

High leucine levels influence on optimal dietary valine and isoleucine levels

Ivan Camilo Ospina Rojas

CJ BIO, Brazil

INTRODUCTION

It has been well known that branched-chain amino acids (BCAA; Val, Leu and Ile) are not only substrates for building block protein, but they are also involved in intracellular signaling pathways on protein anabolism and stimulatory effects on protein synthesis by modulating the activation of mTOR and its downstream effectors (Suryawan et al., 2008). BCAA concentrations quickly increase in the bloodstream after protein intake and are readily available for protein synthesis in skeletal muscle, as BCAA do not have to first-pass hepatic metabolism as other AA (Brosnan and Brosnan, 2006).

BCAA catabolism

All three of the BCAA share common enzymes in their catabolism, as the branched-chain AA aminotransferase (BCAT) enzyme and the branched-chain α -keto acid dehydrogenase (BCKD) complex (Brosnan and Brosnan, 2006). The BCAT reaction takes place in muscle and involves a reversible transfer of Leu, Val, and Ile to their corresponding branched-chain α -keto acids, α -ketoisocaproate (KIC), α -ketoisovalerate (KIV), and α -keto- β -methylvalerate (KMV), respectively (Fig. 1). The KIC, the α -keto acid of Leu, activates the BCKD complex (Harris et al., 2005), which increases an irreversible catabolism of both Val and Ile. The α -keto acids of Val and Ile, KIV and KMV, also activates the BCKD complex, but at a lower efficacy than that of KIC (Brosnan and Brosnan, 2006). Consequently, excess Val or Ile leads to small reductions in plasma concentrations of the other two BCAA (D'Mello and Lewis, 1970; Smith and Austic, 1978), indicating that Val, Ile and/or their α -keto acids do not significantly increase overall BCAA catabolism.

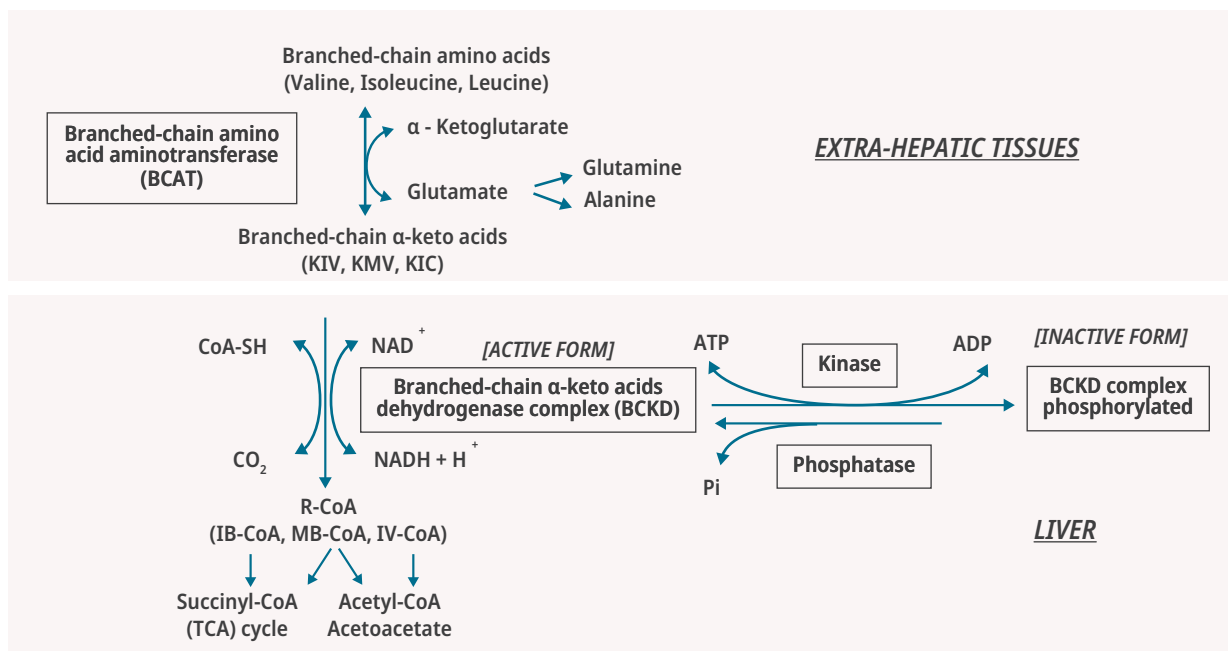


Figure 1. Catabolic pathway of BCAA. KIV, α -ketoisovalerate; KMV, α -keto- β -methylvalerate; CoA-SH, reduced coenzyme A; IB-CoA, isobutyryl-CoA; MB-CoA, α -methylbutyryl-CoA; IV-CoA, isovaleryl-CoA; R-CoA, acyl-CoA.

(Adopted from Brosnan and Brosnan, 2006)

High leucine levels affect the optimal dietary valine and isoleucine levels in broilers fed low-protein diets

The three BCAA exhibit antagonistic interactions among each other when either are provided in excess (Harper et al., 1984), but Leu has the most pronounced effects. Diets high Leu have been shown to increase required optimum levels of the other two BCAA in birds (Smith and Austic, 1978), pigs (Langer et al., 2000) and rats (May et al., 1991). In a previous study, Ospina-Rojas et al., 2017 found that higher Val was needed to optimize the feed intake as dietary Leu increased in broilers fed low-protein diets (Fig. 2), indicating that excess Leu stimulates the Val catabolism.

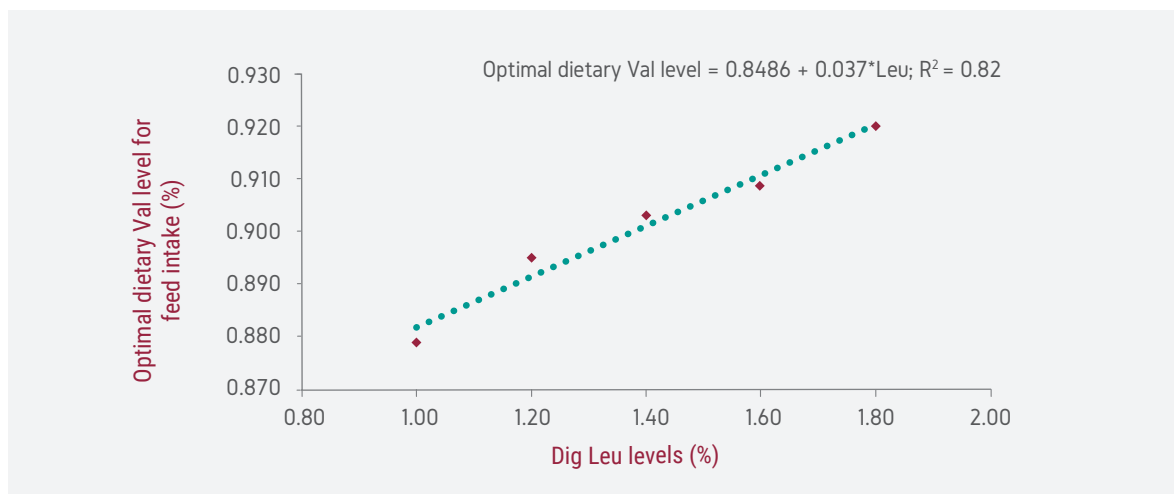


Figure 2. Effects of Leu levels on dietary optimal levels of Val for feed intake in broilers fed low-protein diets.
(Adopted from Ospina-Rojas et al., 2017)

Additionally, a strong relationship between dietary Leu and Val levels was reported on the gain:feed ratio of broilers fed low-protein diets from 1 to 21 d of age (Ospina-Rojas et al., 2019). According to the fitted surface-response model, gain:feed was optimized at low-protein starter diets for broilers with a Leu level of 1.27%, and Val level of 0.91% (Fig. 3), suggesting a Leu:Val ratio of 100:72.

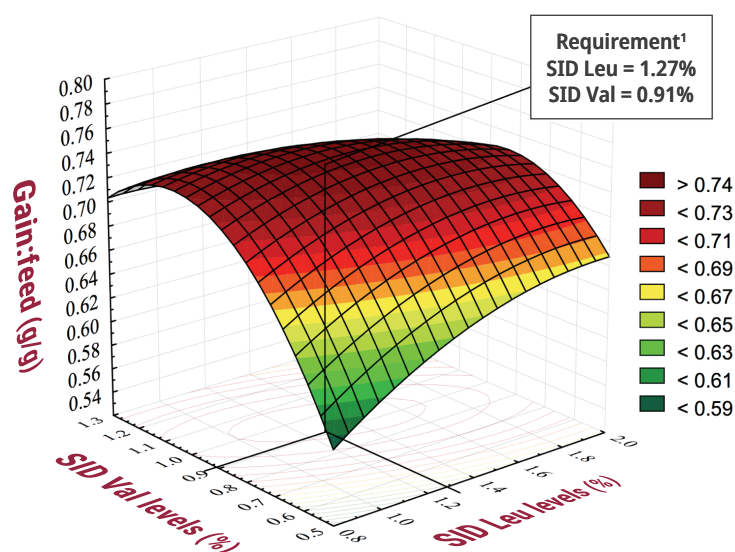


Figure 3. Effect of the standardized ileal digestible (SID) Leu and Val content in low-CP diets on gain:feed of broiler chickens from 1 to 21 d of age.

(Adopted from Ospina-Rojas et al., 2019)

(¹SID Leu and Val requirement estimates are 95% of the response. Color frames represent the gain:feed range in the Z-axis. Contour lines below the surface response indicate a stationary point. The predicted maximum gain:feed (0.744g) was achieved at SID levels of Leu and Val of 1.27 and 0.91%, respectively, in low-protein diets.)

Broilers fed high dietary protein content with AA levels above their minimum requirement did not exhibit reduced performance by high Leu levels (Burnham et al., 1992; Waldroup et al., 2002), whereas the Leu antagonism has been more evident in low-protein diets where some AA are at minimal dietary levels (D'Mello and Lewis, 1970; Allan and Baker, 1972; Smith and Austic, 1978; Ospina-Rojas et al., 2017, 2019). Thus, the magnitude of reduced dietary protein may influence the bird's response to SID Leu levels. The ideal BCAA ratios in diets with high-protein levels may be different from those in low-protein diets. Leucine as a large neutral amino acid (LNAA) shares the same transporters with not only Val and Ile, but also other LNAA, such as Trp, Met, His, Phe, and Tyr in sodium independent (L and y+L) and sodium dependent systems (Bo, Bo+) (Wu, 2013). High protein diets contain some essential and nonessential AA at levels above the bird's requirements, which may reduce the Leu pool and the antagonistic effect of Leu on BCAA metabolism by increasing the competition among Leu and other AA for transport across cell membranes or for entry into the metabolic pathway. The initial BCAA transamination reactions are highly reversible; a high proportion of the branched-chain α -keto acids formed can be reconverted to their respective BCAA and used in protein metabolism, unless Leu and KIC pools are high enough to activate the BCKD complex and increase the irreversible oxidation of the branched-chain α -keto acids (Torres et al., 1995).

Some feed ingredients have disproportionate higher Leu levels compared to Val and Ile, which may create a BCAA imbalance in low-protein diets with a combination of some particular feed ingredients (Fig. 4). Corn's SID Leu content is 11.6% relative to its protein concentration, whereas this ratio is only 6.9% in soybean meal (Rostagno et al., 2011). Leucine concentration in sorghum is three-fold higher than the Val and Ile levels. In addition, corn gluten meal contains high SID Leu level as a percentage of protein content (17%) and low levels of Val and Ile (4%) (Rostagno et al., 2011). Low protein diets decrease levels of the primary protein source and an increased proportion of dietary cereal ingredients, some of which have a high Leu level in relation to their protein contribution. Hence, Leu antagonism effect on the other BCAA may be more significant for birds fed these low-protein diets.

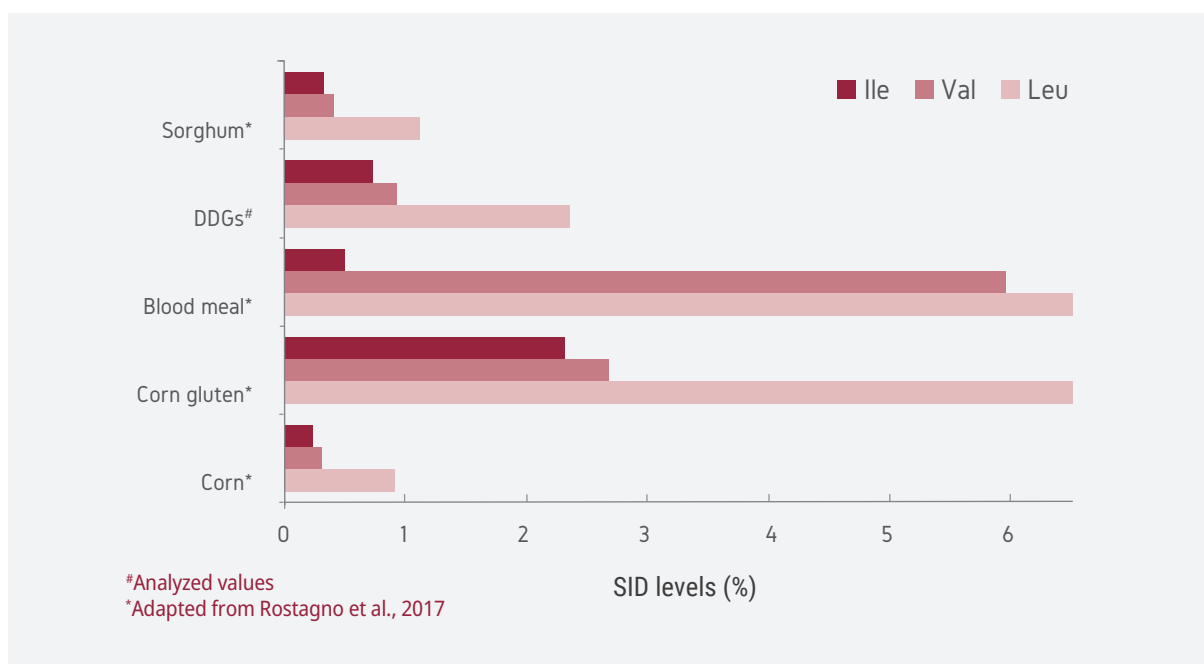


Figure 4. Standardized ileal digestible (SID) levels of Ile, Val, and Leu in some ingredients used in broiler diets.

Inclusion level of corn increases as soybean meal levels decreases in a reduced-protein diet. As corn inclusion increases in low-protein diets, Val and Ile supplementation in these diets is important to support broiler growth by improving BCAA balance and counteracting the activation metabolic pathways that oxidize all BCAA. Special attention should be paid to BCAA ratios in low-protein diets, especially those formulated with particular combinations of feed ingredients with marginally adequate levels of Ile and Val and disproportionally high Leu levels. In some cases, relative Leu content could be high even in low-protein diets resulting in low Val and Ile to Leu ratios that might increase optimal dietary Val and Ile levels. However, broiler recommendations of Val and Ile are generally kept at the same levels in a least-cost feed formulation. In this situation, higher dietary Val and Ile levels may be required to avoid poor performance due to high Leu levels. Low-protein diets without Leu supplementation have resulted in good

broiler performance when Val and Ile requirements were fully met (Ospina-Rojas et al., 2020). This suggests that Val and Ile supplementation with adequate Leu:Val:Ile ratios could be a strategy to maintain broiler growth in low-protein diets by decreasing dietary Leu content and improving BCAA balance. In a recent study, the optimal average ratios for Leu:Val:Ile in low-protein diets were estimated at 100:69:62 from 1 to 14 d, 100:67:61 from 14 to 28, and 100:67:60 from 28 to 42 d (Ospina-Rojas et al., 2020).

Conclusion

The negative effects of high Leu levels are more pronounced in low-protein diets with marginal levels of Val and Ile. Higher dietary Val and Ile levels are required to minimize the antagonistic effect of excess Leu on broiler performance. In addition to marginal Gly+Ser levels, the antagonistic effect of BCAA could be the reason for why low-CP diets do not always result in bird performance similar to that of birds receiving the control diet.

REFERENCES

- Allan, N. K., and D. H. Baker. 1972. Quantitative efficacy of dietary isoleucine and valine for chick growth as influenced by variable quantities of excess dietary leucine. *Poult. Sci.* 51:1292-1298.
- Brosnan, J. T., and M. E. Brosnan. 2006. Branched-chain amino acids: enzyme and substrate regulation. *J. Nutr.* 136:2075-2115.
- Burnham, D., G. C. Emmans, and R. M. Gous. 1992. Isoleucine requirements of the chicken: the effect of excess leucine and valine on the response to isoleucine. *Br. Poult. Sci.* 33:71-87.
- D'Mello, J. P. F., and D. Lewis. 1970. Amino acid interactions in chick nutrition. 2. Interrelationships between leucine, isoleucine, and valine. *Br. Poult. Sci.* 11:313-323.
- Harper, A. E., R. H. Miller, and K. P. Block. 1984. Branched-chain amino acid metabolism. *Ann. Rev. Nutr.* 4:409-454.
- Harris, R. A., M. Joshi, N. H. Jeoung, and M. Obayashi. 2005. Overview of the molecular and biochemical basis of branched-chain amino acid catabolism. *J. Nutr.* 135:1527S-1530S.
- Langer, S., M. F. Fuller. 2000. Interactions among the branched-chain amino acids and their effects on methionine utilization in growing pigs: Effects on nitrogen retention and amino acid utilization. *Br. J. Nutr.* 83:43-48.
- May, R. C., N. Piepenbrock, R. A. Kelly, and W. E. Mitch. 1991. Leucine-induced amino acid antagonism in rats: muscle valine metabolism and growth impairment. *J. Nutr.* 121(3):293-301.
- Ospina-Rojas, I. C., A. E. Murakami, C. R. A. Duarte, G. R. Nascimento, E. R. M. Garcia, M. I. Sakamoto, and R. V. Nunes. 2017. Leucine and valine supplementation of low-protein diets for broiler chickens from 21 to 42 days of age. *Poult. Sci.* 96:914-922.
- Ospina-Rojas, I. C., A. E. Murakami, C. R. A. Duarte, P. C. Pozza, R. M. Rossi, and A. Gasparino. 2019. Performance, diameter of muscle fibers, and gene expression of mechanistic target of rapamycin in pectoralis major muscle of broilers supplemented with leucine and valine. *Can. J. Anim. Sci.* 99:168-178.
- Ospina-Rojas, I. C., P. C. Pozza, R. J. B. Rodrigueiro, E. Gasparino, A. S. Khatlab, A. E. Murakami. 2020. High leucine levels affecting valine and isoleucine recommendations in low-protein diets for broiler chickens. *Poult. Sci.* in press.
- Rostagno, H.S., Albino, L.F.T., Donzele, J.L., Gomes, P.C., de Oliveira, R.F., Lopes, D.C., Ferreira, A.S., Barreto, S.L.T., Euclides, R.F. 2011. Brazilian tables for poultry and swine: feed composition and nutritional requirements. 3rd ed. UFV, Viçosa, Minas Gerais, Brazil.
- Smith, T. K., and R. E. Austic. 1978. The branched-chain amino acid antagonism in chicks. *J. Nutr.* 108:1180-1191.
- Suryawan, A., A. S. Jeyapalan, R. A. Orellana, F. A. Wilson, H. V. Nguyen, and T. A. Davis. 2008. Leucine stimulates protein synthesis in skeletal muscle of neonatal pigs by enhancing mTORC1 activation. *Am. J. Physiol. Endocrinol. Metab.* 295:E868-E875.
- Torres, N., A. R. Tovar, and A. E. Harper. 1995. Leucine affects the metabolism of valine by isolated perfused rat hearts: relation to branched-chain amino acid antagonism. *J. Nutr.* 125:1884-93.
- Waldroup, P. W., J. H. Kersey, and C.A. Fritts. 2002. Influence of branched chain amino acid balance in broiler diets. *Int. J. Poult. Sci.* 1: 136-144.
- Wu, G. 2013. Degradation of Amino acids. Pages 118-122 in *Amino acids. Biochemistry and Nutrition*. Taylor & Francis Group, London, New York.