Differences in amino acid imbalance, antagonism and toxicity: Importance of dietary amino acid controlling in feed

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Introduction

With the development of the livestock industry, maximization of production efficiency is considered as the greatest concern, and feed cost reduction and increase of feed efficiency , which account for the largest proportion of various production costs, are considered as top priority. Accordingly, the development of animal nutrition has led to the management of micronutrients in the actual feed formulation, and furthermore, it has led to the simulation of feed nutrients by considering the actual digestion and utilization rate of individual feed ingredients in livestock. This precision feed formulation was naturally developed for the purpose of reducing feed production costs while maintaining or improving feed efficiency. Thus, the change in the price of feed ingredients (corn, soybean meal, etc.) has a profound effect on the final feed formulation. In particular, the increase in prices of relatively expensive dietary protein ingredients such as soybean meal is coupled with the need for feed cost reduction, and limits the amount of that ingredient in feed. However, in order to achieve the fundamental purpose of the livestock industry of "producing animal protein for human prosperity and survival", difficulties in the use of various feed protein ingredients such as economy, environment and safety have been overcome through the addition of exogenous essential amino acids. In addition, the kinds of essential amino acids that can be used reflect rapidly changing grain prices and the latest livestock trends, leading to the distribution of various essential amino acid products for feed.

Currently, there are a total of 8 feed grade essential amino acids available ; L-Lys, L-Met, L-Thr, L-Trp, L-Val, L-Ile, L-Arg and L-His by the recently developed natural fermentation technology. The supply of essential amino acids is such that it meets the needs of producers to reduce feed cost. And the addition of essential amino acids for feed is expanding not only due to the uncertainty and volatility in the price of protein raw materials, but also in conjunction with large global trends such as reducing nitrogen emissions to the environment, prohibiting the use of antibiotics, and animal welfare.

However, despite the clear global trend of expanding the use of amino acids, there is much that is still unknown about any specific interactions or antagonism of any essential amino acid, and their effect on animal performance.

Definitions of amino acid imbalance, antagonism and toxicity and specific examples

Since Willcock & Hopkins (1906) emphasized the metabolic importance of individual amino acid balances in 1906, there has been a need for supplementation of insufficient dietary amino acids from a variety of nutritional perspectives including reports of potential toxicities (Harper, 1956, Park, 2006). These studies focus on various nutritional and functional effects that appear when amino acids are added in conjunction with recent changes and regulations in feed ingredient composition.

1) Amino acid imbalance

Park (2006) defined the detrimental effect that occurs when a 2nd limiting amino acid or an amino acid mixture without the 1st limiting amino acid is supplemented to a diet deficient in one or more essential amino acids. The reduction in growth that occurs through the amino acid imbalance is characterized by mitigating the sluggish growth when supplemented with amino acids. Therefore, in order to prevent amino acid imbalance, it means that the 1st limiting amino acid must be used indispensably, and from this principle, the concept of an ideal protein is applied to feed formulation (water bottle theory).

A common characteristic of an amino acid imbalanced diet is a noticeable reduction in feed intake. When limited amino acids are supplied to the blood through the digestive tract, the enzyme activity involved in the catabolism of these amino acids increases,

causing additional amino acid deficiency, and consequently adversely affecting the synthesis of metabolites related to feed intake in the brain (Gietzen, 1993). The summary of the growth reduction pathway by amino acids is shown in the figure below (Fig. 1).
In addition, essential amino acids have been believed to cause amino acid imbalance, but those such as alanine, glycine, serine, proline, glutamate and aspartate are also known to cause growth retardation (Savage and Harper, 1964; Tews et al., 1979, 1980).

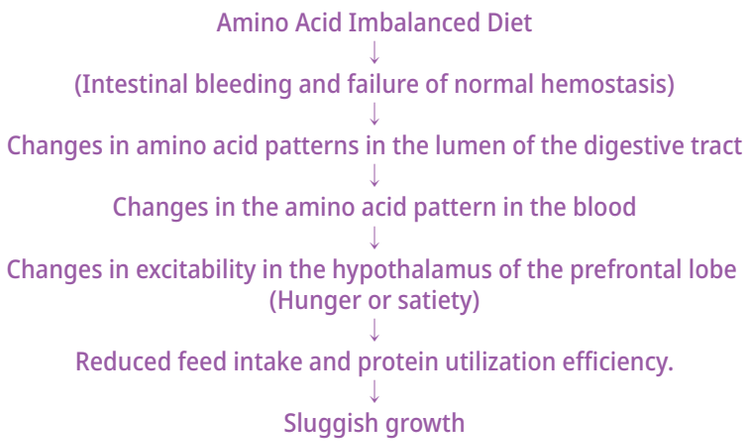

Figure 1. Growth reduction pathway due to dietary amino acid imbalance

2) Amino acid antagonism

Harper (1956) defines the antagonism of amino acids as harmful interactions in which the intake of an amino acid in excessive amounts increases the requirement for structurally similar amino acids. The antagonism of these amino acids occurs between amino acids that are similar in form (metabolism). Even a small amount of amino acid can adversely affect thephysiological metabolism. Antagonisms occur more frequently than amino acid imbalances. The main difference between an amino acid antagonism and imbalance is that it occurs when certain amino acids are consumed in excess of the required amount for maintenance and metabolism. In the case of an imbalance, it is only necessary to compensate for the deficiency of a specific amino acid. The antagonism of well-known amino acids is summarized in Table 1.

Table 1. Types and symptoms of amino acid antagonism

Antagonisms	Symptom
Lys & Arg	✓ Excess Lys increases the activity of renal arginase to increase the catabolism of Arg, thereby reducing the synthesis of creatine and Arg content in urine.
	✓ (Thr and aminoisobutyric acid prevent the increase in arginase activity.)
	✓ The proper ratio of Arg and Lys depends on the species and phase.
	✓ Excess Lys reduces Arg content in plasma, but does not affect liver, kidney, and muscle concentration.
	✓ Excessive intake of Lys induces a decrease in feed intake and feed efficiency.
BCAA (Leu & Val & Ile)	✓ Excess Leu was observed to decrease the growth of chicks.
	✓ Egg production rate and egg weight of laying hens decreased when Leu was exceeded and recovered by addition of Ile and Val.
	✓ With Leu in lactating sows, addition of Val and Ile improved the growth of weaning piglet and protein content in sow milks.
	✓ The addition of Leu and Val decreases the level of Ile in the plasma.
	✓ The use of high corn content has high Leu, but Ile and Val show relatively low content (most BCAA antagonism in pigs and chickens is observed only in diets with excess Leu)
Met & Thr	✓ Excessive intake of Met induces Thr deficiency.
	✓ The increase in Met increases the activity of Thr and Ser dehydratase.
Arg+Gly & Met	✓ Excessive intake of Arg and Gly increases the requirement of Met.
	✓ (Increase of Arg increases creatine synthesis through guanidinoacetic acid formation, and at this time, the demand for methyl group required for conversion from guanidinoacetic acid to creatine increases)
	✓ In general diet, Arg and Gly are abundant, but Met is often limited.

One of the most well-known amino acid antagonisms is Arg deficiency due to excess Lys. Lys is a generally 1st-restricted amino acid (in pig), and has been used as an index amino acid in the realization of an ideal protein theory because of its ease of use (simple nutritional functionality). And in the last 10 years, the supply of Lys for feed has increased beyond demand, making it the most popular amino acid additive. On the other hand, there is no doubt about the necessity of Arg based on the proven functionality, but the supply required for use was very limited. However, since the supply of feed grade Arg has recently become available similar to other general amino acids, perhaps we should reconsider the appropriate ratio of Arg and Lys. In particular, the recent rapid breeding improvement of breeders is accompanied by an increase in Lys demand for protein accumulation in the body, so there is no doubt about the need for re-validation of the appropriate ratio of Arg.
Meanwhile, the BCAAs imbalance composed of Leu, Val and Ile is also one of the important antagonists. The basis of this antagonistic inducing mechanism lies in the sharing of catabolic enzymes necessary for metabolism of amino acids with a similar structure with branched chain groups (Fig. 2). In other words, the excess of dietary Leu increases the demands of Val and Ile. The decrease in dietary CP content due to the recent rise in the price of feed ingredients, the regulation of nitrogen excretion and antibiotic use, and the emphasis on animal welfare, etc. are causing a serious antagonism of dietary BCAAs along with the increase in the actual dietary Leu content. The availability of dietary Val and Ile is seriously deteriorating. Against this background, verification of clear equilibrium values for individual BCAAs has recently emerged as a major topic in animal nutrition. As in the case of Arg, the difficulty of applying in feed formulations due to the shortage of existing Val and Ile sources has been resolved, and now the time has come to require sufficient review of the BCAA balance in the low CP feed formulation.

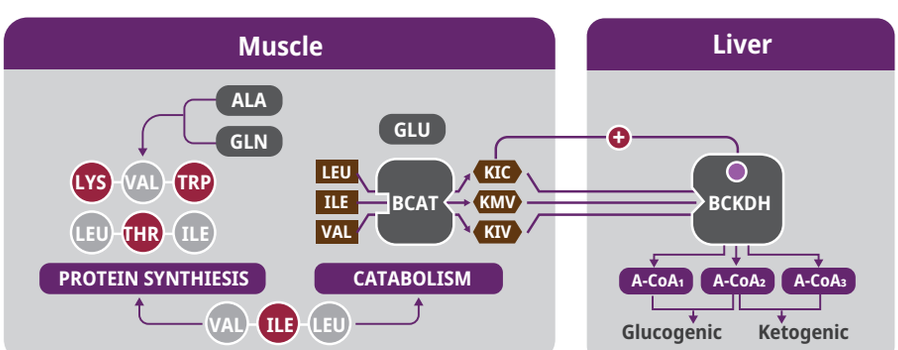

Figure 2. Metabolic process of branched chain amino acids (BCAA) in muscle and liver (ref. from CJ BIO Val handbook) BCAT; BCAA Transaminase, BCKDH; BC α-Keto acid Dehydrogenase, KIV Keto iso Valeric acid, KMV; Keto Methyl Valeric acid, KIC; Keto iso caproic acid

3) Amino acid toxicity :

Harper (1956) defines amino acid toxicity as a condition resulting from supplying an unpreventable excess of individual amino acids by supplementing the diet with other amino acids or groups of amino acids. As mentioned above, in recent feed formulations that control micronutrient content, toxicity due to an excess of amino acids practically does not occur. However, here, only some important toxicities are briefly mentioned.
Among the toxicity of amino acids, the most widely known is the toxicity of Met (Harper et al., 1970; FASEB, 1992). Toxicity due to Met excess is caused by inducing a relative deficiency of substances necessary for Met metabolism, so it has a mechanism different from toxicity caused by excess of sulfur amino acids such as Cyst(e)ine produced through Met metabolism. To understand the toxicity of Met, it is first necessary to understand the metabolism of Met. As the first step in the metabolism of methionine in the body, it is converted to Homocysteine through S-Adenosylmethionine (SAM) and S-Adenosylhomocysteine using three kinds of enzymes. Homocysteine again combines with serine to produce Cystathionine, which is synthesized as cysteine through the separation of NH4 and α-ketobutyrate (Fig. 3).

The basic mechanism of growth reduction and physiological (biochemical) toxicity due to excessive intake of Met is recognized as the essential cause of excessive intake of Met per The basic mechanism of physiological (biochemical) toxicity and physiological (biochemical) toxicity due to excessive intake of Met is recognized as the essential cause of excessive intake of Met per unit Serine required for the conversion process from Homocysteine to Cystathionine. And the reduction (deficiency) of this serine required for Met metabolism causes toxicity by increasing cellular oxidation through oxidation promotion by homocysteine, a metabolite of Met, and/or inhibition of the synthesis of Nitric oxide (NO), an antioxidant (Benevenga and Harper, 1970).
In addition, the mechanisms for inducing toxicity of Met known to date include induction of deficiency of other amino acids (Ser, Thr, Gly), occurrence of hemolytic anemia, and genetic diseases.

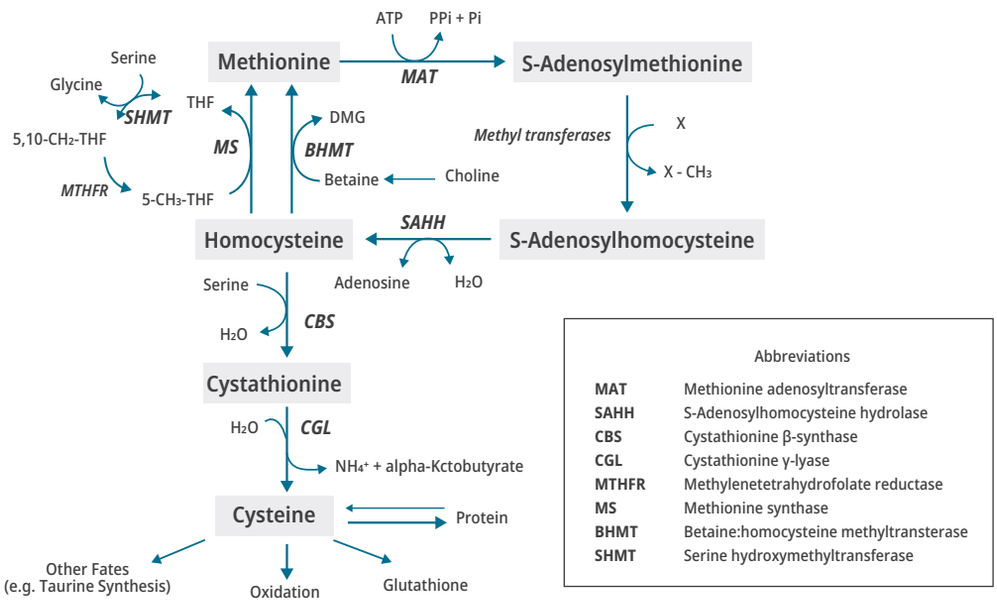

Figure 3. Metabolic pathway of L-Methionine (Brosnan and Brosnan, 2006)

Conclusion

It is known that amino acid imbalance and antagonism, excluding amino acid toxicity, generally occur in low crude protein (CP) feeds due to restrictions on the use of dietary protein ingredients. However, in the case of feed formulations of the classical period when the quality of feed was evaluated only with CP content, it strongly suggests that side effects caused by these amino acids are caused if the content of essential amino acids is not considered, even if the feed has a normal level of CP content. In other words, since the dietary CP content is a method of indirectly estimating the protein content from the amount of nitrogen contained in the raw material, it also includes various non-protein nitrogens such as urea, ammonia, nucleotide, and vitamins that contain nitrogen rather than protein. Therefore, there is no consideration for the content of amino acids required for biosynthesis of proteins in the body, and it is not known whether essential amino acids are contained in a balance even with a high CP content. In addition, most of the feed ingredients we commonly use are often supplementary protein sources that do not contain a balance of essential amino acids necessary for protein production in animals. Therefore, the addition of essential amino acids is indispensable from the viewpoint of maximum effect at the aforementioned minimum cost, and the range of use of essential amino acids and the appropriate level of addition are in accordance with the current dietary CP level and the performance of livestock should continuously be reviewed.

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