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IMPORTANCE OF GLUTAMINE AND METHIONINE IN GROWTH PERFORMANCE, VILLUS CHARACTERISTICS, AND PRESENCE OF INTESTINAL POLYAMINES IN WEANED PIGLETS

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ABSTRACT

Glutamine (Gln) and methionine (Met) are involved in the synthesis of polyamines, which are essential for the functioning of intestinal epithelial cells of weaned piglets (*Sus scrofa domestica* L.). Two experiments were conducted with 21-day-weaned piglets. In the first, the dietary inclusion of Gln (0 and 1.5 %) and Met (0.05 and 1.05 %) was evaluated during the first post-weaning week. Villus height (VH), Lieberkühn's crypt depth (LCD), putrescine, spermidine, and spermine concentration, and total polyamines in the duodenum, jejunum, and ileum were measured. The average daily gain (ADG), average daily feed intake (ADFI), and feed efficiency (FE) were calculated. A randomized complete block design with a 2 × 2 factorial arrangement was used. In the second experiment, the addition of glutamine at four levels (0, 0.7, 1.4, and 2.1 %) in the diet was evaluated for three post-weaning weeks. ADG, ADFI, and FE were measured, and a randomized complete block design was used. In the first experiment, glutamine and methionine levels showed no effect on VH and LCD ($p > 0.05$). The concentration of spermidine and total polyamines in the jejunum improved ($p \leq 0.05$) with glutamine. Regarding growth performance, the level of 1.5 % glutamine in the diet improved the values of ADG and FE ($p \leq 0.05$), without affecting ADFI ($p > 0.05$). In the second experiment, glutamine levels increased ADG and FE ($p \leq 0.01$) during the first week, without modifying ADFI ($p > 0.05$); growth performance in the second and third weeks was similar ($p > 0.05$).

Keywords: functional amino acids, intestinal integrity and functionality.

INTRODUCTION

Weaning causes economic losses in pig farms; piglets *(Sus scrofa domestica* L.) in the first week post-weaning lose weight, consume little feed, and have diarrhea (Cranwell, 1995; Campbell *et al*., 2013). A possible cause of these negative effects is the atrophy of intestinal villi, since the shedding of intestinal cells is greater than their renewal, which decreases the digestion and absorption of nutrients (Pluske *et al*., 1997; Campbell *et al*., 2013).

Polyamines are essential for the growth and proliferation of intestinal epithelial cells by increasing their maturation and renewal (Johnson, 1996; Kusano *et al*., 2008; Flynn *et al*., 2009). Putrescine, spermine, and spermidine are polyamines from colostrum and sow's milk that contribute to gut maturation in lactating piglets (Cheng *et al*., 2006). Low concentration or absence of polyamines in the diet of piglets generates changes in the function and structure of the intestine after weaning (Rezaei *et al*., 2016).

Glutamine (Gln) and methionine (Met) participate in polyamine synthesis (Wu *et al*., 1997; Rezaei *et al*., 2013). Gln is a non-essential amino acid (AA), but in situations of prolonged stress (weaning or acute illness), it is not synthesized in sufficient quantity, becoming a conditionally essential AA (Wang *et al*., 2009; Wu *et al*., 2014). As for Met, Shoveller *et al*. (2005) and Wu *et al*. (2014) indicate that it is a sulfur-branched essential AA whose main function is to initiate protein synthesis. In order to reduce weaning stress, the use of antibiotics, probiotics, prebiotics, and even the addition of AA in the diet has been studied (Campbell *et al*., 2013).

Gln is the AA with the most beneficial post-weaning effects, as it is versatile in cell physiology and metabolism (Wu *et al*., 2007). Gln is abundant in the 39 proteins of living plant and animal tissues, but there is no established requirement to include it in balanced feed for pigs at any stage. However, recent studies indicate that the addition of 1 % Gln in the diet prevents intestinal atrophy and improves immune function, as well as the performance of weaned piglets (Li *et al*., 2007). However, the combined effect that Gln and Met have on the diet of weaned piglets is not completely clear.

In the present study, the response of Gln and Met addition was evaluated, individually and combined, in diets for weaned piglets on growth performance, intestinal villus length, and intestinal polyamines concentration in the first week after weaning.

MATERIALS AND METHODS

The present research was conducted at the Swine Experimental Unit of the Institute of Agricultural Sciences of the Autonomous University of Baja California, Mexico. Animal handling was carried out in accordance with the ethical and biosafety standards of the Council for International Organizations of Medical Sciences (CIOMS, 1986), complying with the Mexican standard (NOM-062-ZOO-1999) for the use of animals in experimentation (DOF, 2001).

Experiment 1

Eighty piglets [Yorkshire × (Landrace × Duroc)], 21 days old, were randomly distributed in four diets (1: addition of 0 % Gln and 0.05 % Met; 2: 1.5 % Gln and 0.05 % Met; 3: 0 % Gln and 1.05 % Met; and 4: 1.5 % Gln and 1.05 % Met) (Table 1) with five replicates. The experimental unit consisted of four animals of similar weight and sex, and a randomized complete block design with a 2 × 2 factorial arrangement was used. The animals were housed in weaning cages with metal walls (120 × 110 cm base, 70 cm height), plastic floors, and automatic waterers, with free access to water and feed.

Table 1. Composition of the experimental diets for piglets (*Sus scrofa domestica* L.) (Experiment 1).

Ingredients (%)	Control	Glutamine	Methionine	Gln + Met
Wheat	66.8	66.8	66.8	66.8
Soybean meal (PC 47.5 %)	27	27	27	27
L-lysine	0.35	0.35	0.35	0.35
L-threonine	0.1	0.1	0.1	0.1
DL-methionine	0.05	0.05	1.05	1.05
L-glutamine	0	1.5	0	1.5
Calcium carbonate	1.26	1.26	1.26	1.26
Dicalcium phosphate	1.24	1.24	1.24	1.24
Iodized salt	0.25	0.25	0.25	0.25
Antibiotic	0.1	0.1	0.1	0.1
Copper sulfate	0.05	0.05	0.05	0.05
Starch	2.5	1	1.5	0
Vitamins and minerals*	0.3	0.3	0.3	0.3
Total	100	100	100	100
	Calculated analysis			
Metabolizable energy (Mcal kg^{-1})	3.17	3.17	3.17	3.1
Protein	20.78	20.78	20.78	20.78
True digestible lysine	1.37	1.37	1.37	1.37
True digestible threonine	0.87	0.87	0.87	0.87
Methionine + true digestible cysteine	0.38	0.38	1.36	1.36
Calcium	0.8	0.8	0.8	0.8
Available phosphorus	0.4	0.4	0.4	0.4

*Vitamin premix composed of 3000 IU vitamin A, 300 IU vitamin D3, 30 IU vitamin E, 2 mg vitamin K, 1.8 mg thiamine, 0.11 mg vitamin B12, 3.6 mg riboflavin, 0.55 mg folic acid, 0.15 mg biotin, 10 mg Ca pantothenate, and 35 mg niacin. **The Cu-free mineral premix was composed of 600 mg Mg, 0.3 % K, 0.35 mg I, 80 mg Fe, 60 mg Mn, 0.15 mg Se, and 40 mg Zn. Penicillin was the antibiotic added.

The growth performance was measured during one week after weaning by means of the following variables: average daily gain (ADG, g: difference between initial weight and weekly weight divided by the seven days of the week), average daily feed intake (ADFI, g d^{-1}: daily difference between feed offered and rejected), and feed efficiency (FE: ratio between ADG and ADFI).

Experiment 2

In this experiment, 112 piglets were used, with a similar age as in experiment 1. The animals were distributed in four diets (Table 2) with different concentrations of Gln added to the diet (1: no Gln; 2: 0.7 %; 3: 1.4 %; and 4: 2.1 %), with seven replicates. The experimental unit had four pigs of similar weight and sex. The experimental design consisted of randomized complete blocks. Diets were formulated to meet nutritional requirements (NRC, 2012) with ingredients and proportions similar to experiment 1,

Table 2. Composition of the experimental diets for piglets (*Sus scrofa domestica* L.) (Experiment 2).

Ingredients (%)	Level 1	Level 2	Level 3	Level 4
Wheat	66.8	66.8	66.8	66.8
Soybean meal (PC 47.5 %)	27	27	27	27
L-lysine	0.35	0.35	0.35	0.35
L-threonine	0.1	0.1	0.1	0.1
DL-methionine	0.05	0.05	0.05	0.05
L-glutamine	0	0.7	1.4	2.1
Calcium carbonate	1.26	1.26	1.26	1.26
Orthophosphate	1.24	1.24	1.24	1.24
Iodized salt	0.25	0.25	0.25	0.25
Copper sulfate	0.05	0.05	0.05	0.05
Starch	2.5	1.9	1.2	0.5
Vitamins and minerals*	0.3	0.3	0.3	0.3
Total	100	100	100	100
Calculated analysis				
Metabolizable energy (Mcal kg^{-1})	3.17	3.17	3.17	3.1
Protein	20.78	20.78	20.78	20.78
True digestible lysine	1.37	1.37	1.37	1.37
True digestible threonine	0.87	0.87	0.87	0.87
Methionine + true digestible cysteine	0.38	0.38	1.36	1.36
Calcium	0.8	0.8	0.8	0.8
Available phosphorus	0.4	0.4	0.4	0.4

*Vitamin premix composed of 3000 IU vitamin A, 300 IU vitamin D3, 30 IU vitamin E, 2 mg vitamin K, 1.8 mg thiamine, 0.11 mg vitamin B12, 3.6 mg riboflavin, 0.55 mg folic acid, 0.15 mg biotin, 10 mg Ca pantothenate, and 35 mg niacin. **The Cu-free mineral premix was composed of 600 mg Mg, 0.3 % K, 0.35 mg I, 80 mg Fe, 60 mg Mn, 0.15 mg Se, and 40 mg Zn. No antibiotics were added.

with the inclusion of Gln at different levels and without antibiotics. Throughout the study, animals had free access to water and feed. Growth performance was measured with the same variables as in experiment 1 for three weeks post-weaning.

Samples from the intestinal tract

After one week of weaning, 20 piglets from Experiment 1 (three males and two females per treatment) were slaughtered by suffocation with carbon dioxide inside a box, and the entire small intestine was extracted. A longitudinal cut was made to eliminate food residues, cleaning with sterile 0.9 % sodium chloride solution and delimiting the duodenum, jejunum, and ileum. Then, from two sites of each segment, intestinal mucosa was sampled and placed in a 2 mL microtube by scraping with a slide. Another sample was also taken for polyamine analysis. Samples were collected within 15 min after animal slaughter, identified, and immediately stored at -82 °C until analysis.

Intestinal histology

Sections of 2 cm^2 of the three segments of the small intestine were obtained and processed by embedding and kerosene cutting and stained with hematoxylin and eosin. Ten measurements of villus height (VH) and crypt depth of Lieberkühn (LCD) were performed with an optical microscope on each intestinal segment in five pigs per treatment.

Polyamine concentration

Polyamines from the intestinal mucosa were isolated according to Clarke and Tyms (1986). To establish the standards for the polyamines putrescine (Put), spermidine (Spd), and spermine (Spn), the procedure adopted followed the methodology described by Bardocz and White (1998). Polyamines were quantified by high-performance liquid chromatography (HPLC) in a chromatograph (Hewlett Packard 1100 series) with a fluorescence detector, an analytical column of 5 mm internal diameter, and a length of 10 cm. The concentration was obtained using the methodology described by Saarinen (2002), using two mobile phases. Mobile phase A consisted of ammonium acetate (Sigma A-8920) 0.2 M, pH 5; HPLC grade water (J.T. Baker 4218-0) and HPLC acetonitrile (J.T. Baker 9017-03) (10:60:30). Mobile phase B was 0.2 M ammonium acetate pH 5, water (J.T. Baker 9180-02), and acetonitrile (J.T. Baker 9180-02) (10:5:85). Excitation and emission fluorescence lengths were 250 and 540 nm, respectively.

The statistical analysis of growth performance, polyamine concentration, and intestinal villus height was performed with the GLM procedure of the SAS version 9.1 statistical program (SAS Institute Inc., Cary, NC, USA), under a randomized complete block design. Any difference whose p was lower than or equal to 0.05 was considered significant.

RESULTS AND DISCUSSION

Experiment 1

The analysis of variance (Table 3) showed that in the first post-weaning week, the addition of 1.5 % Gln to the diet individually improved ($p \leq 0.05$) ADG and FE without affecting ADFI ($p > 0.05$). The inclusion of Met in the diet did not affect growth performance ($p > 0.05$). An interaction ($p \leq 0.01$) between Gln and Met was observed in ADG and FE. The results of previous studies of Gln addition in piglet diets (Wu *et al*., 1996; Haynes *et al*., 2009; Cabrera *et al*., 2013) are inconsistent, with a general tendency to increase ADG and FE, which is consistent with the results observed in the first week of this experiment.

There were no differences (Table 4) in villus height or crypt depth in the different segments of the small intestine ($p \geq 0.059$), which contrasts with results from other researchers (Wu *et al*., 1996; Lee *et al*., 2008; Cabrera *et al*., 2013) where they included Gln to prevent intestinal atrophy in pigs and mice. However, an increasing trend

Table 3. Effect of the addition of glutamine (Gln) and/or methionine (Met) in the first post-weaning week in diets for piglets (*Sus scrofa domestica* L.) on average daily gain (ADG), average daily feed intake (ADFI), and feed efficiency (FE).

Control	Glutamine	Methionine	Gln + Met	Probability value		
				Gln	Met	Gln*Met
		ADG (g d^{-1})				
8.0^{c} ± 0.01	60^{a†} ± 0.01	37^{b} ± 0.01	32^{b} ± 0.01	0.006	0.894	0.001
		ADFI (g d^{-1})				
109 ± 0.01	121 ± 0.01	120 ± 0.01	121 ± 0.19	0.112	0.114	0.138
		FE (ADG $ADFI^{-1}$)				
0.14^{c} ± 0.12	0.45^{a†} ± 0.11	0.28^{b} ± 0.13	0.23^{cb} ± 0.11	0.001	0.241	0.001

†Values with different letters on the same line are different ($p \leq 0.05$).

Table 4. Response to the addition of glutamine (Gln) and/or methionine (Met) in the first post-weaning week in piglet (*Sus scrofa domestica* L.) diets on Lieberkühn's crypt depth (LCD) and intestinal villus height (VH).

Segment	Diet 1	Diet 2	Diet 3	Diet 4	Probability		
					Gln	Met	Gln*Met
			Depth (LCD; µm)				
Duodenum	271 ± 38.1	287 ± 12.4	293 ± 12.1	280 ± 26.7	0.336	0.181	0.547
Jejunum	333 ± 28.2	264 ± 14.6	273 ± 12.9	281 ± 37.6	0.257	0.434	0.158
Ileum	293 ± 26.5	276 ± 16.5	267 ± 27.4	234 ± 33.9	0.293	0.162	0.754
			Height (VH; µm)				
Duodenum	259 ± 19.6	303 ± 18.2	320 ± 26.3	317 ± 25.5	0.364	0.108	0.292
Jejunum	272 ± 15.3	325 ± 15.1	291 ± 8.9	281 ± 28.5	0.183	0.417	0.059
Ileum	284 ± 18.9	272 ± 21.1	266 ± 9.1	244 ± 26.2	0.308	0.253	0.803

Diet 1: addition of 0 % Gln and 0.05 % Met; diet 2: 1.5 % Gln and 0.05 % Met; diet 3: 0 % Gln and 1.05 % Met; diet 4: 1.5 % Gln and 1.05 % Met. The mean and standard error of each treatment are presented.

($p \geq 0.059$) in VH in the jejunum was observed. This indicates the need to increase the number of replicates (in the present research there were five replicates with four piglets each per treatment), improve the precision of the measurements, or increase the weeks of evaluation (only the first week, the most critical at weaning, was evaluated) in future research on this subject. The variables analyzed (VH and LCD) indicate the integrity and capacity of the intestine to digest and absorb nutrients. This integrity and capacity are impaired when piglets are weaned (Duan *et al*., 2016). Therefore,

normal maintenance of intestinal morphology by individual inclusion of 1.5 % Gln during the first post-weaning week improves these functions (Baba *et al*., 2005; Basson, 2007; Hou *et al*., 2010).

An increase (Table 5) in the concentration of spermidine (Spd) and total polyamines in the jejunum was observed, presumably due to increased polyamine synthesis in enterocytes. This is a result of increased activity of ornithine decarboxylase, an enzyme responsible for polyamine synthesis (Wu *et al*., 2000a). The intestinal concentration of polyamines would suggest that Gln enhances the activity of epithelial cells (Chen *et al*., 2014). The results indicate that Gln is a conditionally essential AA, especially in stressful situations such as weaning (Wu, 2009; Duan *et al*., 2016).

Table 5. Jejunal concentration of spermidine and total polyamines (mmol g^{-1}) with addition of glutamine (Gln) and/or methionine (Met) to diets for piglets (*Sus scrofa domestica* L.) in the first post-weaning week.

Met (%)	Gln (%)		Mean
	0	1.5	
	Spermidine		
0.05	3.28	4.14	3.71
1.05	3.46	3.58	3.52
Mean	3.37[b]	3.86[a]	
	Total polyamines		
0.05	8.25	9.36	8.81
1.05	8.33	8.76	8.54
Mean	8.29[b]	9.06[†a]	

[†]Means with different letters in the same row are different ($p \leq 0.05$).

Gln is important in the intestinal synthesis of polyamines, essential nutrients for cell division and proliferation. However, weaning piglet diets contain little or no ornithine (direct precursor of polyamines), whose main precursor is arginine (Arg), which is synthesized from Gln (Wu *et al*., 2000b; Wu *et al*., 2014). Polyamine synthesis from Arg is the main pathway for enterocyte turnover during weaning (Rezaei *et al*., 2013). In other words, the absence of polyamines reduces small intestinal turnover. Since it is economically unfeasible to include polyamines in the diet, AA precursors of these essential nutrients must be added (Cheng *et al*., 2006; Pegg, 2008). However, in the present study, a higher concentration of spermidine and total polyamines was observed only with Gln.

Finally, although there was no effect of Met in the present study on growth performance, histology, and intestinal concentration of polyamines, it could be explained because

some authors consider that Met is not metabolized by the intestinal mucosa (Wu *et al*., 1996; Chen *et al*., 2009; Chen *et al*., 2014). However, Stoll *et al*. (1998) reported that approximately 50 % of dietary Met is metabolized in the first intestinal step, originating cysteine. Most of the circulating cysteine is derived from endogenous synthesis.

The activation of polyamine synthesis is facilitated by ornithine decarboxylase (ODC) and S-adenosylmethionine decarboxylase (SAMD). The activities of these enzymes occur within a few hours after feed intake (Moore and Swendseid, 1983; Shoveller *et al*., 2005). The response time of SAMD depends on ODC activity, since SAMD requires putrescine (a product of ODC activity) to form spermidine and spermine (Brosnan and Brosnan, 2006).

In the liver and intestine, SAMD activity reaches its peak before ODC activity, implying that putrescine concentration is insufficient for SAMD to produce spermidine and spermine (Moore and Swendseid, 1983). The coenzyme S-adenosyl methionine, a precursor of SAMD, is composed of adenosine triphosphate (ATP) and Met; therefore, weaning in piglets is a limiting factor for SAMD synthesis, since the organism is in a state of negative energy balance due to low or no feed intake at that stage (Gong *et al*., 2008).

Experiment 2

In the first week after weaning (Table 6), dietary Gln levels increased average daily weight gain ($p \leq 0.0084$) and feed efficiency ($p \leq 0.0103$). The best response was obtained by adding 2.1 %. These results are not related to ADFI but to a higher nutrient absorption (Gln) due to the increase in the concentration of this AA in the feed, since in the first week the intake was similar between diets ($p \leq 0.1933$).

In the second and third post-weaning weeks, no significant differences ($p > 0.05$) were observed between the levels of Gln inclusion in the diet for any variable; however, it influenced ADG and FE (due to greater absorption and better utilization of nutrients) in the first week so that the accumulated weight of the piglets at the end of the study period was 50 % higher ($p \leq 0.001$) than the initial one. In contrast, Wu *et al*. (1996) observed an improvement in FE during the second post-weaning week by adding different doses of Gln at 1 % as the dose of best response, without observing differences in ADG, ADFI, and FE at weeks 1 and 3.

Glutamine is also important for other metabolic processes in animals. Gln, via glutamate, forms α-ketoglutarate, which is involved in the synthesis of oxaloacetate, and in turn, in the formation of glucose via the Krebs cycle (Hou *et al*., 2010). Gln is the main energetic substrate of ATP in constantly multiplying cells: erythrocytes, lymphocytes, macrophages, and renal cells (Wu *et al*., 1996; Rezaei *et al*., 2013). This AA stimulates various growth factors in the damaged mucosa and enhances activity in signaling pathways, which helps repair the intestinal barrier (Wang *et al*., 2008).

The mucosa of the intestinal epithelium is rich in glycoproteins synthesized from glucosamine 6-phosphate, in which Gln participates (Basson, 2007). Therefore, a good supply of glutamine must be ensured in the diet of piglets at weaning. The addition of

Table 6. Response of glutamine (Gln) addition level during the first three post-weaning weeks in diets for piglets (*Sus scrofa domestica* L.) on average daily weight gain (ADG), average daily feed intake (ADFI) and feed efficiency (FE).

Variable	Dietary glutamine level (%)				*p* value
	0	0.7	1.4	2.1	
			First week		
ADG (g)	-10.9 ± 0.01	2.9 ± 0.01	12 ± 0.01	28.9 ± 0.01	0.0084
ADFI (g d^{-1})	119 ± 0.01	129 ± 0.01	130 ± 0.01	135 ± 0.01	0.1933
FE	-0.089 ± 0.02	0.021 ± 0.03	0.094 ± 0.06	0.21 ± 0.08	0.0103
			Second week		
ADG (g)	123 ± 0.01	122 ± 0.01	135 ± 0.01	142 ± 0.01	0.8266
ADFI (g d^{-1})	241 ± 0.01	243 ± 0.01	218 ± 0.01	214 ± 0.01	0.2979
FE	0.52 ± 0.01	0.49 ± 0.01	0.63 ± 0.01	0.67 ± 0.01	0.2602
			Third week		
ADG (g)	170 ± 0.01	174 ± 0.02	182 ± 0.01	184 ± 0.01	0.9104
ADFI (g d^{-1})	341 ± 0.02	346 ± 0.02	349 ± 0.01	364 ± 0.01	0.7956
FE	0.49 ± 0.03	0.47 ± 0.04	0.51 ± 0.03	0.52 ± 0.02	0.6756
			Accumulated time (day 1 to 21)		
ADG (g)	94 ± 0.01	100 ± 0.01	110 ± 0.01	118 ± 0.01	0.5818
ADFI (g d^{-1})	234 ± 0.01	239 ± 0.01	232 ± 0.01	238 ± 0.01	0.4289
FE	0.31 ± 0.02	0.33 ± 0.03	0.41 ± 0.01	0.47 ± 0.01	0.3154
			Weight (kg)		
Initial	4.71 ± 0.12	4.69 ± 0.13	4.73 ± 0.14	4.72 ± 0.12	0.9969
Final	6.69 ± 0.12	6.77 ± 0.14	7.04 ± 0.14	7.21 ± 0.12	0.0461
Accumulated	1.98 ± 0.01	2.1 ± 0.01	2.31 ± 0.01	2.48 ± 0.01	0.001

Mean and standard error of means are presented for each treatment.

Gln in the diet prevents arginine (Arg) deficiency during weaning in piglets; Arg is an essential AA for young animals and is synthesized from Gln in pigs (Wu *et al*., 1996; Kim and Wu, 2004, 2009; Cabrera *et al*., 2013). Arg reduces plasma urea concentrations, increases plasma creatine and ornithine levels in pigs, and increases polyamine synthesis (Wu *et al*., 2005; Wu *et al*., 2009). Arg requirements in young mammals, including piglets, are particularly high (0.75 %) (He *et al*., 2009).

In summary, dietary addition of Gln prevents intestinal injury and improves nutrient absorption in post-weaned piglets. The effects of Gln are associated with intestinal cell proliferation (indicated by increased polyamines), which improves the growth performance of piglets in the first post-weaning week (Lobley *et al*., 2001).

CONCLUSIONS

The addition of 1.5 % glutamine in the diet improves weight gain and feed efficiency of newly weaned piglets and increases the concentration of spermidine and total

polyamines in the jejunum during the first week after weaning, without affecting the height and depth of intestinal villi or the concentration of putrescine and spermine. The best response to the addition of glutamine on weight gain and feed efficiency was observed in the first post-weaning week. There was no effect of adding methionine to the diet on growth performance, intestinal villi, or polyamine concentration.

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