Branched-chain amino acid interactions in growing pig diets[1]

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ABSTRACT: The branched-chain amino acids (BCAA) Leu, Ile, and Val share the first steps of their catabolism due to similarities in their structure. The BCAA are reversibly transaminated in skeletal muscle through the activity of branched-chain aminotransferase and then transported to the liver. They undergo an irreversible decarboxylation catalyzed by the branched-chain α-keto acid dehydrogenase complex. Both enzymes are common to Leu, Ile, and Val and increased enzymatic activity stimulated by an excess of one of them will increase the catabolism of all BCAA, which can result in antagonisms. Leucine and its keto acid are the most potent stimulators of BCAA catabolic enzymes. Moreover, BCAA and large neutral amino acids (LNAA) share common brain transporters. Research has shown that high concentrations of BCAA, especially Leu, can decrease the absorption of LNAA, such as Trp, which is a precursor of serotonin and can have a significant impact in feed intake regulation. Finally, high Leu concentrations have the ability to overstimulate the mTOR signaling pathway, resulting in an inhibitory effect on feed intake. Most of the research conducted to evaluate the impact of BCAA on growth performance of pigs seems to agree that high levels of Leu decrease weight gain, mostly due to a reduction in feed intake. However, some studies, mostly with finishing pigs, observed no evidence for an impact on growth performance even with extremely high levels of Leu. It could be hypothesized that these inconsistencies are driven by the entire dietary amino acid profile as opposed to only considering the level of Leu. Grow-finish diets typically contain high levels of Leu, but the other BCAA are also well above the requirement and could potentially mitigate the negative impact of Leu on BCAA catabolism. Indeed, some studies suggest that when diets contain high levels of Leu, more Ile and Val are needed to optimize growth performance. However, the precise relationship between BCAA and their balance in swine diets is not fully understood. More research is needed to understand and quantify the relationship between LNAA and BCAA.

Key words: antagonism, branched-chain amino acids, pig, performance

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INTRODUCTION

Formulation of diets with low crude protein (CP) while maintaining adequate amino acid supply through the addition of crystalline amino acids is a well-established practice in swine diets.

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The use of crystalline amino acids reduces diet costs and nitrogen excretion while maintaining growth performance. Today, L-Lys, L-Thr, DL-Met, L-Trp, and L-Val are commonly used in the swine industry. After Val, Ile is likely the next limiting amino acid in corn–soybean meal diets (Figueroa et al., 2003). However, while Val and Ile are limiting in low CP corn–soybean meal diets, Leu is usually in excess due to its high concentration in corn and corn by-products (NRC, 2012). The branched-chain amino acids (BCAA) Leu, Ile, and Val are structurally similar and share the first steps of their catabolism. Therefore, excess of one BCAA, particularly Leu, may result in increased degradation of all three BCAA. The objective of this review is to summarize the current state of knowledge on BCAA metabolism and their interactions on growth performance of pigs.

BCAA METABOLISM AND ANTAGONISM

The metabolism of BCAA is well described (Harper et al., 1984). While most amino acids are metabolized in the liver, BCAA are transported to the skeletal muscle to be degraded. Through the action of branched-chain aminotransferase (BCAT), BCAA are reversibly converted to α-keto acids. The α-keto acids of Ile, Leu, and Val are α-keto-β-methylvalerate, α-ketoisocaproate, and α-ketoisovalerate, respectively. The transamination also forms glutamate, which can be transformed to glutamine or alanine and used in protein synthesis. In the next step, the α-keto acids are transported to the liver, where they are irreversibly decarboxylated by branched-chain α-keto acid dehydrogenase complex (BCKD). The final products of this reaction are ketogenic (for α-ketoisocaproate), glucogenic (for α-ketoisovalerate), or both (for α-keto-β-methylvalerate) and can be used in the TCA cycle.

Both enzymes, BCAT and BCKD, are common to all three BCAA. Stimulation of enzymatic activity by one of the BCAA will increase the catabolism of all BCAA, possibly creating antagonisms among them. The most potent stimulator of BCAT and BCKD is Leu and its α-keto acid, α-ketoisocaproate (Harper et al., 1984). Excessive Val and Ile seem to have a lesser effect on increasing the catabolism of the other BCAA (D'Mello and Lewis, 1970). The first study to demonstrate BCAA antagonism was conducted in 1955 with rats (Harper et al., 1955). Researchers observed that including 3% L-Leu to a low CP diet impaired growth and supplementation of L-Ile could partially alleviate the decrease in growth. Allen (1971) and Allen and Baker (1972) demonstrated in chicks that excess Val does not affect the utilization of Ile or Leu; however, excess Ile and especially Leu impair the utilization of the other BCAA and cause reduction in feed intake and growth. A similar observation was made by Harper et al. (1984) in rats, where excess Leu reduced growth and supplementation of Ile and Val was able to partially reverse the decrease in growth.

In a recent study (Wessels et al., 2016), nursery pigs with an initial body weight (BW) of 10.4 kg were fed diets with 100%, 186%, or 353% standardized ileal digestible (SID) Leu:Lys. In this experiment, 186% SID Leu:Lys was enough to produce a reduction ADFI and the effect was even more pronounced with 353% SID Leu:Lys (9% or 23% reduction compared to 100% SID Leu:Lys). Feeding high Leu diets increased Leu and reduced Ile and Val in plasma and several other tissues and increased the activity of BCKD in most tissues. Taken together, results indicate that high Leu increases the catabolism not only of itself but of the other BCAA. Interestingly, pigs fed 353% SID Leu:Lys diets had decreased plasma serotonin and numerically lower brain serotonin. A possible explanation for the decrease in serotonin is the lower concentration of Trp observed in the brain of piglets fed the 353% SID Leu:Lys diet. BCAA and other large neutral amino acids (LNAA), such as Trp, His, Phe, and Tyr, share the same brain transporters (Pardridge, 1977). Increasing levels of one of the LNAA raises its brain uptake and decreases the uptake of the other LNAA (Fernstrom, 2013). Taken together, these data may suggest that excessive Leu may decrease the absorption and utilization of Trp, which ultimately results in reduced serotonin activity in the brain and decreased feed intake (Henry et al., 1992). It is well reported that low dietary Trp has profound effects on feed intake (Ettle and Roth, 2004; Gonçalves et al., 2015). However, Wessels et al. (2016) hypothesized that Trp and serotonin were not the main drivers of reduced feed intake because pigs fed the 186% SID Leu:Lys diet had similar brain Trp concentration to pigs fed 100% SID Leu:Lys but lower feed intake. Instead, the reduction in appetite was attributed to excessive mTOR activation, stimulating anorectic signals (Cota et al., 2006), and deficiency of Val and Ile caused by increased catabolism due to excess Leu.

A study was conducted by Millet et al. (2015) to evaluate the interaction between BCAA and Trp for nursery pigs (initially 9.9 kg). Treatments consisted of two ratios of SID Val:Lys (63% or 70%), SID Leu:Lys (97% or 192%), SID Ile:Lys (54% or 66%), and SID Trp:Lys (18% or 23%). High concentrations of dietary Leu negatively affected growth performance (Table 1), but some of the performance was recovered with the addition of high Val concentrations. Addition of Ile did not improve performance. Interestingly, there was an interaction between Leu and Trp due to a negative effect of adding Trp to a high Leu diet compared with a low Leu diet. This may indicate some degree of antagonism between the BCAA and Trp.

EFFECTS OF BCAA ON GROWTH PERFORMANCE

Kerr et al. (2004) fed nursery pigs (7 kg initial BW) diets with increasing levels of spray-dried blood cells (SDBC), an ingredient with very high concentration of Leu and Val and low concentration of Ile. Diets contained 2.5% or 5% SDBC and were supplemented with or without L-Ile. Pigs fed diets with 2.5% SDBC without or with L-Ile had similar average daily gain (ADG), average daily feed intake (ADFI), and gain-to-feed ratio (G:F; Table 2). However, pigs fed diets with 5% SDBC without L-Ile had reduced ADG, ADFI, and G:F. The inclusion of L-Ile to the 5% SDBC diets resulted in performance similar to the 2.5% SDBC diets. Comparable results were observed in other experiments (Kerr et al., 2004). These results suggest that diets with moderate levels of Leu can be fed to nursery pigs without compromising growth performance as long as Ile is above the requirement. Diets with 136% SID Leu:Lys (2.5% SDBC) did not reduce growth

Table 1. Effects of changing BCAA and Trp for nursery pigs, adapted from Millet et al. (2015)[1]

	Treatment							
Item	Control	Control +Val	Control +Val +Trp	Control +Leu	Control +Leu +Val	Control +Leu +Val +Ile	Control +Leu +Val +Trp	Control +Leu +Val +Ile +Trp
Diet composition, %								
SID Lys	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11
SID Leu:Lys	97	97	97	192	192	192	192	192
SID Ile:Lys	54	54	54	54	54	66	54	66
SID Val:Lys	63	70	70	63	70	70	70	70
SID Trp:Lys	18	18	23	18	18	18	23	23
Results								
ADG[2], g	695	659	695	511	623	625	589	626
ADFI[3], g	1,142	1,110	1,142	974	1,055	1,058	1,055	1,034
G:F[4], g/kg	609	594	609	525	591	591	558	605

[1]A total of 32 pigs (initially 9.9 kg BW) were fed dietary treatments in a cross-over design during 8 wk.
[2]ADG, $P < 0.05$ for Leu and Leu × Val; $P > 0.05$ for Val, Ile, Trp, Leu × Trp, and Ile × Trp.
[3]ADFI, $P < 0.05$ for Val, Leu, and Val × Leu; $P > 0.05$ for Ile, Leu × Trp, and Ile × Trp.
[4]G:F, $P < 0.05$ for Val, Leu, and Val × Leu; $P > 0.05$ for Ile, Trp, Leu × Trp, and Ile × Trp.

Table 2. Effects of spray-dried blood cells (SDBC) in diets with or without L-Ile for nursery pigs, adapted from Kerr et al. (2004)[1]

	2.5% SDBC		5% SDBC				
Item	-L-Ile	+L-Ile	-L-Ile	+L-Ile	Low-CP control	High-CP control	SEM
Diet composition, %							
CP	21.0	21.0	21.0	21.0	21.0	24.7	—
SID Lys	1.25	1.25	1.25	1.25	1.25	1.25	—
SID Leu:Lys	136	136	150	150	122	141	—
SID Ile:Lys	52	66	46	66	66	74	—
SID Val:Lys	74	74	83	83	71	78	—
SID Trp:Lys	18	18	18	18	18	21	—
Results[2]							
ADG, g	419[a]	399[ab]	336[c]	393[ab]	388[b]	382[b]	9.8
ADFI, g	505[x]	481[x]	440[y]	479[x]	481[x]	473[x]	13.9
G:F, g/kg	831[a]	838[a]	759[b]	824[a]	817[a]	818[a]	16.4

[1]A total of 936 pigs (initially 7.3 kg BW) were used in a 16-d trial with 12 replicates per treatment.
[2]Means with different superscripts differ ([a,b,c]$P < 0.05$) or tend to differ ([x, y]$P < 0.10$).

performance, but diets with 150% SID Leu:Lys (5% SDBC) impaired growth. It is important to observe that 136% SID Leu:Lys diets had Ile:Lys at or above the requirement (52% or 66% Ile:Lys), whereas the diet with 150% Leu:Lys without added L-Ile was below the Ile:Lys requirement (46% Ile:Lys).

In a summary of Ile requirement studies, Htoo (2012) observed that experiments where diets contained high levels of SDBC and consequently high SID Leu:Lys, i.e., >150%, the estimated SID Ile:Lys requirements were considerably higher than in trials where SID Leu:Lys was held at more moderate levels (diets not containing blood products), regardless of BW and genetics. Data from 12 trials were combined to create a regression equation to estimate the SID Ile:Lys requirement based on the dietary SID Leu:Lys (Figure 1). The equation suggests that as Leu increases, Ile requirement increases proportionately. For example, in a diet with 110% SID Leu:Lys, the SID Ile:Lys requirement would be ~54% and if the SID Leu:Lys is 200%, the SID Ile requirement increases to 61% of Lys. However, it should be acknowledged that the regression equation was constructed with data from different classes of pigs, from ~6 to 113 kg BW, and there is not sufficient evidence to support the response of different classes of pigs to BCAA is comparable. Moreover, although the equation can be useful from a practical standpoint, the statistical procedures used to produce it were not described.

Gloaguen et al. (2013) fed nursery pigs (11.3 kg initial BW) diets with increasing SID Leu:Lys from 80% to 130%. The Ile:Lys ratio was 52%. Results show that 80% SID Leu:Lys reduced ADFI and ADG. However, no evidence for differences were observed between 90% and 130% SID Leu:Lys. This indicates that Leu levels 10% below the NRC (2012) requirement estimates do not seem to impact growth performance. Moreover, 130% SID Leu:Lys was not sufficient to produce a reduction in feed intake. Note the SID Ile:Lys in this study was not in excess but very close to the estimated requirement for nursery pigs. In another study (Gloaguen et al. 2011), nursery pigs (initially 11.7 kg BW) were fed diets with two levels of SID Val:Lys (60% or 70%) and two levels of SID Leu:Lys (111% or 165%). Treatments were created by replacing soybean meal with corn gluten meal. There were significant SID Val:Lys and Leu:Lys effects (Table 3). Increasing SID Val:Lys from 60% to 70% improved growth performance, indicating that the requirement was >60%. Pigs fed diets with high SID Leu:Lys had decreased growth performance, and the reduction was much more severe when SID Val:Lys was deficient. However, it can be hypothesized that other differences between soybean meal and corn gluten meal were confounded and could play a role in the observed results.

Another experiment was conducted (Gloaguen et al., 2011) to determine the SID Val:Lys requirement of nursery pigs (initially 12.1 kg BW) when Leu is in excess (169% SID Leu:Lys). The estimated SID Val:Lys requirement was 72%. Although this observation is higher than the NRC (2012) requirement estimates, it is similar to the observations of Barea et al. (2009), conducted in the same laboratory using a diet with 118% SID Leu:Lys, and to other SID Val:Lys studies with moderate SID Leu:Lys levels (Soumeh et al., 2015, Clark et al., 2017). Therefore, it seems that 169% SID Leu:Lys was not enough to cause an increase in the Val requirement for nursery pigs. Wiltafsky et al. (2010) also conducted two experiments with nursery pigs with high SID Leu:Lys ratios ranging from 102

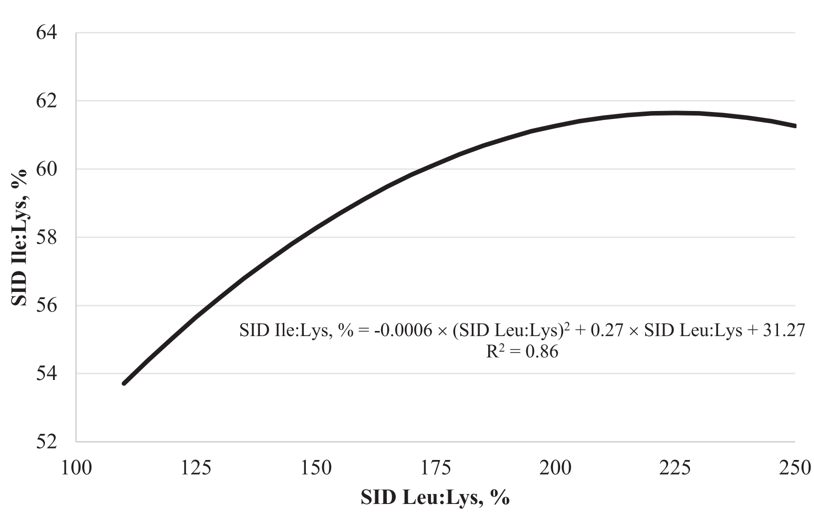

Figure 1. Regression equation of the estimated SID Ile:Lys requirement as a function of SID Leu:Lys, adapted from Htoo (2012).

to 204% in Exp. 1 or 99% to 198% in Exp. 2. In Exps. 1 and 2, diets were marginal for Ile (44% SID Ile:Lys) or Val (55% SID Val:Lys), respectively. In both experiments, there was a linear reduction in ADFI and ADG in response to increasing SID Leu:Lys. Contrary to Gloaguen et al. (2011, 2013), the authors observed important reductions in feed intake even with intermediate SID Leu:Lys, i.e., around 150%. It can be hypothesized that the feed intake decrease was observed with lower SID Leu:Lys by Wiltafsky et al. (2010) because diets were limiting in Ile or Val, which exacerbated the effects of excess Leu.

Duan et al. (2016) studied the effects of BCAA ratios on growth performance of nursery pigs (Table 4). The authors compared diets with 20% CP and Leu:Ile:Val ratios of 1:0.51:0.63 and 17% CP diets with ratios of 1:1:1, 1:0.75:0.75, 1:0.51:0.63, or 1:0.25:0.25 Leu:Ile:Val. Results show that reducing CP from 20% to 17% while maintaining the 1:0.51:0.63 ratio did not affect growth performance. Pigs fed diets with 1:0.25:0.25 ratio had poorer performance than the other treatments. However, it is important to observe that the 1:0.25:0.25 treatment had 200% SID Leu:Lys but only 50% SID Ile:Lys and 50% SID Val:Lys, much lower than the estimated requirement. Conversely, all other treatments also had moderately high SID Leu:Lys but Ile and Val levels well above the estimated requirement. Thus, this seems to support the fact that negative effects of high Leu are more evident when the other BCAA are below the estimated requirement. Moreover, although not statistically significant, ADFI decreased by 15% for the 1:0.25:0.25 treatment and an SID Leu:Lys of 141% (1:0.51:0.63 treatment) did not produce a reduction in ADFI.

Data for grow-finish pigs are less abundant. Morales et al. (2016) fed growing pigs (31.8 kg initial BW) a basal diet with 99% SID Leu:Lys, 58% SID Ile:Lys, and 73% SID Val:Lys, the basal diet supplemented with L-Leu (137% SID Leu:Lys, 58% SID Ile:Lys, and 73% SID Val:Lys), or the

Table 3. Effects of SID Leu:Lys and SID Ile:Lys on growth performance of nursery pigs, adapted from Gloaguen et al. (2011)[1,2]

SID Leu:Lys, %	111		165			Probability, $P<$		
SID Val:Lys, %	60	70	60	70	SEM	Val:Lys	Leu:Lys	Val:Lys × Ile:Lys
Initial BW, kg	11.8	12.2	11.3	11.6	1.6	0.19	0.34	0.90
Final BW, kg	18.6	22.0	16.4	20.4	2.2	0.01	0.01	0.54
ADG, g	325[b]	465[a]	242[c]	420[a]	85	0.01	0.01	0.28
ADFI, g	634[b]	736[a]	563[c]	715[a]	69	0.01	0.04	0.24
G:F, g/kg	0.51[b]	0.63[a]	0.44[c]	0.59[a]	0.09	0.01	0.01	0.39

[1]A total of 64 pigs (initially 11.7 kg) were used in a 21-d trial with 16 replicates per treatment.

[2]Differences in SID Leu:Lys were obtained by replacing soybean meal with corn gluten meal.

Table 4. Effects of BCAA ratio on growth performance of grow-finish pigs, adapted from Duan et al. (2016)[1]

CP	20%	17%				
SID[2] Leu:Ile:Val	1:0.51:0.63	1:1:1	1:0.75:0.75	1:0.51:0.63	1:0.25:0.25	SEM
Diet composition, %						
SID Lys	1.23	1.23	1.23	1.23	1.23	—
SID Leu:Lys	141	100	120	141	200	—
SID Ile:Lys	72	100	90	72	50	—
SID Val:Lys	89	100	90	89	50	—
SID Trp:Lys	16	16	16	16	16	—
Results[2]						
Initial weight, kg	9.9	9.9	9.7	9.8	9.9	0.35
Final weight, kg	36.7[a]	33.4[ab]	35.6[a]	36.6[a]	31.2[b]	0.66
ADG, kg	0.62[a]	0.55[ab]	0.60[a]	0.63[a]	0.50[b]	0.03
ADFI, kg	1.15	1.12	1.06	1.16	0.99	0.14
G:F, g/kg	539[xy]	491[x]	566[y]	543[xy]	505[xy]	0.18

[1]A total of 40 pigs (initially 9.9 kg) were used in a 45-d trial with eight replicates per treatment.

[2]Means with different superscripts differ ([a,b,c] $P < 0.05$) or tend to differ ([x, y] $P < 0.10$).

basal diet supplemented with L-Leu, L-Ile, and L-Val (133% SID Leu:Lys, 74% SID Ile:Lys, and 95% SID Val:Lys). Ratios were calculated from the analyzed diet composition. There was no evidence for differences in performance across dietary treatments, which indicates that 137% SID Leu:Lys was not sufficient to provoke a reduction in feed intake in growing pigs. However, it is important to acknowledge that both Ile and Val were above the estimated requirements.

Hyun et al. (2003) fed finishing pigs (initially 78.4 kg BW) corn–soybean meal diets (171% SID Leu:Lys) or corn–soybean meal diets supplemented with 2.1% L-Leu (424% SID Leu:Lys). Other ratios were 66% SID Ile:Lys, 20% SID Trp:Lys, 66% SID Met and Cys:Lys, and 62% SID Thr:Lys. Valine level was not reported. Pigs fed diets with added L-Leu had significantly lower ADG (829 vs. 930 g), but there was no evidence for differences in ADFI (2.75 vs. 2.89 kg). It is important to observe that the Leu levels in the L-Leu supplemented diet were extremely high and do not correspond to practical conditions. Also, although not significant, there was a 5% numerical reduction in ADFI.

In another finishing study, Hyun et al. (2007) fed finishing pigs (73 kg initial BW) in a 2 × 3 factorial treatment structure with two levels of SID Lys (0.5% or 0.7%) and three levels of SID Leu (1%, 2%, or 3%). Diets were corn–soybean meal based and treatments were achieved by manipulating the inclusion of feed-grade L-Lys and L-Leu. Calculated ratios were not provided, but analyzed values resulted in Leu:Lys of 218%, 365%, and 501% with 0.5% Lys and 166%, 244%, and 330% with 0.7% Lys. Other amino acid levels were above the estimated requirement. Interestingly, growth performance was not affected by Lys or Leu levels. In this study, even the highest SID Leu:Lys of 501% did not impact ADFI. A similar finding was observed by Cisneros et al. (1996), where no evidence for differences were observed in growth performance of finishing pigs fed diets with extremely high SID Leu:Lys, >500%. However, it is important to note that in this study there was a numeric reduction in ADFI of 9%.

Rojo et al. (2011) conducted an experiment using growing pigs (42.4 kg initial BW) fed a corn–soybean meal diet (control), control supplemented with L-Leu, control supplemented with L-Leu and L-Ile, or control supplemented with L-Leu, L-Ile, and L-Val. Ratios of SID Leu:Lys, SID Ile:Lys, and SID Val:Lys were 128%, 61%, and 68% in control; 192%, 61%, and 68% in control supplemented with L-Leu; 192%, 62%, and 68% in control supplemented with L-Leu and L-Ile; and 192, 62, and 74% in control supplemented with L-Leu, L-Ile, and L-Val. The Trp:Lys was 18% for all treatments. There was a reduction in ADG in all treatments compared to the control. However, there was no evidence for differences in feed intake among treatments, which is in agreement with Hyun et al. (2007) and Cisneros et al. (1996).

Several studies were conducted to evaluate the effects of increasing distillers dried grains with solubles (DDGS) for grow-finish pigs. Although they were not designed as BCAA trials, data can be utilized to evaluate the effects of increasing SID Leu:Lys due to the amino acid profile of DDGS. Increasing DDGS will also result in high Val and Ile content, but not to the same extent as Leu. However, it should be recognized that there are a number of confounding factors when doing such evaluation. Whitney et al. (2006) fed grow-finish pigs (28.4 kg initial BW) diets with 0%, 10%, 20%, or 30% DDGS. The inclusion of L-Lys HCl was held constant for all treatments. Ratios of SID Leu:Lys were not reported but they can be estimated to range from ~150% to >250%, depending on the feeding phase. Overall, there was no evidence for differences in ADFI, although the inclusion of DDGS linearly reduced ADG and G:F. This suggests that the high SID Leu:Lys in these diets did not affect ADFI. The observed reduction in ADG and G:F could have been caused by overestimating amino acid content and digestibility or underestimating energy level of the DDGS source. In a study by Graham et al. (2014), grow-finish pigs (initially 46.1 kg BW) were fed diets with 0%, 20%, or 40% DDGS. The inclusion of L-Lys HCl was increased in diets with increasing DDGS. The SID Leu:Lys ranged from ~150% to 250%, depending on the feeding phase. Similar to Whitney et al. (2006), feeding high levels of DDGS did not have any negative impact on ADFI. It appears that high levels of DDGS can be used without negative impact on performance parameters (Stein and Shurson, 2009). It is unclear why high levels of Leu do not seem to impact feed intake as much in grow-finish compared with nursery pigs. It can be hypothesized that in the available research Val and Ile are also in a level high enough that the negative impact of exacerbated catabolism caused by excessive Leu is reduced. However, it is important to note that cost-effective practical diets are currently formulated with high inclusion of feed-grade AA to replace intact protein sources as well as alternative ingredients such as DDGS. Using this strategy, diets can be formulated with Val and Ile close to the estimated requirement, while Leu can fluctuate to levels well above the estimated requirement and may potentially impact growth performance.

Taken together, results suggest that there is strong evidence to support the negative effects of feeding high Leu levels when diets are marginal or below the Ile and/or Val estimated requirements. However, the effects on pigs fed diets with adequate or high Ile and Val, such as corn–soybean meal-DDGS grow-finish diets, are less clear. Furthermore, there is also no definition of exactly where the breakpoint is, i.e., at what SID Leu:Lys ratio growth performance is impaired. Similarly, other ratios, such as among BCAA and between BCAA and LNAA, are not fully understood.

Conflict of interest statement. None declared.

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