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Histidine dose-response effects on lactational performance and plasma amino acid concentrations in lactating dairy cows: 1. Metabolizable protein-adequate diet

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ABSTRACT

The objective of this experiment was to determine the effect of increasing digestible His (dHis) doses on milk production, milk composition, and plasma AA concentrations in lactating dairy cows fed diets that meet or exceed their energy and metabolizable protein (MP) requirements. In a companion paper (Räisänen et al., 2021) results are presented on the effect of increasing dHis dose with an MP-deficient basal diet. In this experiment, 16 Holstein cows (72 ± 15 d in milk) were used in a replicated 4 × 4 Latin square design experiment with four 28-d periods. Treatments were as follows: (1) control, total mixed ration (TMR) with 1.8% dHis of MP (TMR1; dHis1.8); (2) a different TMR with 2.2% dHis (TMR2; dHis2.2); (3) TMR2 supplemented with rumen-protected His (RP-His) to supply 2.6% dHis (dHis2.6); and (4) TMR2 supplemented with RP-His to supply 3.0% dHis of MP (dHis3.0). Estimated dHis intakes calculated at the end of the experiment were 46, 58, 69, and 79 g/d for dHis1.8, dHis2.2, dHis2.6, and dHis3.0, respectively. Contrasts were used to compare TMR1 with TMR2 and to test the linear and quadratic effects of RP-His inclusion rate on TMR2. We detected no effects of TMR or dHis dose on dry matter intake or milk yield, whereas energy-corrected milk (ECM) yield was quadratically increased, being greatest for cows on treatment dHis2.6. Milk true protein and lactose concentrations and milk true protein yield were not affected by TMR or dHis dose. Milk fat concentration and yield increased quadratically, and lactose yield tended to increase quadratically with increasing dHis dose. Calculated apparent efficiency of His utilization decreased quadratically with increasing dHis supply. Further, plasma concentration of His was greater for cows on TMR2 compared with TMR1. When an MP-adequate diet was fed to dairy cows, milk true protein concentration and yield were not affected by dHis supply, but milk fat and ECM yields of dairy cows were optimized at dHis supply of 69 g/d or 2.65% of MP.
Key words: histidine, milk production, plasma amino acid, dairy cow

INTRODUCTION

Modifying dairy cow diets to supply less total protein but balanced AA supply may be a powerful tool in decreasing the negative environmental effect of nitrogen excretion from dairy operations while decreasing feed costs and maintaining milk production (Hristov et al., 2015). The true requirements of the dairy cow are for AA and not protein; therefore, the focus should shift from supplying dietary protein to providing the cow with digestible AA for optimal production (Patton et al., 2014). The National Research Council dairy model from 2001 has recommendations for the supply of digestible (**d**)Lys and dMet, but studies have suggested His to be another AA that may enhance milk and milk protein yields (Lee et al., 2012a; Giallongo et al., 2015, 2017). This is thought to be due to the lower His:Met ratio in microbial protein synthesized in the rumen compared with the same ratio in milk protein (Kim et al., 1999). Thus, His deficiency is even more apparent in situations in which the cow is more reliant on microbial protein to meet AA needs (Lee et al., 2012b); for example, when low-protein or grass silage–based diets are fed. Indeed, several studies have shown that His supplementation increases milk production, milk protein production, or both of cows fed a MP-deficient diet (Lee et al., 2012a; Giallongo et al.,

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2015; Zang et al., 2019). Abomasal infusion of His has been shown to increase milk and milk protein yields of cows on grass silage–based diets (Vanhatalo et al., 1999; Kim et al., 2001; Huhtanen et al., 2002). Further, a long-term experiment with low and high His supply on MP-adequate corn silage–based diets showed that decreased dHis supply (49 vs. 68 g/d) compromises the lactational performance of dairy cows, even when the MP requirements of the cow are met (Giallongo et al., 2017). These experiments indicate that His deficiency is more apparent in diets supplying less RUP (i.e., grass silage–based or MP-deficient diets), but even in situations in which the diet is adequate in MP, His deficiency can limit milk and milk protein production.

There is some evidence that a long-term His deficiency may compromise the DMI of the cow, and supplying additional His increases not only milk and milk protein production but also DMI (Lee et al., 2012a; Giallongo et al., 2015; Giallongo et al., 2017). Indeed, deficiencies, excesses, and imbalances of dietary protein and AA can lead to suppressed intake (Mercer et al., 1990). This effect of His on DMI may be related to AA acting as signaling molecules on the brain (Anthony and Gietzen, 2013; Heeley and Blouet, 2016) and through various intake-regulating metabolites (van den Broek et al., 2018). For example, His, along with other AA, has been associated with glucagon-like peptide-1 (**GLP-1**) and neuropeptide Y (**NPY**), which are appetite-regulating gut peptides in monogastric animals (Van den Broek et al., 2018). In addition, histamine, which is directly derived from His by cleavage of a carboxyl group by histidine decarboxylase mainly in mast cells and basophils of the immune system, gastric cells, and neurons, has been linked to several functions in the body, one of which is as a neurotransmitter (Brosnan and Brosnan, 2020). There is some evidence in monogastric animals of the role of histamine as an anorexic neurotransmitter that has receptors on the hypothalamus (Mercer et al., 1990; Yoshimatsu et al., 2002). The role of histamine in energy homeostasis has also been demonstrated in ruminants (Kurose and Terashima, 2007). However, there are no experiments measuring histamine concentration in the serum of lactating cows supplemented with rumen-protected His (**RP-His**).

Studies on the effects of incremental levels of dHis on milk and milk protein production as well as DMI in lactating dairy cows are lacking, and the effects of MP level on the production responses to different levels of His supplementation has not been previously demonstrated. Two experiments were therefore designed to supplement incremental levels of RP-His to lactating dairy cows on an MP-adequate (current study) or an MP-deficient diet (companion paper, Räisänen et al., 2021). The objective of this experiment was to assess the effect of increasing dHis dose on lactational performance and plasma His concentration of lactating cows fed an MP-adequate, His-deficient diet or an MP-adequate diet supplemented with 1 of 2 additional dHis doses. We hypothesized that incremental dHis supply would increase DMI, milk yield (**MY**), and milk protein yield as well as plasma His concentrations linearly.

MATERIALS AND METHODS

Animals, Housing, and Experimental Design

The animals involved in this experiment were cared for according to the guidelines of the institutional animal care and use committee at The Pennsylvania State University. The committee approved the experiment and all procedures involving animals.

A total of 16 lactating cows, of which 4 were primiparous (72 ± 15 DIM, 611 ± 70 kg of BW, 46.7 ± 7.8 kg/d MY, at the beginning of the experiment), were used in a replicated 4 × 4 Latin square design experiment. The cows were assigned to 4 blocks based on parity, DMI, and MY. The duration of each experimental period was 28 d with 3 wk of adaptation and 1 wk of sampling. The experiment was conducted in the tie-stall barn of the Dairy Research and Teaching Center of The Pennsylvania State University. The barn was equipped with forced-air ventilation, individual rubber mats, and water bowls with free access to water. Cows were milked twice daily, at 0630 and 1900 h. Before morning milking, the cows had access to an exercise area for 1 h. Diets were mixed using a mobile mixer (Rissler Mobile TMR Mixer Model 1050; I. H. Rissler) and were fed once daily at 0800 h.

Diet and Treatments

The experimental diets were formulated to supply adequate MP and 4 incremental levels of dHis, according to NRC (2001), based on actual AA analysis of the dietary feed ingredients (University of Missouri–Columbia's Agricultural Experiment Station Chemical Laboratories, Columbia, MO). The following treatments were tested in this experiment: dHis (as % of MP) at (1) 1.80 (**dHis1.8**), (2) 2.2 (**dHis2.2**), (3) 2.6 (**dHis2.6**), and (4) 3.0% (**dHis3.0**). Two basal diets (Table 1) were formulated to meet the energy and MP requirements of a lactating Holstein cow with an average BW of 638 kg, DMI of 26 kg/d, MY of 47.0 kg/d, and milk fat and milk true protein contents of 3.29% and 2.85%, respectively. The 2 TMR were different only in the amount of feather meal and blood meal (Table 1), and subsequently dAA supply estimated using NRC (2001; Table 2). One of the TMR was formulated to

supply 1.8% dHis of MP (**TMR1**), or around 46 g of dHis/d, and was fed to the control group (dHis1.8), whereas the other TMR supplied 2.2% dHis of MP (**TMR2**), or around 58 g of dHis/d, and was fed to the other 3 treatment groups (dHis2.2, dHis2.6, and dHis3.0). Treatments dHis2.6 and dHis3.0 were top-dressed with RP-His (experimental product, Ajinomoto Co. Inc.) to provide an additional 11 and 22 g of dHis/d, respectively (Table 2). The amount of dHis supplied from RP-His was based on a bioavailability estimation by Räisänen et al. (2020). All diets were supplemented with RP-Met (Mepron, Evonik Operations GmbH) and RP-Lys (AjiPro-L, Ajinomoto Co. Inc.) to meet or exceed the recommendations for dLys and dMet, of 6.6 and 2.2% of MP, respectively (NRC, 2001; Schwab et al., 2005).

Sample Collection and Measurements

Feed and TMR Sampling. Weights of feed offered and refusals were recorded daily, and feeding rate was adjusted to yield refusals equal to 10% of intake. Fresh TMR samples were collected twice weekly, immediately after being prepared and as feed was delivered to the cows. Refusal samples and forages were also collected twice weekly, and weekly composites of the TMR, refusals, and forages was prepared. Concentrate feeds were sampled weekly. The feed samples were stored at −20°C and subsequently dried in a forced-air oven at 55°C for 72 h for DM determination. Dried samples were ground using a Wiley mill (Thomas Scientific) through a 1-mm screen, and 1 composite sample for each period (TMR) or the entire experiment (individual feed ingredients) was prepared on an equal weight basis for further analysis. Composited samples of the individual feed ingredient were sent to Cumberland Valley Analytical Services (Waynesboro, PA) for wet chemistry analysis of OM, NDF (Van Soest et al., 1991), ADF (method 973.18; AOAC International, 2000), CP (method 990.03; AOAC International, 2000), ether extract (method 954.02; AOAC International, 2000), ash (method 942.05; AOAC International, 2000) and Ca and P (method 985.01; AOAC International, 2000). Starch was analyzed as described in Hall (2009). Composite samples of blood and feather meal were analyzed for protein fractions and RUP digestibility determined in vitro according to Calsamiglia and Stern (1995) by Rock River Laboratories Inc. (Watertown, WI). Individual feed ingredients were analyzed for AA with ion-exchange chromatography by Evonik Operations (AOAC International, 1995; European Commission, 2009). Chemical composition of the TMR was reconstituted from analyzed composition of the individual feed ingredients and their inclusion in the TMR (Table 1).

Table 1. Ingredient and chemical composition of the experimental diets used in the experiment

	Diet[1]	
Composition	TMR1	TMR2
Feed ingredients, % of DM		
Corn silage[2]	44.1	44.3
Alfalfa haylage[3]	14.9	14.9
Straw/hay mix[4]	4.47	4.48
Ground corn	8.93	8.96
Roasted soybeans	6.95	6.97
SoyPLUS[5]	2.48	2.49
Porcine RBC[6]	—	1.49
Hydrolyzed feather meal[7]	4.96	3.48
Whole cottonseed	5.95	5.97
Molasses[8]	4.96	4.98
Mineral mix[9]	1.53	1.53
Mepron[10]	0.18	0.14
AjiPro-L[11]	0.57	0.28
Chemical composition,[12] % of DM		
CP	16.8	17.1
NDF	32.3	32.1
ADF	21.1	20.9
NFC	42.5	42.5
Starch	28.0	28.0
NE_L,[13] Mcal/kg	1.57	1.58
Ash	4.69	4.68
Ca	1.27	1.26
P	0.35	0.35

[1]TMR1 was formulated to supply digestible His (dHis) at 1.8% of MP requirements, and TMR2 to supply dHis at 2.2% of MP requirements.

[2]Corn silage was 41.3% DM and contained (DM basis) 7.6% CP, 38.7% NDF, and 41.8% starch.

[3]Alfalfa hay was 33.4% DM and contained (DM basis) 19.6% CP, 43.7% NDF, and 2.49% starch.

[4]Straw/hay mix was 81.4% DM and contained (DM basis) 12.5% CP, 64.5% NDF, and 3.2% starch.

[5]Landus Cooperative.

[6]Porcine red blood cells (West Central Cooperative) contained DM-basis 106% CP. Rumen undegradable protein, 75.5% of CP; intestinal digestibility, 80.5% of RUP [determined in vitro according to Calsamiglia and Stern (1995) method by Rock River Laboratories Inc. (Watertown, WI)].

[7]Hydrolyzed feather meal (Papillon Agricultural Company LLC) contained DM-basis 94.4% CP. Rumen undegradable protein, 71.1% of CP; intestinal digestibility, 50.5% of RUP [determined in vitro according to Calsamiglia and Stern (1995) method by Rock River Laboratories Inc. (Watertown, WI)].

[8]Westway Feed Products.

[9]Mineral/vitamin Premix (Cargill Animal Nutrition, Cargill Inc.) contained (%, as-is basis) limestone, 36.75; dry corn distillers grains with solubles, 29.00; NaCl, 24.85; MgO (54% Mg), 4.15; Bio-Phos (Rootwise), 2.45; zinc sulfate, 0.96; mineral oil, 0.5; vitamin E, 0.37; manganese sulfate, 0.37; copper sulfate, 0.26; ferrous sulfate, 0.16; Se, 0.13; vitamin A, 0.03; vitamin D_3, 0.013; calcium iodate, 0.008; cobalt carbonate, 0.005.

[10]Evonik Operations GmbH.

[11]Ajinomoto Co. Inc.

[12]Unless indicated otherwise, values were calculated using the chemical analysis (Cumberland Valley Analytical Services Inc., Waynesboro, PA) of individual feed ingredients and their inclusion rates in the diet.

[13]Values estimated based on NRC (2001).

Table 2. Net energy of lactation, protein fractions, and AA supply and balance[1] in mid-lactation dairy cows fed a MP-adequate diet supplying incremental levels of digestible (d)His

	Treatment[2]			
Item	dHis1.8	dHis2.2	dHis2.6	dHis3.0
NE_L, Mcal/d				
Requirement	38.2	39.5	40.5	38.7
Supply	36.4	37.6	36.8	36.4
Balance	−1.8	−1.9	−3.7	−2.3
Protein fraction balance, g/d				
MP				
Requirement	2,530	2,624	2,606	2,547
Supply	2,494	2,680	2,633	2,600
Balance	−36	56	27	53
Supplied/requirement	0.99	1.02	1.01	1.02
RDP and RUP				
RDP supply	2,318	2,135	2,085	2,061
RDP balance	−237	−246	−242	−241
RUP supply	1,812	1,957	1,904	1,877
RUP balance	−53	79	38	72
AA balance, g/d				
dHis				
Supply from basal diet	46	58	58	57
Supply from RP-His[3]	—	—	11	22
Total supply	46	58	69	79
dMet				
Requirement[4]	56	58	57	56
Supply from basal diet	40	42	40	40
Supply from RP-Met[3]	21	18	18	18
Balance	5	2	1	2
dLys				
Requirement[4]	167	173	172	168
Supply from basal diet	135	154	151	149
Supply from RP-Lys[3]	34	19	19	19
Balance	2	0	−2	0
Other AA supplied,[1] g/d				
dArg	111	117	115	114
dIle	116	118	115	114
dLeu	207	230	227	224
dPhe	120	131	129	127
dThr	114	120	118	116
dVal	134	147	144	143
Total digestible EAA	1,078	1,154	1,135	1,121

[1]Values were estimated using NRC (2001) based on actual averaged DMI, milk yield and composition, and BW of cows during last 7 d of each experimental period.

[2]The 4 treatments supplied dHis at 1.82, 2.21, 2.65, and 3.10% of MP, respectively, from 2 basal diets and rumen-protected His (RP-His) product (dHis1.8: TMR1; dHis2.2: TMR2; dHis2.6: TMR2 + 11 g/d of dHis from RP-His; dHis3.0: TMR2 + 22 g/d of dHis from RP-His). Both basal diets were supplemented with RP-Lys and RP-Met.

[3]The amounts dHis, dMet, and dLys from RPAA products were calculated based on the bioavailability estimations in Räisänen et al. (2020) for RP-His or provided by the manufactures for RP-Met and RP-Lys.

[4]Requirements of dMet and dLys were calculated as 2.2 and 6.6% of MP requirements, respectively (NRC 2001; Schwab et al., 2005).

Milk Yield, Body Weight, and Milk Sampling. Milk yield and BW of the cows were recorded daily at each milking. Milk samples from 2 consecutive p.m. and a.m. milkings were collected during the last week of each experimental period in 20-mL tubes with 2-bromo-2-nitropropane-1,3-diol and analyzed for fat, true protein, MUN, and lactose concentrations by Dairy One Laboratory (Ithaca, NY). A separate 45-mL milk sample was collected and stored at −20°C for analysis of milk casein and NPN fractions after compositing on an equal volume basis per cow and experimental period. Milk fat was separated from the samples by centrifuging at 5,000 × *g* and 10°C for 15 min. The fat-free milk samples were precipitated with 2.5 mL of 65% TCA (final TCA concentration of 5% wt/vol), kept on ice for 30 min and centrifuged at 20,000 × *g* and 4°C for 15 min to separate milk protein. The supernatant representing NPN and the pellet representing casein were

freeze-dried (VirTis Ultra 35L; SP Scientific) and analyzed for N with a Costech ECS 4010 C/N/S elemental analyzer (Costech Analytical Technologies Inc.).

Fecal and Urine Sampling. Eight fecal and urine samples each were collected every 6 h over the last 3 d of each experimental period (at 0500, 1100, 1700, and 2300 h on d 1; at 0800, 1400, and 2000 h on d 2; and at 0200 h on d 3) to represent a 24-h feeding cycle. Fecal samples (approximately 500 g each) were collected by rectal stimulation and immediately dried at 55°C to constant weight. The dried samples were ground in a Wiley mill (Thomas Scientific) through a 1-mm screen and composited on an equal weight basis per cow and period. Composited fecal samples were analyzed for total N using Costech ECS 4010 C/N/S elemental analyzer (Costech Analytical Technologies Inc.), indigestible NDF, ADF, and NDF with Ankom 200 fiber analyzer (Ankom Technology Corp.) and starch (Hall, 2009) to determine total-tract N, NDF, ADF, and starch digestibility. Indigestible NDF was used as a total-tract digestibility marker (Schneider and Flatt, 1975). Composited TMR and fecal samples for each period and cow were incubated for 12 d in the rumen for analysis of indigestible NDF (Huhtanen et al., 1994; Lee et al., 2012a).

Urine samples were collected by stimulation of the vulva and filtered through 2 layers of cheesecloth. Aliquots of urine samples were added to 2 *M* sulfuric acid to reach a pH <3.0, diluted 1:10 with distilled water and stored at −20°C until analysis. Urine samples were composited on an equal volume basis per cow and period and analyzed for allantoin (Chen et al., 1992), uric acid (Uric acid kit 1045; Stanbio Laboratory Inc.), urea N (**UUN**; Urea nitrogen kit 580; Stanbio Laboratory Inc.) and creatinine (Creatinine kit 420; Stanbio Laboratory Inc.). Another aliquot of the composite urine samples was freeze-dried (VirTis Ultra 35L; SP Scientific) and analyzed for N using a Costech ECS 4010 C/N/S elemental analyzer (Costech Analytical Technologies Inc.). Daily urinary volume was estimated based on urinary creatinine concentration, assuming a creatinine excretion rate of 29 mg/kg of BW (Hristov et al., 2011). Estimated daily urine output was used to calculate daily excretions of total N, UUN, and purine derivates (allantoin and uric acid).

Blood Sampling. Blood samples were collected from the tail vein or artery of the cows 4 times on 2 consecutive days in wk 4 of each experimental period, at 1100 and 1700 h on d 1 and at 1400 and 2000 h on d 2. Blood plasma was collected into heparinized Vacutainer tubes (Becton, Dickinson and Co.) and blood serum into Vacutainer tubes containing silica clot activator (SST tube; Becton, Dickinson and Co.). In addition, whole-blood samples were collected at 1100 and 1400 h into Vacutainer tubes containing EDTA and analyzed for hemoglobin concentration on the day of sampling. Plasma and serum were separated by centrifugation at 1,500 × *g* and 4°C for 15 min and at 1,800 × *g* and 20°C for 30 min, respectively. Composited plasma samples (1 sample/cow and period) were analyzed for AA concentration by Evonik Operations GmbH as described above. Blood serum samples (collected at 1700 h) were analyzed for GLP-1; inter- and intraassay coefficients of variation (**CV**) <10 and <15%; Bovine GLP-1 Competitive ELISA, EKB01721, Biomatik USA), NPY; inter- and intraassay CV <10 and <12%; Bovine NPY ELISA Kit No. EKC31744, Biomatik USA), insulin (inter- and intraassay CV <10 and <10%; Bovine Insulin ELISA, Kit No. 10-1201-01, Mercodia AB) and histamine (inter- and intraassay CV <10 and <12%; pan-species ELISA, Kit No. EKU04794, Biomatik USA).

Calculated Histidine Pools and Efficiency of Utilization. Apparent recovery of dHis in blood and milk His pools were calculated based on the individual cow DMI, MY, and milk composition data during the experiment and estimated dHis intake according to NRC (2001). The amount of His in plasma and blood pools was calculated based on an assumed blood volume of 6.7% of BW, and plasma volume of 68% of blood volume (Reynolds, 1953), and by extrapolating the amount of His in 1-methylhistidine (**MH**) and hemoglobin, using their plasma and blood concentrations, respectively. The amount of His in these metabolites was based on the proportion of His molecular weight in the molecular weight of the metabolite in question. It is noted that other His-containing metabolites, 3-MH and carnosine, were not analyzed in the current experiment but are included in the His pool calculations in our companion paper (Räisänen et al., 2021). Histidine concentration in milk CP was assumed to be 2.7%, based on an averaged value from Lee et al. (2015). Apparent recovery of dHis in milk His pool was calculated as milk His (g) ÷ dHis intake (g) × 100. Apparent recovery of dHis in blood was calculated as total His in blood (g) ÷ dHis intake (g) × 100, where total His in blood was the sum of plasma His (g), His in 1-MH, and His in hemoglobin. Apparent recovery of dHis in blood and milk His pools was calculated as [total blood His (g) + milk His (g)] ÷ dHis intake (g) × 100. Last, apparent efficiency of His utilization ($\mathbf{Eff_{His}}$) was calculated as described in Lapierre et al. (2020):

$$\mathrm{Eff_{His}} = \frac{\text{sum of His in true exported proteins (g)}}{\left[\text{digestible His flow (g)} - \text{endogenous urinary loss}\right]},$$

where the sum of His in true exported proteins includes milk true protein yield and estimated scurf and metabolic fecal protein calculated as detailed in Lapierre et al. (2020).

Statistical Analysis

Data were analyzed using the MIXED procedure of SAS (release 9.4, SAS Institute Inc.). Milk yield and DMI from the last 7 d of each experimental period were analyzed as a repeated measure. The best covariance structure for repeated measures was chosen based on the lowest Akaike information criterion, and was first-order autoregressive for DMI and BW and compound symmetry for MY and feed efficiency. The statistical model included the repeated term (day), period, parity, and treatment. Parity × treatment interactions were not significant and were excluded from the model. Square and cow within square were random effects, and all others were fixed. Milk composition, milk component yields, ECM, ECM feed efficiency, plasma AA, nutrient intake and digestibility, excretion of N compounds, and serum metabolites data were analyzed with the same model without the repeated term. Milk composition data were weighted averages based on the milk production at each milking. Orthogonal and polynomial contrasts were used to test the effect of TMR (TMR1 vs. TMR2) and linear and quadratic effects of dHis dose with TMR2. Differences were considered at $P \leq 0.05$, and trends were declared at $0.05 < P \leq 0.10$. Data are presented as least squares means.

RESULTS AND DISCUSSION

Two experimental TMR (TMR1 and TMR2, Table 1) were fed to the cows in this study. Diets differed in the amount of feather meal (5.0 vs. 3.5% of DM), and blood meal (0 vs. 1.5% of DM) but had similar composition of major nutrients. TMR1 was formulated to be low in dHis (1.8% of MP) by replacing blood meal with a greater concentration of feather meal. The effect of TMR was included in the statistical analysis, and the effect of dHis dose was tested with TMR2 only, as discussed below.

Nutrient intakes and balances were estimated using NRC (2001) at the end of the experiment based on the actual DMI and production of the cows and nutrient analysis of feed ingredients collected during the experiment. As shown in Table 2, the energy supply from the basal diets was slightly deficient as percentage of NE_L requirements according to NRC (2001); for cows on treatments dHis1.8 (95%), dHis2.2 (95%), dHis2.6 (91%), and dHis3.0 (94%). However, the cows on all treatments produced more than the NRC (2001)-predicted NE_L-allowable milk (+2.7, +2.7, +5.2, and +3.3, respectively). Treatment dHis1.8 was slightly deficient in MP supply from the basal diet (around 99% of MP requirements).

Dry Matter Intake and Production Variables

In the current experiment, we detected no effects ($P \geq 0.14$) of TMR or dHis dose on DMI or MY (Table 3). There was a quadratic effect ($P \leq 0.02$) for increased ECM yield and ECM feed efficiency with increasing dHis dose.

Earlier research reported no effects of postruminal supply of His on DMI in cows fed grass silage–based diets (Korhonen et al., 2000; Kim et al., 2001) or RP-His supplementation of cows fed MP-deficient, corn silage–based diet with incremental levels of His (Zang et al., 2019). However, previous long-term studies (8–10 wk) from our laboratory have shown a positive effect of His on DMI in high-producing, mid-lactation cows fed both MP-adequate (Giallongo et al., 2017) and MP-deficient diets (Lee et al., 2012a; Giallongo et al., 2015). Giallongo et al. (2017) observed a 1.7-kg-greater DMI of cows on a diet supplying 68 g/d of dHis compared with cows on a diet supplying 49 g/d of dHis. Similarly, cows supplied with 59 g/d of dHis ate 1.7 kg less DM than cows supplied with 75 g/d of dHis (Giallongo et al., 2015). Lee et al. (2012a) reported a tendency for a greater intake (+1.3 kg/d of DMI) in cows receiving 59 g/d of dHis than in cows supplied with 44 g/d of dHis. In a Latin square experiment, in which high levels of feather meal were included to induce His deficiency, DMI was decreased by 1.6 and 1.9 kg/d for high-protein and standard-protein diets, respectively (Stahel et al., 2014). The decrease in DMI was attributed to His deficiency, but the authors also noted that reduced DMI may have been caused in part by decreased palatability due to the high inclusion of feather meal (Stahel et al., 2014). The short-term nature of the current experiment; that is, 28-d periods compared with 8- to 10-wk experiments conducted by Lee et al. (2012a) and Giallongo et al. (2015, 2017), may have contributed to the lack of effect on DMI (Giallongo et al., 2017).

Milk yield was not affected by dHis dose in the current experiment, whereas the highest ECM yield was achieved by cows receiving 69 g/d of dHis (+2.0 kg/d compared with dHis supply of 58 g/d). Positive MY and ECM responses to His supplementation have been inconsistent across studies. Abomasal infusion of 6 g/d of His in cows fed a grass silage–based diet increased MY by 1.8 kg (Korhonen et al., 2000), whereas infusion of His with or without Lys and Met resulted in an average increase of 0.9 kg in MY in low-producing cows fed a grass silage–based diet (Vanhatalo et al., 1999).

Table 3. Lactational performance and BW of mid-lactation dairy cows fed a MP-adequate diet supplying incremental levels of digestible (d)His

Item	Treatment[1]				SEM[2]	*P*-value[3]		
	dHis1.8	dHis2.2	dHis2.6	dHis3.0		TMR1 vs. TMR2	Linear	Quadratic
DMI, kg/d	23.2	23.9	23.3	23.0	1.42	0.25	0.14	0.92
Milk yield, kg/d	41.2	42.6	43.0	42.0	2.71	0.23	0.76	0.34
Feed efficiency,[4] kg/kg	1.79	1.78	1.87	1.81	0.063	0.95	0.59	0.37
Milk fat, %	3.63	3.66	3.84	3.64	0.147	0.76	0.72	0.04
Fat, kg/d	1.49	1.53	1.65	1.52	0.109	0.38	0.65	0.005
Milk true protein, %	2.76	2.78	2.75	2.75	0.063	0.54	0.21	0.86
Protein, kg/d	1.14	1.17	1.18	1.15	0.072	0.25	0.77	0.29
Milk lactose, %	4.82	4.83	4.90	4.82	0.046	0.75	0.88	0.14
Lactose, kg/d	1.98	2.04	2.12	2.02	0.141	0.25	0.88	0.06
MUN, mg/dL	11.3	12.3	12.2	12.2	0.44	0.05	0.83	0.88
ECM,[5] kg/d	37.7	38.8	40.8	38.4	2.56	0.23	0.78	0.007
ECM feed efficiency, kg/kg	1.62	1.61	1.72	1.64	0.027	0.87	0.22	0.02
Milk NE_L,[6] Mcal/d	28.1	28.9	30.4	28.6	1.91	0.23	0.77	0.007
SCC,[7] $\times 10^3$ cells/mL	49.7	64.6	50.3	61.9	20.14	0.12	0.19	0.69
BW, kg	617	620	620	616	17.3	0.91	0.88	0.89

[1]The 4 treatments supplied dHis at 46, 58, 69, and 79 g/d, respectively, from 2 basal diets and rumen-protected His (RP-His) product (dHis1.8: TMR1; dHis2.2: TMR2; dHis2.6: TMR2 + 11 g/d of dHis from RP-His; dHis3.0: TMR2 + 22 g/d of dHis from RP-His). Both basal diets were supplemented with RP-Lys and RP-Met.

[2]Largest SEM published in table. n = 447 for DMI, n = 420 for MY and feed efficiency, n = 64 for milk composition variables (n represents number of observations used in the statistical analysis). Data are presented as LSM.

[3]Contrasts: effect of TMR without RP-His supplementation (TMR1: dHis1.8 vs. TMR2: dHis2.2); linear and quadratic effects of dHis dose with TMR2. Significance is declared at $P \leq 0.05$.

[4]Milk yield ÷ DMI.

[5]Calculated according to Sjaunja et al. (1990).

[6]Milk NE_L (Mcal/d) = kg of milk × (0.0929 × % fat + 0.0563 × % true protein + 0.0395 × % lactose); NRC (2001).

[7]Statistical analysis was performed on log-transformed data.

However, there was no effect of L-His infusion on ECM in either experiment. A short-term duodenal infusion of 13.6 g/d of His increased MY by 1.1 kg and ECM yield by 0.9 kg (Hadrová et al., 2012). Intravenous infusion of increasing doses of L-His to cows fed grass silage–based diets also increased MY quadratically by 3.4 kg/d (no His infusion vs. 6 g/d infused His), or linearly from 25.9 (no His) to 28.4 kg/d (9 g/d infused His) when infused together with Met and Lys (Kim et al., 2001). High-producing cows supplied with adequate MP (in the form of TMR and casein infusion) and infused with incremental levels of His for 6 d increased MY quadratically from 38.6 (no His infusion) to 42.8 kg/d (30.4 g/d infused His) as reported by Ouellet et al. (2014) or linearly from 32.2 (no His infusion) to 36.8 kg/d (22.8 g/d infused His) with 14-d infusions (Lapierre et al., 2014). A more recent experiment with similar design showed a 4.5 kg/d increase in MY when 0 to 22.8 g/d of dHis was abomasally infused in Holstein cows (Lapierre et al., 2020). Histidine was shown to increase MY in high-producing dairy cows fed an MP-deficient corn silage–based diet by 1.6 kg/d (Lee et al., 2012a) and 2.5 kg/d (Giallongo et al., 2015) and in cows on an MP-adequate diet by 2.9 kg/d (Giallongo et al., 2017). In the latter experiment, ECM yield was also greater for cows supplied with 68 versus 49 g/d of dHis (Giallongo et al., 2017). Further, Zang et al. (2019) observed a 1.5 kg/d increase in MY with no RP-His supplementation versus 246 g/d of RP-His, respectively, on a MP-deficient corn silage–based diet. Further, the magnitude of MY and ECM responses to incremental levels of RP-His were greater with a MP-deficient diet (Räisänen et al., 2021), compared with the current experiment with MP-adequate diet. These data, together with the current experiment and data from our companion paper (Räisänen et al., 2021), indicate that the length of His deficiency or supplementation, type of basal diet, and possible deficiencies in MP, other dAA, or both will affect the extent of MY and ECM responses to His supplementation.

Milk fat concentration and yield increased quadratically ($P \leq 0.04$) with dHis dose (Table 3). Neither milk true protein concentration nor yield was affected by TMR or dHis dose ($P \geq 0.21$). Lactose concentration was also similar across treatments ($P \geq 0.14$), whereas lactose yield tended to increase quadratically ($P = 0.06$) with increasing dHis dose. Cows on TMR1 had a lower ($P = 0.05$) MUN concentration than cows on TMR2.

Fat concentration has not been affected by His supplementation with a fat-coated RP-His product in previous experiments (Lee et al., 2012a; Giallongo et

Table 4. Milk casein and NPN fractions in mid-lactation dairy cows fed a MP-adequate diet supplying incremental levels of digestible (d)His

	Treatment[1]					*P*-value[3]		
Item	dHis1.8	dHis2.2	dHis2.6	dHis3.0	SEM[2]	TMR1 vs. TMR2	Linear	Quadratic
Casein, mg/mL	43.6	43.7	41.9	43.3	1.16	0.95	0.49	0.14
Casein, % of total milk N	92.9	93.7	93.2	93.0	0.58	0.18	0.19	0.89
Casein yield, kg/d	1.80	1.85	1.80	1.82	0.154	0.42	0.52	0.57
NPN, mg/mL	3.31	2.94	3.11	3.33	0.247	0.16	0.16	0.62
NPN, % of total milk N	7.05	6.28	6.76	7.04	0.576	0.18	0.19	0.89
NPN, kg/d	0.136	0.125	0.134	0.142	0.0116	0.33	0.17	0.73

[1]The 4 treatments supplied dHis at 46, 58, 69, and 79 g/d, respectively, from 2 basal diets and rumen-protected His (RP-His) product (dHis1.8: TMR1; dHis2.2: TMR2; dHis2.6: TMR2 + 11 g/d of dHis from RP-His; dHis3.0: TMR2 + 22 g/d of dHis from RP-His). Both basal diets were supplemented with RP-Lys and RP-Met.

[2]Largest SEM published in table. n = 64 (n represents number of observations used in the statistical analysis). Data are presented as LSM.

[3]Contrasts: effect of TMR without RP-His supplementation (TMR1: dHis1.8 vs. TMR2: dHis2.2); linear and quadratic effects of dHis dose with TMR2. Significance is declared at $P \leq 0.05$.

al., 2017; Zang et al., 2019). The numerically greater MY and greater milk fat concertation for cows on dHis2.6 resulted in greater milk fat yield compared with the other treatments. This is in contrast to previous findings, in which milk fat concentration has been reported to decrease with increasing His supply, most likely due to dilution effect of increased MY, as discussed in the companion paper (Räisänen et al., 2021). Histidine supplementation has had varying effects on milk protein content in lactating dairy cows. Some experiments, in line with our data, did not report any effect of His on milk true protein concentration when His was supplemented to MP-adequate (Giallongo et al., 2017) or MP-deficient (Lee et al., 2012a; Zang et al., 2019) corn silage–based diets, or postruminally infused in cows fed grass silage–based diets (Korhonen et al., 2000; Kim et al., 2001). Others have observed an increase in true protein concentration (from 2.94 to 3.0%) with postruminal infusion of His in cows fed a grass silage–based diet (Huhtanen et al., 2002), or with RP-His supplementation on an MP-deficient corn silage–based diet (from 3.16 to 3.26%; Giallongo et al., 2015). In contrast to data from our current experiment but in line with data in our companion paper (Räisänen et al., 2021), milk protein yield has been consistently higher with His supplementation: around a 5 to 6% increase in cows with RP-His supplementation of a corn silage–based, MP-deficient diet (Giallongo et al., 2015; Zang et al., 2019) and 7 to 9% increase when His was infused postruminally (Korhonen et al., 2000; Huhtanen et al., 2002). Postruminal infusion of His increased milk protein yield by around 20% in 3 short-term, crossover experiments at adequate MP supply (Ouellet et al., 2014; Lapierre et al., 2014, 2020). In a longer-term experiment with MP-adequate diets, in which cows received a diet with dHis at 68 g/d, milk protein yield was 10% greater compared with that when cows were fed a diet supplying 49 g/d dHis (Giallongo et al., 2017). The lack of milk protein response in the current study indicates that the supplemental His was not used for milk protein synthesis, as also shown by the decreased apparent recovery of dietary dHis in milk His discussed below. Furthermore, the greater MUN concentration in cows fed TMR2 reflects the greater digestible AA intake and subsequent metabolism of excess AA to urea N, rather than to milk true protein.

Milk casein and NPN fractions and yields (Table 4) were similar between TMR1 and TMR2 and were not affected by His dose ($P \geq 0.14$). This is in accordance with the data observed for milk true protein concentrations and yields as well as MUN concentration, with no changes in milk protein and N content. In line with our data, Hadrová et al. (2012) reported no difference in casein concentration of milk true protein. However, in contrast to our data, milk true protein yield and casein and casein fraction yields were greater in cows infused duodenally with His in a short-term experiment, indicating a stimulatory effect of dHis on casein synthesis, as also discussed in Vanhatalo et al. (1999).

Plasma AA Concentrations and Calculated His Pools

Plasma His concentration was around 1.8 times greater ($P < 0.001$; Table 5) for cows on TMR2 than for cows on TMR1, but there was no effect of dHis dose on plasma His concentration. Similarly, Lys, Phe, Asn, branched-chain AA (**BCAA**), and the sums of EAA and total AA were greater ($P \leq 0.02$) for cows fed TMR2 compared with cows fed TMR1, and there was a quadratic response ($P = 0.05$) to dHis dose in plasma concentration of Val, and a tendency ($P \leq 0.09$) for Arg and the sum of EAA. Estimated His pools, apparent recovery of dHis in blood and milk, and Eff_{His} are presented in Table 6. Digestible His recovery in milk and blood, and recovery in total His pool (the sum of blood and milk His pools) were greater ($P < 0.001$) for

Table 5. Plasma AA concentration (μM) in mid-lactation dairy cows fed a MP-adequate diet supplying incremental levels of digestible (d)His

	Treatment[1]					*P*-value[3]		
Item	dHis1.8	dHis2.2	dHis2.6	dHis3.0	SEM[2]	TMR1 vs. TMR2	Linear	Quadratic
Met	19.0	18.4	17.3	17.9	0.69	0.48	0.35	0.32
Lys	72.8	84.2	79.6	83.1	3.14	<0.001	0.40	0.12
Thr	86.9	86.6	83.3	82.5	2.16	0.92	0.13	0.90
Arg	79.2	77.3	74.4	79.5	2.03	0.47	0.72	0.06
Ile	154	133	127	133	3.7	<0.001	0.72	0.26
Leu	157	205	198	207	4.5	<0.001	0.97	0.23
Val	330	397	372	393	8.1	<0.001	0.41	0.05
His	36.9	65.7	65.3	68.2	2.39	<0.001	0.39	0.28
Phe	45.9	51.7	52.0	52.7	1.59	0.007	0.64	0.79
ΣEAA	982	1,119	1,069	1,117	18.9	<0.001	0.60	0.09
Gly	271	263	251	262	8.06	0.35	0.58	0.15
Ser	88.9	89.2	86.8	89.0	3.03	0.95	0.82	0.46
Pro	102	101	100	99.2	2.53	0.77	0.58	0.90
Ala	282	281	283	263	15.0	0.93	0.25	0.15
Glu	50.1	49.5	49.0	47.8	2.28	0.77	0.53	0.73
Tau	30.9	31.5	30.9	31.0	1.21	0.69	0.70	0.86
Asn	35.9	40.1	37.8	38.7	1.42	0.02	0.28	0.41
Gln	216	211	210	210	4.11	0.32	0.82	0.92
Citr	67.1	64.2	64.2	66.4	1.59	0.19	0.43	0.41
Tyr	42.6	43.5	43.4	43.8	1.76	0.65	0.89	0.83
Orn	44.1	44.3	42.9	44.9	2.01	0.84	0.98	0.12
ΣNEAA	1,231	1,213	1,200	1,196	28.5	0.53	0.55	0.99
Total AA	2,213	2,331	2,269	2,312	36.1	0.02	0.48	0.26
1-MH[4]	14.2	15.0	15.1	14.9	0.50	0.16	0.87	0.86

[1]The 4 treatments supplied dHis at 46, 58, 69, and 79 g/d, respectively, from 2 basal diets and rumen-protected His (RP-His) product (dHis1.8: TMR1; dHis2.2: TMR2; dHis2.6: TMR2 + 11 g/d of dHis from RP-His; dHis3.0: TMR2 + 22 g/d of dHis from RP-His). Both basal diets were supplemented with RP-Lys and RP-Met.

[2]Largest SEM published in table. n = 64 (n represents number of observations used in the statistical analysis). Data are presented as LSM.

[3]Contrasts: effect of TMR without RP-His supplementation (TMR1: dHis1.8 vs. TMR2: dHis2.2); linear and quadratic effects of dHis dose with TMR2. Significance is declared at $P \leq 0.05$.

[4]1-Methylhistidine.

cows fed TMR1 than for cows fed TMR2. Digestible His recovery in the blood His pool and dHis recovery in the total His pool (%) decreased quadratically ($P \leq 0.04$) with dHis dose. The apparent efficiency of His utilization was greater ($P < 0.001$) for cows fed TMR1 than for cows fed TMR2 and decreased quadratically ($P = 0.005$) with dHis dose.

The increase in plasma His concentration in cows fed TMR2 compared with cows fed TMR1 was expected because TMR1 was formulated to be deficient in dHis. However, the lack of effect on plasma His concentration of an additional 11 and 22 g/d of dHis in treatments dHis2.6 and dHis3.0 on TMR2 was unexpected. Data from our companion paper with an MP-deficient diet supplemented with incremental levels of dHis showed a linear increase in plasma His concentration with increasing dHis dose with a similar RP-His product (Räisänen et al., 2021). Similarly, a recent study with incremental doses of RP-His added to an MP-deficient corn silage–based diet supplying 44 g/d dHis reported a linear increase in plasma His concentration, from 33.2 to 64.1 μM (Zang et al., 2019). Further, postruminal infusion of graded levels of His at 0, 2, 4, or 6 g/d with a grass silage–based diet (supplying 49 g/d His at the omasum) linearly increased plasma His concentration from 23 to 64 μM (Korhonen et al., 2000). However, in both of those studies, MY of the cows was relatively low, averaging 31.7 kg/d (Zang et al., 2019) or 28.0 kg/d (Korhonen et al., 2000), compared with that of cows in the current experiment (averaging 42.5 kg/d). There may have been a lower uptake of plasma His by the mammary gland in lower-producing cows, and thereby a greater plasma concentration of His at greater dHis doses in the former experiments.

Interestingly, in Lee et al. (2012a), cows fed an MP-adequate diet with a dHis supply of 54 g/d had a plasma His concentration of 48.4 μM, which was similar to that of cows fed an MP-deficient diet with 59 g/d of dHis (41.1 μM). On the other hand, Giallongo et al. (2017) reported a 2.4 times greater plasma His concentration in cows fed an MP-adequate diet supplying dHis at 68 g/d (similar to TMR2 in the current experiment) compared with cows fed an MP-adequate diet that supplied 49 g/d of dHis (similar to TMR1 in the current experiment). However, in line with the current experiment, plasma His concentration was similar

Table 6. Estimated digestible (d)His intake, His pools, and apparent recovery of dHis in milk of mid-lactation dairy cows fed a MP-adequate diet supplying incremental levels of dHis

	Treatment[1]					*P*-value[3]		
Item	dHis1.8	dHis2.2	dHis2.6	dHis3.0	SEM[2]	TMR1 vs. TMR2	Linear	Quadratic
Estimated dHis intake,[4] g/d	46.3	59.3	69.0	80.0	3.99	<0.001	<0.001	<0.001
Estimated dHis supply from RP-His, g/d	—	—	11.0	12.0	—	—	—	—
Milk His, g/d[5]	31.0	31.8	32.2	31.4	1.97	0.25	0.77	0.29
Apparent dHis recovery in milk His pool,[6] %	67.5	54.3	46.9	39.2	0.90	<0.001	<0.001	0.005
Blood His pools								
Plasma His,[7] g	0.161	0.290	0.289	0.298	0.0139	<0.001	0.54	0.46
His in 1-methylhistidine,[7] g	0.062	0.068	0.067	0.065	0.0043	0.11	0.25	0.15
His in hemoglobin,[7] g	3.12	3.19	3.20	3.17	0.098	0.12	0.78	0.51
Total His blood pool,[8] g	3.34	3.55	3.56	3.53	0.109	<0.001	0.88	0.64
Apparent dHis recovery in blood pool,[9] %	7.29	6.10	5.21	4.46	0.268	<0.001	<0.001	0.04
Apparent dHis recovery in total His pool,[10] %	74.8	60.4	52.2	43.7	0.94	<0.001	<0.001	0.003
Eff_{His}[11]	0.941	0.749	0.647	0.548	0.0147	<0.001	<0.001	0.005

[1]The 4 treatments supplied dHis at 46, 58, 69 and 79 g/d, respectively, from 2 basal diets and rumen-protected His (RP-His) product (dHis1.8: TMR1; dHis2.2: TMR2; dHis2.6: TMR2 + 11 g/d of dHis from RP-His; dHis3.0: TMR2 + 22 g/d of dHis from RP-His). Both basal diets were supplemented with RP-Lys and RP-Met.

[2]Largest SEM published in table. n = 64 (n represents number of observations used in the statistical analysis). Data are presented as LSM.

[3]Contrasts: effect of TMR without RP-His supplementation (TMR1: dHis1.8 vs. TMR2: dHis2.2); linear and quadratic effects of dHis dose with TMR2. Significance is declared at $P \leq 0.05$.

[4]Estimated using NRC (2001) based on the individual cow DMI, MY, and milk composition during the experiment and includes dHis from basal diet and RP-His.

[5]Calculated as milk CP × His milk concentration, % of milk CP × MY (g/d). Milk His concentration was assumed to be 2.7% of milk CP.

[6]Calculated as milk His (g) ÷ dHis intake (g) × 100.

[7]Calculated based on an assumed blood volume of 6.7% of BW and plasma volume of 68% of blood volume.

[8]Sum of plasma His (g), His in 1-methyl His and blood hemoglobin.

[9]Calculated as total His in blood (g) ÷ dHis intake (g) × 100.

[10]Calculated as [total His in blood (g) + milk His (g)] ÷ dHis intake (g) × 100.

[11]Calculated as sum of His in true exported proteins (g) ÷ [dHis flow (g) – urinary excretions (g)]. For details, see Material and Methods section.

(averaging 45 μ*M*) between cows that received a basal diet supplying 67 g/d of dHis (MP-adequate diet) and those that received an MP-deficient diet supplying 56 or 75 g/d of dHis with RP-His (Giallongo et al., 2015).

Our results indicate a saturation of plasma His concentration at dHis supplementation levels above 58 g/d (Fleming et al., 2019), as well as an increased tissue uptake of plasma His at greater production levels for dHis2.6 treatment (Bequette et al., 2000). Interestingly, studies in chicks (Robbins et al., 1977) and piglets (Li et al., 2002) measuring His requirements in growing animals reported that serum His levels remained stable regardless of increasing dietary supply of His. This was attributed to tissue uptake of free His for gain and for synthesis of carnosine (Li et al., 2002). In line with this, the proportion of estimated dHis recovered in the combined blood His and milk His pools in the current study decreased linearly, showing that part of the ingested and absorbed His was directed elsewhere in the body or manure and was not used for synthesis of milk protein. Indeed, a recent crossover experiment showed a linear increase in muscle His concentration with increasing His dose (Zang et al., 2019), whereas Giallongo et al. (2017) reported a 2-fold increase in muscle His concentration in cows receiving 68 versus 49 g/d dHis. This indicates that part of the absorbed supplemental His can be directed to tissues other than the mammary gland.

The lack of response in plasma His concentration and milk protein yield to dHis dose discussed above in the current experiment is most likely a result of a decreased mammary blood flow, and thereby decreased uptake of His by the mammary gland with increasing dietary supply of dHis (Bequette et al., 2000; Cant et al., 2018), and an increased hepatic removal of His (Raggio et al., 2004). Recent data from Lapierre et al. (2020) showed that net liver removal of His decreased with decreased dHis supply, revealing the underlying reason for a more efficient His use when dHis supply is limited. In line with this concept, Eff_{His} decreased quadratically with increasing dHis dose in the current experiment. According to Lapierre et al. (2020), a target Eff_{His} would be around 0.77, such that TMR1 in the current experiment would be His-deficient, whereas the Eff_{His} for TMR2 was close to the target efficiency. Based on data in our companion paper (Räisänen et al., 2021), where an MP-deficient diet was supplemented with incremental levels of dHis, the overall calculated dHis recovery

Table 7. Intake and apparent total-tract digestibility of nutrients in mid-lactation dairy cows fed a MP-adequate diet supplying incremental levels of digestible (d)His

	Treatment[1]					*P*-value[3]		
Item	dHis1.8	dHis2.2	dHis2.6	dHis3.0	SEM[2]	TMR1 vs. TMR2	Linear	Quadratic
Nutrient intake, kg/d								
DM	23.5	24.3	23.9	23.6	1.56	0.16	0.22	0.86
OM	22.0	22.8	22.4	22.2	1.46	0.11	0.22	0.86
CP	3.95	4.15	4.08	4.04	0.256	0.04	0.22	0.85
NDF	7.61	7.85	7.47	7.38	0.490	0.87	0.28	0.81
ADF	4.36	4.35	4.29	4.23	0.282	0.93	0.28	0.78
Starch	6.58	6.80	6.69	6.61	0.437	0.16	0.23	0.86
Apparent digestibility, %								
DM	66.1	70.1	70.1	70.3	0.42	<0.001	0.76	0.80
OM	66.8	70.8	70.7	71.0	0.40	<0.001	0.84	0.66
CP	63.9	68.9	69.9	69.7	0.89	<0.001	0.46	0.73
NDF	44.5	48.4	47.6	48.7	0.79	<0.001	0.98	0.24
ADF	42.1	46.5	44.9	46.4	0.87	<0.001	0.55	0.10
Starch	97.0	97.5	97.3	97.4	0.10	<0.001	0.37	0.30

[1]The 4 treatments supplied dHis at 46, 58, 69 and 79 g/d, respectively, from 2 basal diets and rumen-protected His (RP-His) product (dHis1.8: TMR1; dHis2.2: TMR2; dHis2.6: TMR2 + 11 g/d of dHis from RP-His; dHis3.0: TMR2 + 22 g/d of dHis from RP-His). Both basal diets were supplemented with RP-Lys and RP-Met.

[2]Largest SEM published in table. n = 64 (n represents number of observations used in the statistical analysis). Data are presented as LSM.

[3]Contrasts: effect of TMR without RP-His supplementation (TMR1: dHis1.8 vs. TMR2: dHis2.2); linear and quadratic effects of dHis dose with TMR2. Significance is declared at $P \leq 0.05$.

in milk was greater compared with the current data but decreased linearly with increasing dHis dose. Together, our data further confirm the concept of decreased efficiency of AA use by the mammary gland for milk protein with increasing dAA supply and is affected by the MP supply and overall balance of absorbed AA (Raggio et al., 2004; Lee et al., 2015; Omphalius et al., 2020).

The greater plasma concentration of other AA, specifically BCAA (+13%), EAA (+12%), and total AA (+4%), in cows on TMR2 can be attributed to the inclusion of blood meal in that diet, and, thereby, greater supply of dEAA with TMR2 (Table 2). Similar results for plasma BCAA concentrations were reported by Giallongo et al. (2017) with MP-adequate diets similar to TMR1 and TMR2 in the current experiment, in which blood meal was replaced by feather meal to decrease the dHis content of the diet. Blood meal has been reported to contain up to 22% BCAA on an as-fed basis compared with 16.3% in feather meal (Li et al., 2011). Further, the RUP digestibility of blood meal is greater than that of feather meal, as discussed below.

Nutrient Digestibility and Nitrogen Utilization

The nutrient intake of cows (Table 7) did not differ among dHis doses ($P \geq 0.22$) or between TMR1 and TMR2 ($P \geq 0.11$), except for a lower ($P = 0.04$) CP intake for cows fed TMR1 compared with TMR2. However, apparent total-tract digestibility of all nutrients was lower ($P < 0.001$) for cows fed TMR1 compared with cows fed TMR2. Nitrogen intake was greater ($P = 0.04$) and UUN excretion tended to be greater ($P = 0.07$) for cows fed TMR2 (Table 8). Fecal N excretion was greater ($P = 0.02$) for cows fed TMR1 and fecal N and total excreta N as percentage of N intake was greater ($P \leq 0.02$) for cows on TMR1.

In line with the current data, Giallongo et al. (2017) observed lower digestibility of DM, OM, CP, and NDF in cows receiving a low-His diet (similar to TMR1) compared with cows receiving a diet supplying 68 g/d of dHis (similar to TMR2). The lower digestibility of CP was attributed to lower RUP digestibility of feather meal compared with blood meal (low-His vs. high-His diet, respectively), whereas lower NDF digestibility was a result of the greater NDF content of feather meal compared with blood meal (Giallongo et al., 2017). Indeed, the NDF content of feather meal in the current experiment was 23%, whereas blood meal had 1.4% NDF. Further, the RUP digestibility in the current experiment was markedly lower for feather meal compared with blood meal (50.5 vs. 80.5%), resulting in an overall lower CP digestibility of TMR1. This was also reflected in the greater fecal and total N excretion for cows fed TMR1 compared with cows fed TMR2. The difference in RUP digestibility of the feather meal and blood meal, and thereby a greater supply of dLeu (around +23 g/d) and dVal (around +13 g/d) from TMR2, were also reflected in the plasma concentration of BCAA as discussed above. In accordance with our data, previous experiments have shown no positive effect of BCAA on milk or milk protein yields (Korhonen

Table 8. Nitrogen utilization and purine derivatives (PD) excretion in mid-lactation dairy cows fed a MP-adequate diet supplying incremental levels of digestible (d)His

	Treatment[1]					*P*-value[3]		
Item	dHis1.8	dHis2.2	dHis2.6	dHis3.0	SEM[2]	TMR1 vs. TMR2	Linear	Quadratic
N intake, g/d	632	665	656	650	42.5	0.04	0.34	0.92
N excretion or secretion, g/d								
Urinary N	213	224	220	218	14.8	0.37	0.63	0.99
Urinary urea N	126	142	147	138	9.96	0.07	0.83	0.29
Fecal N	229	206	197	196	12.7	0.02	0.26	0.83
Total excreta N	442	431	417	414	25.1	0.48	0.27	0.89
Milk N	178	183	185	181	11.3	0.25	0.77	0.29
N excretion and secretion	620	614	602	595	35.2	0.68	0.24	0.88
As proportion of N intake, %								
Urine N	34.5	34.1	33.7	34.2	1.53	0.88	0.97	0.82
Urinary urea N	20.3	21.8	22.6	21.6	0.94	0.30	0.93	0.48
Fecal N	36.1	31.0	30.0	30.1	0.89	<0.001	0.37	0.76
Total excreta N	70.6	65.2	63.7	64.2	1.77	0.02	0.60	0.71
Milk N	28.4	27.8	28.5	27.8	0.41	0.31	0.77	0.19
N excretion and secretion	99.0	93.0	92.2	92.0	1.65	0.007	0.63	0.98
Urine output, kg/d	19.5	19.8	19.5	19.4	1.45	0.69	0.52	0.95
Urinary PD excretion, mmol/d								
Uric acid	83.3	87.4	83.1	86.8	6.51	0.60	0.82	0.58
Allantoin	539	536	518	532	36.2	0.93	0.79	0.63
Total PD	622	624	601	618	40.7	0.98	0.79	0.60

[1]The 4 treatments supplied dHis at 46, 58, 69, and 79 g/d, respectively, from 2 basal diets and rumen-protected His (RP-His) product (dHis1.8: TMR1; dHis2.2: TMR2; dHis2.6: TMR2 + 11 g/d of dHis from RP-His; dHis3.0: TMR2 + 22 g/d of dHis from RP-His). Both basal diets were supplemented with RP-Lys and RP-Met.

[2]Largest SEM published in table.

[3]Contrasts: effect of TMR without RP-His supplementation (TMR1: dHis1.8 vs. TMR2: dHis2.2); linear and quadratic effects of dHis dose with TMR2. Significance is declared at $P \leq 0.05$.

et al., 2002; Curtis et al., 2018). Instead, part of the additional EAA supplied from TMR2 was oxidized in the liver and removed through urea N as discussed above. Indeed, the daily excretion of UUN followed a similar pattern as the MUN concentration discussed above and is in line with greater N intake by cows fed TMR2 versus TMR1. Responses in lactational performance to BCAA have been variable across experiments and seem to be dependent on energy and protein or AA supply from the basal diet (Appuhamy et al., 2011).

Blood Serum Metabolites

There was a tendency ($P = 0.10$) for a greater histamine concentration in cows fed TMR1 versus TMR2 and a linear increase ($P = 0.03$) in blood histamine concentration with dHis dose. No differences ($P \geq 0.26$) in serum concentration of insulin, NPY, GLP-1, or blood hemoglobin were observed when comparing cows on TMR1 with cows on TMR2, nor was there any effect of dHis dose on these parameters (Table 9).

Table 9. Concentration of serum hormones and blood metabolites of mid-lactation dairy cows fed a MP-adequate diet supplying incremental levels of digestible (d)His

	Treatment[1]					*P*-value[3]		
Item	dHis1.8	dHis2.2	dHis2.6	dHis3.0	SEM[2]	TMR1 vs. TMR2	Linear	Quadratic
Glucagon-like peptide-1, n*M*	12.0	13.0	12.7	15.4	1.16	0.54	0.22	0.14
Neuropeptide Y, n*M*	3.24	3.99	3.45	3.62	0.528	0.26	0.49	0.65
Insulin, p*M*	198	214	185	196	25.3	0.66	0.52	0.63
Histamine, n*M*	10.7	9.38	10.2	11.2	0.714	0.10	0.03	0.50
Hemoglobin, g/dL	9.56	9.60	9.63	9.63	0.211	0.64	0.79	0.87

[1]The 4 treatments supplied dHis at 46, 58, 69, and 79 g/d, respectively, from 2 basal diets and rumen-protected His (RP-His) product (dHis1.8: TMR1; dHis2.2: TMR2; dHis2.6: TMR2 + 11 g/d of dHis from RP-His; dHis3.0: TMR2 + 22 g/d of dHis from RP-His). Both basal diets were supplemented with RP-Lys and RP-Met.

[2]Largest SEM published in table. n = 64 (n represents number of observations used in the statistical analysis). Data are presented as LSM.

[3]Contrasts: effect of TMR without RP-His supplementation (TMR1: dHis1.8 vs. TMR2: dHis2.2); linear and quadratic effects of dHis dose with TMR2. Significance is declared at $P \leq 0.05$.

Histidine and other AA (such as Arg, Asp, Ser, and Thr) have been associated with GLP-1 (a satiety-inducing gut peptide) and NPY (a feed intake-stimulating peptide) in monogastric animals (Haas et al., 2008; van den Broek et al., 2018). The lack of response in DMI and lack of effect of His dose on the feed intake regulating hormones can be attributed to the overall balanced dietary supply of AA across treatments in the current experiment (Mercer et al., 1990). Further research is warranted to specifically investigate the mechanisms and effects of His and other AA on feed intake both on neurological and endocrinological level in lactating dairy cows.

To our knowledge, there are no previous reports on plasma histamine concentration in lactating dairy cows. However, studies in monogastric animals have shown an increased histamine concentration with increasing dietary His supply and with increased plasma His concentration (Mercer, et al., 1990; Li et al., 2002; Kasaoka et al., 2004). The linear increase of serum histamine concentration in the current experiment indicates that part of the His absorbed in plasma was converted to histamine, which may partly explain the lack of linear increase in plasma His concentration at higher dHis doses, as discussed above. Histamine has been reported to play a role in His-induced depression in feed intake in monogastric animals. A protein-deficient diet with low His content fed to rats led to an increased serum His concentration and a subsequent increase in His and histamine concentrations in the brain (Mercer et al., 1989). The depressed intake under His deficiency was attributed to the increase in brain His and histamine, and its effects on the hypothalamus (Mercer et al., 1989, 1990). More recent studies have shown that His supplementation increases the transportation of His to the brain and its conversion to histamine, causing a subsequent decrease in feed intake (Yoshimatsu et al., 2002; Kasaoka et al., 2004). Other studies in nonruminant animals have shown a positive effect of His on voluntary feed intake, as discussed in Giallongo et al. (2015). The lack of effect of His dose on plasma His concentration as well as DMI in the current experiment does not offer clarification of the possible role of His and histamine in feed intake regulation in ruminants.

Furthermore, and as mentioned above, the His deficiency of TMR1 may not have been severe in the current experiment, as indicated by the lack of difference in hemoglobin concentration across treatments. This may explain the lack of effect of His on DMI. It has been suggested that under His deficiency there is an increased catabolism of hemoglobin (Mercer et al., 1989), which would provide additional His to support the animal's His needs. Indeed, a decrease in blood hemoglobin in His-deficient cows was observed in Giallongo et al. (2017), but it took around 6 wk before there were any significant differences in blood hemoglobin between cows on His-adequate versus His-deficient diets. Therefore, it is possible that 4 wk is not enough time to trigger a severe His deficiency in cows fed diets supplying 46 g/d dHis, therefore, the DMI, production, and plasma AA responses to increasing His doses might not have been apparent in the current experiment. Additionally, the overall balanced dietary supply of MP and dAA may have masked the possible effects of His and histamine on feed intake regulation.

CONCLUSIONS

In the conditions of the current experiment, the greatest milk fat and ECM yields were achieved with a dHis supply of 2.65% of MP or 69 g/d, whereas neither concentration nor yield of milk true protein was affected by dHis dose. The lack of plasma response to increasing dHis dose above dHis supply of 58 g/d was unexpected and needs further investigation. Histidine deficiency was not apparent in lactating dairy cows in this short-term experiment, and therefore long-term experiments are needed to establish His metabolism and requirements, and the effect of His deficiency on DMI and milk production in lactating dairy cows fed an MP-adequate diet.

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REFERENCES

Anthony, T. G., and D. W. Gietzen. 2013. Detection of amino acid deprivation in the central nervous system. Curr. Opin. Clin.

Nutr. Metab. Care 16:96–101. https://doi.org/10.1097/MCO.0b013e32835b618b.
AOAC International. 1995. Official Method of Analysis. 16th ed. AOAC International.
AOAC International. 2000. Official Methods of Analysis. 17th ed. AOAC International.
Appuhamy, J. A. D. R. N., J. R. Knapp, O. Becvar, J. Escobar, and M. D. Hanigan. 2011. Effects of jugular-infused lysine, methionine, and branched-chain amino acids on milk protein synthesis in high-producing dairy cows. J. Dairy Sci. 94:1952–1960. https://doi.org/10.3168/jds.2010-3442.
Bequette, B. J., M. D. Hanigan, A. G. Calder, C. K. Reynolds, G. E. Lobley, and J. C. MacRae. 2000. Amino acid exchange by the mammary gland of lactating goats when histidine limits milk production. J. Dairy Sci. 83:765–775. https://doi.org/10.3168/jds.S0022-0302(00)74939-3.
Brosnan, M. E., and J. T. Brosnan. 2020. Histidine metabolism and function. J. Nutr. 150(Suppl. 1):2570S–2575S. https://doi.org/10.1093/jn/nxaa079.
Calsamiglia, S., and M. D. Stern. 1995. A three-step in vitro procedure for estimating intestinal digestion of protein in ruminants. J. Anim. Sci. 73:1459–1465. https://doi.org/10.2527/1995.7351459x.
Cant, J. P., J. J. M. Kim, S. R. L. Cieslar, and J. Doelman. 2018. Symposium review: Amino acid uptake by the mammary glands: Where does the control lie? J. Dairy Sci. 101:5655–5666. https://doi.org/10.3168/jds.2017-13844.
Chen, X. B., Y. K. Chen, M. F. Franklin, E. R. Ørskov, and W. J. Shand. 1992. The effect of feed intake and body weight on purine derivative excretion and microbial protein supply in sheep1. J. Anim. Sci. 70:1534–1542. https://doi.org/10.2527/1992.7051534x.
Curtis, R. V., J. J. M. Kim, J. Doelman, and J. P. Cant. 2018. Maintenance of plasma branched-chain amino acid concentrations during glucose infusion directs essential amino acids to extra-mammary tissues in lactating dairy cows. J. Dairy Sci. 101:4542–4553. https://doi.org/10.3168/jds.2017-13236.
European Union. 2009. Commission regulation (EU) No 152/2009 of 27 January 2009 laying down the methods of sampling and analysis for the official control of feed. Official Journal of the European Union. Accessed May 18, 2021. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32009R0152.
Fleming, A. J., K. A. Estes, H. Choi, B. A. Barton, C. A. Zimmerman, and M. D. Hanigan. 2019. Assessing bioavailability of ruminally protected methionine and lysine prototypes. J. Dairy Sci. 102:4014–4024. https://doi.org/10.3168/jds.2018-14667.
Giallongo, F., M. T. Harper, J. Oh, C. Parys, I. Shinzato, and A. N. Hristov. 2017. Histidine deficiency has a negative effect on lactational performance of dairy cows. J. Dairy Sci. 100:2784–2800. https://doi.org/10.3168/jds.2016-11992.
Giallongo, F., A. N. Hristov, J. Oh, T. Frederick, H. Weeks, J. Werner, H. Lapierre, R. A. Patton, A. Gehman, and C. Parys. 2015. Effects of slow-release urea and rumen-protected methionine and histidine on performance of dairy cows. J. Dairy Sci. 98:3292–3308. https://doi.org/10.3168/jds.2014-8791.
Haas, H. L., O. A. Sergeeva, and O. Selbach. 2008. Histamine in the nervous system. Physiol. Rev. 88:1183–1241. https://doi.org/10.1152/physrev.00043.2007.
Hadrová, S., L. Křížová, M. Richter, J. Třináctý, and M. Dračková. 2012. The effect of duodenal infusion of histidine on milk yield, milk composition, and plasma amino acids in dairy cows. J. Anim. Feed Sci. 21:555–565. https://doi.org/10.22358/jafs/66129/2012.
Hall, M. B. 2009. Determination of starch, including maltooligosaccharides, in animal feeds: Comparison of methods and a method recommended for AOAC collaborative study. J. AOAC Int. 92:42–49. https://doi.org/10.1093/jaoac/92.1.42.
Heeley, N., and C. Blouet. 2016. Central amino acid sensing in the control of feeding behavior. Front. Endocrinol. (Lausanne) 7:148. https://doi.org/10.3389/fendo.2016.00148.
Hristov, A. N., K. Heyler, E. Schurman, K. Griswold, P. Topper, M. Hile, V. Ishler, E. Fabian-Wheeler, and S. Dinh. 2015. Case study: Reducing dietary protein decreased the ammonia emitting potential of manure from commercial dairy farms. Prof. Anim. Sci. 31:68–79. https://doi.org/10.15232/pas.2014-01360.
Hristov, A. N., C. Lee, T. Cassidy, M. Long, K. Heyler, B. Corl, and R. Forster. 2011. Effects of lauric and myristic acids on ruminal fermentation, production, and milk fatty acid composition in lactating dairy cows. J. Dairy Sci. 94:382–395. https://doi.org/10.3168/jds.2010-3508.
Huhtanen, P., K. Kaustell, and S. Jaakkola. 1994. The use of internal markers to predict total digestibility and duodenal flow of nutrients in cattle given six different diets. Anim. Feed Sci. Technol. 48:211–227. https://doi.org/10.1016/0377-8401(94)90173-2.
Huhtanen, P., A. Vanhatalo, and T. Varvikko. 2002. Effects of abomasal infusions of histidine, glucose, and leucine on milk production and plasma metabolites of dairy cows fed grass silage diets. J. Dairy Sci. 85:204–216. https://doi.org/10.3168/jds.S0022-0302(02)74069-1.
Kasaoka, S., N. Tsuboyama-Kasaoka, Y. Kawahara, S. Inoue, M. Tsuji, O. Ezaki, H. Kato, T. Tsuchiya, H. Okuda, and S. Nakajima. 2004. Histidine supplementation suppresses food intake and fat accumulation in rats. Nutrition 20:991–996. https://doi.org/10.1016/j.nut.2004.08.006.
Kim, C.-H., J.-J. Choung, and D. G. Chamberlain. 1999. Determination of the first-limiting amino acid for milk production in dairy cows consuming a diet of grass silage and a cereal-based supplement containing feather meal. J. Sci. Food Agric. 79:1703–1708. https://doi.org/10.1002/(SICI)1097-0010(199909)79:12<1703::AID-JSFA424>3.0.CO;2-5.
Kim, C.-H., J.-J. Choung, and D. G. Chamberlain. 2001. Estimates of the efficiency of transfer of L-histidine from blood to milk when it is the first-limiting amino acid for secretion of milk protein in the dairy cow. J. Sci. Food Agric. 81:1150–1155. https://doi.org/10.1002/jsfa.923.
Korhonen, M., A. Vanhatalo, and P. Huhtanen. 2002. Evaluation of isoleucine, leucine, and valine as a second-limiting amino acid for milk production in dairy cows fed grass silage diet. J. Dairy Sci. 85:1533–1545. https://doi.org/10.3168/jds.S0022-0302(02)74223-9.
Korhonen, M., A. Vanhatalo, T. Varvikko, and P. Huhtanen. 2000. Responses to graded postruminal doses of histidine in dairy cows fed grass silage diets. J. Dairy Sci. 83:2596–2608. https://doi.org/10.3168/jds.S0022-0302(00)75153-8.
Kurose, Y., and Y. Terashima. 2007. Roles of central histaminergic system in glucose metabolisms and food intake in sheep. Anim. Sci. J. 78:66–69. https://doi.org/10.1111/j.1740-0929.2006.00406.x.
Lapierre, H., G. E. Lobley, and D. R. Ouellet. 2021. Histidine optimal supply in dairy cows through determination of a threshold efficiency. J. Dairy Sci. 104:1759–1776. https://doi.org/10.3168/jds.2020-19205.
Lapierre, H., D. R. Ouellet, and G. E. Lobley. 2014. Estimation of histidine requirement in lactating dairy cows. J. Dairy Sci. 97:757–758.
Lee, C., F. Giallongo, A. N. Hristov, H. Lapierre, T. W. Cassidy, K. S. Heyler, G. A. Varga, and C. Parys. 2015. Effect of dietary protein level and rumen-protected amino acid supplementation on amino acid utilization for milk protein in lactating dairy cows. J. Dairy Sci. 98:1885–1902. https://doi.org/10.3168/jds.2014-8496.
Lee, C., A. N. Hristov, T. W. Cassidy, K. S. Heyler, H. Lapierre, G. A. Varga, M. J. de Veth, R. A. Patton, and C. Parys. 2012a. Rumen-protected lysine, methionine, and histidine increase milk protein yield in dairy cows fed a metabolizable protein-deficient diet. J. Dairy Sci. 95:6042–6056. https://doi.org/10.3168/jds.2012-5581.
Lee, C., A. N. Hristov, K. S. Heyler, T. W. Cassidy, H. Lapierre, G. A. Varga, and C. Parys. 2012b. Effects of metabolizable protein supply and amino acid supplementation on nitrogen utilization, milk production, and ammonia emissions from manure in dairy cows. J. Dairy Sci. 95:5253–5268. https://doi.org/10.3168/jds.2012-5366.
Li, D. F., J. H. Zhang, and L. M. Gong. 2002. Optimum ratio of histidine in the piglet ideal protein model and its effects on the body metabolism. Arch. Tierernaehrung 56:199–212. https://doi.org/10.1080/00039420214187.

Li, X., R. Rezaei, P. Li, and G. Wu. 2011. Composition of amino acids in feed ingredients for animal diets. Amino Acids 40:1159–1168. https://doi.org/10.1007/s00726-010-0740-y.

Mercer, L. P., S. J. Dodds, M. R. Schweisthal, and J. D. Dunn. 1989. Brain histidine and food intake in rats fed diets deficient in single amino acids. J. Nutr. 119:66–74. https://doi.org/10.1093/jn/119.1.66.

Mercer, L. P., S. J. Dodds, M. D. Weber, and J. D. Dunn. 1990. Histidine, histamine, and the neuroregulation of food intake: A review and hypothesis. Nutrition 6:273–277.

NRC. 2001. Nutrient Requirements of Dairy Cattle. 7th ed. National Academies Press.

Omphalius, C., H. Lapierre, J. Guinard-Flament, P. Lamberton, L. Bahloul, and S. Lemosquet. 2019. Amino acid efficiencies of utilization vary by different mechanisms in response to energy and protein supplies in dairy cows: Study at mammary-gland and whole-body levels. J. Dairy Sci. 102:9883–9901. https://doi.org/10.3168/jds.2019-16433.

Ouellet, D. R., G. E. Lobley, and H. Lapierre. 2014. Histidine requirement of dairy cow determined by the indicator amino acid oxidation (AAO) technique. J. Dairy Sci. 97:757.

Patton, R. A., A. N. Hristov, and H. Lapierre. 2014. Protein feeding and balancing for amino acids in lactating dairy cattle. Vet. Clin. North Am. Food Anim. Pract. 30:599–621. https://doi.org/10.1016/j.cvfa.2014.07.005.

Raggio, G., D. Pacheco, R. Berthiaume, G. E. Lobley, D. Pellerin, G. Allard, P. Dubreuil, and H. Lapierre. 2004. Effect of level of metabolizable protein on splanchnic flux of amino acids in lactating dairy cows. J. Dairy Sci. 87:3461–3472. https://doi.org/10.3168/jds.S0022-0302(04)73481-5.

Räisänen, S. E., C. F. A. Lage, M. E. Fetter, A. Melgar, A. M. Pelaez, H. A. Stefenoni, D. E. Wasson, S. F. Cueva, X. Zhu, M. Miura, and A. N. Hristov. 2021. Histidine dose-response effects on lactational performance of lactating dairy cows: 2. Metabolizable protein-deficient diet. J. Dairy Sci. 104:9917–9930. https://doi.org/10.3168/jds.2020-20189.

Räisänen, S. E., C. M. M. R. Martins, K. Nedelkov, J. Oh, M. T. Harper, X. Chen, C. Parys, R. A. Patton, M. Miura, and A. N. Hristov. 2020. Bioavailability of rumen-protected methionine, lysine and histidine assessed by fecal amino acid excretion. Anim. Feed Sci. Technol. 268:114595. https://doi.org/10.1016/j.anifeedsci.2020.114595.

Reynolds, M. 1953. Measurement of bovine plasma and blood volume during pregnancy and lactation. Am. J. Physiol. 175:118–122. https://doi.org/10.1152/ajplegacy.1953.175.1.118.

Robbins, K. R., D. H. Baker, and H. W. Norton. 1977. Histidine status in the chick as measured by growth rate, plasma free histidine and breast muscle carnosine. J. Nutr. 107:2055–2061. https://doi.org/10.1093/jn/107.11.2055.

Schneider, B. H., and W. P. Flatt. 1975. The Evaluation of Feeds through Digestibility Experiments. University of Georgia Press.

Schwab, C. G., P. Huhtanen, C. W. Hunt, and T. Hvelplund. 2005. Nitrogen requirements of cattle. In Nitrogen and Phosphorus Nutrition of Cattle and the Environment. E. Pfeffer and A. N. Hristov, ed. CAB International.

Sjaunja, L. O., L. Baevre, L. Junkkarinen, J. Pedersen, and J. Setälä. 1990. A Nordic proposal for an energy corrected milk (ECM) formula. Pages 156–157 in 27th Session of the International Commission for Breeding and Productivity of Milk Animals, Paris, France. Wageningen Academic Publishers.

Stahel, P., N. G. Purdie, and J. P. Cant. 2014. Use of dietary feather meal to induce histidine deficiency or imbalance in dairy cows and effects on milk composition. J. Dairy Sci. 97:439–445. https://doi.org/10.3168/jds.2013-7269.

van den Broek, M., L. J. M. de Heide, M. Emous, R. B. Wijma, N. J. G. M. Veeger, A. Wolthuis, A. J. Laskewitz, M. R. Heiner-Fokkema, A. C. Muller Kobold, B. H. R. Wolffenbuttel, and A. P. van Beek. 2018. Satiety and gastrointestinal hormones during a Mixed Meal Tolerance Test after gastric bypass surgery: association with plasma amino acid concentrations. Surg. Obes. Relat. Dis. 14:1106–1117. https://doi.org/10.1016/j.soard.2018.05.010.

Van Soest, P. J., J. B. Robertson, and B. A. Lewis. 1991. Methods for dietary fiber, neutral detergent fiber, and nonstarch polysaccharides in relation to animal nutrition. J. Dairy Sci. 74:3583–3597. https://doi.org/10.3168/jds.S0022-0302(91)78551-2.

Vanhatalo, A., P. Huhtanen, V. Toivonen, and T. Varvikko. 1999. Response of dairy cows fed grass silage diets to abomasal infusions of histidine alone or in combinations with methionine and lysine. J. Dairy Sci. 82:2674–2685. https://doi.org/10.3168/jds.S0022-0302(99)75524-4.

Yoshimatsu, H., S. Chiba, D. Tajima, Y. Akehi, and T. Sakata. 2002. Histidine suppresses food intake through its conversion into neuronal histamine. Exp. Biol. Med. (Maywood) 227:63–68. https://doi.org/10.1177/153537020222700111.

Zang, Y., L. H. P. Silva, M. Ghelichkhan, M. Miura, N. L. Whitehouse, M. L. Chizzotti, and A. F. Brito. 2019. Incremental amounts of rumen-protected histidine increase plasma and muscle histidine concentrations and milk protein yield in dairy cows fed a metabolizable protein-deficient diet. J. Dairy Sci. 102:4138–4154. https://doi.org/10.3168/jds.2018-15780.