Beyond Lysine and Methionine: What Have We Learned About Histidine?

Ranga Appuhamy
Department of Animal Science
Iowa State University
Ames, IA

Introduction

Amino acids are the building blocks of protein synthesis. Of 20 amino acids usually taking part in protein synthesis, the body is able to produce only 10 in adequate quantities. Therefore, the other 10 amino acids (arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine) must be obtained in the diet and thus called essential amino acids. It is now a common knowledge that a deficiency of one or multiple essential amino acids would significantly limit milk protein synthesis in lactating dairy cows. Lysine and methionine are considered the most limiting amino acids for dairy cows in North America, as commonly used feeds such as corn and soybean are deficient in those two amino acids. Nonetheless, marked increases in prices of those conventional feeds in recent years have prompted many considerations about alternative feeds for dairy cows. In this context, partial replacement of corn with other cereal grains such as barley and wheat has been recognized as a promising strategy. Moreover, along with greater demand of forage inventory, nutrient management in dairy farms has promoted growing more and more cereal-grain cover crops such as rye, oats, wheat, triticale, and barley. Those crops uptake more nutrients from manure and better tolerate cold weather in winter and fall than corn. Nonetheless, cereal cover crop forages contain 20 to 30% greater rumen degradable protein than corn silage indicating an increased contribution of microbial protein to the amino acid supply for milk production. Bergen et al. (1968) demonstrated that rumen microbial proteins were deficient in histidine compared to the requirements of protein synthesis in the body. There have been several studies focused on the impact of supplementation of histidine in dairy cows fed grass silage and other cereal grain supplements. However, the conclusions particularly about the limitations of methionine and lysine were mixed. For instance, Vanhatalo et al. (1999) and Korhonen et al. (2000) concluded that histidine was the first limiting amino acid, while neither methionine nor lysine were the second limiting, when grass silage-based diets were supplemented with cereal grains. On the other hand, Kim et al. (2000) concluded that not only histidine but also methionine and lysine were limiting for milk protein production in cows consuming similar diets. We hypothesized that bringing those literature data into one place and conducting a global statistical analysis would help us more accurately understand the limitations of histidine relative to that of methionine and lysine in cows consuming other cereal forages and grains than corn. Therefore, we conducted a meta-analysis using data from controlled-studies where histidine was supplemented with or without methionine and lysine in lactating dairy cows fed grass silage and other cereal grain-based diets.

Materials & Methods

Twenty-five observations (treatment means) of dry matter intake, diet composition, milk yield and composition, and amino acid dose were obtained from seven studies (Choung et al., 1995; Vanhatalo et al., 1999; Kim et al, 2000; Korhonen et al., 2000; Kim et al., 2001; Huhtanen et al., 2002; Haque et al., 2012). These studies included abomasal or intravenous infusion of histidine relative to a control group (saline infusion). A summary of basic characteristics of the diet and cows are given in Table 1. All the studies except one (Haque et al. 2012) used silage made of perennial rye grass, timothy grass or meadow fescue grass as the only forage. Barley grain was the primary concentrate supplement in all the studies. The average sample size was four cows and ranged from two to six cows per treatment. The 25 observations altogether represented a population of 107 early- and mid-lactating multiparous Holstein (52%) and Ayrshire (48%) cows in Finland, United Kingdom, and France. The site of amino acid infusion was however confounded in breed as all the Holstein cows received amino acids via intravenous infusions, whereas all the Ayrshire cows received them via abomasal infusions.

Of 25 observations, 12 observations were related to infusion of histidine without methionine or lysine. Three of those histidine infusions also included leucine but they were still considered to include only histidine (**His**) as the effects of leucine were negligible. Six and seven observations were related to infusions of histidine with methionine and lysine (**His+ML**) and with methionine, lysine, and tryptophan (**His+ML+Trp**), respectively. Table 2 gives the dose of individual amino acids infused in each treatment group. Infusion of histidine alone or with other Infusion of histidine alone or with other amino acids did not change milk fat yield compared to that of control cows. Infusion of histidine alone however decreased milk fat content by 0.17 (P = 0.001). In line with milk yield increments, infusion of histidine alone increased milk lactose yield by 36.6 g/d (P < 0.001). The additions of tryptophan methionine, and lysine nullified that effect (P = 0.619). Infusion of histidine alone did not change milk lactose percentage (P = 0.244) but infusion of histidine with methionine and lysine or with methionine and lysine plus tryptophan reduced milk lactose percentage in additive manner (-0.06±0.03 and -0.26±0.05 percentage units, respectively).

The mean effects of His, His+ML, or His+ML+Trp on a given response (e.g., milk yield) was calculated in terms of mean difference (MD), which is the difference in the response variable between control and amino acid infusion treatment in each individual study.

MD=Mean response(control)-
Mean response (treatment)

The MD were then combined and summarized across all the studies using the metafor package in R software as described in Appuhamy et al. (2013). The present approach of meta-analysis accounts for the random variability of individual studies. A preliminary data analysis revealed that the site of infusion (or breed) had a significant impact on the production responses to amino acid infusions (Table 3). For instance, cows receiving intravenous infusions were related to a significantly greater milk yield increases than cows receiving abomasal infusions. Therefore, the effects of His, His+ML, and His+ML+Trp on each response of interest were adjusted for the variability in the site of infusion by including it in the statistical models.

Results

The mean changes in DMI, milk yield, and milk component yields for supplementation of His alone or with other amino acids are given in Table 4. Supplementation of histidine alone at a dose of 6.5 g/d increased DMI by 0.25 kg/d (P = 0.002). Addition of methionine and lysine or methionine and lysine plus tryptophan to histidine infusions did not significantly change that increment. When adjusted to the site of infusion, supplementation of histidine alone was related to a 0.94±0.16 kg/d increase in milk yield (P<0.001). Again, the additions of other amino acids did not change the milk yield increment. In line with the milk yield increase, protein yield increased by 35.0 g/d for the histidine supplementation (P < 0.001). Addition of methionine and lysine to histidine did not change the protein yield increment (P = 0.466) but addition of them with tryptophan tended to further increase the protein yield increment to 74.4 g/d (P = 0.069). Supplementation of histidine alone tended to increase milk protein content by 0.04 percentage units (P = 0.081) compared to the milk protein content of control cows (3.0%, Table 1). Addition of methionine, lysine, and tryptophan to histidine further increased milk protein content increment to 0.21 percentage units.

Conclusions

Regardless of the site of infusion (or breed), supplementation of histidine alone (6.5 g/d) increased DMI (0.25 kg/d), milk yield (0.94 kg/d), milk protein yield (35 g/d), milk protein content (0.04 percentage units) and milk lactose yield (37 g/d)), and decreased milk fat content (0.17 percentage units). Supplementation of histidine (6.5 g/d) with methionine (8.2 g/d) and lysine (16.1 g/d) did not affect those changes. However, addition of tryptophan into a mixture of histidine (6.5 g/d), methionine (7.3 g/d), and lysine (25.8 g/d) further improved milk protein yield and milk protein content by 74.4 g/d and 0.21 percentage units, respectively. Again, the real cause of those improvements were not clear, as the supplementation of tryptophan was confounded in different lysine: methionine ratios. Overall, this meta-analysis supports previous observation that histidine is significantly limiting for milk protein production in dairy cows consuming grass silage and cereal grain-based diets. Moreover, it is likely that a tryptophan deficiency or an improper ratio of lysine and methionine could also be limiting for milk protein production in those cows.

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Table 1. A summary of the data

Variable	Mean	Minimum	Maximum
---Diet---			
DMI, kg/d	17.0	13.6	19.9
NE_L, Mcal/d	26.0	21.6	32.7
Grass silage, % of DM	58.2	0.0*	74.6
Barley grain, % of DM	17.1	4.8	23.3
Crude Protein, % of DM	16.8	12.9	20
NDF, % of DM	41.6	27.4	47.9
---Animals---			
BW, kg	551	509	621
DIM	82	35	179
Milk yield, kg/d	23.8	14.2	32.7
Milk protein, %	3.0	2.7	3.7
Milk fat, %	4.3	3.3	5.9
Lactose, %	4.8	4.3	5.0

Table 2. Mean dose of amino acids (g/d) in each infusion treatment

Infusion	Histidine	Methionine	Lysine	Tryptophan	Lysine: methionine ratio
His	6.5	0	0	0	NA
His+ML	6.5	8.2	16.1	0	1.96
His+ML+Trp	7.2	7.3	25.8	3.3	3.53

Table 3. Mean changes in DMI and production performance of cows having abomasal or intravenous infusions compared to control cows

Response	Abomasal	Intravenous	SEM	*P*-value
DMI, kg/d	0.20	0.28	0.09	0.583
Milk yield, kg/d	0.90	1.90	0.08	<0.001
Milk protein yield, g/d	37.8	61.0	10.3	<0.001
Milk fat yield, g/d	-7.90	19.0	11.6	0.096
Milk lactose yield, g/d	33.8	84.5	11.9	0.003

Table 4. Mean (±Standard error) changes in DMI and production performances of lactating dairy cows for infusion of histidine alone (+His), histidine plus methionine and lysine (His+ML), and histidine plus methionine, lysine, and tryptophan (His+ML+Trp), when adjusted for the site of infusion

Variable	Infusion Treatment		
	His (n = 12)	His+ML (n = 6)	His+ML+Trp (n = 7)
DMI, kg/d	0.25±0.08	0.18±0.06	0.29±0.18
Milk yield, kg/d	0.94±0.16	0.90±0.11	0.64±0.36
Milk protein			
Yield, g/d	35.0±7.9	41.8±9.6	74.4±22.7
%	0.04±0.02	0.06±0.03	0.21±0.09
Milk fat			
Yield, g/d	-5.1±10.7	-4.5±15.7	-34.7±28.7
%	-0.17±0.05	-0.03±0.09	-0.21±0.16
Milk lactose			
Yield, g/d	36.6±10.2	27.9±12.2	-13.8±27.7
%	-0.02±0.02	-0.06±0.03	-0.26±0.05