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META-ANALYSIS OF THE EFFECT OF GLUTAMINE DIETARY INCLUSION ON PRODUCTIVE PERFORMANCE IN PIGLETS

META-ANÁLISIS DEL EFECTO DE LA INCLUSIÓN ALIMENTICIA DE GLUTAMINA SOBRE EL DESEMPEÑO PRODUCTIVO EN LECHONES

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Resumen

La glutamina no es considerada un aminoácido esencial; sin embargo, juega un rol importante en la salud y crecimiento de neonatos y adultos. En lechones el destete genera atrofia de las vellosidades intestinales y retraso en el crecimiento. Varios trabajos han demostrado que la suplementación de glutamina (0,2-2 %) disminuye los efectos adversos del estrés post-destete en lechones. El objetivo de este manuscrito fue evaluar el tamaño de efecto de la suplementación de glutamina sobre el rendimiento productivo de lechones, la consistencia de su efecto y la influencia de otros factores mediante el uso de meta-análisis. La administración de glutamina mejora la conversión alimenticia ($p < 0,001$), y los lechones que reciben glutamina convierten mejor el alimento cuando la suplementación duró entre 7 a 14 días ($p = 0,0023$), pues requieren 121,6 *g* menos de alimento en comparación con el grupo control para hacer 1 *kg* de peso vivo. Cuando la suplementación se realiza por un periodo de 15 a 30 días y 7 a 30 días, el ahorro de alimento es de 70,6 *g* ($p < 0,001$) y 87,3 *g* ($p < 0,001$) por *kg* de peso vivo respectivamente. La ganancia diaria de peso es superior en 20,3 *g/día* ($p = 0,0029$) frente al grupo control entre los 7 a 30 días de suplementación y de 28,2 *g/día* ($p = 0,0002$) entre los 15 a 30 días. La edad y peso del lechón al inicio de la suplementación, el nivel de lisina, la proteína cruda y el número de repeticiones por tratamiento influyen en el efecto de la glutamina sobre las variables evaluadas.

Palabras clave: nutrición, dieta, nutrientes, aminoácidos, cerdos

Abstract

Glutamine is not considered an essential amino acid; however, it plays an important role in the health and growth of neonates and adults. In piglets, weaning generates atrophy of the intestinal villi and growth retardation. Several

studies have shown that glutamine supplementation (0.2-2%) decreases the adverse effects of post-weaning stress in piglets. The aim of this article was to evaluate the effect size of glutamine supplementation on the productive performance of piglets, the consistency of their effect and the influence of other factors through the use of meta-analysis. The administration of glutamine improves the feed conversion (p <0.001), the piglets that receive glutamine convert the feed better when the supplementation lasted between 7 to 14 days (p =0.0023), since they require 121.6 g less of feed in comparison with the control group to make 1 kg of body weight. When the supplementation is done for a period of 15 to 30 days and 7 to 30 days, the saving of feed is 70.6 g (p <0.001) and 87.3 g (p <0.001) per kg of body weight, respectively. The daily weight gain is higher in 20.3 g/day ($p = 0.0029$) compared to the control group between 7 to 30 days of supplementation and 28.2 g/day ($p = 0.0002$) between 15 to 30 days. Age and weight of the piglet at the beginning of the supplementation, level of lysine, crude protein and the number of repetitions per treatment influence on the effect of glutamine on the variables evaluated.
Keywords: nutrition, diet, nutrients, amino acids, pigs

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1 Introduction

Wetting, stress by transportation and thermal stress increase the incidence of diseases, especially when they occur simultaneously (Varley and Wiseman, 2001). During the weaning process, stress can be induced by separation of the mother's piglet, relocation and mixture of litters, additionally there may be sudden changes in the diet that reduce or eliminate the food consumption in the first few hours of life (Wijtten et al., 2011; Campbell et al., 2013). Stress during weaning alters the development of the barrier functions of the gastro-intestinal tract that leads to permanent harmful consequences for intestinal health during the life of the pig (Moeser et al., 2017; Pluske et al., 2018). To combat the negative effects of weaning on the health of piglet, several strategies have been implemented, including weaning age management, environmental conditioning, nutritional manipulation and antibiotic use through a diet (Lalles et al., 2007; Gresse et al., 2017; Solà-Oriol and Gasa, 2017). Antibiotics applied in the diet may allow weaned piglet to reduce pathogenic burden and promote growth (Cromwell, 2002). However, due to the possible contribution of antibiotics to the development of antibiotic-resistant bacterial lines (Smith et al., 2010), their use is being limited. Glutamine dietary supplementation decreases health problems, prevents intestinal atrophy, maintains antioxidant status, decreases incidence of diarrhea, resulting in increased weight gain and improved efficiency (Haynes et al., 2009; Zhong et al., 2011; Wang et al., 2014; Watford, 2015). Similar results have also been reported in broiler chicken (Nassiri Moghaddam and Alizadeh-Ghamsari, 2013; Jazideh et al., 2014; Nascimento et al., 2014; Manvailer et al., 2015; Muro et al., 2015; Olubodun et al., 2015; Ribeiro Jr et al., 2015; Luquetti et al., 2016; Maiorka et al., 2016; Namroud et al., 2017).

Glutamine is the preferred fuel of intestinal cells and the immune system (Horio et al., 2008; Sakiyama et al., 2009; Zhong et al., 2012), supplementation of this amino acid aims to maintain intestinal function through weaning (Curi et al., 2007). Research shows that glutamine is an amino acid that is abundant in physiological fluids and body proteins and is a regulator of the genetic expression (Wu et al., 2011; Xi et al., 2011). Glutamine serves as an energy substrate for rapidly dividing cells and the construction of polypeptides and proteins (Rhoads and Wu, 2009), as it is an essential precursor of bioactive molecules (Boza et al., 2000). Endogenous production of Gln in mammals is insufficient during adverse conditions and there is evidence that Gln supplementation may be necessary in feeding young animals during states of poor nutrition (Wu et al., 1996; Chamorro et al., 2010). Numerous studies have investigated glutamine dietary supplementation in order to improve the productive performance of the piglet. However, several have been the levels of dietary inclusion and experimental circumstances under which these studies have been developed.

The aim of this article was to evaluate the size of Gln supplementation on the productive yield of piglets, the consistency of its effect and the influence of other factors by using the statistical meta-analysis tool.

2 Materials and methods

2.1 Source of information (data)

An electronic search of scientific articles was conducted in double-blind peer-reviewed indexed journals in the following electronic bases: CAB direct, Elsevier biobase-CABS, Google Scholar, MEDLINE, PubMed, Science Direct (Journal), Scopus, Academic Search Complete, CAB Abstract, Directory of Open Access Journals. A combination of keywords was used: glutamine, amino acids, diet, food, nutrition, piglets, weaning and their English equivalents, without date restrictions.

2.2 Inclusion criteria

Items in which glutamine was administered exclusively in piglets through a diet were selected. The articles had to include information regarding the number of experimental units (replications) per treatment, and the experiments needed include at least 2 treatments (including the control group: without Gln), weight and age of the piglet at the beginning of the study period, level of glutamine included in the food and duration of supplementation, level of lysine and raw protein in the food used (covariates). In addition, it should have included at least one of the interest response variables: daily weight gain (GDP), average daily food consumption (CDPA), and food conversion (CA). They should include mean (average) and some measure of variation (standard deviation (SD), standard error (SE)).

Table 1. Descriptive statistics (covariates)

	Average	Minimum	Maximum	Mode
Inclusion level of Gln in food (%)	0.96	0.20	2.00	1.00
Duration of supplementation (days)	16.34	7.00	30.00	14.00
Living weight (kg) onset of the supplementation	6.34	4.96	9.22	5.78
Age of supplementation (kg)	22.91	17.00	28.00	21.00
Lysin level in the diet (%)	1.33	1.17	1.60	1.30
Level of RP in the diet (%)	21.32	18.08	23.74	21.09
N° replications/treatment	5.42	2.00	12.00	3.00
N° replications/control	5.39	2.00	12.00	3.00

RP= Raw protein

2.3 Statistical analysis

A total of 13 scientific articles that met the above-mentioned inclusion criteria were found (Wu et al., 1996; Lee et al., 2003; Domeneghini et al., 2004; Zhou et al., 2006; Zou et al., 2006; Abreu et al., 2010; Hsu et al., 2010; Shan et al., 2012; Xiao et al., 2012; Wang et al., 2014; He et al., 2016; Duttlinger et al., 2019). The data of the variables of interest were obtained from all 13 manuscripts, and it is important to mention that the meta-analysis technique considers all articles that meet the inclusion criteria (13) and does not sample them, as one of its purposes is to have the largest n number (number of repetitions) as possible. MIX 2.0 Pro was used for statistical data processing in Microsoft Excel (Bax, 2016). The size of the effect of glutamine supplementation was determined by mean difference (MD) between the treatment group and the control, with 95% confidence intervals. Heterogeneity was assessed by the inconsistency index $\left(I^2\right)$ (Cochran, 1954; Higgins and Thompson, 2002). If there was heterogeneity, meta-regressions were carried out in order to explain the origin of such variability (Borenstein et al., 2011).

A random effects model was used as recommended by Sauvant et al. (2008). 9 meta-analyses were carried out from the 13 scientific articles (n=1902 animals). The variables analyzed were daily weight gain, average daily food consumption and food conversion. In each variable, 3 meta-analyses were performed according to the duration of glutamine supplementation: 7 to 30 days, 7 to 14 days and 15 to 30 days. This research did not follow the protocols established by PRISMA-P (Moher et al., 2015) as these were developed for human studies. This meta-analysis study follows a methodology of animal science studies, as detailed in several published articles in which meta-analysis was used in swine nutrition (Apple et al., 2007; Kiefer and Sanches, 2009; Sales, 2011; Andretta et al., 2012; Létourneau-Montminy et al., 2012; Remus et al., 2015; Hung et al., 2017; Metzler-Zebeli et al., 2012; Torres-Pitarch et al., 2017; Zeng et al., 2017; Torres-Pitarch et al., 2019).

3 Results

Table 1 summarizes the main descriptive statistics calculated (covariates) from the 13 research articles used. The DWG, ADFC, and FC response variables in each of the evaluated periods are presented in Table 2.

The average size of the effect (expressed in mean difference) of Gln supplementation in piglets on the productive yield are presented in Table 3. The results of the inconsistency index, and heterogeneity test between studies is shown in Table 4.

The results of the meta-regressions to determine the influence of each of the covariates on the pro-

Table 2. Summary of the variables response of productive parameters

Productive parameter	**Meta-analysis**	**Variable summary response**			
		Treatment		Control	
		Mean	SD	Mean	SD
DWG *(kg/day)*	7 to 30 days	0.22	0.12	0.20	0.11
	7 to 14 days	0.16	0.10	0.15	0.09
	15 to 30 days	0.31	0.10	0.29	0.10
ADFC *(kg/day)*	7 to 30 days	0.33	0.17	0.33	0.15
	7 to 14 days	0.25	0.12	0.26	0.10
	15 to 30 days	0.46	0.16	0.44	0.14
FC *(kg/kg)*	7 to 30 days	1.81	0.89	1.94	1.12
	7 to 14 days	1.98	1.08	2.14	1.37
	15 to 30 days	1.51	0.28	1.61	0.32

SD= standard deviation

ductive variables of interest in each period are presented in Table 5 (Gln inclusion level and duration of supplementation); Table 6 (live weight and age when the supplementation started); Table 7 (lysine level and raw protein in the diet) and Table 8 (number of replications).

Table 3. Effect of glutamine supplementation

Productive parameter	Meta-analysis	Effect size			
		MD	CI		*p*
DWG *(kg/day)*	7 to 30 days	0.0203	0.0070	0.0336	0.0029
	7 to 14 days	0.0146	−0.0041	0.0332	0.1252
	15 to 30 days	0.0282	0.0133	0.0431	0.0002
ADFC *(kg/day)*	7 to 30 days	0.0058	−0.0052	0.0168	0.3023
	7 to 14 days	−0.0033	−0.0128	0.0063	0.5030
	15 to 30 days	0.0237	0.0024	0.0450	0.0295
FC *(kg/kg)*	7 to 30 days	−0.0873	−0.1271	−0.0474	0.0000
	7 to 14 days	−0.1216	−0.1999	−0.0433	0.0023
	15 to 30 days	−0.0706	−0.1120	−0.0290	0.0008

MD= mean difference
CI= confidence interval
p = probability value

Table 4. Inconsistency index

Productive parameter	Meta-analysis	I^2 (%)
DWG *(kg/day)*	7 to 30 days	81.78
	7 to 14 days	87.40
	15 to 30 days	36.87
ADFC *(kg/day)*	7 to 30 days	48.75
	7 to 14 days	20.76
	15 to 30 days	45.79
FC *(kg/kg)*	7 to 30 days	21.20
	7 to 14 days	42.33
	15 to 30 days	0.00

4 Discussion

Glutamine works as an energy source for the growth of enterocytes, thus reducing the intestinal wall atrophy and the damage of the intestinal epithelium (Wang et al., 2014, 2015). Piglets receiving Gln food supplementation improve the protection of the intestinal barrier which leads to increased resistance to pathogens (Peng et al., 2004), and increased activity of digestive enzymes (Shan et al., 2012), consequently the increased nutrient utilization and the improvement in the productive performance (Jiang et al., 2009; Johnson and Lay Jr, 2017). The above can be seen in this research paper, as it was found that the food supplementation of Gln improved (p <0.001) the food conversion into piglets in any of the periods evaluated. It emphasizes that the piglets that receive Gln convert the food better when supplementation lasted between 7 to 14 days (MD= -0.1216; p =0.0023). Supplemented piglets require 121.6 *g* less food compared to the control group to make 1 *kg* of body weight between 7 to 14 days. When supplementation was done for a longer period (15 to 30 days) the food savings are 70.6 *g* to make a *kg* of body weight and 87.3 *g* when the Gln was supplemented between 7 to 30 days. With regard to the daily weight gain, Gln causes an increase in gain of 20.3 *g/day* (p =0.0029) over the DWG of the control group between 7 and 30 days of supplementation, and 28.2 *g/day* (p =0.0002) between 15 to 30 days.

The ADFC variable only has a significant increase when Gln administration was 15 to 30 days, consuming an additional 23.7 grams per day compared to the witness group. Similarly, in broiler chickens it was found that food supplementation of glutamine allows a more efficient use of ingested nutrients, improving the productive performance (Namroud et al., 2017), associated with the effect of Gln on the length of intestinal villi (Abdulkarimi et al., 2019). This will require less food to lead pigs to the market weight or shorten the days needed to reach the market weight, representing significant savings for the pig industry. In addition, Gln supplementation has shown to favor the immune system of piglets by ensuring better health and thus preserving nutrients for growth (Johnson et al., 2006; Zhong et al., 2012).

Table 5. Meta-regression for Gln inclusion level (%) duration of supplementation (days)

Productive parameter	Meta-regression	Gln inclusion level (%)				Duration of supplementation (days)			
		Intercept		Regression Coef.		Intercept		Regression Coef.	
		Estimated	p	Estimated	p	Estimated	p	Estimated	p
DWG *(kg/day)*	7 to 30 days	0.024	0.007	0.006	0.503	0.041	<0.001	−0.001	0.002
	7 to 14 days	0.025	0.010	0.005	0.578	0.094	<0.001	−0.007	<0.001
	15 to 30 days	0.014	0.505	0.011	0.577	0.121	0.002	−0.004	0.013
ADFC *(kg/day)*	7 to 30 days	0.003	0.762	−0.003	0.737	−0.019	0.002	0.002	<0.001
	7 to 14 days	0.004	0.700	−0.010	0.372	−0.025	0.064	0.002	0.117
	15 to 30 days	0.048	0.176	−0.025	0.475	0.097	0.018	−0.003	0.069
FC *(kg/kg)*	7 to 30 days	−0.050	0.044	−0.021	0.434	−0.063	0.143	−0.0002	0.927
	7 to 14 days	−0.050	0.051	−0.025	0.456	−0.260	0.260	0.015	0.390
	15 to 30 days	−0.054	0.599	−0.016	0.873	−0.080	0.638	0.0004	0.953

p = probability value

Regarding the heterogeneity between studies, it is reported that only in DWG (7 to 30d and 7 to 14d) the variability is high (> 75%). In the other variables, heterogeneity is between low to moderate (< 50%). In order to explain the variability between studies, meta-regressions were performed between the response variable and each of the co-variables indicated above. Gln inclusion level (%) in the diet for piglets has no impact (p >0.05) on any of the productive variables evaluated. The most commonly used level is 1%; however, the values range from 0.1 a 2%. Studies in chicken report that supplementation of high levels of glutamine negatively affects the production performance because they cause a reduction in the food consumption, as shown in the results found when a 4% level was used. Ad-

Table 6. Meta-regression body weight (kg) and age (days) at the beginning of Gln supplementation

Productive parameter	Meta-regression	Live weight at the beginning of the supplementation (kg)				Age at the beginning of the supplementation (days)			
		Intercept		Coef. Regression		Intercept		Coef. Regression	
		Estimated	*p*	Estimated	*p*	Estimated	*p*	Estimated	*p*
DWG *(kg/day)*	7 to 30 days	−0.086	<0.001	0.019	<0.001	0.043	0.041	−0.001	0.528
	7 to 14 days	−0.138	<0.001	0.029	<0.001	0.020	0.629	0.001	0.797
	15 to 30 days	0.027	0.428	0.000	0.979	0.047	0.229	−0.001	0.589
ADFC *(kg/day)*	7 to 30 days	−0.020	0.118	0.004	0.114	−0.020	0.324	0.001	0.343
	7 to 14 days	−0.015	0.286	0.002	0.449	−0.014	0.586	0.000	0.716
	15 to 30 days	0.030	0.399	−0.001	0.839	0.072	0.119	−0.002	0.284
FC *(kg/kg)*	7 to 30 days	0.124	0.169	−0.030	0.032	0.066	0.386	−0.006	0.074
	7 to 14 days	0.227	0.103	−0.050	0.035	0.415	0.005	−0.025	0.001
	15 to 30 days	0.133	0.415	−0.029	0.209	−0.026	0.860	−0.002	0.767

p = probability value

ditionally, high levels of Gln create an imbalance with the other amino acids in the diet affecting their intestinal absorption, despite the evidence of increased intestinal villi size (Bartell and Batal, 2007).

The duration of supplementation (days) significantly influences (p <0.05) DWG (all evaluated periods) and ADFC (7 to 30 days). The live weight of the piglet at the beginning of the supplementation also has a significant effect (p <0.05) on DWG and FC in periods of 7 to 30 days and 7 to 14 days. It is observed that as the live weight of the piglet increases, the DWG increases and the FC decreases. The body weight values range from 4 to 16 kg with an average of 6.89 kg. The age of the piglet at the beginning of the supplementation only has an influence on FC when the supplementation lasted between 7 to 14 days. Of the studies used, it was found that the age range of the beginning of Gln supplementation is between 17 to 28 days, with 21 days being the most frequent. It is important to consider that natural Gln constitutes only 10% of the amino acid content of the total protein in a conventional pig diet, being necessary the supplementation to achieve maximum growth and facilitate normal functioning, particularly in hypercatabolic states (Wu, 2014) that occur during weaning of piglets due to social and environmental stress (Spreeuwenberg et al., 2001).

Table 7. Meta-regression for lysine level (%) and raw protein in the diet (%)

Productive parameter	Meta-regression	**Lysine level in the diet** (%)				**RP level in diet** (%)			
		Intercept		Regression Coef.		Intercept		Regression Coef.	
		Estimated	*p*	Estimated	*p*	Estimated	*p*	Estimated	*p*
DWG *(kg/day)*	7 to 30 days	−0.145	<0.001	0.126	<0.001	−0.152	<0.001	0.009	<0.001
	7 to 14 days	−0.165	<0.001	0.140	<0.001	−0.215	<0.001	0.012	<0.001
	15 to 30 days	0.185	0.019	−0.118	0.043	0.192	0.015	−0.008	0.036
ADFC *(kg/day)*	7 to 30 days	−0.041	0.335	0.033	0.337	−0.022	0.59	0.001	0.593
	7 to 14 days	−0.028	0.591	0.019	0.654	−0.021	0.643	0.001	0.715
	15 to 30 days	0.183	0.051	−0.121	0.089	0.293	0.008	−0.013	0.014
FC *(kg/kg)*	7 to 30 days	−0.137	0.495	0.052	0.725	−0.716	0.002	0.029	0.004
	7 to 14 days	−0.162	0.482	0.075	0.669	−1.370	<0.001	0.057	<0.001
	15 to 30 days	−0.219	0.721	0.106	0.809	−0.285	0.430	0.010	0.552

p = probability value
RP= Raw protein

Table 8. Meta-regression number of replications

Productive parameter	Meta-regression	Number of replications			
		Intercept		Regression Coef.	
		Estimated	*p*	Estimated	*p*
DWG *(kg/day)*	7 to 30 days	−0.006	0.143	0.005	<0.001
	7 to 14 days	−0.010	0.022	0.006	<0.001
	15 to 30 days	0.030	0.071	−0.001	0.819
ADFC *(kg/day)*	7 to 30 days	0.008	0.209	−0.002	0.153
	7 to 14 days	0.006	0.393	−0.003	0.079
	15 to 30 days	0.064	<0.001	−0.009	0.024
FC *(kg/kg)*	7 to 30 days	−0.036	0.211	−0.007	0.245
	7 to 14 days	−0.032	0.313	−0.009	0.199
	15 to 30 days	−0.070	0.384	0.001	0.972

p = probability value

Dietary formulation factors also have significant effect on DWG, ADFC and FC after the Gln supplementation in piglets. The level of lysine (p <0.05) and raw protein (p <0.05) affects DWG over the 3 periods evaluated. It is evident that as the level of lysine and RP increases the DWG also increases for the periods 7 to 30 days and 7 to 14 days. However, in the period 15 to 30 days there is a reduction in the DWG. In addition, the RP level affects ADFC when supplementation lasted between 15 and 30 days (p =0.014) and FC when Gln administration was from 7 to 30 days (p =0.004) and 7 to 14 days (p <0.001). In this work, the RP and lysine values of the diets used in piglets were between 18 to 23% and 1.17 a 1.6%, respectively. One strategy to improve the use of protein in piglets and prevent intestinal disorders is to reduce the level of raw protein with adequate free amino acid supplementation (synthetic) (Le Floc'h et al., 2018).

Gloaguen et al. (2014) confirms the effectiveness of this strategy and the possibility of formulating diets with low RP levels (13.5%) piglets between 10 and 20 *kg* of body weight. Additionally, diets with moderate protein restriction (13-15.3%) proved to be beneficial for the health of the gut microbiota, metabolic activity in the large intestine and for the improvement in the function of the piglet intestinal barrier (Peng et al., 2017). The reduction of RP content allows to reduce the nitrogen consumption and prevents the excess of amino acids, therefore, prevents metabolic overloads.

Finally, the number of replications influenced the DWG in the periods 7 to 30 (p <0.001) and 7 to 14 days (p <0.001), as well as the ADFC when supplementation lasted between 15 and 30 days (p =0.024). The number of replications in the different works used for this study ranged from 2 to 12, 3 being the most used. This confirms the importance stated by Aaron and Hays (2004) of considering an appropriate number of individuals to be used in experimental studies in pigs. In the face of an inadequate number of replications per treatment, significant differences may not be detected, leading to a waste of time and money for the researcher.

5 Conclusion

Glutamine supplementation improves the productive performance in piglets, being an excellent option to be used in weaning diets to reduce the stress occurring in this stage.

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