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ORIGINAL ARTICLE

Short-term supplementation of isocaloric meals with L-tryptophan affects pig growth

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Abstract L-Tryptophan (Trp) and some of its metabolites regulate the circadian rhythm in mammals. We aimed to investigate the effects of short-term supplementation of Trp in isocaloric meals on growth performance using the parameters of multiple blood biomarkers and free amino acids in growing pigs. A total of 32 Landrace × Yorkshire barrows with a mean body weight of 8.64 (±1.13) kg were randomly assigned to four groups and then fed with various concentrations of Trp diets daily. Our results showed that sequential supplementation of different concentrations of Trp in isocaloric meals decreased the feed:gain (F:G) ratio ($P = 0.079$) and plasma urea and albumin ($P = 0.019$), whereas the level of total protein did not. Among the essential and conditionally essential amino acids, the concentrations of histidine, isoleucine, proline, threonine, arginine, and valine in the plasma decreased ($P < 0.05$), whereas the concentrations of Trp, glycine, serine, and methionine increased ($P < 0.01$). In addition, concentrations of branched chain amino acids also significantly decreased ($P = 0.004$), while the rate of conversion of Trp to branched chain amino acids increased ($P < 0.001$). Taken together, we show that administration of a high concentration of Trp in breakfast with decreasing concentrations of Trp in lunch and dinner positively affected feed utilization and improved feed efficiency, at least in part, through the optimization of amino acid interconversions and nitrogen utilization.

Keywords Tryptophan · Feed efficiency · Sequence of isocaloric meals · Amino acid profile · Pig

Introduction

L-Tryptophan (Trp) is an essential amino acid and a nutrient additive in the corn–soybean based diet for pigs. More than 90% of the Trp is degraded to acetyl acid and pyruvic acid, which then participates in the metabolic cycle for energy. Catalyzed by Trp hydroxylase, 5% of Trp is used

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to produce the neurotransmitters 5-hydroxy-Trp generated serotonin (5-HT) and melatonin in the brain. 5-HT and melatonin participate in a variety of physiological processes, including regulation of appetite, digestive process, gastrointestinal motility, circadian rhythm, and emotional response control (Sodhi and Sanders-Bush 2004). Thus, Trp and its metabolites have essential roles in various physiological functions in both animals and humans.

Imbalance of Trp metabolism can lead to symptoms such as decrease in feed intake and growth rate (Moehn et al. 2012). A metabolite of Trp, 6-sulfatoxy-melatonin, which can be detected in the urine, is an indicator of change of circadian rhythm. In urine, 6-sulfatoxy-melatonin can be measured with acrophase (maximum) at 06:00 AM when compared to the change caused by Trp concentrations in blood with acrophase (maximum) at around 03:00 AM in the breast-fed infant (Cubero et al. 2005). Overall, Trp in the milk might be one of the key compounds that regulates the circadian clock in infants, as it is converted, in part, to melatonin. In growing pigs, the optimum Trp:lysine ratio is 0.17 (Susenbeth 2006). Additionally, Trp and melatonin in the blood have been shown to affect the circadian rhythm and are important for sustaining the synchronization of neuromodulatory process and providing the growing animal a physiological advantage in performance and health. A nutritional study in humans showed that the intake of Trp at breakfast affected the circadian typology and sleep habits of children and young adults aged 2–25 years (Harada et al. 2013).

In a previous study, we found that a high level of dietary Trp (0.7%) negatively affects the small intestinal structure (Tossou et al. 2016). In this study, we hypothesized that a sequence of isocaloric meals with different concentrations of Trp would positively affect feed efficiency through optimization of amino acid and nitrogen utilization in growing pigs. We determined the effects of short-term supplementation of different amounts of Trp in isocaloric meals with regard to the growth performance, blood parameters, and free amino acid profiles in growing pigs.

Materials and methods

The animal experiments were performed following the guidelines for animal welfare, and the protocol was reviewed and approved by the Institute of Subtropical Agriculture (ISA), the Chinese Academy of Sciences (CSC).

A total of 32 Landrace × Yorkshire barrows with a mean body weight of 8.64 ± 1.13 kg were randomly assigned to four groups: Trp15 (control), Trp60, Trp90-30, and Trp30-90. Each pig represented a replicate and was housed in an individual pen. Four diets were prepared containing 0.15, 0.30, 0.60, and 0.90% Trp and were designated Trp15, Trp30, Trp60, and Trp90, respectively (Table 1). The barrows in the Trp15 and Trp60 groups were fed the Trp15 and Trp60 diets, respectively, at 08:00, 12:00, and 17:00 h daily. Pigs in the Trp90-30 group were fed with the Trp90 diet at 08:00 h, the Trp60 diet at 12:00 h, and the Trp30 diet at 17:00 h, while the Trp30-90 group was fed with the Trp30 diet at 08:00 h, the Trp60 diet at 12:00 h, and the Trp90 diet at 17:00 h (Table 2). The pigs were feed restricted, and the daily food amount was adjusted to approximately 1/3 of an individual's total body weight (BW) and was provided over the course of three meals daily for 14 days with equal amounts of feed given at each meal for each group. All of the diets were based on maize and soybean, and followed the National Research Council requirements for swine (NRC 2012), and the nutrients administered were adequate.

Table 1 Components of experimental diets provided to pigs (on an as-fed basis)

Ingredients	Trp15	Trp30	Trp60	Trp90
Corn (8% CP; <13% H_2O)	64.61	64.96	65.12	65.37
Soybean meal (43% CP)	19.50	19.00	18.20	17.30
Whey powder (11% CP)	4.50	4.50	4.50	4.50
Fish meal 279	5.50	5.50	5.50	5.50
Soybean oil	2.40	2.40	2.70	3.00
Lysine	0.55	0.55	0.58	0.60
Methionine	0.18	0.18	0.18	0.20
Threonine	0.18	0.18	0.19	0.20
Tryptophan	0.00	0.15	0.45	0.75
Dicalcium phosphate	0.76	0.76	0.76	0.76
Limestone flour	0.52	0.52	0.52	0.52
NaCl	0.30	0.30	0.30	0.30
Premix[a]	1.00	1.00	1.00	1.00
Total	100.00	100.00	100.00	100.00
Nutrient level[b], %				
Digestible energy (MJ/kg)	14.65	14.63	14.63	14.62
Crude protein	18.08	18.05	18.06	18.05
Lysine	1.23	1.23	1.23	1.23
Methionine + cystine	0.68	0.68	0.68	0.68
Threonine	0.73	0.73	0.73	0.73
Tryptophan	0.15	0.30	0.60	0.90

Trp15 breakfast, lunch, and dinner with 0.15% tryptophan, Trp30 breakfast, lunch, and dinner with 0.30% tryptophan, Trp30-90 breakfast with 0.30%, lunch with 0.60%, and dinner with 0.90% tryptophan, Trp90-30 breakfast with 0.90%, lunch with 0.60%, and dinner with 0.30% tryptophan

[a] Supplied per kilogram of diet: $CuSO_4 \cdot 5H_2O$ 19.8 mg; KI 0.20 mg; $FeSO_4 \cdot 7H_2O$ 400 mg; $NaSeO_3$ 0.56 mg; $ZnSO_4 \cdot 7H_2O$ 359 mg; $MnSO_4 \cdot H_2O$ 10.2 mg; vitamin K (menadione) 5 mg; vitamin B_2 15 mg; vitamin B_{12} 30 mg; vitamin A 5400 IU; vitamin D_3 110 IU; vitamin E 18 IU; choline chloride 80 mg; antioxidants 20 mg; fungicide 100 mg

[b] Nutrient level as calculated value

Table 2 Amount of supplemental tryptophan added to isocaloric pig meals

Meal[a]	Treatment			
	Trp15 (%)	Trp60 (%)	Trp90-30 (%)	Trp30-90 (%)
Breakfast	0.15	0.60	0.90	0.30
Lunch	0.15	0.60	0.60	0.60
Dinner	0.15	0.60	0.30	0.90

[a] Meals were offered at 08:00, 12:00, and 17:00 h for breakfast, lunch and dinner, respectively

The diets were determined by calculating the content of digestible energy, crude protein, and apparent ileal digestible limiting amino acids (Lys, Met + Cys, Thr; Table 1). Trp with a purity of 98.42% was purchased from Kaisheng New Materials Co. LTD (Shandong, China). The animals were given free access to water. During the experiment, sunrise time was from 5:45 to 5:30, while sunset time was from 19:00 to 19:20. The animal received natural sunlight through the window, the area of which is 25% of the walls in the room.

Body weight and feed intake were recorded at the end of the trial as previously described (Yin et al. 2014). Based on these data, pigs' performance such as average daily gain (ADG), average daily feed intake (ADFI), and feed/gain (F:G) ratio were calculated (Xie et al. 2015). On day 14, after 12 h of fasting, blood samples (about 5 mL from each piglet) were obtained by anterior vena cava puncture. After the samples were centrifuged at $3000\times g$ at 4 °C for 15 min, the plasma was collected and stored at −20 °C for subsequent analysis(Yin et al. 2010, 2015).

The plasma sample was used to assess total protein, albumin, urea, glucose, and triglyceride levels, which were measured with commercial kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China) in accordance with the manufacturer's instructions. Plasma amino acid (AA) concentration was determined by an ion-exchange AA analyzer (Hitachi L-8800 Auto-Analyzer, Tokyo, Japan) as previously described (Fang et al. 2009).

Statistical analyses

Differences between groups were tested with a one-way ANOVA for completely randomized designs with four treatments and eight replicates per treatment using the GLM procedure using the SAS statistical software (SAS Institute Inc., Cary, NC, USA). Statistical significance was considered to be at $P < 0.05$.

Results

The effects of different daily patterns of supplemental Trp on performance are shown in Table 3. The results revealed that F:G showed decreasing trend affected by Trp supplementation ($P = 0.079$). Compared with the control group, the F:G ratio decreased by 14.87, 21.02, and 11.79% in the Trp60, Trp90-30, and Trp30-90 groups, respectively. No difference was observed in final BW, daily feed intake, and daily gain.

Plasma urea and albumin were significantly affected by treatment ($P < 0.05$), whereas the level of total protein was not. A changing trend was observed in plasma glucose levels ($P = 0.086$), and the highest was in the Trp90-30 group compared to the control. No significant differences in plasma triglyceride content between treatments were found in this study (Table 4).

The majority of the amino acid plasma levels were affected by the different treatments of Trp supplementation ($P < 0.05$) excluding alanine, glutamic acid, lysine, ornithine, and phenylalanine (Table 5). Among the essential amino acids, the levels of histidine, isoleucine, proline, threonine, and valine in the Trp supplement group were significantly lower than those in the control group, with those of Trp30-90 being lower than those of the control group, and those of Trp90-30 being even lower (Fig. 1). Plasma arginine levels exhibited a similar trend ($P = 0.057$). Pigs in the supplemental Trp group showed higher glycine, serine, and methionine plasma levels than those in the control group ($P < 0.05$).

Table 3 Effect of different patterns of supplemental tryptophan on the growth performance of growing pigs fed three meals daily

Items	Trp15	Trp60	Trp90-30	Trp30-90	SEM	P value
Initial BW (kg)	8.26	8.19	8.17	8.28	0.15	0.993
Final BW (kg)	11.98	12.19	12.30	11.73	0.31	0.940
Daily feed intake (g)	480.36	458.93	444.05	403.57	17.99	0.529
Daily gain (g)	265.18	285.71	295.24	246.43	16.09	0.765
Feed:gain	1.95	1.66	1.54	1.72	0.06	0.079

Values are expressed as mean ± SEM, $n = 8$ pigs in each experimental group

Trp15 breakfast, lunch, and dinner with 0.15% tryptophan, Trp30 breakfast, lunch, and dinner with 0.30% tryptophan, Trp30-90 breakfast with 0.30%, lunch with 0.60%, and dinner with 0.90% tryptophan, Trp90-30 breakfast with 0.90%, lunch with 0.60%, and dinner with 0.30% tryptophan, BW body weight

Table 4 Effect of different patterns of supplemental tryptophan on the plasma biochemical index of pigs fed three meals daily

Items	Trp15	Trp60	Trp90-30	Trp30-90	SEM	*P* value
Total protein (g/L)	49.31	48.49	50.45	46.28	0.68	0.208
Albumin (g/L)	23.70	24.56	28.43	24.10	0.61	0.019
Urea (mmol/L)	3.61	2.37	2.54	3.09	0.16	0.010
Glucose (mmol/L)	3.89	3.90	4.80	3.78	0.16	0.086
Triglyceride (mmol/L)	0.41	0.41	0.32	0.29	0.03	0.280

Values are expressed as mean ± SEM, $n = 8$ pigs in each experimental group

Trp15 breakfast, lunch, and dinner with 0.15% tryptophan, Trp30 breakfast, lunch, and dinner with 0.30% tryptophan, Trp30-90 breakfast with 0.30%, lunch with 0.60%, and dinner with 0.90% tryptophan, Trp90-30 breakfast with 0.90%, lunch with 0.60%, and dinner with 0.30% tryptophan

Table 5 Effect of different patterns of supplemental tryptophan on the free amino acid profile in the plasma (μmol/mL) of pigs fed three meals daily

Amino acids	Trp15	Trp60	Trp90-30	Trp30-90	SEM	*P* value
Alanine	729.83	950.20	843.28	770.70	37.21	0.142
Arginine	74.56	58.85	48.17	56.48	3.68	0.057
Aspartic acid	28.40	32.59	21.79	15.46	1.62	<0.001
Glutamic acid	208.98	251.59	240.99	212.92	8.56	0.203
Glycine	1121.22	1905.95	1898.78	1550.67	86.28	<0.001
Histidine	36.01	24.53	23.96	26.53	1.78	0.029
Isoleucine	72.01	42.60	34.47	32.29	4.73	0.002
Leucine	100.15	111.55	95.16	80.96	3.95	0.050
Lysine	253.51	270.490	223.07	212.57	10.97	0.232
Methionine	41.79	69.14	59.41	41.75	3.63	0.006
Ornithine	62.54	68.96	56.45	56.49	2.83	0.372
Phenylalanine	57.06	56.29	51.59	53.90	1.55	0.619
Proline	838.71	456.08	327.78	185.49	31.50	0.014
Serine	135.69	183.45	167.96	138.75	6.25	0.006
Taurine	210.38	290.02	160.77	140.71	19.10	0.020
Threonine	300.06	174.47	179.66	94.98	23.17	0.007
Tryptophan	12.04	46.20	45.74	41.41	3.91	<0.001
Tyrosine	45.73	54.72	45.26	34.46	2.53	0.042
Valine	106.54	74.14	52.99	49.30	6.60	0.001
BCAA[a]	278.7	228.3	182.6	162.5	13.52	0.004
Trp: BCAAs	0.044	0.200	0.253	0.260	0.022	<0.001

Values are mean ± SEM, $n = 8$

Trp15 breakfast, lunch, and dinner with 0.15% tryptophan, Trp30 breakfast, lunch, and dinner with 0.30% tryptophan, Trp30-90 breakfast with 0.30%, lunch with 0.60%, and dinner with 0.90% tryptophan, Trp90-30 breakfast with 0.90%, lunch with 0.60%, and dinner with 0.30% tryptophan

[a] BCAAs means branched chain amino acids including isoleucine, leucine, and valine (Pascucci et al. 2009)

The plasma content of nine non-essential amino acids was also assessed in this study. However, only the level of plasma tyrosine changed significantly by treatment ($P = 0.042$). The amount of branched chain amino acids (BCAA) decreased significantly ($P = 0.004$), whereas the rate of Trp to BCAA conversion increased ($P < 0.001$).

Discussion

Building mature and balanced circadian rhythm may improve growth performance in animals. The metabolites of Trp are key modulators regulating the development of the circadian clock system in young animals. In the present study, we show that short-term supplementation of

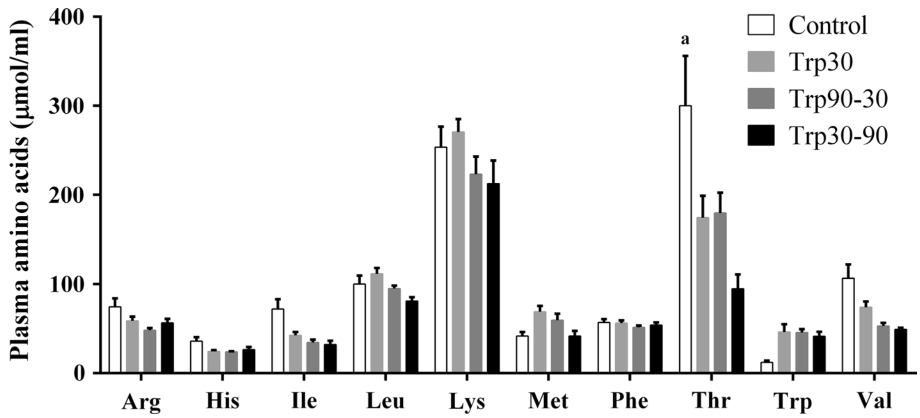

Fig. 1 Effects of different patterns of supplemental tryptophan on plasma essential amino acids in growing pigs fed three meals daily. $n = 8$. *Arg* L-arginine, *His* L-histidine, *Ile* L-isoleucine, *Leu* L-leucine, *Lys* L-lysine, *Met* L-methionine, *Phe* L-phenylalanine, *Thr* L-threonine, *Trp* L-tryptophan, *Val* L-valine, *Trp15* breakfast, lunch, and dinner with 0.15% tryptophan, *Trp30* breakfast, lunch, and dinner with 0.30% tryptophan, *Trp30-90* breakfast with 0.30%, lunch with 0.60%, and dinner with 0.90% tryptophan, *Trp90-30* breakfast with 0.90%, lunch with 0.60%, and dinner with 0.30% tryptophan

isocaloric meals with various concentrations of Trp optimizes the amino acid interconversions, which increases the nitrogen utilization in our pig models.

Trp is used in mammals for the synthesis of melatonin, a hormone that induces the anticipation of the daily onset of darkness (Shibuya et al. 1977). Melatonin production begins at 21:00 PM and falls to its lowest level by approximately 09:00 AM (Arendt 2011). The rhythm of melatonin production suggests that functions of Trp and melatonin in mood control vary depending on the time at which Trp is ingested. Interestingly, the effects of high levels of Trp in food in humans have been reported to result in elevated mood, calmness, and drowsiness, while decreasing one's appetite for carbohydrates and pain threshold; it also improves memory (Heine 1999; Silber and Schmitt 2010).

Recently, the effect of Trp intake at breakfast has received considerable attention, and it is thought that if Trp is ingested early in the day, it might help children maintain a morning-type diurnal rhythm, high sleep quality, and good mental health by increasing the metabolism of Trp to melatonin at night (Harada et al. 2013). In the present study, we found that short-term supplementation of decreased levels of dietary Trp at successive meals improved growth performance. This may be due to the increasing efficiency of dietary nitrogen uptake in the pigs (Xie et al. 2015). We will continue to investigate the molecular basis of Trp-induced nitrogen uptake and utilization in piglets.

It has been previously demonstrated that higher dietary tryptophan:lysine ratios in wheat–barley–soybean meal improves growth in growing pigs (Naatjes et al. 2014). To understand how Trp could actually affect the coordination of amino acid interconversions in vivo, we fed the pigs with the meals containing geometric levels of Trp and noticed that a high concentration of Trp supplied at the breakfast and lower amounts of Trp at lunch and dinner improved the final body weight and resulted in a decreasing trend in F:G, which can be explained by the relatively low plasma urea levels in Trp-fed pigs. Lower measurements of plasma urea suggest a high efficiency of dietary nitrogen use (Brown and Cline 1974). Importantly, the plasma levels of 12 of 17 amino acids exhibited significant changes after Trp treatment. Specifically, the isocaloric meals with different Trp concentrations decreased the plasma content of ten amino acids which include seven large neutral amino acids (LNAAs). Plasma Trp content was increased after supplementation of high Trp concentrations and a sequence of meals with different amounts of Trp after 12 h of fasting. Upregulation of Trp in the circulation can boost protein synthesis as well as other metabolic functions, such as the synthesis of melatonin, serotonin and picolinic acid, which in turn regulate feed intake (FI) (Eder et al. 2001; Cortamira et al. 1991).

Albumin is one of the most abundant proteins in the blood and a good indicator of animal's overall health (Kragh-Hansen 1981; Ha and Bhagavan 2013). It is known that a portion of Trp in the blood binds to albumin (Demain et al. 1972). Thus, animals maintain a balanced albumin level to ensure the resistance to disease and healthy growth (Klonoff-Cohen et al. 1992), possibly, in part, due to a proper and balanced amount of Trp which is albumin bound.

Author contributions HL designed the study, analyzed data, and drafted the manuscript with CAH. MB and MCT conducted the research. KX and FL participated in the experimental design and statistical analysis. XK provided essential materials. XW and YY participated in the experimental design and helped draft the manuscript. Additionally, HL had final responsibility for content while all authors read and approved the final manuscript.

Compliance with ethical standards

Ethical standards The protocol for this study was approved by the Committee on the Ethics of Animal Experiments of the Institute of Subtropical Agriculture, Chinese Academy of Sciences (Permit Number: 201506-11), and it was conducted out in accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the Institute of Subtropical Agriculture, Chinese Academy of Sciences.

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Conflict of interest The authors declare that they have no conflict of interest.

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