietary δ-aminolevulinic acid supplement on growth performance and hematological changes in weaned pigs. Journal of the Korean Society of Food Science and Nutrition 33:1606-1610. [in Korean]

NRC (National Research Council). 2012. Nutrient requirements of swine. 11th Rev. ed. National Academy Press, Washington, D.C., USA.

Ogun AS, Valentine M. 2019. Biochemistry, heme synthesis. StatPearls, Treasure Island, FL, USA.

Palade LM, Habeanu M, Marin DE, Chedea VS, Pistol GC, Grosu IA, Taranu I. 2019. Effect of dietary hemp seed on oxidative status in sows during late gestation and lactation and their offspring. Animals 9:194.

Pedrosa-Gerasmio IR, Kondo H, Hirono I. 2019. Dietary 5-aminolevulinic acid enhances adenosine triphosphate production, ecdysis and immune response in Pacific white shrimp, *Litopenaeus vannamei* (Boone). Aquacul Ture Research 50:1131-1141.

Phour M, Ghai A, Rose G, Dhull N, Sindhu SS. 2018. Role of aminolevulinic acid in stress adaptation and crop productivity. Internal Journal Current Microbiology Applied Science 7:1516-1524.

Sato K, Matsushita K, Takahashi K, Aoki M, Fuziwara J, Miyanari S, Kamada T. 2012. Dietary supplementation with 5-aminolevulinic acid modulates growth performance and inflammatory responses in broiler chickens. Poultry Science 91:1582-1589.

Smith AD, Wilk A. 2012. Extracellular heme uptake and the challenges of bacterial cell membranes. Current Topics Membrances 69:359-392.

Sonhom R, Thepsithar C, Jongsareejit B. 2012. High level production of 5-aminolevulinic acid by *Propionibacterium acidipropionici* grown in a low-cost medium. Biotechnology Letters 34:1667-1672.

Tang N, Zhu Y, Zhuang H. 2015. Antioxidant and anti-anemia activity of heme iron obtained from bovine hemoglobin. Food Science and Biotechnology 24:635-642.

Terry MJ, Smith AG. 2013. A model for tetrapyrrole synthesis as the primary mechanism for plastid-to-nucleus signaling during chloroplast biogenesis. Frontiers Plant Science 4:14.

Val-Laillet D, Elmore JS, Baines D, Naylor P, Naylor R. 2018. Long-term exposure to sensory feed additives during the gestational and postnatal periods affects sows' colostrum and milk sensory profiles, piglets' growth, and feed intake. Journal of Animal Science 96:3233-3248.

Wan D, Zhang YM, Wu X, Lin X, Shu XG, Zhou XH, Li Y. 2018. Maternal dietary supplementation with ferrous N-carbamylglycinate chelate affects sow reproductive performance and iron status of neonatal piglets. Animal 12:1372-1379.

Wang JP, Kim HJ, Chen YJ, Yoo JS, Cho JH, Kang DK, Kim IH. 2009. Effects of delta-aminolevulinic acid and vitamin C supplementation on feed intake, backfat, and iron status in sows1. Journal of Animal Science 87:3589-3595.

Wang JP, Kim IH. 2012. Effects of iron injection at birth on neonatal iron status in young pigs from first-parity sows fed delta-aminolevulinic acid. Animal Feed Science and Technology 178:151-157.

Wang JP, Yan L, Lee JH, Zhou TX, Kim IH. 2011. Effects of dietary delta-aminolevulinic acid and vitamin C on growth performance, immune organ weight and ferrum status in broilerchicks. Livestock Science 135:148-152.

Xiong JL, Wang HC, Tan XY, Zhang CL, Naeem MS. 2018. 5-aminolevulinic acid improves salt tolerance mediated by regulation of tetrapyrrole and proline metabolism in *Brassica napus* L. seedlings under NaCl stress. Plant Physiology Biochemistry 124:88-99.

Yan L, Kim IH. 2011. Evaluation of dietary supplementation of delta-aminolevulinic acid and chitooligosaccharide on growth performance, nutrient digestibility, blood characteristics, and fecal microbial shedding in weaned pigs. Animal Feed Science and Technology 169:275-280.

Yan L, Lee JH, Meng QW, Ao X, Kim IH. 2010. Evaluation of dietary supplementation of delta-aminolevulinic acid and chito-oligosaccharide on production performance, egg quality and hematological characteristics in laying hens. Asian-Australasian Journal of Animal Science 23:1028-1033.

Youdim MBH, Gerlach M, Riederer P. 2009. Iron deficiency and excess in the brain: Implications for cognitive impairment and neurodegeneration. pp. 95-123. In Iron Deficiency and Overload: Bacic Biology to Clinical Medicine edited by Yehuda S, Mostofsky DI. Humana Press, Totowa, NJ, USA.